

# **THE 'CHG TRIAL'**

The effectiveness of 2% chlorhexidine gluconate in 70% isopropyl alcohol in the prevention of CVC-related infections in outpatient haemodialysis patients compared to routinely used chlorhexidine gluconate solutions: A pilot multi-centre randomised trial

A thesis presented to the  
University of Dublin, Trinity College Dublin,  
for the Degree of Doctor in Philosophy.

Margaret McCann

2014



## DECLARATION

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

I agree to deposit this thesis in the University's open access institutional repository or allow the library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

Signature: \_\_\_\_\_

Margaret McCann

Date: \_\_\_\_\_

# SUMMARY

## Background

The use of central venous catheters (CVC) in the outpatient haemodialysis population in Ireland is high. Due to the presence of this invasive medical device, this patient population are at an increased risk of healthcare-associated infections, an adverse event that has a profound impact on patient health and safety. Preventing CVC-related infections is key to keeping patients safe. The use of antiseptic solutions for CVC hub and exit site care is one strategy used in the prevention of catheter-related infections. A Cochrane Review undertaken as part of this thesis identified a lack of randomised evidence to inform decisions about the effectiveness of antiseptic solutions as exit site and catheter hub cleansing agents in haemodialysis patients. Additionally, a critical analysis of the randomised control trial (RCT) evidence found no RCTs that directly compared different strengths or formulations of chlorhexidine gluconate (CHG), so that the most effective and appropriate strength and formulation of CHG is not known. Despite this, a number of national and international bodies recommend the use of 2% CHG in 70% isopropyl alcohol as an antiseptic solution for the maintenance of CVCs.

The aims of this pilot multi-centre trial were twofold. The first was to test the trial methods in preparation for a study to evaluate the effectiveness of 2% CHG in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent in the reduction of CVC-related infection in outpatient haemodialysis patients, in comparison to other formulations of CHG that were in routine use at the time in Ireland. The second was to evaluate the feasibility of undertaking a future multi-national, multi-centre study on this topic.

## Study Design

Using a pragmatic design, this thesis reports on a pilot multi-centre parallel randomised controlled, open label, trial. A central telephone randomisation service used computer generated stratified allocation sequences to allocate intervention and comparator solutions. Primary outcomes were catheter-related infections (catheter-related bloodstream infections [CRBSI], catheter-associated bloodstream infections [CABSIs] and local access infections). Three outpatient haemodialysis units agreed to participate in the trial. The target population was haemodialysis patients with permanent cuffed tunnelled CVCs, over the age of 18 who required long term haemodialysis and who

attended for dialysis on an outpatient basis. In total, 105 of the 149 eligible patients gave informed consent to enter this trial (70% response rate), with 53 randomly assigned to the intervention group (who received 2% CHG in 70% isopropyl alcohol) and 52 to the comparator group (who received 0.5% CHG in 70% isopropyl alcohol [ $n=42$ ] or 0.05% aqueous CHG [ $n=10$ ]). Findings are based on an 'intention-to-treat' analysis.

## Findings

Methods used in this trial were appropriate for evaluating the effectiveness of 2% CHG in alcohol. Proposed amendments to the main study protocol include refining the research question, modifying the study's inclusion and exclusion criteria and refining primary and secondary outcomes. This trial did not show a difference between 2% CHG in alcohol and the comparator solution in the prevention of catheter-related infections (relative risk [RR] 0.49, 95% CI 0.18 to 1.34;  $p=0.15$ ), CRBSI (RR 0.49, 95% CI 0.05 to 5.25;  $p=0.55$ ), CABSIs (RR 0.25, 95% CI 0.03 to 2.12;  $p=0.16$ ) and local access infection (RR 0.74, 95% CI 0.17 to 3.13;  $p=0.68$ ). Given the small sample size and low event numbers, this is not unexpected.

Four participants in the intervention group experienced an adverse reaction (skin sensitivity reaction) to 2% CHG in 70% isopropyl alcohol; three participants withdrew from this trial because the intervention stained their clothes. No adverse reactions were observed in the comparator group. This pilot trial confirms that the main study is feasible, but only if the right conditions exist around funding, availability of appropriate dialysis research sites and standardisation of trial methodology.

Given this pilot trial's small sample size and low frequency of events, no conclusions for changes in practice can be drawn, but findings from this trial add to the evidence and can be used in a future meta-analysis of the evidence-based literature. The trial is registered on the International Standard Randomised Controlled Trial Number Register (ISRCTN2657745). Trial interventions (ChlorPrep® with tint and Sani-Cloth CHG 2% medical device wipes) were provided free of charge by CareFusion and PDI. Neither company had any involvement in the planning or conduct of the trial.

## ACKNOWLEDGEMENTS

My thesis would not have been possible without the help from a number of individuals. I would like to take this opportunity to thank:

The trial participants for taking part in this trial, it was a privilege meeting them during my weekly visits to the units.

My supervisors for their advice, guidance and council, I am forever grateful for the hard work associated with supervising this thesis:

- Professor Michael Clarke for his words of wisdom, patience and support and whose guidance made every problem surmountable;
- Dr Fidelma Fitzpatrick for her expertise, encouragement and clinical input, which was immeasurable;
- Professor Cecily Begley for her support, encouragement and input into this PhD thesis.

Professor George Mellotte for agreeing to act as trial Sponsor, without which, this trial would not have been possible. For his guidance, expertise and support on clinical issues during the planning, implementation and completion of this trial and thesis.

The dialysis nurse managers, whose support, input, enthusiasm, encouragement and motivation made this trial possible: Cesira McCrohan, Ali Al-lady, Glenda Taylor, Evonne Healy (The Adelaide and Meath Hospital, Dublin, Incorporating The National Children's Hospital at Tallaght [AMNCH]); Fe Delos Santos, Jacqui McEntee, Elaine McGrath, Roland Galang (Beacon Renal); Raj Ramkaun (formerly of Beacon Renal); and Michelle McQuaid and Carolann Flynn (St Vincent's University Hospital).

The dialysis nursing staff at each research site, for embracing this trial and their commitment to implementing the trial protocol. Their input ensured the success of the trial.

Professor Alan Watson for facilitating access to the Beacon Renal Unit and St Vincent's University Hospital haemodialysis unit, and agreeing to act as principal investigator at these research sites.

Dr Suzy Fitzgerald, St Vincent's University Hospital for her expertise and advice on clinical microbiology.

The Consultants and Directors of Nursing at each of the research sites for their support of the trial.

CareFusion (ChloroPrep® with Tint) and PDI (Sani-Cloth CHG 2% medical device wipes) for providing free of charge the investigational medicinal products used in the trial. Special thanks to Simon-Noble Clarke from CareFusion and Ron Tierney from PDI for organising the provision and delivery of these products.

Iskus Health for providing in-service training on the administration of ChloroPrep® with Tint.

Professor Catherine Comiskey, Professor Declan Devane and Dr Jerome Fennell for their work on the Trial Monitoring Committee.

My colleagues in the School of Nursing and Midwifery for their support and guidance during the PhD process.

Dr Catherine McCabe, my colleague and friend, for answering my phone calls in moments of crisis, keeping me calm, focusing my thoughts and pushing me forward.

To Michelle McCann for her exemplar work in inputting the trial data.

Finally, my deepest gratitude to my sisters Bernie and Roisin, in my darkest moments they shined a light that got me over each hurdle I encountered. For their unwavering support at every step of my PhD journey I am eternally grateful.

# TABLE OF CONTENTS

<b>Declaration</b> .....	<b>i</b>
<b>Summary</b> .....	<b>ii</b>
<b>Acknowledgements</b> .....	<b>iv</b>
<b>Table of Contents</b> .....	<b>vi</b>
<b>List of Tables</b> .....	<b>xvi</b>
<b>List of Figures</b> .....	<b>xvii</b>
<b>Glossary of Terms</b> .....	<b>xviii</b>
<b>Abbreviations</b> .....	<b>xx</b>
<b>Chapter 1: Introduction</b> .....	<b>1</b>
1.1 Introduction.....	1
1.2 Overview of the CHG Trial .....	1
1.3 Background & Context to the CHG Trial.....	2
1.4 Critical Analysis of the Literature.....	3
1.5 Routine Practice, Trial Design, Methods & Conduct.....	4
1.6 Results of CHG Trial & Discussion of Findings .....	6
<b>Section 1 Background &amp; Context</b> .....	<b>7</b>
<b>Chapter 2: Patient Safety &amp; Healthcare-Associated Infections</b> ....	<b>8</b>
2.1 Introduction.....	8
2.2 Adverse Events & Patient Safety .....	8
2.3 Patient Safety .....	14
2.4 Healthcare-Associated Infections.....	17
2.5 Infection Prevention & Control .....	23
2.6 The Role of the Renal Nurse.....	26
2.7 Summary .....	29
2.8 Conclusion.....	30
<b>Chapter 3: Haemodialysis Patients with Central Venous Catheters</b> .....	<b>32</b>
3.1 Introduction.....	32
3.2 End Stage Kidney Disease .....	33
3.3 Haemodialysis .....	34
3.4 Vascular Access .....	37
3.5 Central Venous Catheters.....	39
3.5.1 <i>Patient safety &amp; central venous catheter use</i> .....	40
3.5.2 <i>Pathogenesis of CVC-related infection</i> .....	46
3.5.3 <i>CVC-related bloodstream infections: case definitions</i> .....	48
3.6 Interventions Preventing CVC Infections.....	52
3.7 Summary .....	53
3.8 Conclusion.....	54



<b>Section 2</b>	<b>Critical Analysis of the Literature</b>	<b>57</b>
<b>Chapter 4:</b>	<b>Interventions for Preventing Infectious Complications in Haemodialysis Patients with Central Venous Catheters A Cochrane Review</b>	<b>58</b>
4.1	Introduction	58
4.2	Review Objectives	58
4.3	Review Methods	59
4.3.1	<i>Criteria for considering studies for this review</i>	59
4.3.1.1	Types of studies	59
4.3.1.2	Types of participants	59
4.3.1.3	Types of interventions	59
4.3.1.4	Types of outcome measures	60
4.3.2	<i>Search methods for identification of studies</i>	61
4.3.2.1	Electronic searches included	61
4.3.2.2	Searching other resources included	61
4.3.3	<i>Data collection &amp; analysis</i>	62
4.3.3.1	Selection of studies	62
4.3.3.2	Data extraction & management	62
4.3.3.3	Assessment of risk of bias in included studies	62
4.3.3.4	Quality checklist	63
4.3.3.5	Measures of treatment effect	64
4.3.3.6	Assessment of heterogeneity	64
4.3.3.7	Data synthesis	64
4.3.3.8	Subgroup analysis & investigation of heterogeneity	64
4.4	Results	64
4.4.1	<i>Description of studies</i>	64
4.4.2	<i>Interventions</i>	70
4.4.2.1	Topical antimicrobials	70
4.4.2.2	Topical mupirocin ointment	70
4.4.2.3	Topical povidone-iodine ointment	70
4.4.2.4	Topical polysporin ointment	70
4.4.2.5	Topical honey	70
4.4.2.6	Non-medicated dressings	70
4.4.2.7	Tunnelled versus non-tunnelled CVC	70
4.4.2.8	Post-insertion catheter care protocol	71
4.4.2.9	Other interventions	71
4.4.3	<i>Risk of bias in included studies</i>	71
4.4.3.1	Randomisation	71
4.4.3.2	Allocation concealment	71
4.4.3.3	Blinding	72

4.4.3.4	Intention-to-treat.....	72
4.4.3.5	Completeness of follow-up .....	72
4.5	Effects of Interventions .....	72
4.5.1	<i>Topical antimicrobial ointment</i> .....	72
4.5.1.1	Incidence & type of infections.....	72
4.5.1.2	Patient mortality .....	75
4.5.1.3	Survival rate of CVC.....	77
4.5.1.4	Episodes of hospitalisation.....	79
4.5.1.5	Time to development of infection.....	79
4.5.1.6	Adverse reactions .....	80
4.5.2	<i>Topical honey</i> .....	80
4.5.2.1	Incidence & type of infections.....	80
4.5.2.2	Adverse reactions .....	81
4.5.3	<i>Non-medicated dressings</i> .....	81
4.5.3.1	Incidence & type of infections.....	81
4.5.3.2	Adverse reactions .....	82
4.5.4	<i>Tunnelled CVC versus non-tunnelled CVC</i> .....	82
4.5.4.1	Incidence & type of infections.....	82
4.5.5	<i>Post insertion catheter care protocols (haemodialysis nurses using heparin 3 times/week versus intravenous team using heparin 3 times/day)</i> .....	82
4.5.5.1	Incidence & type of infections.....	82
4.5.5.2	Patient mortality .....	82
4.5.6	<i>Other outcomes</i> .....	83
4.6	Discussion .....	83
4.6.1	<i>Summary of main results</i> .....	83
4.6.1.1	Topical antimicrobial ointments .....	83
4.6.1.2	Topical honey.....	84
4.6.1.3	Non-medicated dressings.....	84
4.6.1.4	Other interventions.....	84
4.6.2	<i>Overall completeness &amp; applicability of evidence</i> .....	84
4.6.2.1	Topical antimicrobial ointments .....	84
4.6.2.2	Honey .....	87
4.6.2.3	Dressings .....	88
4.6.2.4	Other interventions.....	90
4.6.2.5	Agreements & disagreements with other studies or reviews.....	90
4.7	Implications for Practice.....	91
4.7.1	<i>Topical antimicrobial ointments &amp; honey</i> .....	91
4.7.2	<i>Dressings</i> .....	92

4.7.3	<i>Other interventions</i> .....	92
4.8	Implications for Research.....	92
4.8.1	<i>All interventions</i> .....	92
4.8.2	<i>Topical antimicrobial ointments &amp; honey</i> .....	93
4.8.3	<i>Dressings</i> .....	93
4.8.4	<i>Other Interventions</i> .....	93
4.9	Conclusions .....	94
<b>Chapter 5: Chlorhexidine Gluconate as an Antiseptic Cleansing Agent for Intravascular Catheters .....</b>		<b>95</b>
5.1	Introduction .....	95
5.2	Chlorhexidine Gluconate as a Skin Antiseptic .....	95
5.3	Randomised Trials of CHG CVC Antiseptic Agents.....	96
5.3.1	<i>Search strategy</i> .....	96
5.3.2	<i>Randomised trials of CHG as a CVC antiseptic agent</i> .....	98
5.4	Systematic Reviews on CVC Antiseptic Agents .....	107
5.5	Guidelines when Randomised Trial was Designed.....	111
5.6	Summary .....	111
5.7	Conclusion .....	114
<b>Section 3 Preparation for Trial: Ascertaining Routine Practice in Haemodialysis Units</b>		
<b>Trial Design, Methods &amp; Conduct.....</b>		<b>117</b>
<b>Chapter 6: Routine Practice in Haemodialysis Units.....</b>		<b>118</b>
6.1	Introduction .....	118
6.2	Routine Practice.....	118
6.3	Variation in Routine Practice .....	121
6.3.1	<i>Variation in infection prevention &amp; control practices</i> .....	121
6.3.2	<i>Variation in renal care practices</i> .....	124
6.4	Routine Practice in Haemodialysis Units in Ireland .....	125
6.4.1	<i>Research methodology</i> .....	126
6.4.1.1	Population .....	126
6.4.1.2	Survey design .....	126
6.4.1.3	Survey implementation .....	126
6.4.1.4	Data analysis.....	127
6.4.1.5	Ethical considerations.....	127
6.4.2	<i>Results</i> .....	127
6.4.2.1	Prevalence of vascular access .....	128
6.4.2.2	Timeline to formation of primary AVF .....	128
6.4.2.3	Access to vascular surgeon for creation of AVF .....	130
6.4.2.4	Dedicated theatre sessions for AVF formation.....	130
6.4.2.5	Infection prevention and control.....	130
6.4.2.6	CVC insertion .....	131
6.4.2.7	CVC care and maintenance.....	132

6.4.3	<i>Survey implications</i> .....	133
6.5	Conclusion.....	139
<b>Chapter 7:</b>	<b>Trial Design</b> .....	<b>142</b>
7.1	Introduction.....	142
7.2	Background & Significance .....	142
7.3	Research Question .....	144
7.4	Aim of Study .....	144
7.5	Primary Objectives.....	145
7.6	Secondary Objectives .....	145
7.7	Methodology .....	145
7.7.1	<i>Theoretical perspectives</i> .....	146
7.7.2	<i>Research methodology</i> .....	146
7.7.3	<i>True experimental design</i> .....	147
7.7.4	<i>Pragmatic versus explanatory approach</i> .....	149
7.8	Clinical Trial of a Medicinal Product for Human Use .....	150
7.9	Implications of EU Clinical Trial Directives .....	152
7.9.1	<i>Trial sponsor, chief investigator &amp; principal investigator</i> .....	152
7.9.2	<i>Good clinical practice &amp; investigational product accountability</i> .....	153
7.9.3	<i>Safety monitoring &amp; recording</i> .....	154
7.9.4	<i>Type of adverse reactions expected in CHG trial</i> .....	157
7.9.5	<i>Safety reports</i> .....	158
7.9.6	<i>Trial monitoring committee</i> .....	158
7.9.7	<i>Trial protocol &amp; standard operating procedures</i> .....	159
7.9.8	<i>Clinical indemnity for CHG trial</i> .....	160
7.9.9	<i>Trial management</i> .....	161
7.9.10	<i>Management of trial documentation</i> .....	161
7.9.11	<i>Trial approval</i> .....	162
7.10	Pilot Study .....	162
7.11	Comparative Groups.....	164
7.12	Validity in Clinical Trials .....	165
7.13	Blinding.....	167
7.14	Randomisation.....	169
7.14.1	<i>Generating randomised allocation sequence</i> .....	169
7.14.2	<i>Allocation concealment</i> .....	170
7.15	Clinical Trial Registration .....	170
7.16	Ethical Considerations .....	171
7.16.1	<i>Clinical equipoise</i> .....	171
7.16.2	<i>Respect for persons &amp; informed consent</i> .....	172
7.16.3	<i>Beneficence</i> .....	173
7.16.4	<i>Justice</i> .....	174
7.16.5	<i>Confidentiality and privacy</i> .....	174
7.17	Summary .....	175

<b>Chapter 8: Trial Methods &amp; Conduct.....</b>	<b>177</b>
8.1 Introduction .....	177
8.2 Research Sites .....	177
8.2.1 <i>Potential research sites</i> .....	178
8.2.2 <i>Confirmed research sites</i> .....	179
8.3 Permission to Access Research Sites.....	180
8.4 Trial Approval.....	180
8.5 Study Population.....	180
8.5.1 <i>Eligibility criteria</i> .....	181
8.6 Sampling.....	182
8.6.1 <i>Sample size calculation</i> .....	182
8.6.2 <i>Sample size for pilot study</i> .....	183
8.7 Recruitment .....	184
8.7.1 <i>Recruitment period &amp; follow-up</i> .....	186
8.8 Randomisation Process .....	186
8.9 Issues Related to Blinding.....	188
8.10 Preparation of Research Site and Staff .....	188
8.11 Trial Interventions .....	191
8.11.1 <i>Control intervention</i> .....	193
8.11.2 <i>Investigational product accountability</i> .....	194
8.11.2.1 Trial intervention.....	194
8.11.2.2 Control intervention .....	196
8.11.3 <i>Administration of trial intervention</i> .....	196
8.11.4 <i>Administration of control intervention</i> .....	197
8.11.5 <i>Standardised CVC care &amp; maintenance</i> .....	198
8.11.6 <i>End of trial</i> .....	198
8.12 Site-Visits.....	199
8.13 Compliance & Trial Deviations .....	200
8.14 Trial Outcomes.....	201
8.14.1 <i>Primary outcome case definitions</i> .....	202
8.14.2 <i>Diagnostic methods used to assess CRBSI &amp; CABSII</i> .....	205
8.14.3 <i>Secondary outcomes</i> .....	206
8.14.4 <i>Outcome reporting requirements</i> .....	207
8.14.5 <i>Monitoring for primary &amp; secondary outcomes</i> .....	208
8.15 Data Collection .....	209
8.15.1 <i>Development &amp; completion of data collection forms</i> .....	210
8.15.2 <i>Data collection interval</i> .....	212
8.15.3 <i>Quality control in data collection</i> .....	213
8.16 Data Management .....	214
8.17 Ethical Issues during the Conduct of the Trial .....	215
8.18 Amendments to Trial Protocol.....	217
8.19 Trial Management Issues.....	217
8.20 Safety Monitoring & Reporting During Trial.....	217
8.20.1 <i>Recording/reporting of adverse events &amp; reactions</i> .....	218
8.20.2 <i>Trial monitoring committee</i> .....	218

8.21	Data Analysis.....	219
8.21.1	<i>Intention-to-treat analysis</i> .....	219
8.21.2	<i>Data entry &amp; cleaning</i> .....	221
8.21.3	<i>Categorical data</i> .....	221
8.21.4	<i>Continuous data</i> .....	222
8.21.5	<i>Survival analysis</i> .....	223
8.21.6	<i>Logistic regression analysis</i> .....	223
8.22	Conclusion.....	225
<b>Section 4</b>	<b>Results &amp; Discussion of Findings.....</b>	<b>226</b>
<b>Chapter 9:</b>	<b>Results.....</b>	<b>227</b>
9.1	Introduction.....	227
9.2	Recruitment & Randomisation .....	228
9.2.1	<i>Lost to follow-up</i> .....	230
9.2.2	<i>Early discontinuation of solution</i> .....	230
9.3	Baseline Characteristics .....	231
9.4	Primary Outcomes .....	236
9.4.1	<i>Primary outcomes sub-comparison 1</i> .....	237
9.4.2	<i>Primary outcomes sub-comparison 2</i> .....	238
9.5	Secondary Categorical Outcomes.....	240
9.5.1	<i>Secondary categorical outcomes sub-comparison 1</i> .....	243
9.5.2	<i>Secondary categorical outcomes sub-comparison 2</i> .....	244
9.6	Secondary Continuous Outcomes.....	245
9.6.1	<i>Secondary continuous outcomes main comparison</i> .....	245
9.6.2	<i>Secondary continuous outcomes sub-comparison 1 &amp; 2</i> .....	247
9.7	Survival Outcomes.....	247
9.7.1	<i>Time to catheter-related events main comparison</i> .....	249
9.7.2	<i>Time to catheter-related events sub-comparison 1 &amp; 2</i> .....	253
9.8	Logistic Regression .....	254
9.9	Causative Organism .....	254
9.10	Vascular Access Prevalence.....	255
9.11	Summary .....	256
9.12	Conclusion: Impact on the Design of the Main Study .....	258
<b>Chapter 10:</b>	<b>Discussion &amp; Feasibility of Study .....</b>	<b>260</b>
10.1	Introduction.....	260
10.2	Catheter-Related Infections .....	260
10.2.1	<i>2% CHG in alcohol &amp; CRBSI</i> .....	262
10.2.2	<i>0.5% CHG in alcohol &amp; CRBSI</i> .....	262
10.2.3	<i>0.05% aqueous CHG &amp; CRBSI</i> .....	264
10.2.4	<i>CHG solutions &amp; exit site infections</i> .....	264
10.2.5	<i>CHG solutions &amp; CRBSI/CABSI causative organisms</i> .....	265
10.2.6	<i>Overview of trial primary objectives</i> .....	266
10.3	Dialysis Event Outcomes .....	268
10.4	Adverse Reactions.....	270
10.5	Vascular Access Prevalence.....	272
10.6	Feasibility.....	272

10.6.1	<i>Research sites for main study</i> .....	273
10.6.2	<i>Standardisation of trial methodology &amp; CVC care practices</i> ....	273
10.6.3	<i>Methodological issues for main study</i> .....	275
10.6.4	<i>Funding for main study</i> .....	279
10.7	<i>Limitations of Pilot Study</i> .....	280
10.8	<i>Summary</i> .....	281
10.9	<i>Conclusion, Implications &amp; Recommendations</i> .....	283
10.9.1	<i>Implications for practice</i> .....	283
10.9.2	<i>Implications for research</i> .....	284
10.9.3	<i>Recommendations for practice</i> .....	285
10.9.4	<i>Recommendations for research</i> .....	286
10.9.5	<i>Conclusion</i> .....	287
	<b>References</b> .....	<b>288</b>
	<b>Appendices</b> .....	<b>329</b>
	<i>Appendix 4.1 Chapter 4 Literature search strategy</i> .....	329
	<i>Appendix 5.1 Overview of CHG RCTs</i> .....	331
	<i>Appendix 5.2 CHG meta-analysis forest plots</i> .....	339
	<i>Appendix 6.1 Routine practice survey</i> .....	342
	<i>Appendix 7.1 National Competent Authority algorithm to determine clinical trials</i> .....	346
	<i>Appendix 7.2 Confirmation of trial sponsor</i> .....	347
	<i>Appendix 7.3 Delegation of tasks and duties related to trial</i> .....	348
	<i>Appendix 7.4 Education/Training for clinical trial design &amp; conduct</i> .....	349
	<i>Appendix 7.5 Confirmation of insurance cover, site OA &amp; OV</i> .....	350
	<i>Appendix 7.6 Confirmation of insurance cover site OB</i> .....	352
	<i>Appendix 7.7 Professional indemnity cover</i> .....	353
	<i>Appendix 7.8 Public liability cover</i> .....	354
	<i>Appendix 7.9 Letter of invite</i> .....	355
	<i>Appendix 7.10 Patient information leaflet</i> .....	356
	<i>Appendix 7.11 Consent Form</i> .....	362
	<i>Appendix 8.1 Research sites dialysis build environment</i> .....	364
	<i>Appendix 8.2 Research site routine CVC care</i> .....	366
	<i>Appendix 8.3 Permanent cuffed CVCs per research site</i> .....	368
	<i>Appendix 8.4 Research sites: letters of permission</i> .....	369
	<i>Appendix 8.5 IMB approval</i> .....	381
	<i>Appendix 8.6 Research ethics committee approval</i> .....	382
	<i>Appendix 8.7 Randomisation instructions</i> .....	383
	<i>Appendix 8.8 Independent microbiologist review record sheet</i> .....	384
	<i>Appendix 8.9 Participants admitted to nephrology ward</i> .....	385
	<i>Appendix 8.10 Order declaration form for unlicensed IMP</i> .....	386
	<i>Appendix 8.11 Ordering procedure for unlicensed IMP</i> .....	387
	<i>Appendix 8.12 Order form ChloroPrep® with Tint: Iskus Health Ltd</i> ....	388
	<i>Appendix 8.13 Order form for Sani-Cloth CHG: PDI</i> .....	389
	<i>Appendix 8.14 Record of medicinal product delivery</i> .....	390

Appendix 8.15 Record of control medicinal product supplies.....	391
Appendix 8.16 Instructions on administration of trial IMPs .....	392
Appendix 8.17 Protocol on use of control IMP.....	394
Appendix 8.18 Instructions on administration of control IMPs .....	396
Appendix 8.19 Trial solutions record Sheet (Example).....	399
Appendix 8.20 Denominator data collection form .....	400
Appendix 8.21 Dialysis event form .....	401
Appendix 8.22 Trial register form .....	402
Appendix 8.23 Baseline collection form.....	404
Appendix 8.24 Adverse event form .....	405
Appendix 8.25 Adverse reaction .....	406
Appendix 8.26 Safety monitoring .....	407
Appendix 8.27 Trial Monitoring Committee .....	408
Appendix 9.1 Eligibility assessment and recruitment.....	409
Appendix 9.2 Lost to follow-up .....	410
Appendix 9.3 Discontinued assigned solution .....	410
Appendix 9.4 Primary outcomes per 100 patient-months main comparison.....	411
Appendix 9.5 Sensitivity analysis for primary outcomes .....	412
Appendix 9.6 Primary outcomes per 100 patient-months sub-comparison 1 .....	413
Appendix 9.7 Primary outcomes per 100 patient-months sub-comparison 2.....	414
Appendix 9.8 Secondary categorical outcomes per 100 patient-months main comparison .....	415
Appendix 9.9 Secondary categorical outcomes <sup>1</sup> .....	416
sub-comparison 1 .....	416
Appendix 9.10 Secondary categorical outcomes per 100 patient-months sub-comparison 1 .....	417
Appendix 9.11 Secondary categorical outcomes.....	418
sub-comparison 2.....	418
Appendix 9.12 Secondary categorical outcomes per 100 patient-months sub-comparison 2.....	419
Appendix 9.13 Continuous secondary outcomes per 100 patient-months main comparison .....	420
Appendix 9.14 Continuous secondary outcomes sub-comparison 1&2	421
Appendix 9.15 Continuous secondary outcomes per 100 patient-months sub-comparison 1 .....	422
Appendix 9.16 Continuous secondary outcomes per 100 patient-months Sub-comparison 2 .....	423
Appendix 9.17 Proportion surviving CVC-related events including survival curves sub-comparison 1.....	424
Appendix 9.18 Proportion surviving CVC-related events including survival curves sub-comparison 2.....	428
Appendix 9.19 Forced entry logistic regression model .....	431
Appendix 9.20 Stepwise entry logistic regression model.....	434
Appendix 9.21 Forced entry and stepwise logistic regression model with subset of predictor variables .....	436





## LIST OF TABLES

Table 4.1 Characteristics of excluded studies .....	65
Table 4.2 Characteristics of included randomised controlled trials: Topical antimicrobials .....	67
Table 4.2 Characteristics of included randomised controlled trials: Topical antimicrobials & non-medicated dressings .....	68
Table 4.2 Characteristics of included randomised controlled trials: Topical Honey & other interventions .....	69
Table 4.3 Topical antimicrobial ointments: CVC Survival time .....	79
Table 4.4 Topical antimicrobial ointments: Time to infection .....	80
Table 4.5 Honey & bacteraemia-free survival period .....	81
Table 6.1 Number of patients attending for haemodialysis .....	127
Table 6.2 Compliance with guideline recommendations .....	129
Table 6.3 Vascular access use .....	130
Table 8.1 Catheter-related bloodstream infections .....	203
Table 8.2 Catheter-associated bloodstream infections .....	204
Table 8.3 Local access infection .....	205
Table 8.4 CDC/NHSN dialysis events outcomes & events .....	207
Table 8.5 Data collection intervals per research site .....	212
Table 8.6 Data collection intervals per trial participants .....	212
Table 9.1 Outcome of randomisation process .....	230
Table 9.2 Baseline characteristics main comparison .....	232
Table 9.3 Baseline characteristics sub-comparison 1 & 2 .....	234
Table 9.4 Primary outcomes main comparison .....	237
Table 9.5 Primary outcomes sub-comparison 1 & 2 .....	239
Table 9.6 Secondary categorical outcomes <sup>1</sup> main comparison .....	241
Table 9.7 Secondary continuous outcomes main comparison .....	246
Table 9.8 Proportion surviving CVC-related events .....	248
Table 9.9 CRBSI & CABS I causative organism main comparison .....	255
Table 9.10 Vascular access prevalence .....	255
Table 10.1 'CHG trial' compared to studies with similar trial arms .....	261
Table 10.2 Comparison of CRBSI case definitions .....	262
Table 10.3 CVC bloodstream infections episodes of <i>S. aureus</i> .....	266

## LIST OF FIGURES

Figure 4.1 Flow chart of citations retrieved from search of different data bases .....	66
Figure 4.2 Exit site & catheter-related bacteraemia: Topical antimicrobial ointment versus no ointment or placebo.....	73
Figure 4.3 Catheter-related bacteraemia: Topical antimicrobial ointment versus no ointment or placebo, subgroup analysis.....	74
Figure 4.4 Mortality related to infection: Topical antimicrobial ointment versus no ointment or placebo, subgroup analysis.....	76
Figure 4.5 Catheter removal due to infection: Topical antimicrobial ointment versus no ointment or placebo, subgroup analysis.....	78
Figure 8.1 Trial participant label .....	190
Figure 8.2 Chloraprep® with Tint 3ml applicator .....	192
Figure 8.3 Sani-Cloth CHG 2% medical device wipes .....	192
Figure 8.4 Sterets® Unisept .....	193
Figure 8.5 Hydrex® Pink 200ml .....	193
Figure 8.6 Hydrex® Pink 600ml .....	193
Figure 8.7 IMP trial label research site OA .....	195
Figure 8.8 IMP trial label research site OB & OV.....	195
Figure 9.1 CONSORT flow diagram: CHG randomised trial .....	229
Figure 9.2 Kaplan-Meier curve: Time to CRBSI.....	249
Figure 9.3 Kaplan-Meier curve: time to CABSII .....	250
Figure 9.4 Kaplan-Meier curve: time to Local access infection .....	251
Figure 9.5 Kaplan-Meier curve: catheter survival .....	252
Figure 9.6 Kaplan-Meier curve: infection-related CVC removal .....	253

## GLOSSARY OF TERMS

**Adverse Event:** Unintended injury or complication caused by medical management, as opposed to an underlying medical condition.

**Antiseptic solution:** Any agent capable of preventing infection by inhibiting the growth of micro-organisms.

**Antimicrobial lock:** Instillation of an antimicrobial solution into the lumen of a dialysis catheter for the entire interdialytic period.

**Antimicrobials:** Any agents capable of destroying or inhibiting the growth of micro-organisms.

**Colonisation:** Positive culture for an organism without invasive infection.

**Denominator data:** Number of the total population from which numerator data is being collected.

**Haemodialysis:** The extra-corporeal circulation of a patient's blood through a dialyser, a semi-permeable membrane fibre that acts as an artificial kidney.

**Healthcare-Associated Infections:** Unintended consequences of treatment in which patients contract an infection while receiving medical treatment in a hospital, an outpatient clinic or other healthcare settings.

**Incidence:** Number of new cases of a disease occurring in a population over a specific period of time.

**Numerator data:** Number of patients with the condition been measured.

**Patient Safety:** Avoidance, prevention and amelioration of adverse outcomes or injuries stemming from the process of healthcare.

**Prevalence:** The total number of cases of a disease present in a population at a single point in time.

**Routine Practice:** Routine practice is the care and management normally provided to patients with a particular condition, which is evidence-based.

**Skin asepsis:** The application of an antiseptic solution prior to catheter insertion and during central venous catheter maintenance that reduces the volume of micro-organisms at the insertion site and catheter hubs, so decreasing the risk of contamination and infection.

**Skin cleansers:** Antiseptic agents used to assist the physical removal of foreign materials such as dirt, micro-organisms, and dead cells from skin.

**Surveillance:** Ongoing systemic collection, analysis and dissemination of data regarding health-associated events that can lead to action being taken to improve health and reduce morbidity and mortality.

**Systematic review:** An attempt to identify, appraise and synthesize research-based literature that meets pre-specified eligibility criteria to answer a given research question.

**Vascular Access:** Access to large blood vessels that facilitates the removal and return of patients' blood, after it has passed through the artificial kidney.

## ABBREVIATIONS

<b>AMNCH</b>	The Adelaide and Meath Hospital, Dublin, Incorporating The National Children's Hospital, Tallaght
<b>AVF</b>	Arterio-venous fistula
<b>AVG</b>	Arterio-venous graft
<b>BSI</b>	Bloodstream infections
<b>CABSI</b>	Catheter-associated bloodstream infections
<b>CDC/NHSN</b>	Centres for Disease Prevention and Control/National Healthcare Safety Network
<b>CHG</b>	Chlorhexidine gluconate
<b>CKD</b>	Chronic kidney disease
<b>CRBSI</b>	Catheter-related bloodstream infections
<b>CVC</b>	Central venous catheter
<b>DOPPS</b>	Dialysis outcomes and practice patterns study
<b>ECDC</b>	European Centre for Disease Prevention and Control
<b>ERA-EDTA</b>	European Renal Association – European Dialysis and Transplant Association
<b>ESKD</b>	End stage kidney disease
<b>HCAI</b>	Healthcare-associated infections
<b>HIQA</b>	Health Information and Quality Authority
<b>HSE</b>	Health Service Executive
<b>ICU</b>	Intensive care unit
<b>IDSA</b>	Infectious Diseases Society of America
<b>IMP</b>	Investigational medicinal product
<b>MRSA</b>	Methicillin Resistant <i>Staphylococcus aureus</i>
<b>MSSA</b>	Methicillin Sensitive <i>S. aureus</i>
<b>NICE</b>	National Institute for Health and Clinical Excellence
<b>NKF-K/DOQI</b>	National Kidney Foundation – Kidney Disease Outcomes Quality Initiative
<b>RCT</b>	Randomised control trial
<b>REC</b>	Research ethics committee
<b>RR</b>	Relative risk
<b>RRT</b>	Renal replacement therapy
<b>SARI</b>	Strategy for the control of antimicrobial resistance in Ireland
<b>SD</b>	Standard deviation
<b>USRDS</b>	United States Renal Data System
<b>VA</b>	Vascular access
<b>WHO</b>	World Health Organisation

# CHAPTER 1: INTRODUCTION

## 1.1 Introduction

The patient population involved in this pilot multi-centre study are haemodialysis patients with central venous catheters (CVC). Advances in technology have increased the complexity of care these patients receive. Due to the presence of invasive medical devices such as a CVC, patients are at an increased risk of adverse events that have a negative impact on their wellbeing and safety. My trial is focused on preventing one type of adverse event: CVC-related infections.

This chapter begins with an overview of this chlorhexidine gluconate (CHG) trial, the 'CHG trial', and an outline of its primary aims. It also provides an overview of the four sections that make up this thesis. The first section provides background and context to the trial. The second section provides a critical analysis of the literature, justifying the focus and scope of the study. The third section focuses on ascertaining routine practice in haemodialysis units in Ireland, essential preparation for this trial, as well as issues relating to trial design, methods and conduct. The final section presents the results of the CHG trial, which are discussed within the context of the wider literature, and conclusions drawn from the trial are outlined.

## 1.2 Overview of the CHG Trial

Patient safety underpins decision-making across all aspects of nursing practices, irrespective of the healthcare setting. Caring for patients receiving haemodialysis raises many important safety issues including the prevention of vascular access-related infection. The use of CVCs as a form of vascular access (VA) is high within the haemodialysis patient population, increasing their risk of healthcare-associated infections (HCAI). CVC-related infections have a negative impact on haemodialysis patients' wellbeing, causing increased mortality and morbidity when compared to patients with other types of VA (Pisoni *et al.* 2009, Goodkin *et al.* 2010). The care and maintenance of a CVC is a challenging area for dialysis nurses and members of the renal multidisciplinary team. My trial is focused on a component of CVC care that is part of everyday dialysis nursing practice.

As the person with most access to a patient's CVC and who is responsible for connecting and disconnecting patients to and from dialysis, three times a week, dialysis nurses implement strategies aimed at preventing the contamination of patients' CVCs. One strategy is the effective cleansing of the CVC exit site and catheter hub using a cutaneous antiseptic solution. Intravascular-catheter guidelines recommend the use of CHG antiseptic solutions for the maintenance of CVCs, including haemodialysis catheters (CARI 2000, CDC 2002, NKF K/DOQI 2006a, Pratt *et al.* 2007, The UK Renal Association 2007, SARI 2009). A number of guidelines recommend a 2% CHG in 70% isopropyl alcohol solution, even though no randomised controlled trials (RCTs) were found that directly compared this solution to other strength/formulations of CHG. The aims of this trial are:

- To test the trial methods in preparation for a study to evaluate the effectiveness of 2% CHG in 70% isopropyl alcohol as an exit site and catheter hub cleansing agent in the reduction of CVC-related infections in outpatient haemodialysis patients, in comparison to the other forms of CHG that were in routine use at the time in dialysis centres in Ireland.
- To evaluate the feasibility of undertaking a future multi-national, multi-centre study on this topic.

The CHG trial was undertaken in three outpatient haemodialysis units in Dublin, The Adelaide and Meath Hospital, Dublin, Incorporating The National Children's Hospital (AMNCH), Beacon Renal and St. Vincent's University Hospital.

### **1.3 Background & Context to the CHG Trial**

Section one of my thesis provides the background and context to the trial. In this section, chapter 2 highlights the global issue of patient safety and the different types of adverse events that patients admitted to healthcare facilities experience. One of these events is HCAI, of which 30% to 70% are estimated to be preventable (Harbarth *et al.* 2003, Michel *et al.* 2007). The chapter explores the impact HCAI have on patient safety and the unnecessary harm they cause, which may lead to mortality or considerable morbidity. Catheter-related infections, although not the most common HCAI, have the second highest number of infection-related deaths (WHO 2011). Also outlined is the



priority given to the prevention of such infections by international and national policy-makers. The burden associated with HCAI and particularly CVC-related infections, for patients and the healthcare exchequer, is emphasised as is the importance of infection prevention and control. Specific CVC infection preventive measures including skin asepsis are described. The chapter discusses the central role of dialysis nurses in preventing CVC-related infection and the expectation that dialysis nursing practices are informed by infection prevention and control practices based on the best evidence.

Chapter 3 provides an outline of End Stage Kidney Disease (ESKD) as a global health issue that is managed through the provision of renal replacement therapy, the most common being haemodialysis. Haemodialysis patients require some form of vascular entry method to access dialysis and, despite being the least preferred choice, CVC use in this population is rising. The chapter discusses CVC-related infections in the context of this vulnerable patient group; highlighting the detrimental impact such infections have on haemodialysis patient safety and wellbeing in comparison to patients who access dialysis via an arterio-venous fistula. CVC-related infections include bloodstream and exit site infections. Risk factors for CVC-related infections are discussed, as are the implications they have for the design of the trial. Lastly, the chapter examines important methodological issues to emerge from the review of the literature and the implications they had for the design of the 'CHG Trial'.

## **1.4 Critical Analysis of the Literature**

Section 2 of this thesis focuses on a critical analysis of the literature relating to interventions for the prevention of CVC-related infections. Chapter 4 describes a Cochrane Review of the worldwide evidence from randomised trials on interventions for the prevention of infectious complications in haemodialysis patients with CVCs. A total of 10 studies (786 participants) reported in 16 publications were included. The review identifies a lack of evidence from randomised trials to inform decisions about the effectiveness of antiseptic solutions as CVC hub and exit site cleansing agents in haemodialysis patients. The review recommends a new trial comparing 2% CHG in 70% isopropyl alcohol versus other alcohol or aqueous concentrations of CHG.

Chapter 5 provides a critical analysis of the CHG trial literature. A total of 17 randomised trials on the effectiveness of CHG-based antiseptic solutions were identified. One study (Astle & Jensen 2005) was undertaken in a haemodialysis setting and compared 0.5% CHG in alcohol to a chlorine-based solution for the prevention of CVC-related infections. Only one trial (Valles *et al.* 2008) compared different strengths of CHG; this three-arm trial compared 0.5% CHG in alcohol and 2% aqueous CHG solution to 10% povidone iodine. I found no published trials that compared 2% CHG in 70% isopropyl alcohol to other formulations or strengths of CHG in the prevention of CVC-related infection. Analysis of the literature suggests that there is strong evidence that CHG antiseptics solutions are more effective than other agents in reducing the risk of catheter-related infections. Although guidelines recommend a 2% CHG in 70% isopropyl alcohol solution for CVC care and maintenance, no randomised trials were found that would provide the evidence justifying such a recommendation. This gap in the existing evidence supports the direction and focus of my trial.

The findings in chapter 4 and 5 shed light on the need to investigate, through a pilot trial, the relative effectiveness of 2% CHG in 70% isopropyl alcohol versus other alcohol or aqueous strengths of CHG for the prevention of catheter-related infections in haemodialysis patients. This pilot multi-centre trial offered the opportunity to explore the feasibility of undertaking a more powerful study, as a multi-national, multi-centre trial. The critical analysis of the literature identifies a number of issues that had important implications for the design of this trial.

## **1.5 Routine Practice, Trial Design, Methods & Conduct**

Section 3 of this thesis discusses essential preparation for the trial and trial design, methods and conduct. Chapter 6 is focused on ascertaining routine practice in haemodialysis units in Ireland. In the chapter, routine practice is described as the care and management that is normally provided to patients with a particular condition and which should be evidence-based. The results of a national survey of routine practice in haemodialysis units in Ireland are also presented. The survey highlights areas where practice differs from guideline recommendations. Dialysis units varied in the strength and formulation of CHG used for cleansing the CVC site and catheter hub. This is in keeping with the critical analysis of the CHG literature that identified a lack

of evidence as to which strength and formulation of CHG is the most effective in preventing CVC-related infections.

Chapter 7 discusses the design of the study and its methodology. The appropriateness of using a pragmatic RCT design is highlighted. In this trial, a 2% CHG in alcohol solution was compared to CHG solutions that were routinely used in haemodialysis units. This study was a trial of a medicinal product for human use; consequently, the EU Clinical Trial Directive (European Community 2001a) and associated legislation had important implications for the design and conduct of this trial. Additionally, the purpose and focus of a pilot design and the importance of this trial in evaluating the feasibility of conducting the main study are discussed.

The overall comparison for the pilot trial was 2% CHG in alcohol versus routine antiseptic solutions, which required sub-comparison groups to reflect the different routine solutions in use. This led to comparisons of 2% CHG in alcohol versus 0.5% CHG in alcohol and 2% CHG in alcohol versus 0.05% aqueous CHG.

Adequate randomisation was achieved through a computer generated randomised allocation sequence that was stratified by routinely used solution and consisted of fixed block sizes of ten. Allocation concealment was achieved through the use of a central telephone randomisation service, with the release of the allocation only after the patient's consent had been obtained and details recorded. Clinical equipoise, respect of persons, beneficence and justice governed the conduct of this trial.

Chapter 8 explores the methods and conduct of the trial. Trial approval was granted by the Irish Medicines Board and an approved Research Ethics Committee (Joint St James's Hospital and AMNCH Research Ethics Committee). Three outpatient haemodialysis units agreed to participate in the trial. The target population was haemodialysis patients with permanent cuffed tunnelled CVCs, over the age of 18 who required long term haemodialysis and who attended for dialysis on an outpatient basis. As this was a pilot study it was not necessary to undertake a sample size calculation. All recruited participants were followed up to trial completion (12 months), primary outcome or death.

Primary outcomes for this study were catheter-related bloodstream infections (CRBSI), catheter-associated bloodstream infections (CABSI) and local access infections. Primary diagnosis was determined by case definitions from the Infectious Disease Society of America and the Centres for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) (CDC/NHSN 2009, Mermel *et al.* 2009). Issues relating to data collection, development of data collection forms, and data analysis are also outlined.

## **1.6 Results of CHG Trial & Discussion of Findings**

In section 4, chapters 9 and 10 describe and discuss the 'CHG Trial' results. In total, 105 of the 149 eligible patients agreed to participate in my trial, a 70% response rate. Overall, 53 participants were randomly assigned to the intervention group (2% CHG in 70% isopropyl alcohol) and 52 to the comparator group (0.5% CHG in 70% isopropyl alcohol or 0.05% aqueous CHG). Comparator participants were treated with a 0.5% in 70% isopropyl alcohol solution ( $n=42$ , sub-comparison 1) or a 0.05% aqueous CHG solution ( $n=10$ , sub-comparison 2). Issues relating to the number of patients not eligible ( $n=52$ ), refusing to participate ( $n=44$ ), or lost to follow-up after recruitment and randomisation ( $n=16$ ) have important implications when calculating the sample size for the main study. Modifications to the design of the trial may be necessary, so that more eligible participants are included. The pilot trial did not show a difference between 2% CHG in alcohol and the comparator solutions in the prevention of CVC-related infections.

Finally, the CHG Trial is the first of its kind in the haemodialysis patient population. This pilot trial confirms that the trial methods used were appropriate and a larger comparator multi-national, multi-centre study is feasible.

**SECTION 1**  
**BACKGROUND & CONTEXT**

## **CHAPTER 2: PATIENT SAFETY & HEALTHCARE-ASSOCIATED INFECTIONS**

### **2.1 Introduction**

The population at the heart of my PhD research project are haemodialysis patients with central venous catheters (CVC). Due to the presence of this invasive medical device, patients are at increased risk of healthcare-associated infections (HCAI); an adverse event that has a profound impact on patient health and safety. This chapter places the randomised trial within the context of patient safety, HCAI and infection prevention and control. Vascular access (VA) care and maintenance, often referred to in the literature as the '*Achilles heel*' of the haemodialysis patient (Konner 1999, Schwab 2007, Riella & Roy-Chaudhury 2013), is one of the most challenging areas of care confronting the renal multidisciplinary team. The central role of dialysis nurses in the prevention of CVC-related infections is also explored in this chapter.

A search of the literature was undertaken using the following databases: PubMed, EMBASE, CINAHL and The Cochrane Library (including the Cochrane Central Register of Controlled Trials). Reference lists of pertinent literature were reviewed for relevant material not identified during the database search. The search strategy was limited to papers published in English; no limits were placed on the year of publication. A number of MeSH and non-MeSH keywords were used including adverse event, patient safety, government policy, infection control, infection prevention, principles; haemodialysis and nurse. Relevant papers ( $n=102$ ) provided a global perspective of adverse events, patient safety, HCAI, the importance of infection prevention and control programmes and the role of the dialysis nurse in the prevention of CVC-related infections. A large proportion of papers (over 200) were linked to a particular adverse event or not relevant to the discussions in this chapter.

### **2.2 Adverse Events & Patient Safety**

Over the last four decades, advances in medical knowledge, treatments and technology have increased the complexity of healthcare provision, increasing the possible risk of harm to patients. "Adverse event" is the most common

term used in the literature to describe this type of harm, which is described as an unintended injury or complication caused by medical management, as opposed to an underlying medical condition. These events can lead to death, prolonged hospitalisation or disability at discharge (Brennan *et al.* 1991, Wilson *et al.* 1995, Baker *et al.* 2004, Michel *et al.* 2007, WHO 2011).

Patient safety emerged as an important global healthcare issue, following publication of a number of retrospective studies exploring adverse events in hospitalised patients. Seminal research in the Harvard Medical Practice Study investigated adverse events in acute care hospitals in New York State (Brennan *et al.* 1991, Leape *et al.* 1991). Using screening criteria, trained nurses and medical record analysts reviewed all medical charts of patients admitted during 1984. Charts identified during this process were independently reviewed by two physicians, for adverse events and occurrence of negligence. This design was subsequently used, in 1992, in the Utah/Colorado study (Thomas *et al.* 2000a).

Both the Harvard (Brennan *et al.* 1991, Leape *et al.* 1991) and the Utah/Colorado studies (Thomas *et al.* 2000a) have comparable findings. Each reviewed randomly selected medical records of patients (30,121 in New York State and 15,000 in Utah/Colorado), from representative acute care hospitals (51 in New York State and 28 in Utah/Colorado) admitted during a specified period of time (1984 and 1992). The adverse event incidence for all hospitalisations in New York State was 4% (95% CI, 3.2 to 4.2) and 3% (SD 0.2%) in Utah/Colorado. In New York State, permanent disability occurred in 2.6% of adverse events. For New York State and Utah/Colorado, 14% and 7% of adverse events led to death. The most frequent type of adverse event was drug events (19%) in New York State and operative events in Utah/Colorado (45%). Both studies reported adverse events associated with wound infection, 14% and 11%, respectively. A higher rate of adverse events was associated with patients aged 65 and over ( $p < 0.000$ ) when compared with patients aged below 65 (Brennan *et al.* 1991).

The Quality in Australian Health Care Study (Wilson *et al.* 1995) was among the first studies outside of the United States (US) to explore adverse events caused by healthcare management. This study, using a modified version of the methodology underpinning the Harvard Study (Brennan *et al.* 1991, Leape *et al.* 1991), reviewed 14,179 admissions, in 1992, from 28 representative

hospitals in New South Wales and South Australia. Overall, 17% ( $n=2353$ , 95% CI, 15% to 18%) of admissions were associated with adverse events, 51% of which were deemed preventable (95% CI, 48% to 54%). This adverse event rate is considerably higher than both US studies. Permanent disability and death were attributed to 14% ( $n=315$ ) and 5% ( $n=112$ ) of adverse events, with hospitalisation extended by an average of 7 days. The rate of permanent disability is higher than in the Harvard study. It was estimated that 470,000 (95% CI, 430,000 to 510,000) annual hospital admissions in Australia were linked to adverse events, accounting for 3.3 million bed-days, per year. Death and permanent disability (greater than 50%) due to adverse events was estimated at 18,000 (95% CI, 12,000 to 23,000) and 17,000 (95% CI, 12,000 to 22,000), respectively. Causes of adverse events were linked to major diagnostic and specialist criteria, but no detailed breakdown was provided.

There are notable differences in adverse event rates between the US and Australian studies. Following a collaborative review (Runciman *et al.* 2000, Thomas *et al.* 2000b) and a re-analysis of data, the comparative rates were 11% for Australia and 3% for Utah/Colorado. This re-analysis witnessed a reduction in the Australian adverse event rate, but considerable differences remained. This may relate to the underlying premise for undertaking these studies. The Australian Study focused on quality improvement and preventability, whereas the US studies were concerned with malpractice litigation and negligence. This may have influenced initial reporting of events and the behaviours of those involved in the two-stage screening process. Additionally, the Harvard Study focused on admissions during 1984, eight years earlier than the Australian study, with the possibility that reporting procedures in medical records may have improved during the intervening years, notwithstanding international differences in reporting mechanisms. Furthermore, the review process, although guided by predetermined criteria, was still open to subject variation among initial screeners of charts and physicians who determined the occurrence of adverse events.

Methods used in the US and Australian studies were used in subsequent studies from England (Vincent *et al.* 2001), Denmark (Schioler *et al.* 2001), New Zealand (Davis *et al.* 2002, 2003), Canada (Baker *et al.* 2004), Spain (Aranaz-Andrés *et al.* 2008, Aranaz-Andrés *et al.* 2009), the Netherlands (Zegers *et al.* 2009) and Sweden (Soop *et al.* 2009). All studies examined randomly selected medical records of patients admitted to representative



hospitals. These national studies were undertaken in different years, the timelines were 1998 (England and New Zealand), 2000 (Canada), 2003 to 2004 (Sweden), 2004 (Netherlands) and 2005 (Spain). Information was not provided as to when the Danish study was done.

Across these national retrospective studies, adverse events ranged from 6% (Netherlands) to 13% (New Zealand) of all hospitalisations. Incidences were higher than the US studies (Brennan *et al.* 1991, Leape *et al.* 1991, Thomas *et al.* 2000a). In England, 6% of adverse events resulted in permanent disability, slightly higher than the Netherlands (5%), but lower than New Zealand (10%). Death due to adverse events ranged from 3% (Sweden) to 21% (95% CI, 7.8 to 33.8; Canada). Preventable adverse events were lowest in New Zealand (35%) and highest in Sweden (70%). Hospitalisation was prolonged by an average of 6 days (Sweden) to 9 days (New Zealand). The relative risk of patients in Spain experiencing an adverse event was higher in those aged 65 years and over (RR 2.5, 95% CI, 2.0 to 3.0;  $p < 0.001$ ). Infections were the second leading cause of adverse events in both Sweden (29%) and Spain (25%); 57% of infections in patients in Spain were deemed to be preventable. As with the Australian study, no detailed account of types of adverse events was provided by the Canadian, Danish, Dutch, English or New Zealand studies.

The Spanish study (Aranaz-Andrés *et al.* 2008, Aranaz-Andrés *et al.* 2009) also explored associations between patient intrinsic and extrinsic risk factors and adverse events. Intrinsic factors included renal failure, diabetes, chronic obstructive pulmonary disease, immunodeficiency and hypertension. Extrinsic factors related to invasive devices including peripheral venous catheters, various types of central venous catheters, urinary bladder catheterisation, and mechanical ventilation. Patients with intrinsic risk factors had more adverse events than patients without these risk factors, 13% and 5% ( $p < 0.001$ ), respectively. Similarly, patients with extrinsic risk factors had more adverse events than those without them, 9% and 3% ( $p < 0.001$ ), respectively.

Extrapolating their findings to NHS hospitals in England and Wales, Vincent *et al.* (2001) estimated that 5% of the 8.5 million patients admitted to hospital experience a preventable adverse event each year. This results in three million additional bed days, costing the NHS around £1 billion each year. The Canadian study (Baker *et al.* 2004) estimated that between 141,250 and

232,250 admissions, out of a total of 2.5 million admissions nationally, resulted in adverse events, in the year 2000, with 70,000 of these adverse events being preventable.

Unlike the studies discussed up to this point, a French study (Michel *et al.* 2007) investigated adverse events using a prospective design, making it difficult to compare its findings with the other studies. Michel *et al.* (2007) collected data in 2004, during a 7-day observation period of each clinical setting. A total of 8,754 patients from 71 hospitals were sampled. The incidence density of adverse events was 6.6 per 1000 hospitalisation days ( $n=255$ , 95% CI, 5.7 to 7.5). The main types of adverse events were perioperative care (42%), care-related infection (22%) and drug events (20%). At least 30% of healthcare-related infections were deemed preventable, similar to the Spanish study (Aranaz-Andrés *et al.* 2009).

In addition to retrospective studies, audits have also been used to estimate the rate of adverse events. A 2004-2005 National Audit Office survey of 256 NHS trust healthcare facilities recorded 974,000 incidents or near misses (National Audit Office 2005). Incidents were defined as “*clinical procedures that resulted, or could have resulted, in unexpected harm to the patient*” (National Audit Office 2005, p. 80). Although hospital acquired infections were seldom reported, it was estimated that they would increase the overall number of incidents by 300,000; 30% of which would be preventable. Economically, patient safety incidents cost the NHS £2 billion a year in extra bed days, with hospital acquired infections adding another £1 billion.

From a European perspective, Conklin *et al.* (2008) in a technical report for the European Commission (EC), extrapolated findings from some of the aforementioned studies (Wilson *et al.* 1995, Vincent *et al.* 2001, Aranaz-Andrés *et al.* 2008) to estimate that across 27 countries 6.7 million (7%) to 15 million (17%) patients discharged from hospital had experienced an adverse event. Of these, 1.1 million (14%) led to permanent disability and 5% (400,000 to 550,000 hospitalisations) resulted in death.

Using a survey approach, the EC (2008a) also carried out an open consultation on patient safety and adverse events in the EU. A total of 184 contributions were received from various groups. Healthcare-associated infections (24%) and medication-related adverse events (24%) received top

ranking for prioritisation in reducing adverse events. When ranked by competent authorities only, HCAI received the highest ranking (33%), followed by medication-related events (27%).

In Ireland, reporting of adverse events is not mandatory. Adverse events are reported to a number of organisations such as the Irish Medicines Board or via the State Claims Agency STARSWeb reporting system. As a result, national data on adverse event incidence is incomplete. In 2011, 85,918 adverse events were reported to the Health Service Executive (HSE) and the State Claims Agency (Health Service Executive & State Claims Agency 2012). Duffy (2012), in an unpublished thesis on *Open disclosure of adverse events in Ireland*, estimated that 14% of hospital admissions in Ireland experienced an adverse event. This estimation was extrapolated from HSE hospital admission and adverse event data. A weakness of this analysis is the use of voluntary reported adverse event data that may not reflect the true national incidence of adverse events. Given the lack of national data on adverse events, the Royal College of Surgeons in Ireland, the Royal College of Physicians in Ireland and the HSE Directorate of Quality and Patient Safety commenced a joint research project on adverse events in Ireland, in 2013. This study, the first of its kind in Ireland, is due to be completed in 2015 (Mudiwa 2013).

Adverse events within the haemodialysis setting include many of those experienced in the general patient population, but more specific events relate to the process of providing modality treatment. These events include equipment malfunction, inappropriate use of chemicals, falls prior to and post modality treatment, errors using technological equipment, deviating from dialysis prescriptions, errors in medication and blood administration, infection prevention and control errors, and medical record and similar name errors. Others include vascular access-related events e.g., clotting, infiltration, poor blood flow, difficult cannulation, dialyser errors, excess blood loss and prolonged bleeding (Garrick *et al.* 2012).

There is limited published literature on adverse events and related mortality in haemodialysis settings. Bray *et al.* (2014), in a retrospective review of the Scottish Renal Registry investigated adverse events causing or contributing to death in those patients receiving renal replacement therapy (RRT) (haemodialysis, peritoneal dialysis and transplantation). HCAI contributed to

10% of deaths in the overall RRT population. Vascular access failure or infection led to 11% of deaths among haemodialysis patients. Preventable death due to adverse events was estimated at 4%, similar to the aforementioned European national adverse events studies.

## 2.3 Patient Safety

Patient safety is defined as “*freedom for a patient from unnecessary harm or potential harm associated with healthcare*” (European Commission 2008a, p. 3). This broad definition is used by EC and WHO policy makers, but the following comprehensive definition, with its strong emphasis on prevention, is also widely quoted in the literature “*patient safety is the avoidance, prevention and amelioration of adverse outcomes or injuries stemming from the process of healthcare*” (Vincent 2006, p. 31).

The first reports that placed patient safety to the forefront of healthcare policy were *To Err is Human: Building a Safer Health System* (Kohn *et al.* 1999) from the Institute of Medicine in the US and *An organisation with a memory: Report of an expert group on learning from adverse events in the NHS* from the Department of Health in the United Kingdom (UK) (2000).

The Institute of Medicine (Kohn *et al.* 1999), extrapolating findings from the Harvard and Utah/Colorado studies, calculated that between 44,000 and 98,000 people die each year in the US from medical errors that could be prevented. Medical errors resulted in patients suffering physical and psychological discomfort; economically, the cost of errors ranged from \$17 billion to \$29 billion, per year, across the US. The strategic plan outlined in the report aimed to reduce preventable errors by shifting the focus of healthcare policy from a blame culture to one that embraced patient safety through quality improvement. Similar recommendations were made in the UK policy report (Department of Health UK 2000), including a mandatory national reporting system for adverse events within the NHS, with the aim of learning from these events. Both reports proved a driver for the emergence of patient safety as a global healthcare issue, led by the World Health Organisation (WHO).

In May 2002, the 55<sup>th</sup> World Health Assembly passed its first resolution linked to patient safety (WHA55.18), recommending that member nations pay more attention to this problem by establishing patient safety and quality care

improvement systems. Building on the work that member nations had achieved in implementing this resolution, the 57<sup>th</sup> World Health Assembly, held in May 2004, recommended the formation of the World Alliance for Patient Safety. This global initiative involved an international alliance of member nations aimed at improving patient safety (WHO 2004).

In response to the WHO and the World Alliance on Patient Safety, the Council of Europe and institutes of the EU made a number of recommendations on patient safety (European Commission 2005, Council of Europe 2006, Council of the European Union 2006, European Commission 2007, Council of the European Union 2009). A common principle underpinning these recommendations was the belief that maintaining the safety of patients should be the cornerstone of healthcare policy. There is an expectation that European states, including Ireland, implement strategies that minimise harm to patients receiving medical treatment. Such strategies include developing national policies on patient safety, creating a culture of safety, promoting education and training of healthcare staff, and empowering patients.

Keeping patients safe is a “*fundamental principle of patient care*” (WHO 2004, p. 4) and a fundamental patient right (European Commission 2005, Council of Europe 2006). This has implications for all areas of healthcare including those providing that care, which includes both the outpatient haemodialysis environment and the care provided by dialysis nurses in the context of this PhD project. Preventing, recording and reporting adverse events and reducing their impact on patient wellbeing when they do occur, are all key components in maintaining patient safety.

All three international bodies (WHO, Council of Europe and EC) place a strong emphasis on the importance of preventing the occurrence of adverse events, which underpins the premise of this PhD project. My research aims to contribute to the knowledge base by investigating the effectiveness of antiseptic skin cleansing solutions for the prevention of CVC-related infections, an important adverse event in the haemodialysis patient population (chapter 3, section 3.5.1). Research recommendations from the Council of Europe (2006) include evaluating the “*real-life effectiveness of interventions to improve patient safety*” (p. 9). Similarly, the European Commission’s (2008a) open consultation on patient safety identified “*real life research*” (p. 7) as a means of providing better evidence for patient safety strategies. This emphasis on *real*

*life research* highlights the need for a pragmatic trial design when evaluating the effectiveness of interventions used in the prevention of adverse events and has important implications for the design of the PhD clinical trial (chapter 7, section 7.7.4).

From a national perspective, developing a quality and safety culture in the Irish healthcare sector has been a key component of government health strategy since 2001 (Department of Health & Children 2001, 2012b, 2012c, 2013). Key strategies include the establishment, in 2007, of the Health Information and Quality Authority (HIQA) and the Commission on Patient Safety and Quality Assurance.

In 2005, the Irish healthcare system was restructured with the establishment of the HSE, a single national body responsible for managing the health service. HIQA's role was to ensure that patient safety and quality underpinned this new management structure. One of HIQA's tasks was setting standards on safety and quality and monitoring their enforcement. In 2012, HIQA published the *National Standards for Safer Better Healthcare*. These standards place a strong emphasis on preventing adverse events and reducing their impact on service users, further emphasising the importance of HCAI infection prevention and control. One of the standards (2.1) requires the delivery of healthcare practices that are underpinned by the best available evidence and information. When applying this standard to the care and maintenance of haemodialysis CVCs the superiority of chlorhexidine gluconate (CHG) over other antiseptic solutions for the prevention of CVC-related infection is evident (chapter 5, section 5.3). However, there is a lack of adequate evidence to determine the formulation of CHG that is the most effective in preventing these infections. Standard 3.1 is also relevant to my PhD. It is focused on protecting service users from the risk of harm, with one of its *Essential Elements* linked to the effective prevention and control of HCAI (Health Service Executive 2013a). Within the context of these two standards, my PhD project contributes to the knowledge and evidence base that will inform local, national and international strategies on the use of CHG antiseptic skin solutions for the prevention of CVC-related infections. This will allow more informed choices, reduce patients' risk of harm, and lead to better patient safety and more efficient use of resources.

The second key safety strategy was the publication of the Commission on Patient Safety and Quality Assurance report (2008) *Building a culture of patient safety*, a strategic plan for ensuring safety and quality within the Irish healthcare service. Following on from the publication of this report, the *Patient Safety First Initiative* was launched in 2010 by the then Minister for Health, Mary Harney. This included the publication of the *National Healthcare Charter, You and Your Health Service* (Health Service Executive 2012). This charter includes a stipulation that patients can expect to access a healthcare service where HCAI are prevented and prevention of such infections is a priority for all healthcare services and providers.

The integration of patient safety and quality into healthcare policy continued, with one of six strategic goals in the *Department of Health's Statement of Strategy 2011-2014* (Department of Health & Children 2012c) focused on patient safety and quality. Measuring the rate of HCAI is one of the indicators used to determine success towards this strategic goal.

## **2.4 Healthcare-Associated Infections**

HCAI are defined by the HSE (Health Service Executive 2007) as unintended consequences of treatment in which patients contract an infection while receiving medical treatment in a hospital, an outpatient clinic or other healthcare settings, for example an outpatient haemodialysis unit. The following WHO (2011) definition clarifies the timeline for the initial occurrence of infection, "*An infection occurring in a patient during the process of care in a hospital or other health-care facility which was not present or incubating at the time of admission. This includes infections acquired in hospital, but appearing after discharge and also occupational infections among staff of the facility*" (p. 6).

The causes of HCAI are multifaceted and may relate to the systems and processes of healthcare provision, the behaviour of healthcare professionals, or both (WHO 2004). The most common sites for HCAI include the urinary tract, lungs, surgical sites and bloodstream. Risk factors for bloodstream infection include invasive devices, such as CVCs used by haemodialysis patients to access dialysis treatment. Various interventions are used to prevent HCAI, but their use is dependent on the susceptible body site, type of invasive device or procedure.

National and international prevalence surveys confirm the global impact of HCAI on patient safety. A review (ECDC 2008) of 30 national point prevalence surveys of acute care hospitals, undertaken in 19 countries between 1996 and 2007, revealed an average EU HCAI prevalence of 7%. Extrapolating data from the review, it was calculated that 4.1 million patients across Europe develop a HCAI each year. Furthermore, HCAI were directly related to 37,000 deaths, each year, and contributed to an additional 110,000 deaths. More than 16 million extra hospitalisation days occur each year as a result of HCAI, with associated healthcare costs estimated at €7 billion per year.

The 2010 European Centre for Disease Prevention and Control (ECDC) (Zarb *et al.* 2012) pilot point prevalence survey included 19,888 patients across 66 acute care hospitals, in 23 countries. HCAI prevalence was 7%, similar to the ECDC review. Between 2011 and 2012, the ECDC (2013) conducted another point prevalence survey that included 231,459 patients from 947 acute care hospitals, across 29 countries. HCAI prevalence was 6% (95% CI, 5.7–6.3), ranging from 2% (Latvia) to 11% (Portugal) across participating countries. When extrapolated to the average daily number of occupied beds per country, the prevalence of HCAI on any given day was 6% (95% CI, 4.5-7.4). In total, 3.2 million (95% CI, 1.9-5.2 million) patients develop at least one HCAI each year, slightly lower than that reported in the 2008 review. Bloodstream infections were the fourth most common HCAI across the two ECDC point prevalence surveys, 14% and 11%, respectively. In the 2011-2012 survey, 39% of bloodstream infections were vascular catheter-related. Catheter-related infections (with or without positive blood culture or positive catheter tip culture) accounted for 7% of all HCAI. Given the high use of CVCs in haemodialysis patients (chapter 3, section 3.4), this highlights the potential risk for catheter-related HCAI in this patient population.

A retrospective study (Klevens *et al.* 2007), using three national healthcare databases, estimated a HCAI prevalence of 4.5 per 100 admissions (1.7 million HCAI), in 2002. Bloodstream infections (14%) were the fourth most common HCAI. At least 1.2 million HCAI occurred outside of ICUs, with bloodstream infections accounting for 133,368. HCAI resulted in 99,000 hospital deaths; 30,655 deaths were linked to bloodstream infections, second only to pneumonia (35,967).



The WHO (2011) in a systematic review of the world wide literature on endemic HCAI, reviewed 131 national or multicentre studies from 23 high-income countries, undertaken between 1995 and 2010. Hospital prevalence of HCAI ranged from 3% to 12%, with a pooled prevalence of 7.6 episodes per 100 patient-months (95% CI, 6.5 to 8.5) among mixed patient populations, similar to the 2010 ECDC survey. A number of studies from high-income countries suggest that catheter-related bloodstream infections had a significant impact on patients. These infections were the third most frequent HCAI, but had the second highest number of HCAI deaths, after pneumonia. An increase in antimicrobial resistance was also associated with HCAI. It was estimated that at least 50% of HCAI were preventable.

In seminal research, Plowman *et al.* (2000) estimated the annual economic burden of HCAI in England at £986 million; £930 million (95% CI, £780-£1010 million) related to inpatient healthcare management costs, with the remaining £56 million linked to post discharge costs. The Centres for Disease Control and Prevention (CDC) (Scott 2009) also estimated that the annual direct costs for HCAI treatment in US hospitals ranged from \$28 to \$33 billion. Costs for treating bloodstream infections varied from \$0.59 to 2.38 billion in total, with per-patient costs ranging from \$6,461 to \$25,849. The cost benefit of preventing at least 20% of HCAI varied from \$5.5 to \$6.8 billion.

The prevalence of HCAI in Ireland was explored in point prevalence surveys in 2006 (Smyth *et al.* 2008) and 2012 (Health Protection Surveillance Centre 2012b). The 2006 survey was undertaken across acute hospitals in the Republic of Ireland, England, Wales and Northern Ireland, with lower HCAI prevalence in Ireland (5%) (Smyth *et al.* 2008). Across all four countries, 7% of HCAI were due to primary bloodstream infections, the fifth most common HCAI. In a risk factor analysis of prevalence data (Humphreys *et al.* 2008), the presence of a CVC was significantly associated with primary bloodstream infection, with an odds ratio of 14.6 (95% CI, 12.0 to 17.6) and 4.14 (95% CI, 2.94 to 5.84) for the presence of a CVC on the day of the survey or within the last seven days. This highlights the link between CVCs and HCAI.

The 2012 national point prevalence survey (Health Protection Surveillance Centre 2012b) included 9,030 patients from 50 hospitals in the Republic of Ireland. The prevalence of hospital-acquired infections was 5%, ( $n=467$ ; 95% CI, 4.7 to 5.6). Bloodstream infections were the fourth most common HCAI

(13%, 66 cases); 67% ( $n=44$ ) were primary bloodstream infections, of which 57% ( $n=25$ ) were related to a CVC. The most common bloodstream infection causative organisms were *Staphylococcus aureus* (19%,  $n=13$ ), *Escherichia coli* (13%,  $n=11$ ) and coagulase negative staphylococci (13%,  $n=9$ ). There appears to be little difference in the prevalence of HCAI in Ireland between 2006 and 2012, but the surveys are not directly comparable because different methodology and case definitions were used. Chapter 3 (section 3.4) and chapter 6 (section, 6.4.2.1) draw attention to the high use of CVCs in the haemodialysis patient population, both nationally and internationally, and the potential increased risk for HCAI in this particular group of patients. These HCAI have serious consequence for patients, as well as for the Irish healthcare system.

Extrapolating data from the 2006 national prevalence survey of HCAI (Smyth *et al.* 2008), the 2008 ECDC review and the report on *The Socio-economic Burden of Hospital Acquired Infection* (Plowman *et al.* 2000), Fitzpatrick (2013) estimates that 29,388 patients admitted to Irish hospitals develop a HCAI. These infections result in 117,552 to 411,432 extra hospitalisation days. Based on an average cost per HCAI of €4,024, the total cost of all HCAI would be nearly €120 million. The number of expected deaths range from 1,081 to 3,820. The importance of preventing HCAI is highlighted in the potential saving whereby approximately €12 million could be saved if 10% of HCAI were prevented.

The preventability of HCAI is explored in a number of studies. Harbarth *et al.* (2003), in a systematic review of intervention studies estimated that the potential preventability of HCAI ranged from 10% to 70%. The episodes of catheter-related bacteraemia decreased from 8.6 episodes per 1000 catheter-days to 3.8 episodes per 1000 catheter-days, a 56% reduction. In a similar study, Umscheid *et al.* (2011) noted that implementing the most up-to-date evidence-based strategies could result in the prevention of 65% to 70% of catheter-associated bloodstream infections; making it the second highest preventable infection, with the highest number of preventable deaths. Preventable catheter-associated bloodstream infections were associated with higher healthcare cost, varying from \$0.96 to \$18.2 billion. The number of lives saved if best infection and control practices were implemented was estimated to be between 5,520 and 20,239.

Given their potential to harm patients and the serious impact they have on the healthcare system and wider society, HCAI were selected for the first World Alliance Global Patient Safety Challenge, titled *Clean Care is Safer Care* (WHO 2005). This challenge, launched in October 2005, focuses on five action areas that enhance safety and decrease the risk of infection. These areas include clean hands, practices, products, environment and equipment. A primary aim of this challenge was to sustain all actions beyond the initial two year period (2005 and 2006). Hand hygiene was identified as a simple action that decreases the risk and incidence of all types of HCAI. Recognising that healthcare professionals' adherence to good hygiene practices was low, hand hygiene guidelines, developed by the WHO (2006), were integrated into the *Clean Care is Safer Care* programme. Member nations were urged to promote the implementation of these guidelines. However, recent HIQA audits (Health Information and Quality Authority 2013a, 2013b, 2013c), highlight noncompliance with hand hygiene practices.

The institutes of the European Union have made various recommendations on HCAI (European Commission 2005, Council of the European Union 2006, European Commission 2007, Council of the European Union 2009). These include developing national, regional and local strategies for the prevention and control of such infections, promoting education and training of healthcare staff and creating or improving surveillance systems.

In response to the threat of HCAI, the Irish Government introduced a number of HCAI-related initiatives. One of the first was the strategy for the control and prevention of antimicrobial resistance in Ireland (Scientific Advisory Committee of the National Disease Surveillance Centre 2001). Recommendations included the surveillance of antimicrobial resistance, monitoring the supply and use of antimicrobials and developing guidelines on their appropriate use, and the development and implementation of infection prevention and control principles in hospital and community healthcare settings. The strategy's many research recommendations include evaluating the effectiveness of different strategies and measures to prevent infection. This PhD project resonates with this recommendation, as it aims to investigate the effectiveness of a particular intervention in the prevention of CVC HCAI.

Another Irish Government initiative was the National Infection Control Action Plan (*Say no to infection*), which was launched in 2007. The plan aimed to reduce HCAI by 20%, methicillin resistant *S. aureus* (MRSA) infection by 30% and antibiotic consumption by 20%. Key components of the campaign included educating healthcare professionals and the public on the steps they must take to reduce these infections, establishing hygiene and infection prevention and control standards, setting specific hospital targets in relation to surgical site infections and CABSIs, and enhanced bacteraemia surveillance, and ICU MRSA surveillance. By 2011, MRSA bloodstream infections had reduced to 264 cases from 588 cases in 2006, a decrease of over 55% (Department of Health & Children 2012a).

In 2009, HIQA published the *National Standards for the Prevention and Control of Healthcare Associated Infections*. The importance of invasive medical-devices, for example CVCs, as a source of HCAI and the potential impact such infections have on patient safety is reiterated in these standards. Standard 8 outlines a number of strategies important in the prevention of HCAI including the implementation of care bundles that have been proven to be effective in the prevention and control of invasive medical device-related infections. Strict aseptic technique and hand hygiene practices when manipulating the invasive medical device are also advocated, as is the education and training of staff in invasive medical device maintenance and care. Standards 6 and 11 are linked to hand hygiene practices and monitoring of antimicrobial resistance.

The *Clean Care is Safer Care* Global Challenge and national standards 6 and 11 stress the importance of clean hands and practices, which had implications for the design of this PhD project. There is an expectation within the *National Standards for the Prevention and Control of Healthcare Associated Infections* (Health Information and Quality Authority 2009) that principles underpinning the prevention and control of HCAI should be embedded in healthcare staff's daily routine. Chapter 6 explores routine practices across haemodialysis units in Ireland, with a particular emphasis on practices relating to infection prevention and control and adherences to best practice guidelines.

The prevention and control of HCAI is a priority of the HSE, who established the National Programme for the Prevention of HCAI and Antimicrobial Resistance, as a joint initiative with the Royal College of Physicians in Ireland.

Preventing medical device-related infection; for example, CVC-related infection is one of the three main focuses of this programme. Reflecting the National Healthcare Charter, this programme reiterates that every patient has the right to access the healthcare system without acquiring a preventable HCAI (Fitzpatrick 2013). This principle is also incorporated into HIQA's (2012a) programme for monitoring healthcare providers' compliance with its *National Standards for the Prevention and Control of Healthcare Associated Infection*. Improving the prevention, control and management of HCAI was designated a key priority in the 2013 HSE National Operational plan, with a specific action focused on preventing medical device-related infections; for example, intravascular line infections. The Operational plan identifies the number and frequency of catheter-related bloodstream infections as important quality and patient safety indicators.

## **2.5 Infection Prevention & Control**

Infection prevention and control is defined in the nursing literature (Royal College of Nursing 2012) as the "*clinical application of microbiology in clinical practice*" (p. 3) and is closely aligned with the discipline of epidemiology (Syndnor & Perl 2011). Infection control, having initially focused on puerperal sepsis and surgical wound infections expanded to scientifically proven programmes that incorporate the core elements of surveillance and the prevention and control of HCAI involving other body sites (Archibald 2012).

The primary aim of infection prevention and control is to implement measures that protect those vulnerable to acquiring infection (WHO 2014). HCAI are largely preventable through the effective implementation of infection prevention and control programmes. The CDC Efficacy of Nosocomial Infection Control (SENIC) study, undertaken in the US between 1974 and 1983, was one of the first studies to illustrate the impact such programmes have on the incidence of HCAI (Hughes 1988).

The principles underpinning infection prevention and control are referred to as standard precautions. These precautions must be applied to all patients, irrespective of the healthcare setting; at all times when in contact with blood, bodily fluid, secretions and excretions (except sweat) and working under the assumption that all contact may result in the transmission of infectious micro-organisms (Weston 2013). Standard precautions include hand hygiene, the

use of personal protection equipment, safe handling and disposal of sharps and waste, spillage management and cleaning/decontaminating equipment and the environment.

Core elements of present day HCAI prevention and control programmes include the surveillance of HCAI and providing feedback to healthcare professionals, appropriate use of antimicrobial agents, the development and implementation of HCAI policies and guidelines that are based on the best available evidence, education of healthcare professionals and the implementation of standard infection prevention and control precautions (SARI 2009, Royal College of Nursing 2012). Specific CVC HCAI preventive measures include:

- Asepsis, which is achieved by using a process that prevents or reduces the risk of micro-organisms gaining entry through the CVC exit site and catheter hubs. As a result, the risk of infection is reduced.
- Aseptic non-touch technique prevents the transmission of infection to patients by maintaining asepsis through the use of hand hygiene, a non-touch technique, and the use of aseptic fields and sterilised equipment. The CVC exit site and catheter hubs should only come into contact with equipment that is sterile.
- Skin asepsis is the application of an antiseptic solution prior to catheter insertion and during CVC maintenance that reduces the volume of micro-organisms at the insertion site and catheter hubs, so decreasing the risk of contamination.
- Appropriate use and management of CVCs including CVC care bundles.

(SARI 2009, Royal College of Nursing 2012)

The ultimate aim of these measures is to prevent catheter device contamination from micro-organisms entering catheter-related equipment, catheter insertion site, catheter hubs and or the bloodstream. Contamination can result from patients' own skin flora (endogenous transmission) or from the hands of healthcare professionals (exogenous or cross infection) (International Federation of Infection Control 2011). The pathogenesis for haemodialysis CVC-related infection is outlined in chapter 3 (section 3.5.2), as are interventions for the prevention of haemodialysis CVC-related infections

(section 3.6). Additionally, my systematic review of the interventions for the prevention of haemodialysis CVC-related infections can be found in chapter 4.

Infection prevention and control strategies are continually evolving. One strategy to emerge over the last 13 years is the use of care bundles in the prevention of HCAI. A care bundle is a group of evidence-based practices, usually three to five, that individually improve care, but when applied collectively and reliably result in greater improvements in patient outcomes, by significantly reducing catheter-related bloodstream infections (Institute for Healthcare Improvement 2006, The Joint Commission 2012). All components of the bundle must be implemented every time the relevant procedure is undertaken. The concept of the care bundle first emerged, in 2001, from the Institute for Healthcare Improvement (IHP) in the US. The IHP central line insertion bundle includes *“hand hygiene, maximal barrier precautions, chlorhexidine skin antisepsis, optimal catheter site selection, with avoidance of using the femoral vein for central venous access in adult patients, daily review of line necessity, with prompt removal of unnecessary lines”* (Resar *et al.* 2012, p. 3).

The effects of care bundles as part of a quality improvement programme in preventing central line HCAI were evaluated in a number of studies, with significant reductions in CVC infection rates ranging from 50% to 74% (Pronovost *et al.* 2006, Koll *et al.* 2008, Apisarnthanarak *et al.* 2010, De Palo *et al.* 2010, Render *et al.* 2011, Palomar *et al.* 2013). Although these studies focused on CVC insertion bundles, similar findings were also reported in studies that investigated the effects of CVC maintenance bundles (Guerin *et al.* 2010, Miller *et al.* 2010).

The importance of maintenance CVC bundles was reinforced by a study at a US Department of Veterans Affairs hospital in Denver (Guerin *et al.* 2010). Although compliance with a CVC insertion bundle was high (94%), the CABS rate remained at 5.7 infections per 1000 catheter-days. The mean dwell time of catheters associated with infection was 14.5 days (median 12), suggesting that events occurring after insertion may result in infection. Following the introduction of a post-insertion care bundle, the infection rate decreased to 1.1 CABS per 1000 catheter-days, highlighting the benefits of using this bundle.

The use of CVC care bundles is not evident in any renal specific guidelines, but their use is advocated in Irish and CDC intravascular catheter-related infection prevention guidelines (SARI 2009, CDC 2011a). CVC use in the outpatient haemodialysis environment is generally associated with long term CVC use; therefore, the components of a haemodialysis CVC care bundle differ somewhat to those used in other healthcare settings. The following elements may be included in a haemodialysis CVC maintenance care bundle: hand hygiene, inspection of insertion site, site care and change of dressing, CHG for skin antisepsis and CVC hub decontamination, use of antimicrobial lock, no routine catheter replacement and promoting the creation and use of an arterio-venous fistula (Department of Health UK 2007, Patel *et al.* 2013).

The elements of CVC maintenance bundles are generally comparable across different healthcare settings. All care bundles recommend the use of CHG as the CVC antiseptic cleansing agent, but inconsistency exists between bundles on the formulation and strength of this solution (Pronovost *et al.* 2006, SARI 2009, CDC 2011a). This inconsistency corroborates the lack of adequate evidence supporting the use of a particular formulation of CHG. As previously mentioned, there is general agreement within the literature that a CHG antiseptic solution is more effective than povidone iodine (chapter 5, section 5.3). However, there is limited published research on the most effective strength or formulation of CHG (chapter 5, section 5.7), with guideline recommendations being based on intellectual argument. This lack of clarity and uncertainty further underpins the need and focus of this PhD project.

## **2.6 The Role of the Renal Nurse**

Nurses are responsible for the quality of nursing care they deliver and are the only healthcare professionals that have direct contact with patients on a 24-hour basis. This affords them the opportunity to interact with other professionals and staff in the delivery of patient care, building a complete picture of the patient's healthcare experience including exposure to potential harm (Brady *et al.* 2009). Patient safety is an important consideration for nurses, irrespective of the healthcare setting and informs decision-making across all aspects of nursing practice. Renal nursing, encapsulating dialysis, nephrology and transplantation nursing, is also focused on keeping patients safe and delivering the most effective care (Bednarski 2009).



Patient safety is enhanced through nursing involvement in a variety of activities including infection prevention and control (International Council of Nurses 2012). The International Council of Nurses (2012, p. 1) position statement on patient safety notes that “*nurses have a responsibility to promote rigorous infection prevention and control programmes*”. Furthermore, nurses have a professional and ethical responsibility to implement practices that are evidence-based and effective in preventing HCAI (Royal College of Nursing 2012). Preventing infection is an important factor that needs to be incorporated into routine practices of all nurses, including those working within the haemodialysis environment.

The care of patients attending outpatient haemodialysis units is the responsibility of dialysis nurses. Patients are referred to the relevant medical practitioner if a healthcare issue is identified following the nurse’s pre-dialysis patient assessment or following assessment of patients during and post the dialysis procedure. The dialysis nurse, in contrast to other healthcare professionals, has the most access to patients’ CVCs and is responsible for their management including assessing and evaluating the exit site each time patients attend for dialysis or when the dressing is changed (McCann *et al.* 2010). International guidelines recommend that only trained experienced dialysis nurses should access and use patients’ CVCs (NKF K/DOQI 2006a, Pratt *et al.* 2007). Vascular access care and maintenance is one of the most challenging areas of care confronting dialysis nurses, who have a central role in preventing CVC-related infections. However, studies (Higgins & Evans 2008, Abdelsatir 2013) suggest that dialysis nurses’ knowledge and practice of infection prevention and control, in the area of VA care, is suboptimal. Ongoing education and training in hand hygiene, aseptic technique and CVC care were recommended. This supports the inclusion of these issues in the education and training programmes provided to the nurses administering the trial interventions in this PhD research project (chapter 8, section 8.10).

A Delphi study, involving members of the American Nephrology Nurses Association and focused on nephrology nursing research priorities, identified *investigating interventions preventing vascular access infection* as one of five research priorities, corroborating the importance of this area of nursing care for renal nurses (Lewis *et al.* 1999). Given the role that dialysis nurses have in the management of a patient’s CVC and the implementation of practices preventing CVC-related infections, it is important that they are actively

involved at local level in the development of evidenced-based CVC care and maintenance policies.

CVC-related infections not only impact on patients, but also have a negative impact on the workload of dialysis nurses and the efficient running of the dialysis unit. Patients are assessed at each dialysis session, by the dialysis nurse, for signs of CVC-related infections. If a patient is suspected of infection, the dialysis nurse is required to conduct a full infection screen involving device and peripheral blood cultures; and nasal, groin and CVC exit site culture swabs. In addition, patients with CVC-related infections, when attending the dialysis unit, require intravenous and topical administration of antibiotics by the dialysis nurse. Furthermore, patients may require hospitalisation, delaying their discharge from the dialysis unit, which delays the dialysis schedule for the next cohort of patients and may require the dialysis nurse to work overtime to discharge the last shift of dialysis patients. Once patients are admitted, the workload of ward based nurses also increases, because of increased patient acuity and morbidity, and longer periods of hospitalisation.

This PhD research project is highly relevant to renal nurses, focusing on a topic that is an important component of everyday dialysis nursing practice. It is also relevant to patient care in other clinical areas, since it assesses interventions that are in daily use across the health service in Ireland, and not just in haemodialysis units. It has direct application to patient care and contributes to the body of knowledge that will help renal nurses make future choices between the interventions assessed in the trial. Overall, the study contributes to the nursing knowledge and evidence-base on the most appropriate strength of CHG antiseptic solution used in the prevention of CVC-related infection. In addition, it was anticipated that the implementation of the study in the dialysis unit would create awareness among dialysis nurses of the importance of actively engaging in clinical research, and encourage dialysis nurses to explore research opportunities within their own dialysis setting.

## 2.7 Summary

Over the last few decades, retrospective and prospective studies clearly identified that patients admitted to healthcare facilities are exposed to preventable adverse events. Such events impact negatively on patient safety, causing unnecessary harm that may result in death, permanent disability and prolonged episodes of hospitalisation. HCAI were among the most common types of adverse events.

HCAI prevalence across Europe on any given day is 6%, with bloodstream infections the fourth most common HCAI (10.7%). Catheter-related infections account for 7% of all European HCAI. In Ireland between 2011 and 2012, the prevalence of HCAI was 5%; 57% of primary bloodstream infections were related to a CVC. The burden associated with HCAI and particularly CVC-related infections, for patients and the healthcare exchequer, underscores the importance of infection prevention and control and the use of preventative strategies and interventions that are based on the best available evidence.

Patient safety and the prevention of HCAI is a priority for global and national healthcare policy-makers. The National Healthcare Charter, the National Programme for Prevention of HCAI and Antimicrobial Resistance and the monitoring programme for the *National Standards for the Prevention and Control of HCAI* state patients have a right to access a healthcare service where HCAI are prevented. HCAI preventative strategies initiated globally as part of the WHO *Clean Care is Safer Care* Global Patient Safety Challenge include clean hands, practices, products, environment and equipment.

Specific CVC preventive measures include skin asepsis, aseptic non-touch technique, and the appropriate use and management of CVCs. CVC care bundles, which are also advocated, are effective in reducing CVC-related bloodstream infection as part of a quality improvement programme, but their use in outpatient haemodialysis units in Ireland is not wide spread. CVC care bundles across different patient populations are somewhat similar, but are inconsistent in the formulation of CHG used for skin asepsis; reflecting the lack of adequate evidence supporting the use of a particular formulation of CHG. This variation in practice and lack of adequate evidence is the driving force behind this PhD research project.

As the healthcare professional with the most frequent access to patients' CVC, the dialysis nurse has a central role in preventing such infections, and thus maintaining patient safety. There is an expectation in health policy that routine practices of all healthcare staff including dialysis nurses are informed by infection prevention and control principles. Finally, patients presenting to the dialysis unit with suspected CVC-related infections may have a negative impact on nursing workload and the efficient delivery of dialysis services to other patients attending the unit. All of which reinforces the importance of preventing the occurrence of such infections.

## 2.8 Conclusion

This chapter highlights the burden that adverse events have on patients and the healthcare system, including expenditure. HCAI are an important adverse event, are largely preventable and cause unnecessary harm to patients. By investigating the effectiveness of antiseptic solutions used for the prevention of CVC medical device-related infections in a patient population that has high, long term use of such devices, this PhD project is in accord with international and national patient safety and HCAI policy agendas. It is also in synergy with SARI's research recommendation that promotes the investigation of the effectiveness of strategies to prevent infection.

Policy-makers advocate the use of "*real life research*" when investigating interventions preventing adverse events; and, with this in mind, the implications for this PhD project are twofold. This study will focus on the effectiveness of a particular intervention used for the prevention of CVC-related infections in the real world setting of outpatient haemodialysis units. Secondly, a pragmatic trial design will ensure this PhD project is focused on the "*real life effectiveness*" of the intervention.

The *National Infection Prevention and Control Standards*, recent audits of hand hygiene compliance within the Irish healthcare system and the knowledge and practice of dialysis nurses in relation to CVC infection prevention and control needed to be considered when designing this trial and protocol. Education and training programmes, provided to dialysis nurses involved in the administration of trial interventions, had to address hand hygiene, aseptic technique and CVC maintenance and care. Additionally, the emphasis within the literature on monitoring antimicrobial resistance had

implications for trial outcomes and the inclusion of types of causative organisms as one of this study's secondary outcomes.

In summary, findings from this PhD research project will contribute to improvements in healthcare, better patient safety and more efficient use of resources by adding to the evidence base that will inform local, national and international strategy in the prevention of CVC-related infections.

## CHAPTER 3: HAEMODIALYSIS PATIENTS WITH CENTRAL VENOUS CATHETERS

### 3.1 Introduction

This PhD research project is focused on the effectiveness of different strengths of an antiseptic solution for the prevention of central venous catheter (CVC)-related infections in haemodialysis patients. To appreciate fully the magnitude and burden of CVC-related infections on patients with end stage kidney disease (ESKD), it is important first to explore the global significance of this disease, including the incidence and prevalence of haemodialysis. The high use of CVCs and their potential to lead to a detrimental impact on haemodialysis patient safety and wellbeing are also explained. Risk factors and pathogenesis for CVC-related infection are discussed as are the various interventions used to prevent them. Finally, implications for the design of new research in this area are highlighted.

A search of the literature was undertaken using the following databases: PubMed, EMBASE, CINAHL and The Cochrane Library (including the Cochrane Central Register of Clinical Trials). Reference lists of pertinent literature were reviewed for relevant material, not identified during the database search. The search strategy was limited to papers published in English; no limits were placed on the year of publication. The following MeSH and non-MeSH keywords were used: haemodialysis, vascular access, central venous catheters, infection, mortality, hospitalisations, haemodialysis units and built environment. A review of article titles and abstracts showed that, as expected, the retrieved papers were not specific to CVC-related infections. Relevant papers were either renal registries reports or prospective and retrospective studies investigating catheter-related infections, with the country of origin including the United States (US), the United Kingdom (UK), Canada and Spain. I identified three published studies from Ireland that specifically related to CVC-related infections (Little *et al.* 2001, Fitzgerald *et al.* 2011, Bajwa *et al.* 2012); and two conference papers (Reddy *et al.* 2010, Smyth *et al.* 2010) were also identified. Another published paper/report, pertinent to this chapter, is a retrospective study on the demands for vascular access in a renal dialysis unit in Ireland (Eguare *et al.* 2006).

## 3.2 End Stage Kidney Disease

Chronic kidney disease (CKD), a gradual and permanent loss of kidney function, is defined as “*abnormalities of kidney structure or function that is present for more than 3 months, with implications for the health of the individual*” (KDIGO CKD Work Group 2013, p. 5). The progression of CKD is classified into 5 stages, with higher stages reflecting increased kidney dysfunction. Stage 5 CKD is described as kidney failure, also known as end stage kidney disease (ESKD), end stage renal failure (ESRF) or end stage renal disease (ESRD) (KDIGO CKD Work Group 2013). For the purpose of this thesis, the term ESKD will be used.

Reporting of incidence and prevalence of ESKD, within renal registries<sup>1</sup>, is usually confined to patients treated with renal replacement therapy (RRT) that is haemodialysis, peritoneal dialysis and transplantation. Ireland has no renal registry, but the National Renal Office undertakes each year a census of ESKD RRT that is not patient linked (National Renal Office 2014). The primary renal diagnosis of incident ESKD varies across countries, the most common being diabetes, ranging from 26% of patients in the UK to 44% in the US. The second most common primary diagnosis is hypertension, varying from 7% (UK) to 28% (US). Other diagnoses include glomerulonephritis, interstitial nephritis, vascular disease, pyelonephritis, obstruction and inherited diseases such as adult polycystic kidney disease (Jha *et al.* 2012, The UK Renal Registry 2013, US Renal Data System 2013). It is not uncommon for primary renal diagnosis to be coded in renal registries as ‘uncertain’ or ‘of unknown aetiology’. There is a dearth of published literature on the primary renal diagnosis of patients with ESKD in Ireland. The primary renal aetiology in a study (Egure *et al.* 2006) on the demands for haemodialysis vascular access included diabetic nephrology (18.8%, 13 of 158 patients), glomerulonephritis (17.4%,  $n=12$ ), renovascular diseases (13%,  $n=9$ ), obstructive uropathy (11.6%,  $n=8$ ) and polycystic kidney disease (8.7%,  $n=6$ ).

---

<sup>1</sup> Renal registries in general collect and analyse data on different aspects of renal disease such as incidence, prevalence, clinical management and outcomes of patients treated with different forms of renal replacement therapy. Data are collected from January 1<sup>st</sup> to December 31<sup>st</sup> each year, analysed and reported on, on an annual basis. Various methods are used to collect these data such as directly downloaded data from renal units or other healthcare databases (e.g., UK Renal Registry, US Renal Data System) or the renal unit manually reports data to the registry via surveys/spreadsheets (e.g., Australia and New Zealand and Canada). On an annual basis, countries across Europe report their registry data to the European ERA-EDTA registry, which is a federation of renal registries involving 51 countries/regions with an overall population of 680 million.

ESKD is a global health issue due to its increasing incidence, prevalence, costs and poor outcomes. It is estimated that more than two million people worldwide require RRT (Couser *et al.* 2011), an increase of over one million since 1996 (Schena 2000). The incidence of ESKD RRT in Ireland is 88 per million of population (p.m.p.) and is predicted to grow annually by 30-40 patients p.m.p. (National Renal Office 2012a, 2014). The unadjusted incidence of ESKD RRT for the UK is 108 p.m.p., which is similar to Australia and other Northern European Countries (Denmark, Finland, Norway and Sweden). In contrast, the unadjusted incidence of ESKD RRT in the US (362 p.m.p.) is higher, having doubled over the last twenty years, exceeding previous projections (Eggers 2011, Bagdasarian *et al.* 2012, The UK Renal Registry 2013, US Renal Data System 2013). The incidence of ESKD in these countries is stabilising.

In a review of ESKD RRT prevalence trends, the number of patients in the US tripled between 1989 ( $n=123,000$ ) to 2007 ( $n=366,000$ ) (Collins *et al.* 2009), with adjusted prevalence of 1,901 p.m.p. at the end of 2011, a 1.7% increase since 2009 (1,738 p.m.p.) (US Renal Data System 2013). Conversely, the unadjusted prevalence for Ireland is much lower at 862 p.m.p. (3,960 patients), eight times greater than that reported in an epidemiological study from 1995 (494 patients, 137 p.m.p.) and comparable to the UK (861 p.m.p.) (Berthoux *et al.* 1999, The UK Renal Registry 2013, National Renal Office 2014).

Differences in incidence and prevalence of ESKD RRT, across countries and regions, may be due to variation in the healthcare system, differences in management strategies especially with regard to conservative treatment, disparity in risk factors for ESKD and their subsequent impact on mortality rates and differences in advanced kidney disease. Completeness of data submitted to and variation between renal registries also needs to be considered when comparing differences across countries and regions.

### **3.3 Haemodialysis**

Haemodialysis involves the extra-corporeal circulation of a patient's blood through a dialyser, a semi-permeable membrane fibre that acts as an artificial kidney. This fibre removes waste products and water from the blood. Vascular access allows blood to go from the patient, pass through the dialyser



and return back to the patient. This process, known as a haemodialysis session, takes three to four hours and is performed three times a week during the life span of the patient or until they receive a transplant.

Outpatient haemodialysis is provided at hospital and satellite dialysis units. Ulrick *et al.* (2004), note that airborne and contact infection transmission routes are affected by the design of the healthcare physical environment, ultimately impacting on healthcare-associated infection (HCAI) rates. A dialysis unit in Ireland consists of a number of dialysis stations that include a dialysis machine, dialysis chair or bed, bed-side table and ancillary equipment or supplies needed for dialysis treatment. In relation to the build environment, dialysis stations should be in increments of three, with the UK Health Building Note (07-Renal Care) recommending a minimum space of 900mm (3ft) between dialysis stations (The Renal Association 2009, Department of Health UK 2013). Sharing of equipment between dialysis stations should be avoided, in order to reduce cross infection.

Maintenance haemodialysis is the modality of RRT for 71% to 90% of new patients (The UK Renal Registry 2013, US Renal Data System 2013). In 2013, 81% ( $n=327$ ) of new ESKD patients in Ireland selected haemodialysis as their treatment modality. This proportion of patients selecting haemodialysis as their first treatment choice is little changed since 1995, when 73% ( $n=181$ ) of ESKD patients opted for haemodialysis (Berthoux *et al.* 1999, National Renal Office 2014).

At the end of 2013, a total of 1,556 patients were receiving haemodialysis in Ireland (339 p.m.p.), five times higher than in 1995 ( $n=309$ ) and a 17% increase since 2007 ( $n=1,329$ ) (Berthoux *et al.* 1999, National Renal Office 2014). This compares to a prevalence of 367 p.m.p., 473 p.m.p. and 1,225 p.m.p. in the UK, countries reporting to the ERA-EDTA registry and the US, respectively (The UK Renal Registry 2013, US Renal Data System 2013, Noordzij *et al.* 2014).

Limited data are available on the average age of haemodialysis patients in Ireland, with one published study (Eguare *et al.* 2006) reporting a median age of 57, with 32% ( $n=22$ ) of patients aged between 70 to 75 years. The UK Renal Registry notes a median age of 66 in 2012, up from 63 in 2000. Patients over 65 years account for 64% of the prevalent UK haemodialysis

population (The UK Renal Registry 2013). The incidence of haemodialysis is higher in males (57%), with similar gender differences noted in prevalent patients (US Renal Data System 2013).

The NHS Reference Cost Report for England (Kerr 2012) values dialysis activity at £505 million, with implied annual patient costs of £20,078 and £24,043 for peritoneal dialysis and haemodialysis, representing a cost differential of 20%. These estimates do not include all costs; for example, transport costs are excluded. Villa *et al.* (2011), using Spanish healthcare costs database, official government documents, existing literature and a forecast of 2010 prevalence of RRT, conducted a cost analysis for each modality of RRT. The annual per patient cost for peritoneal dialysis and haemodialysis patients was €25,825 and €37,968, a 47% cost differential difference between the two modalities (€12,142). Haemodialysis accounted for more than 70% of the aggregate costs of the Spanish RRT programme. Using different cost analysis methodology, Moncasi *et al.* (2011) report similar average annual costs for haemodialysis treatment (€40,136 per patient year).

Exploring modality over time and crossover of patients, the UK Renal Registry estimated that among the patients who started haemodialysis in 2007, 13% were transplanted by 2012 (5 years), 30% remained on haemodialysis and 53% died. Data on cause of death in this cohort of patients was not provided, but the leading causes of death among the prevalent RRT population, were cardiovascular disease (22%), infection (17%) and withdrawal of treatment (19%) (The UK Renal Registry 2013).

In the US, the 2011 rate of adjusted hospitalisation for haemodialysis patients was 1.8, 0.51, 0.47 and 0.10 hospitalisations per patient year for all-causes, cardiovascular disease, overall infection and vascular access infection. The rate of infection-related hospitalisation is 462 admissions per 1000 patient years, a 43% increase since 1993, but unchanged since 2009. Vascular access infection-related hospitalisations, although 75% higher in 2010 (103 per 1000 patient years) when compared to 1993 (59 per 1000 patient years), fell 24% since 2005 (135 admissions per 1000 patient years). Conversely, bacteraemia/sepsis episodes of hospitalisation increased between 2005 and 2011 from 102 to 123 hospitalisations per 1000 patient years (US Renal Data System 2012, 2013). This difference between these two types of episode in

the US may be linked to changes in the coding within the renal data surveillance system. During 2011, the rate of all-cause rehospitalisation among haemodialysis patients was 36%, with 34% and 31% of rehospitalisations within 30 days of discharge due to patients with overall infection and vascular access (VA) infection (US Renal Data System 2013).

### **3.4 Vascular Access**

An essential component of long term haemodialysis is the establishment of the vascular access (VA) that will enable patients to undergo dialysis treatment. Patients require some type of VA that facilitates the removal and return of patients' blood, after it has passed through the artificial kidney. A good VA should be easy to use, safe and efficient, with minimum risk of complications. It should provide repeated and reliable access to large blood vessels capable of providing sufficient blood flow to meet the needs of a blood pump speed of 300-350 ml/min, which ensures an effective dialysis session (Butterly & Schwab 2001, The NHS Information Centre 2011a). Types of VA used to access patients' vasculature, include an arterio-venous fistula (AVF)<sup>1</sup>, arterio-venous graft (AVG)<sup>2</sup> or a CVC<sup>3</sup>.

None of the various types of VA have all of the above characteristics for a "good VA", but the AVF is associated with fewer complications and has better patient outcomes when compared to an AVG or CVC (The UK Renal Association 2011a). The AVF has a lower risk of infection as it is created using native vessels, unlike the AVG and CVC, which involve the use of synthetic non-biological material, with a CVC having external attachments (Bagdasarian *et al.* 2012). Consequently, an AVF is the gold standard in VA with international guidelines recommending an AVF prevalence of greater than 65% (US) or 85% (UK) (NKF K/DOQI 2006a, The UK Renal Association

---

<sup>1</sup> AVF involves a surgical anastomosis between an artery and vein, usually in the arm either below or above the elbow. The flow of arterial blood and associated arterial pressure causes the vein to enlarge. This change in anatomical structure enables the vein to be cannulated with a large needle, facilitating the removal and return of blood by the blood pump in speeds of up to 350 ml per minute. It takes approximately 6-8 weeks for an AVF to mature.

<sup>2</sup> AVG involves the use of an artificial graft usually Polytetrafluoroethylene (PTFE) that involves an anastomosis between an artery and vein. The graft is usually placed either below or above the elbow and the graft material is cannulated for dialysis.

<sup>3</sup> CVC is a large tube inserted via the skin into a large vein, usually situated in the patient's neck. This tube is connected to the dialysis circuit during the dialysis session, allowing blood to flow to and from the patient via the dialyser.

2011a). However, the Dialysis Outcomes Practice Patterns Studies<sup>1</sup> (Ethier *et al.* 2008, Dialysis Outcomes Practice Pattern Study 2010) note a higher incidence of CVC use compared to AVF. This is also reflected in national renal registry reports, with 80% of patients commencing haemodialysis via a CVC in the US compared to 60% and 81% of UK and Canadian patients, respectively (The UK Renal Registry 2013, US Renal Data System 2013, Canadian Institute for Health Information 2014). There is no National Renal Registry on incidence and prevalence of VA use in Ireland.

A higher incidence of CVC use may be linked to late referral to the nephrology team, delayed access to a VA surgeon, delay between surgical evaluation and creation of AVF, delay between AVF creation and first cannulation and an ever increasing older ESKD patient population who experience higher rates of vascular access disease and diabetes resulting in an inadequate vasculature for AVF formation. Furthermore, in an increasingly older patient population, low output cardiac failure and increased frailty may also be an indication for CVC use (Mendelssohn *et al.* 2006, Ethier *et al.* 2008, Amerling 2012, Grubbs *et al.* 2014). Patient preference may be another contributing factor, whereby patients decline to consent to the formation of an AVF. Patients may fear the pain associated with AVF cannulation or the possibility of an altered body image due to the appearance of the AVF (Stack 2010, Xi *et al.* 2011, National Renal Office 2012b). These potential explanations for a high incidence of CVC use are supported by findings from the National Renal Office 2012 annual ESKD Census. On 31<sup>st</sup> November 2012, 16% of the 1557 patients on dialysis in Ireland who were suitable for, and willing to consent to, AVF creation had not yet had the procedure (National Renal Office 2012b). In this census survey, 27% of patients without an AVF were adjudged not to be suitable for this on technical grounds, or declined to consent to the procedure. A further 7%, although dialysing via a CVC, had had an AVF created that had not yet matured to a sufficient degree to be used.

---

<sup>1</sup> The DOPPS project commenced in 1996 and is an international longitudinal observational study of haemodialysis practices. It is designed to evaluate which dialysis practices are associated with the best patient outcomes including mortality, hospitalisation, quality of life and vascular access survival. Data are collected using a uniform data collection system from nationally representative samples from each of the participating centres. DOPPS 1 collected data from 1996-2001; DOPPS 2 from 2002-2004, DOPPS 3 from 2005-2008, DOPPS 4 from 2009-2011 and DOPPS 5 from 2012-2015. DOPPS 5 collected data from a representative and random sample of 465 units in 19 countries (Australia, Belgium, Canada, China, France, Germany, Japan, Italy, New Zealand, Spain, Sweden, UK, US and six Middle Eastern Countries).

Between 1996 and 2010, the prevalence of AVF use in the US has increased from 24% to 56%, primarily in response to the Fistula First Initiative (Ethier *et al.* 2008, Dialysis Outcomes Practice Pattern Study 2010). The proportion of prevalent haemodialysis patients using an AVF in European countries participating in DOPPS has decreased between DOPPS 1 (1996-2001) and DOPPS 4 (2010). For example, AVF prevalence in Italy decreased from 90% to 74% (Ethier *et al.* 2008, Dialysis Outcomes Practice Pattern Study 2010).

The CVC as a VA choice is considered inferior to other means of VA, with NKI K/DOQI (2006a) guidelines recommending that it should be used for no more than 10% of patients. This recommendation is rarely met, with the proportion of haemodialysis patients using a CVC in many European DOPPS countries increasing between DOPPS 1 (1996-2001) and DOPPS 4 (2010) (Ethier *et al.* 2008, Dialysis Outcomes Practice Pattern Study 2010). For example, the use of CVCs in Germany increased from 4% to 19%. This over-reliance on a CVC is also evident in national renal registries, with prevalence of 18% in the US and 22% in the UK (The UK Renal Registry 2012, US Renal Data System 2012). As there was no National Renal Registry data on CVC use in Ireland, CVC prevalence use was reviewed during fieldwork, undertaken in 2009, as part of this PhD research project. Based on completed data from 17 dialysis units (total of 1,294 patients), CVC prevalence was 53%. Eguare *et al.* (2006), reported a similar CVC use (54%,  $n=85$ ) among 158 Irish haemodialysis patients.

### **3.5 Central Venous Catheters**

CVCs used in haemodialysis patients can be non-tunnelled or tunnelled. A non-tunnelled catheter, known as short term, temporary, non-cuffed or acute catheter, is intended for short-term haemodialysis use, for periods of less than 2 weeks. On the other hand, tunnelled catheters, often referred to as long-term, chronic, permanent or cuffed catheters are generally used when patients require more than two to three weeks haemodialysis (McCann *et al.* 2010).

Haemodialysis CVCs can be inserted into multiple insertion sites relatively easily, while non-tunnelled catheters can be inserted at the bedside. Unlike an AVF, a CVC requires no maturation time and can be used immediately after a chest x-ray and, from a patient's perspective, access to dialysis does not require repeated cannulation (McCann *et al.* 2010). CVCs are, however,

problematic in that they are associated with increased mortality risk and high morbidity due to infection. Other complications include thrombosis formation, central venous stenosis, mal-positioning, and kinking of the catheter, all of which can cause problems with catheter blood flow (Murphy 2011).

A dual-lumen, tunnelled, permanent-cuffed CVC is the catheter of choice for chronic haemodialysis patients. For patients with ESKD, the CVC insertion site is patient-dependent, the preferred site being the right internal jugular vein because of its direct route to the atrium. The femoral vein is the least preferred site and is primarily used for non-tunnelled short-term use and patients who are bed-bound or critically ill, with bleeding tendencies and/or cardiac or respiratory failure (McCann *et al.* 2010). Due to the high risk of venous stenosis, the subclavian vein is not recommended in patients who may require the formation of permanent VA at a later date (NKF K/DOQI 2006a, Vanholder *et al.* 2010, The UK Renal Association 2011b).

A tunnelled CVC is percutaneously tunnelled from the vein insertion site to a distant exit site and held in position by a cuff that is affixed to the catheter. The presence of the cuff acts as an anchor and a barrier to bacteria at the exit site, preventing bacteria migrating down the tunnel. It is also affixed to the skin by sutures, which are removed 7-14 days after insertion (McCann *et al.* 2010). The CVC is locked between dialysis treatment using either heparin (Ashley 2009) or an antimicrobial lock solution such as trisodium citrate (O'Horo *et al.* 2011).

### **3.5.1 Patient safety & central venous catheter use**

As discussed in chapter 2 (sections 2.4 and 2.5), prevention of healthcare-associated infections (HCAI), including those due to CVCs, is an important component of a healthcare facility's patient safety and infection prevention programme. Given that a large portion of haemodialysis patients have a CVC as a means for VA for their dialysis, they are at a higher risk of HCAI than patients with an AVF. The threat to patient safety is best illustrated by the burden that CVCs and infection-related mortality have on this patient population.

In the field of haemodialysis, the type of VA may contribute independently to patient mortality, as seen in a number of observational studies that report a one- to three-fold increase in the risk of death with a CVC when compared to

an AVF (Dhingra *et al.* 2001, Pastan *et al.* 2002b, Polkinghorne *et al.* 2004, Allon *et al.* 2006, Moist *et al.* 2008). Findings from these studies are supported by a number of DOPPS studies (Pisoni *et al.* 2009, Goodkin *et al.* 2010) that, after adjustment for case mix, co-morbid conditions and laboratory values, found that patients with CVCs have a 32% higher relative risk of death than patients with an AVF. Indeed, there is an 80% increased risk of death for patients who convert to a CVC, while those patients who converted from a CVC to permanent access (AVF and AVG) have a 30% lower risk of death when compared to those that did not (Bradbury *et al.* 2009). A systematic review of cohort studies confirms that haemodialysis patients using a CVC have a higher risk for mortality when compared to patients with an AVF (Ravani *et al.* 2013). However, Grubbs *et al.* (2014) following a review of 117,277 incident haemodialysis patients on the US Renal Data System suggests that mortality differences may not be solely attributed to access type. The health status of patients' may also be a potential mediator of the association between vascular access and mortality.

Haemodialysis patients from the US have a higher adjusted mortality risk than patients from participating European DOPPSs countries. This is thought to be attributed to a 20% higher adjusted mortality risk associated with facilities that have a higher use of CVCs (Pisoni *et al.* 2009, Robinson & Port 2009). DOPPS (Wikstrom *et al.* 2010) reviewed haemodialysis practices in Sweden to obtain an estimate of patient life-years, and identified that practices related to reducing the use of CVCs and increasing patient albumin were associated with the largest patient-year gains. Similar findings were also reported when DOPPS estimated patient life-years in the US (Port *et al.* 2004).

In a prospective cohort study involving all Scottish haemodialysis patients (Bray *et al.* 2012), patients with a CVC were found to have a three-fold higher risk of infection-related death than other forms of VA. These findings are similar to those reported in the Choices for Healthy Outcomes in Caring for ESKD (CHOICE) study (Astor *et al.* 2005) and other prospective studies (Dhingra *et al.* 2001, Allon *et al.* 2003).

Leading risk factors for bacteraemia in haemodialysis patients are tunnelled CVCs, history of previous tunnelled CVCs, bacteraemia and immunosuppressive therapy (Hoen *et al.* 1998, Taylor *et al.* 2008, Bagdasarian *et al.* 2012, Martin-Pena *et al.* 2012). CVC infections include

bacteraemia (bloodstream infections), exit site and tunnel infections. The CDC (2011b) estimate that 37,000 catheter-associated bloodstream infections (CABSI) occurred among US outpatient haemodialysis patients in 2008. An audit of vascular access use in the UK <sup>1</sup> (The NHS Information Centre 2011a) reveal a relative risk for access-related infection that is 6 times higher in patients with a CVC than in patients with an AVF. In comparison to patients with CVCs, patients with an AVF have lower episodes of VA-related bacteraemia, 6 and 8 episodes per 100 patients, respectively (The NHS Information Centre 2011b). A weakness of the UK vascular audit process is its dependence on dialysis units completing and returning the relevant spreadsheet. Compliance varies from year to year, resulting in a lack of consistency in the number of units reporting VA figures; for example, 45 out of 65 dialysis units returned completed data for 2011. A strength of these audits is that they are patient-linked, enabling them to be linked to the UK Renal Registry.

Findings from these audits are supported by both prospective and retrospective observational studies (Stevenson *et al.* 2000, Saeed Abdulrahman *et al.* 2002, Weijmere *et al.* 2004, Develter *et al.* 2005, Mokrzycki *et al.* 2006, Mazonakis *et al.* 2009, Al-Solaiman *et al.* 2011, Martin-Pena *et al.* 2012). In these studies, VA-related bacteraemia range from 0.14 to 0.44 episodes per 1000 catheter days for AVF and 0.34 to 8.18 per 1000 catheter days for tunnelled CVCs. Non-tunnelled CVCs have a higher risk of catheter-related infections than tunnelled CVCs.

I identified only three studies reporting episodes of CVC-related bacteraemia in Irish dialysis units, which had been published before the end of 2013. Little *et al.* (2001), investigated all tunnelled haemodialysis CVCs inserted over a three-year period ( $n=336$  patients,  $n=573$  catheters); the rate of catheter-related sepsis was 1.3 episodes per 1000 catheter days. Reddy *et al.* (2010), in a 12-month study investigating dialysis nursing practices in the maintenance of haemodialysis patients CVC ( $n=52$ ) noted a CVC bacteraemia rate of 0.64 per 1000 catheter days (1.94 per 100 patient-months). Changes in dialysis nursing practices included two-person dialysis connection and disconnection, the use of antimicrobial CVC lock solution and valved bungs. Information on

---

<sup>1</sup> The UK Vascular Access Audit is managed by the UK Renal Registry whereby dialysis centres in England, Wales and Northern Ireland submit completed questionnaires on vascular access use. This audit is dependent on dialysis units' compliance in completing and returning the relevant questionnaires.



the type of CVC dressing and skin antiseptic agent used to cleanse the CVC site was not reported, but personal communication (Reddy 2014) with a member of the research team indicates the use of a 0.05% aqueous chlorhexidine gluconate solution for skin asepsis and a transparent semi-permeable polyurethane CVC dressing. The episodes of catheter-related bacteraemia in both these studies are lower than those reported in the international literature (Develter *et al.* 2005, Mokrzycki *et al.* 2006, Al-Solaiman *et al.* 2011). The third study involved the piloting of the CDC/National Healthcare Safety Network (NHSN) dialysis event protocol<sup>1</sup> (Bajwa *et al.* 2012). Dialysis events, including bloodstream infection were more common in patients with CVCs than patients with AVFs ( $p < 0.001$ ). A weakness of this study is the lack of clarity on the event rate for access-related bacteraemia. All three of these Irish studies were prospective observational studies that used different definitions for catheter-related bacteraemia, limiting comparability.

The CDC/NHSN protocol has been used in a number of international studies (El-Saed *et al.* 2011, Quori *et al.* 2011) that report episodes of access-associated bacteraemia relating to AVF and CVC. Episodes of bacteraemia range between 0.6 to 1.3 per 100 patient-months for an AVF and 4.4 to 9.8 per 100 patient-months for a CVC. These studies again illustrate that a CVC poses a higher risk for bacteraemia than an AVF.

The most common causative organism for bacteraemia in haemodialysis patients with CVCs is gram positive cocci, such as *Staphylococcus aureus* and coagulase negative staphylococcus (*Staphylococcus epidermidis*). Other causative organisms include *Enterococcus* sp., *Pseudomonas* sp. and *Candida* sp. (The NHS Information Centre 2011b, Ramanathan *et al.* 2012).

In a number of prospective observational studies involving haemodialysis patients (Engemann *et al.* 2005, Nissenon *et al.* 2005, Reed *et al.* 2005), VA was the source of *S. aureus* bacteraemia in 83% to 88% of episodes. A majority of patients (70%) with methicillin resistant *S. aureus* (MRSA)

---

<sup>1</sup> CDC/NHSN protocol is a surveillance protocol for dialysis events related to vascular access. These events are specific to patients attending outpatient haemodialysis settings and include hospitalisation, intravenous (IV) antimicrobial start and positive blood cultures. In relation to VA-related infection the protocol provides three types of case definitions for local access infection; access-associated bacteraemia and vascular access infection. The use of this type of surveillance is widespread in outpatient haemodialysis units in the US. A number of European and non-European countries have also used this surveillance system.

bacteraemia had a CVC. Episodes of MRSA and methicillin sensitive *S. aureus* (MSSA) bacteraemia ranged from 33% to 38% and 62% to 66%, respectively. MRSA bacteraemia had significantly higher initial hospitalisation costs than MSSA bacteraemia (\$21,251 vs. \$13,978;  $p=0.01$ ). In comparison to MSSA bacteraemia, patients with MRSA bacteraemia had increased length of hospitalisation (mean 16.6 days vs. 9.3 days).

There has been a decline in the number of bloodstream infections caused by MRSA in recent years; but it remains a significant cause of healthcare-associated bloodstream infections, in particular vascular device-associated bacteraemia (Health Protection Surveillance Centre 2012a). Data relating to 2009-2010 from a joint study by the Health Protection Agency and the UK Renal Registry (The UK Renal Registry 2011) highlight the continued threat MRSA bacteraemia poses to haemodialysis patient safety. The incidence of MRSA is 100-fold higher in dialysis patients than in the general patient population and a further six-fold higher in haemodialysis patients with a CVC than in patients with an AVF. The median rate of MRSA bacteraemia is 0.25 per 100 prevalent dialysis patients, with 63% of episodes of MRSA bacteraemia occurring in haemodialysis patients with a CVC. The median rate of MSSA is 1.27 per 100 dialysis patients, again 6-fold higher in patients with a CVC when compared to those with an AVF.

Although there are a number of reports on the surveillance of *S. aureus* across different healthcare settings in Ireland, few relate specifically to the outpatient haemodialysis environment. In unpublished literature from an outpatient haemodialysis unit in Dublin, Smyth *et al.* (2010) reported that 9% ( $n=3$  of 35) of catheter-related bloodstream infections (CRBSI) were due to *S. aureus*. Limitations of this prospective three-month audit include lack of information on the total number of patients with CVCs, resulting in non-reporting of CRBSI event rate for that period. In Reddy *et al.* (2010) study, 85% of isolates were *S. aureus*, 7% of which were MRSA. This is not much different from 2001, where 69% of catheter sepsis were due to *S. aureus* (18% of isolates were MRSA) with 27.5% linked to coagulase negative staphylococcus (Little *et al.* 2001).

Similar findings are also reported in an Irish retrospective study investigating *S. aureus* bloodstream infections in haemodialysis patients over a 12 year period from January 1998 to December 2009 (Fitzgerald *et al.* 2011). The

overall rate of *S. aureus* bloodstream infections was 17.9 per 100 patient-years (range 9.7-36.8), with the rate of MRSA bloodstream infections being 5.6 per 100 patient-years (range 0.9-13.8). Overall, 69% of episodes were due to MSSA, while 31% were caused by MRSA, slightly higher than that reported by Little *et al.* (2001), Reddy *et al.* (2010) and Smyth *et al.* (2010). The haemodialysis CVC was the source of infection in 83% of episodes, similar to that reported by Reed *et al.* (2005). Infective complications occurred in 11% of episodes including metastatic abscess, septic arthritis and osteomyelitis, with infective endocarditis being the most common (7.6%).

Other types of CVC-related infection include exit site infection, which can vary from 8.2 to 16.75 per 1000 catheter days and 0.35 to 8.3 per 1000 catheter days for non-tunnelled and tunnelled catheters respectively (Stevenson *et al.* 2000, Saeed Abdulrahman *et al.* 2002, Weijmere *et al.* 2004). These compare to localised tunnel/exit site infection of 1.81 per 1000 catheter days (5.49 per 100 patient-months) reported by Reddy *et al.* (2010).

In a Canadian observational study (Harwood *et al.* 2008) investigating the predictors of positive CVC exit site infections in haemodialysis patients, no patient characteristics were associated with an exit site infection. The type of dressing (dry gauze versus semi-permeable transparent;  $p=0.007$ ) and antiseptic cleansing solution (10% povidone-iodine solution versus 2% chlorhexidine gluconate;  $p=0.007$ ) were positively associated with an exit site infection.

CVC-related infections impact negatively on CVC survival, hospitalisation and overall cost of care. Premature removal of a CVC due to clinical evidence of CVC infection varied from 32% to 55% for tunnelled catheters and 49% to 59% for non-tunnelled catheters (Kairaitis & Gottlieb 1999, Weijmere *et al.* 2004, Alomari & Falk 2007). There is limited published literature on the removal rate of CVCs due to related infections, in Ireland. Unpublished Irish literature (Smyth *et al.* 2010) suggests that over a three month period 23% ( $n=8$ ) of CVCs were removed as a result of CRBSI, slightly lower than the published literature. The mean survival time of a CVC from catheter insertion to CRBSI was 406 days. This compares to published data suggesting a median CVC survival time ranging from 66 to 310 days (Develter *et al.* 2005, Perl *et al.* 2006).

When compared to patients with an AVF, data from DOPPS I and II (Ng *et al.* 2011), indicate that CVC use confers the highest risk for both all-cause (RR 1.30, 95% CI 1.09 to 1.54), VA-related (RR 1.49, 95% CI 1.06 to 2.11) and infection-related hospitalisations (RR 1.47, 95% CI 0.92 to 2.36). Similar findings were noted in a prospective observational study (Lacson *et al.* 2010), involving 79,545 patients attending Fresenius Medical Care dialysis units in North America. In Ireland, the rate of hospitalisation was higher in patients with CVCs than in patients with an AVF (23.81 per 100 patient-months versus 3.52 per 100 patient-months) (Bajwa *et al.* 2012).

In a Canadian cost analysis study (Lee *et al.* 2002) of ongoing care of haemodialysis patients, the cost for VA-related care was more than five times higher for patients with a long-term CVC or graft compared to those with a functioning AVF. Furthermore, costs associated with the management of patients with catheter-related bacteraemia were calculated to be US \$45,000 (Reed *et al.* 2005).

### **3.5.2 Pathogenesis of CVC-related infection**

There are numerous risk factors for CVC-related infection, which can be patient or dialysis related. Patient-related factors include altered responses to infection due to the immunosuppressive nature of ESKD, as a result of uraemia-associated phagocyte dysfunction, deficits in cell-mediated immunity and antibody production. Other factors include aging, poor patient hygiene, iron overload, low serum albumin level, co-morbidities such as diabetes and malignancies, local skin conditions, *S. aureus* carriage and, in the case of haemodialysis patients, the constant need to access the vascular system for treatment (Hoen *et al.* 1998, Nielsen *et al.* 1998, Powe *et al.* 1999, Taylor *et al.* 2004, Patel *et al.* 2010, Fitzgibbons *et al.* 2011, The Joint Commission 2012).

Dialysis-related factors include dialyser bio-incompatibility, use of less pure dialysate, conditions/technique involved in catheter placement, duration of catheter placement, frequency of manipulations, insertion site protocol, insertion site selection, number of dialysis uses, training of staff and type of catheter (Young *et al.* 2005, Fitzgibbons *et al.* 2011).

The pathogenesis of haemodialysis CVC infection is linked to two major routes, extra-luminal or intra-luminal. Inserting the catheter through the skin breaches the body's natural defence causing local trauma, increasing the patient's susceptibility to the extra-luminal route for CVC infection. This pathway involves the migration of flora from the patients' own skin through the catheter exit site and onto the outer surface of the catheter, resulting in colonisation of the catheter tip. The intra-luminal route involves direct contamination of the catheter or infusion solutions during dialysis. For example, contamination of the catheter hub may occur due to multiple manipulations associated with long term catheter use for haemodialysis, exposing the catheter hubs to the patient's skin flora or contamination from healthcare workers' hands (Crnich & Maki 2002b, 2002a, Safdar *et al.* 2002, Casey *et al.* 2003, Safdar & Maki 2004). Effective preventive strategies need to include interventions that minimise contamination of the CVC exit site and catheter hubs. Furthermore, a CVC can become colonised during an episode of bacteraemia linked to an infection elsewhere in the body, which seeds at the CVC. Dispersal of microorganism or clumps of biofilm can result in metastatic infections elsewhere in the body, for example, endocarditis (The Joint Commission 2012, Kallen 2013).

Inner lumen contamination of a haemodialysis catheter was the focus of a Spanish prospective observational study (Rodríguez-Aranda *et al.* 2011) involving 51 haemodialysis patients. Bacterial colonisation of the inner lumen occurred more frequently in patients with CRBSI than non-infective patients (74% vs. 4.4%,  $p < 0.001$ ). The overall mean time from catheter insertion to colonisation was 378 days (SD 365.3), for patients with CRBSI and non-infective patients the mean time was 391 days (SD 388.3) and 287 days (SD 135.1), respectively. The overall median time between colonisation and CRBSI was 28 days; but variations in interval times were noted in CRBSI, caused by different microorganisms. The time from catheter insertion to CRBSI was 443 days (SD 378.8), higher than the 405 days reported in unpublished audit by Smyth *et al.* (2010).

Another pathway to the development of catheter-related infections is linked to microorganisms gaining access to the intra-luminal or extra-luminal surface of the catheter, adhering to the surface and producing a biofilm that incorporates the microorganism; thus, protecting it from the host defences and from antimicrobial agents (Liangos *et al.* 2006). This pathway was the focus of a

US prospective observational study (Ramanathan *et al.* 2012), which investigated microbiological growth and biofilm thickness on the outer and luminal surfaces of haemodialysis tunnelled catheters in 76 patients. Patients with catheter-related bacteraemia had significantly thicker biofilm on all catheter surfaces than non-infective patients. Biofilm thickness in this group of patients was also significantly thicker on the outer aspect of the catheter compared to the luminal inner surface. Furthermore, the external surface of the catheter had the highest yield of microorganism growth. An acknowledged limitation of the study is linked to patients suspected with catheter-related infection receiving intravenous antimicrobial agents through the catheter prior to its removal; thus, it is unclear what impact this may have had on subsequent culturing of the catheter section. The possible cause of this significant growth of microorganism and biofilm particularly on the outer surface of the catheter may be attributed to contamination of the catheter via the exit site, highlighting the need for strict aseptic technique and skin asepsis while manipulating the catheter during dialysis.

### **3.5.3 CVC-related bloodstream infections: case definitions**

To minimise HCAI in haemodialysis patients with a CVC, it is essential that infection prevention and control within the haemodialysis environment takes an evidence-based approach to ensure optimal management of CVCs. This includes accurate diagnosis and monitoring of bloodstream infections using standardised case definitions and, adopting components of an infection prevention and control programme and quality improvement initiatives (chapter 2, section 2.5) that are aimed at ensuring safe and effective healthcare (Health Information and Quality Authority 2009).

Bloodstream infections can be classified according to surveillance or clinical case definitions. Surveillance definitions include the European Centre for Disease Prevention (ECDC 2012), the CDC/NHSN central line-associated bloodstream infection (CABSI), also known as laboratory-confirmed bloodstream infection (CDC/NHSN 2009) and the CDC/NHSN Dialysis Event Module Bloodstream Infections (CDC/NHSN 2009). Prior to the establishment of the ECDC, the Hospital in Europe Link for Infection Control through Surveillance (HELICS) developed case definitions relevant to CVC-related infections.

The HELICS (2004) protocol includes case definitions for bloodstream infection and CVC-related infection, developed for the surveillance of nosocomial infections in Intensive Care Units (ICU). The case definition relating to bloodstream infection is not concerned with the source of the infection, but the case definition for CVC-related infection addresses three issues. The first two relate to local and general CVC-related infection, both of which do not require positive blood cultures, lack clarity on what constitutes a CVC culture and are very broad definitions. The third is linked to CVC-related bloodstream infection. The HELICS definitions, while suitable for surveillance of bloodstream infection rates specific to ICU patients, may not be suitable for clinical diagnosis or research-based activities, especially in the field of outpatient haemodialysis care, as it may result in decreased specificity<sup>1</sup> (Kallen 2013).

The CDC/NHSN surveillance case definition for CABSIs differs from HELICS in that it was developed for different inpatient areas, including inpatient dialysis units (CDC/NHSN 2009). Laboratory-confirmed bloodstream infections criteria are used to classify primary bloodstream infections, which are classified as CABSIs if the central line was in place 48 hours before the onset of the infection. Greater detail on this case definition is provided in chapter 8 (section 8.14.1). The advantage of this definition is that it removes any clinical uncertainties relating to secondary bloodstream infections and common skin contaminants. Culturing of the catheter tip is not a criterion for CABSIs. A case definition on clinical sepsis is also provided, but this only applies to neonates and infants under the age of one. A potential weakness of this definition is that it may over-estimate the true rate of CVC-related infections due to difficulty in differentiating central line infections from remote unrecognised infections. Other limitations include inter-observer variability and a lack of standardisation in the surveillance process (The Joint Commission 2012).

The CDC/NHSN<sup>2</sup> (CDC/NHSN 2009) was the first organisation to develop a surveillance protocol that includes dialysis events related to vascular access use, including CVC use. These events are specific to patients attending outpatient haemodialysis settings and include hospitalisation, the start of an intravenous (IV) antimicrobial and positive blood cultures. As outlined in chapter 8 (section 8.14.3), the dialysis event surveillance protocol also

---

<sup>1</sup> Specificity is the ability to identify correctly those who do not have the condition.

<sup>2</sup> CDC/NHSN updates the dialysis event protocol on a regular basis, the trial protocol is informed by the CDC/NHSN protocol published in 2009.

includes three infection-related case definition outcomes: local access infection; access-associated bacteraemia and vascular access infection. Although simple and easy to use, these case definitions lack the specificity necessary for clinical diagnosis and may not be sufficiently robust for research studies. However, an advantage of the dialysis events protocol is the reporting of dialysis events per 100 patient-months and the collection of denominator data (number of CVCs) on the first two working days of each month. This is less labour-intensive than collecting denominator data for line days (reported as 1000 catheter line days) that requires counting the number of patients with one or more CVCs at the same time each day during a specific month. This is not suited to an outpatient haemodialysis setting as patients visit the unit every second day. The use of the dialysis events surveillance protocol is widespread in outpatient haemodialysis units in the US, with a number of European and non-European dialysis units also reporting its use (Tokars *et al.* 2002, Klevens *et al.* 2005, George *et al.* 2006, Klevens *et al.* 2008, El-Saed *et al.* 2011, Bajwa *et al.* 2012).

The Infectious Diseases Society of America (IDSA) (Mermel *et al.* 2009), in their 2009 update on clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection, recommended a specific clinical case definition for catheter-related bloodstream infections (CRBSI); chapter 8 (section 8.14.1) provides greater detail on this particular case definition. Clinical findings alone, due to their poor sensitivity<sup>1</sup> and specificity<sup>2</sup>, are not sufficient or reliable for diagnosing CRBSI (Mermel *et al.* 2009, SARI 2009). A diagnosis of CRBSI is dependent on a number of measures including culturing the tip of the CVC and blood cultures. The semi-quantitative catheter segment culture is a method that cultures the outside of the catheter segment, while the quantitative segment catheter culture is concerned with the intra-luminal spread of organism. The quantitative culture method is labour-intensive and time consuming. It has been reported that the semi-quantitative method has high sensitivity, especially in recently inserted catheters. For long-term catheters, the semi-quantitative culture method may be less sensitive to intra-luminal spread of organisms, when compared to the quantitative catheter culture method. However, there is much debate within the literature as to which method is the more sensitive (Bouza *et al.* 2005, Safdar *et al.* 2005, Mermel *et al.* 2009, SARI 2009). Indeed, both approaches

---

<sup>1</sup> Sensitivity is the ability to identify correctly those who have the condition.

<sup>2</sup> Specificity is the ability to identify correctly those who do not have the condition.



are recommended by the European Renal Dialysis Association best practice guidelines (Vanholder *et al.* 2010).

CRBSI can be diagnosed without removal of the CVC, using blood culture diagnostic methods including simultaneous quantitative cultures of blood and differential time-to-positivity cultures. The simultaneous quantitative cultures of blood are labour-intensive and expensive. Differential time-to-positivity cultures are dependent on drawing positive simultaneous blood cultures from the CVC and peripheral vein (Blot *et al.* 1998, Raad *et al.* 2004, Allon 2009). However, it is not always feasible to draw peripheral blood cultures from haemodialysis patients. First of all, peripheral cultures cannot be obtained from vessels intended for future AVF formation. Secondly, patients' vasculature may be so poor that a peripheral sample cannot be obtained. In these circumstances, a peripheral sample may be obtained, during dialysis, from the dialysis circuit lines. However, there is a lack of clarity as to whether there is any difference between cultures drawn directly from the catheter and from the dialysis circuit lines (Mermel *et al.* 2009, Vanholder *et al.* 2010).

The strength of the CRBSI case definition lies in its precision and the inclusion of specific requirements detailing what constitutes a CVC culture. As outlined above, these include specific laboratory testing and, as a result, diagnosis is less open to interpretation, making CRBSI case definitions more suited for clinical research activity (Association for Professionals in Infection Control and Epidemiology 2009). The precision of this case definition can also be a weakness as a number of specialised blood culture tests are required to confirm CRBSI diagnosis, tests that may not routinely be undertaken in hospital laboratories aligned to outpatient haemodialysis units or tests requiring specific blood culture samples that may not be attainable from haemodialysis patients. In addition, there is a reluctance to remove the CVC, as it is the patient's only form of vascular access for haemodialysis, making it impossible to culture the tip of the catheter (The Joint Commission 2012, Kallen 2013).

Finally, SARI (2009) in its published guidelines on the prevention of intravascular catheter-related infections in Ireland recommends the use of CABSIs and CRBSI case definitions in the diagnosis and monitoring of bloodstream infections. Specific reference is also made to the outpatient

haemodialysis setting and the use of the CDC/NHSN dialysis events outcomes in the surveillance of infection within this patient population.

### **3.6 Interventions Preventing CVC Infections**

CVC-related infections are potentially modifiable, thus highlighting the importance of implementing evidence-based infection prevention and control interventions that may contribute to limiting the occurrence of such infections. There is no published literature on the practices underpinning VA management and care in haemodialysis settings in Ireland.

As outlined in chapter 2 (section 2.5), prevention of CVC-related infections is multifaceted, incorporating the education of healthcare personnel about guidelines to prevent catheter-related infections and the implementation of evidence-based interventions when caring for the CVC exit site and catheter hubs, both high risk areas for contamination and colonisation. A variety of interventions are used to prevent haemodialysis CVC-related infections suggesting confusion regarding best practice in this area. Examples of these interventions include the use of various prophylactic antibiotics prior to catheter insertion, antimicrobial-catheter locking solutions, antimicrobial-impregnated catheters, antiseptic solutions to clean the exit site, topical antimicrobial ointments and dressings to cover the exit site (Sesso *et al.* 1998, Johnson *et al.* 2002, Chatzinikolaou *et al.* 2003, Le Corre *et al.* 2003, McIntyre *et al.* 2004, Percival *et al.* 2005). International guidelines offer conflicting advice on interventions preventing CVC-related infections in haemodialysis patients, thereby compounding the confusion for clinicians (CARI 2000, CDC 2002, ERA-EDTA 2002, Jindal *et al.* 2006, NKF K/DOQI 2006b, SARI 2009). There is a lack of clarity on the interventions used in dialysis units in Ireland due to the lack of published paper/reports on VA and infection prevention and control practices in these units.

Haemodialysis patients with CVCs are at increased risk of HCAI that impact on patient safety and lead to an increased incidence of death due to infection and costly lengthy periods of hospitalisations. As discussed earlier in this chapter, such infections are often associated with economically and clinically significant complications. Consequently, it is incumbent on members of the renal team (including haemodialysis nurses) to identify and implement evidence-based infection prevention and control interventions that will limit the

impact of such infections on the physical and mental wellbeing of patients and the costs associated with their treatment. As the number of haemodialysis patients using a CVC continues to grow and, with it, the need for a robust evidence-base for practice, a systematic review of the worldwide evidence was necessary in order to summarise the evidence available on interventions for preventing CVC-related infections in this patient population. This systematic review, conducted using the Cochrane Renal Group methodology framework, is presented in Chapter 4.

### **3.7 Summary**

ESKD is a global health issue that is managed either conservatively or through the provision of some form of renal replacement therapy, the most common being haemodialysis. Incidence and prevalence of this disease continues to increase across the well-resourced parts of the world, with a marked increase in patients aged over 75 years.

Haemodialysis VA can be problematic for patients with ESKD, with a higher incidence of CVCs than AVFs. Despite being the less preferred VA choice, the use of CVCs is also rising among the prevalent patient population. The most widely used catheter for chronic haemodialysis patients is a dual-lumen tunnelled permanent cuffed CVC.

Haemodialysis patients with CVCs are at increased risk of HCAI when compared to non ESKD patients. CVC-related infections include bloodstream infections (bacteraemia), exit site and tunnel infections. By far the most significant infection when considering patient safety is a bloodstream infection. Patients with a CVC have a higher risk of mortality (including infection-related mortality), higher incidence of VA-related infection (in particular, bloodstream infections) and higher rates of hospitalisation and healthcare costs than patients dialysed via an AVF. CVC-related infections also have a negative impact on catheter survival.

Patients with CVCs have a raised risk of infection due to the nature of their disease, which decreases their immune response to infection. Other factors include co-morbidities such as diabetes mellitus and malignancy, immunosuppressive therapy, low serum albumin level, duration of catheter, history of previous tunnelled catheters and previous catheter infection

especially bloodstream infections. Another risk factor for CVC-related infection relates to the technique used in catheter placement. Poor techniques can result in early manifestation of CVC bloodstream infections.

Catheter insertion involves breaching the body's natural defence, exposing the patient to the risk of flora migrating from their own skin, through the catheter exit site and onto the exterior surface of the catheter leading to colonisation of the catheter tip. Direct contamination of the catheter hubs occurs as a result of multiple manipulation of the catheter during dialysis, whereby the catheter hubs may be exposed to the patient's own flora or contaminated from healthcare workers' hands. These potential portals of entry for infection reinforce the need for strict aseptic technique when manipulating the catheter during dialysis. This review of the literature indicates that exit site infections were positively associated with the type of CVC dressing and antiseptic cleansing solution used in the maintenance of the catheter; this underlines the importance of using effective interventions that prevent exit site and catheter hub contamination.

National standards advocate the use of evidence-based interventions for the prevention and control of catheter associated HCAI (Health Information and Quality Authority 2009). Furthermore, national and international bodies offer guidance on a breadth of interventions for the prevention of catheter-related infections; however, there lacks general consensus on what is best practice in a number of areas of practice (CARI 2000, CDC 2002, ERA-EDTA 2002, Jindal *et al.* 2006, NKF K/DOQI 2006b, SARI 2009). This chapter highlights the need for a systematic review on the world-wide evidence on the effects of interventions to prevent infectious complications in haemodialysis patients.

### **3.8 Conclusion**

This chapter shows that preventing CVC-related infections is a multifaceted task, making it imperative that the protocol for the randomised trial that is part of this PhD research project incorporates the provision of routine care that includes key components of an effective preventive strategy, such as education of healthcare staff, hand hygiene, and aseptic technique. However, there is a dearth of published literature on the practices underpinning VA practices and infection prevention and control practices in Irish haemodialysis settings. Therefore, in order to place the findings of this study in the context of

these settings, a descriptive survey of routine VA practices was undertaken (Chapter 6).

The chapter also highlights issues that have implications for the design of this randomised trial. Age, sex, primary renal diagnosis and risk factors for CVC infections warrant inclusion in the baseline data collection form. As patients are at risk of post insertion-related catheter infection, this has implications for the trial exclusion criteria. The key outcomes identified in this review of the literature will inform the outcomes of this study. These include bloodstream infections, exit site infections, mortality, VA-related mortality, hospitalisation, VA-related hospitalisation, CVC survival, causative organisms and prevalence of vascular access.

Studies discussed in this chapter, including those from Ireland, which investigated CVC-related infections, used various case definitions to classify and diagnose CVC-related infections. This limits their comparability. From a research activity perspective the most robust case definitions for the diagnosis of CVC-related infection are CRBSI and CABSIs. The most precise classification system for the diagnosis of CVC-related infections is the CRBSI clinical case definition, proposed by the IDSA. This definition does have limitations, particularly for use in the haemodialysis patient population. It requires specific tests that may not routinely be available in hospital laboratories aligned to the outpatient haemodialysis sites for this randomised trial or tests requiring specific blood cultures that may not be obtainable from haemodialysis patients. Culturing the tip of the CVC is one of the diagnostic tests advocated in the definition; but this is not always feasible due to a reluctance to remove the patient's only form of vascular access for haemodialysis. Given these limitations, it would be prudent to include the CDC/NHSN CABSIs surveillance case definition for the diagnosis of bloodstream infections in this study also. Culturing the catheter tip is not a requirement and any clinical uncertainties relating to common skin contaminants and secondary bloodstream infections are removed. A third case definition that warrants inclusion is the outpatient haemodialysis specific CDC/NHSN surveillance dialysis event protocol case definitions. Although this protocol may not be sufficiently robust for research activity, it is used in outpatient haemodialysis settings in America and Europe and will allow comparability of trial findings to the international literature. The dialysis event

protocol definition for local access infection will be used to diagnose exit site infections that occur in trial participants.

CABSI and CRBSI case definitions are normally associated with line days for denominator data, but the collection of such data is not suited for an outpatient haemodialysis setting. An alternative approach that best suits the use of such rigorous case definitions, within a robust randomised trial such as this PhD outpatient haemodialysis study is the reporting of CABSI, CRBSI, local access infections and dialysis events per 100 patient-months. This requires the collection of denominator data (number of CVCs) on the first two working days of each month.

Finally, given the ever increasing use of CVCs in the haemodialysis patient population and the associated risk of infection, it is imperative that effective interventions are used to prevent CVC-related infections. However, various interventions are used in the care and maintenance of haemodialysis CVCs, suggesting inconsistent implementation of best practice guidelines and/or uncertainty regarding best practice in this area. This lack of clarity highlights the need to conduct a systematic review of the world-wide evidence on interventions for the prevention of infectious complications in haemodialysis patients with CVCs. This systematic review is presented in the following chapter and provides evidence that underpins the direction and focus of this randomised trial.

**SECTION 2**  
**CRITICAL ANALYSIS OF THE LITERATURE**

# **CHAPTER 4: INTERVENTIONS FOR PREVENTING INFECTIOUS COMPLICATIONS IN HAEMODIALYSIS PATIENTS WITH CENTRAL VENOUS CATHETERS A COCHRANE REVIEW**

## **4.1 Introduction**

As outlined in chapter 3 (section 3.4), central venous catheters (CVCs) play a prominent role in haemodialysis vascular access. This is reflected in renal registry survey reports, with 60% of patients in the United Kingdom (UK) commencing haemodialysis via a CVC compared to 81% and 80% of Canadian and American patients, respectively (The UK Renal Registry 2013, US Renal Data System 2013, Canadian Institute for Health Information 2014). Access through a CVC is associated with catheter-related infections, increased patient hospitalisation and death due to infection. Various interventions are used in the care and maintenance of haemodialysis CVCs. This variation may be due to inconsistent implementation of best practice guidelines, uncertainty regarding best practice in this area, or both.

This chapter focuses on a Cochrane Review of the worldwide evidence from randomised trials on interventions for the prevention of infectious complications in haemodialysis patients with CVCs. This review was published in The Cochrane Library in Issue 1, 2010 (McCann & Moore 2010) and its research recommendations guided the direction and focus of the randomised trial. This chapter follows the format of the publication in The Cochrane Library.

## **4.2 Review Objectives**

To evaluate the benefits and harms of prophylactic topical antimicrobials, topical antiseptics, medicated dressings and non-medicated dressings on the incidence of infectious complications among haemodialysis patients with CVCs.



## 4.3 Review Methods

### 4.3.1 Criteria for considering studies for this review

#### 4.3.1.1 Types of studies

Trials eligible for this review were all randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical record numbers, date of birth or other predictable methods) looking at the effect of prophylactic antimicrobials, topical antiseptics, medicated dressings and non-medicated dressings on the incidence of infectious complications among haemodialysis patients with CVC.

#### 4.3.1.2 Types of participants

##### Inclusion criteria

- Adults and children with End Stage Kidney Disease (ESKD) who had, or were about to commence, either short-term or maintenance haemodialysis using tunnelled or non-tunnelled CVCs as vascular access.
- Children were defined as up to the age of 18 years of age or as defined by the eligible trial.

##### Exclusion criteria

- Adults and children whose vascular access for haemodialysis included antimicrobial-impregnated CVC or CVC using locking solutions, which have antimicrobial properties. These interventions are the focus of another Cochrane Review, '*Antimicrobial lock solutions for preventing catheter-related infections in haemodialysis*' (Arechabala *et al.* 2013).
- Adults and children with ESKD whose CVC was used for purposes other than haemodialysis.

#### 4.3.1.3 Types of interventions

Studies containing the following comparisons were eligible for the review:

- Skin cleansers versus no skin cleansers.
- Skin cleansing using different cleaning solutions.
- Different cleaning techniques.
- Antibiotics versus no antibiotics.
- Antibiotics using different modes of administration oral/intravenous/topical.
- Antibiotics using different dosages.
- Antibiotics using different durations.
- Antibiotics using different starting points.

- Topical antimicrobial versus no topical antimicrobial.
- Topical antimicrobial using different durations.
- Different topical antimicrobial agents.
- Different non-medicated topical dressings.
- Different medicated dressings.
- Non-medicated and medicated dressings.
- Different frequencies of dressing changes.
- Different health care staff who inserted CVC.
- Different insertion techniques.
- Different health care staff accessing CVC.
- Different techniques used to access CVC.

Studies describing intranasal application of mupirocin in haemodialysis patients were not considered and are included in a Cochrane Review on mupirocin ointment for preventing *S. aureus* infections in nasal carriers (Van Rijen *et al.* 2008).

The following definitions were used:

- Antimicrobials are any agents capable of destroying or inhibiting the growth of micro-organisms (NKF K/DOQI 2006a).
- Skin cleansers such as antiseptic agents help in the physical removal of foreign materials such as dirt, micro-organisms, and dead cells.
- Antiseptics are any agents capable of preventing infection by inhibiting the growth of micro-organisms. These agents are routinely thought of as topical agents for application to the skin (NKF K/DOQI 2006a).

#### 4.3.1.4 *Types of outcome measures*

The following outcomes were to be assessed.

##### Primary outcomes

- Incidence and type of infectious complication.
- Patient mortality.
- Survival rate of CVC.

## Secondary outcomes

- Time to development of infection.
- Episodes of hospitalisation.
- Patient morbidity.
- Quality of life.

### **4.3.2 Search methods for identification of studies**

The following sources were used to identify relevant studies.

#### *4.3.2.1 Electronic searches included*

1. The Cochrane Renal Group's Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. CENTRAL and the Renal Group's Specialised Register contain the hand searched results of conference proceedings from general and speciality meetings. This searching is an ongoing activity across The Cochrane Collaboration and is both retrospective and prospective (Master List 2009). Therefore, conference proceedings were not specifically searched separately for this review. The Cochrane Renal Group's Module in *The Cochrane Library* provides the most up-to-date list of conference proceedings searched by that Group (Renal Group 2009 *et al.* 2009).
  2. MEDLINE, using the optimally sensitive strategy developed for The Cochrane Collaboration for the identification of RCTs (Lefebvre *et al.* 2008) with a specific search strategy developed with input from the Cochrane Renal Group's Trial Search Coordinator.
  3. EMBASE, using a search strategy adapted from that developed for The Cochrane Collaboration for the identification of RCTs (Lefebvre *et al.* 2008) together with a specific search strategy developed with input from the Cochrane Renal Group's Trial Search Co-ordinator.
- See Appendix 4.1 for electronic search strategies.

#### *4.3.2.2 Searching other resources included*

1. Reference lists of nephrology textbooks, review articles and relevant studies.
2. Correspondence seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

### **4.3.3 Data collection & analysis**

#### *4.3.3.1 Selection of studies*

The search strategy was used to obtain titles and abstracts of studies that might be relevant to the review. These titles and abstracts were screened independently by me and another colleague. Studies that were not applicable to the inclusion criteria for this review were discarded, but studies and reviews that might include relevant data or information on studies were retained initially. Retrieved abstracts and, if necessary the full text, of these reports were independently assessed to determine which studies satisfied the inclusion criteria.

#### *4.3.3.2 Data extraction & management*

My colleague and I both carried out data extraction independently, using standard data extraction forms. It was planned that studies reported in languages other than English would be translated before assessment. Where more than one publication of a study was found, reports were grouped together and the most recent or most complete dataset was used for the review. Any discrepancy between published versions is highlighted. Any further information required from the original author was requested through written or electronic correspondence and any relevant information obtained in this manner was included in the review. Disagreements between the two reviewers were resolved in consultation with the Cochrane Renal Group.

#### *4.3.3.3 Assessment of risk of bias in included studies*

My colleague and I independently assessed the quality of studies to be included without blinding to authorship or journal, using the checklist developed for the Cochrane Renal Group. Disagreements were resolved by discussion with the Cochrane Renal Group. The quality items assessed were allocation concealment, blinding (participants, investigators, outcome assessors and data analysis), intention-to-treat analysis and completeness of follow-up.

#### 4.3.3.4 *Quality checklist*

The following quality categories were used:

##### Allocation concealment

- Adequate (A) - Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study;
- Unclear (B) - Randomisation stated, but no information on method used is available;
- Inadequate (C) - Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

##### Blinding

- Blinding of investigators: Yes/no/not stated;
- Blinding of participants: Yes/no/not stated;
- Blinding of outcome assessor: Yes/no/not stated;
- Blinding of data analysis: Yes/no/not stated.

These groups are considered not blinded if the treatment group could be identified for more than 20% of participants because of treatment side effects.

##### Intention-to-treat

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment;
- Yes: Not stated but confirmed on study assessment;
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation);
- No: Stated but not confirmed upon study assessment;
- Not stated.

##### Completeness of follow-up

- Percentage of randomised (or quasi-randomised) participants excluded or lost to follow-up.

#### 4.3.3.5 *Measures of treatment effect*

For dichotomous outcomes (mortality, presence of infection), results are presented as risk ratios (RR) with 95% confidence intervals (CI). It was planned that if continuous scales were used to measure the effects of treatment (e.g. catheter survival), the mean difference (MD) would be used, or the standardised mean difference (SMD) if different scales were used.

#### 4.3.3.6 *Assessment of heterogeneity*

Heterogeneity was analysed using a Chi<sup>2</sup> test on N-1 degrees of freedom, with a P-value of 0.05 used for statistical significance, and with the I<sup>2</sup> test (Higgins *et al.* 2003). I<sup>2</sup> values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

#### 4.3.3.7 *Data synthesis*

Data were pooled using the random-effects model, but the fixed effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers.

#### 4.3.3.8 *Subgroup analysis & investigation of heterogeneity*

Subgroup analysis was used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age and renal pathology. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy. It was planned that adverse effects would be tabulated and assessed with descriptive techniques, because they are likely to differ between the agents.

## 4.4 Results

### 4.4.1 Description of studies

The search of CENTRAL, MEDLINE, EMBASE and the Cochrane Renal Group's specialised register yielded 81 titles and abstracts (Figure 4.1). Letters and emails seeking information on published and unpublished RCTs were sent to medical and nursing nephrology experts. Following this process, one additional study was identified (Quadri & Huraib 1999). After an initial review, 64 studies were excluded because they were RCTs evaluating other interventions (e.g. catheter locking solutions), involved a different patient

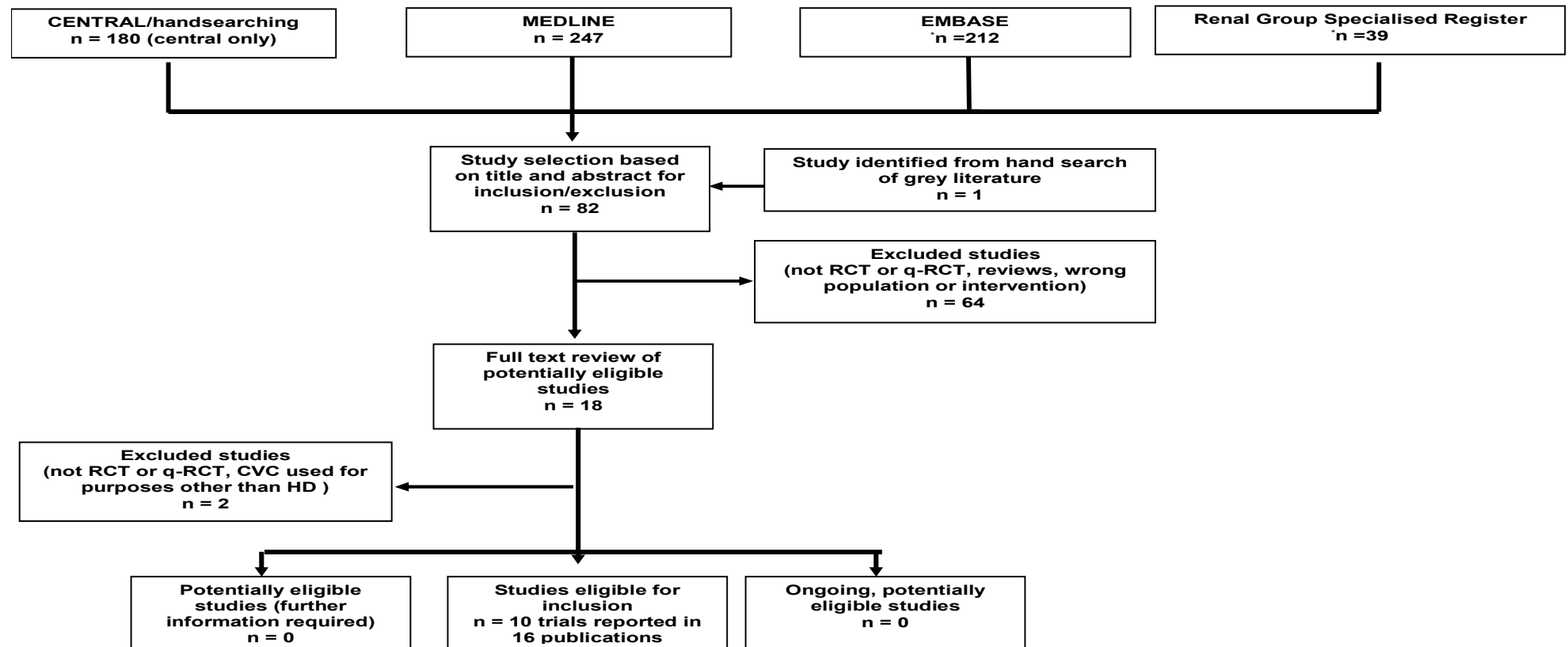
population (e.g. peritoneal dialysis population) or were not RCTs. Full text versions of the remaining 18 reports were obtained and assessed. Two papers were excluded at this stage. One was not an RCT and the second involved the use of CVC for purposes other than haemodialysis (Table 4.1).

**Table 4.1 Characteristics of excluded studies**

Study	Rationale for Exclusion
Comerota 2004	Not a RCT
Dahlberg 1996	Used CVC for purposes other than haemodialysis

In total 10 studies (786 participants), reported in 16 publications were included in this review, and their characteristics are given in Table 4.2 (Levin *et al.* 1991, Huraib *et al.* 1994, Sesso *et al.* 1998, Quadri & Huraib 1999, Johnson *et al.* 2002, Le Corre *et al.* 2003, Lok *et al.* 2003, Kamaliah *et al.* 2004, Johnson *et al.* 2005, Atapour & Shahidi 2006). Attempts were made to seek further information on study methods, but one author could not be contacted (Huraib *et al.* 1994). The authors of four studies were contacted for further information (Quadri & Huraib 1999, Le Corre *et al.* 2003, Kamaliah *et al.* 2004, Atapour & Shahidi 2006), and, of these, one author (Quadri & Huraib 1999) responded and provided information that was included in the review. All studies were published in English between 1986 and 2006. The studies were conducted in seven countries (Australia, Brazil, Canada, Iran, Malaysia, Saudi Arabia and the United States [US]).

Figure 4.1: Flow chart of citations retrieved from search of different data bases





**Table 4.2 Characteristics of included randomised controlled trials: Topical antimicrobials**

Study/Country	Participants (treatment/control)	Intervention	Control	Outcomes
Levin <i>et al.</i> (1991), Canada	129 (63/66)	Topical povidone-iodine ointment applied to CVC exit site	No ointment applied	Exit site infection Septicaemia Morbidity/Mortality Catheter tip colonisation Incidence of <i>S. aureus</i> nasal carriers Catheter duration Catheter days at risk Catheter days at risk in <i>S. aureus</i> nasal carriers
Sesso <i>et al.</i> (1998), Brazil	136 (69/67)	Topical calcium mupirocin ointment applied to CVC exit site	No ointment applied	<i>S. aureus</i> colonisation <i>S. aureus</i> infection Exit site colonisation and infection Bacteraemia due to <i>S. aureus</i> Duration of CVC Episodes of hospitalisation
Johnson <i>et al.</i> (2002), Australia	50 (27/23)	Topical calcium mupirocin ointment (2%) applied to CVC exit site	No ointment applied	Exit site infection Catheter-related bacteraemia Adverse reactions and cost Catheter survival Time to development of infection <i>S. aureus</i> colonisation Mupirocin resistance

**Table 4.2 Characteristics of included randomised controlled trials: Topical antimicrobials & non-medicated dressings**

Study/Country	Participants (treatment/control)	Intervention	Control	Outcomes
Lok <i>et al.</i> (2003), Canada	162 (83/79)	Topical polysporin triple ointment applied to CVC exit site	Placebo ointment applied to CVC exit site	Exit site infection Tunnel infection Bacteraemia Patient mortality Time to development of infection Morbidity related to infection Episodes of hospitalisation Catheter removal due to infection <i>S. aureus</i> nasal exit site carriage
Kamaliah <i>et al.</i> (2004), Malaysia	31 (17/14)	Topical mupirocin ointment applied to CVC exit site	No ointment applied	Exit site infection Catheter-related bacteraemia Bacterial colonisation Duration of catheter placement Survival rate of CVC Mortality
<b>Non-medicated dressing</b>				
Le Corre <i>et al.</i> (2003), Canada	58 (29/29)	Polyurethane semi-permeable transparent dressing applied to CVC exit site	Dry gauze dressing applied to CVC dressing	Exit site infection Local infection Bacteraemia Quality of life Cost related to each type of dressing Skin condition

**Table 4.2 Characteristics of included randomised controlled trials: Topical Honey & other interventions**

Study/Country	Participants (treatment/control)	Intervention	Control	Outcomes
Quadri & Huraib (1999), Saudi Arabia	49 (23/26)	Topical Manuka honey applied to CVC exit site	Topical povidone-iodine ointment applied to CVC exit site	Catheter related bacteraemia Catheter exit site Catheter days Adverse effects
Johnson <i>et al.</i> (2005), Australia	101 (51/50)	Topical Medihoney applied to CVC exit site	Calcium mupirocin ointment applied to CVC exit site	Catheter-related infection Catheter exit infection Causative organism Mupirocin resistance among <i>S. aureus</i> isolate
<b>Other interventions</b>				
Atapour & Shahidi (2006), Iran	30 (14/15) 1 patient from the treatment group was excluded	Tunnelled CVC	Non-tunnelled CVC	Exit site infection Catheter-related bacteraemia Life time of catheter
Huraib <i>et al.</i> (1994), Saudi Arabia	40 (20/20)	Catheter care done by dialysis nurse, using heparin three times a week as a CVC lock	Catheter care done by hospital intravenous team using heparin three times a day as a CVC lock	Exit site infection Bacteraemia Causative organism Duration of catheter function

## **4.4.2 Interventions**

### *4.4.2.1 Topical antimicrobials*

Five studies (379 patients) randomised patients to a topical antimicrobial ointment, or to either no ointment or placebo (Levin *et al.* 1991, Sesso *et al.* 1998, Johnson *et al.* 2002, Lok *et al.* 2003, Kamaliah *et al.* 2004).

### *4.4.2.2 Topical mupirocin ointment*

Three studies (217 patients) evaluated the effect of topical mupirocin ointment versus no ointment (Sesso *et al.* 1998, Johnson *et al.* 2002, Kamaliah *et al.* 2004). Sesso *et al.* (1998) only focused on catheter-related infections caused by *Staphylococcus aureus*.

### *4.4.2.3 Topical povidone-iodine ointment*

Levin *et al.* (1991) (129 patients) compared povidone-iodine ointment with no ointment.

### *4.4.2.4 Topical polysporin ointment*

The HIPPO Study (2003) (162 patients) investigated polysporin triple ointment versus a placebo.

### *4.4.2.5 Topical honey*

Two studies (150 patients) compared topical honey ointment versus an antimicrobial ointment (Quadri & Huraib 1999, Johnson *et al.* 2005): Johnson (2005) (101 patients) compared Medihoney versus mupirocin ointment and Quadri & Huraib (1999) (49 patients) compared Manuka honey versus povidone-iodine ointment.

### *4.4.2.6 Non-medicated dressings*

One study (58 patients) compared a transparent dressing versus a dry dressing (Le Corre *et al.* 2003).

### *4.4.2.7 Tunnelled versus non-tunnelled CVC*

Atapour & Shahidi (2006) (30 patients) compared tunnelled CVCs versus non-tunnelled CVCs.

#### 4.4.2.8 *Post-insertion catheter care protocol*

Huraib *et al.* (1994) (40 patients) compared two different post-insertion catheter care protocols.

#### 4.4.2.9 *Other interventions*

No RCTs investigating the effect of the following interventions were found: skin cleansers versus no skin cleansers, different cleansing solutions, different cleaning techniques; use of antibiotics and different modes of administration, dosage, duration and starting points; medicated dressings; different frequencies of dressing change; different health care staff who inserted CVC and different techniques used to access CVC.

### 4.4.3 **Risk of bias in included studies**

#### 4.4.3.1 *Randomisation*

Method of randomisation was not stated in three of the 10 studies (Huraib *et al.* 1994, Quadri & Huraib 1999, Kamaliah *et al.* 2004). The randomisation methods used in the remaining seven studies were:

- Computer generated random number list (Sesso *et al.* 1998, Johnson *et al.* 2002, Le Corre *et al.* 2003, Johnson *et al.* 2005).
- Independent central randomisation facility using a computer generated random number list (Lok *et al.* 2003).
- Sequenced allocation using designation box (Levin *et al.* 1991).
- Every other case randomly assigned to one of two groups, tunnelled or non-tunnelled CVCs (Atapour & Shahidi 2006).

#### 4.4.3.2 *Allocation concealment*

Allocation concealment was adequate in four studies (Sesso *et al.* 1998, Johnson *et al.* 2002, Lok *et al.* 2003, Johnson *et al.* 2005) and unclear in five (Levin *et al.* 1991, Huraib *et al.* 1994, Quadri & Huraib 1999, Le Corre *et al.* 2003, Kamaliah *et al.* 2004). Allocation concealment was inadequate in one study (Atapour & Shahidi 2006) as allocation was determined by every other case with no attempt to conceal the allocation process.

#### 4.4.3.3 Blinding

- *Blinding of participants:* Two studies stated that the participants were blinded (Quadri & Huraib 1999, Lok *et al.* 2003). For the remaining studies, blinding was either not possible or not reported.
- *Blinding of investigators:* Two studies stated that the investigators were blinded (Quadri & Huraib 1999, Lok *et al.* 2003). For the remaining studies, blinding was either not possible or not reported.
- *Blinding of outcome assessors:* Four studies stated that the outcome assessors were blinded (Sesso *et al.* 1998, Johnson *et al.* 2002, Lok *et al.* 2003, Johnson *et al.* 2005). For the remaining studies, this was not reported.
- *Blinding of data assessors:* One study stated that the data assessors were blinded (Lok *et al.* 2003). For the remaining studies, this was not reported.

#### 4.4.3.4 Intention-to-treat

Analysis was based on intention-to-treat in five studies (Sesso *et al.* 1998, Quadri & Huraib 1999, Johnson *et al.* 2002, Lok *et al.* 2003, Johnson *et al.* 2005).

#### 4.4.3.5 Completeness of follow-up

The completeness of follow-up ranged from 55% (Le Corre *et al.* 2003) to 100% (Huraib *et al.* 1994, Sesso *et al.* 1998, Quadri & Huraib 1999, Johnson *et al.* 2002, Kamaliah *et al.* 2004, Johnson *et al.* 2005). In addition to those studies with 100% follow-up, two studies had over 90% completeness of follow-up (Levin *et al.* 1991, Atapour & Shahidi 2006).

## 4.5 Effects of Interventions

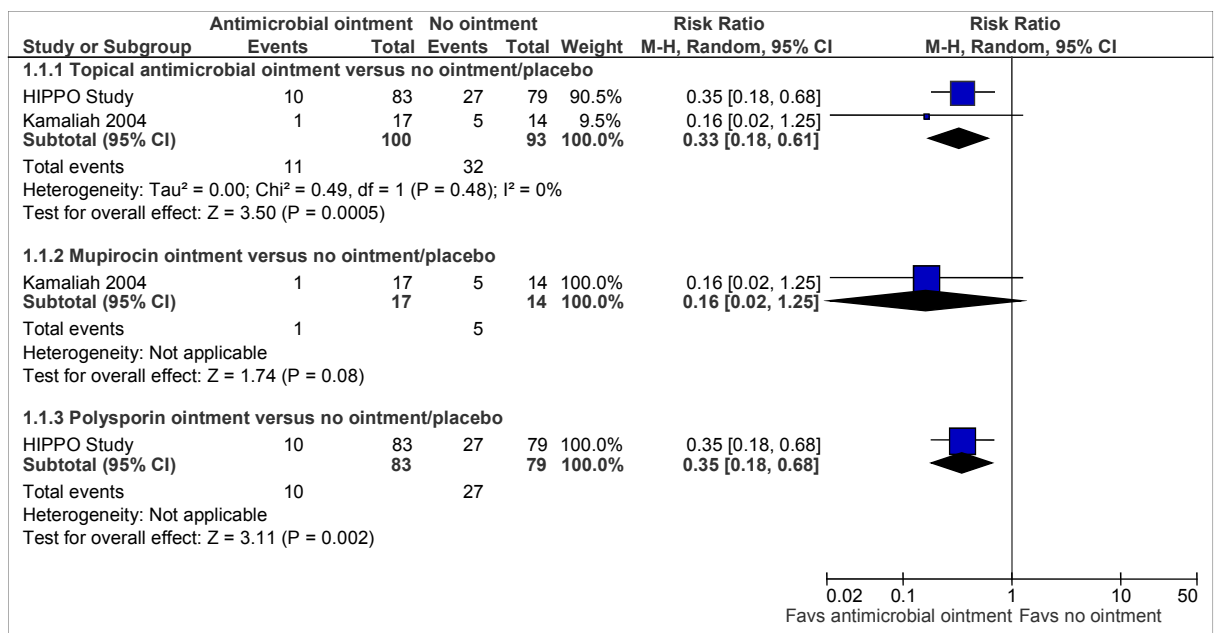
### 4.5.1 Topical antimicrobial ointment

#### 4.5.1.1 Incidence & type of infections

The risk of CVC infection (exit site and catheter-related bacteraemia) was significantly reduced by topical antimicrobial ointments when compared to no ointments or placebo (figure 4.2, analysis 1.1.1; 2 studies, 193 patients: RR 0.33, 95% CI 0.18 to 0.6). The outcome of this analysis is dominated by the HIPPO Study, which had a weighting of 90.5%. There was no significant heterogeneity between the two studies ( $\text{Chi}^2 = 0.49$ ,  $P = 0.48$ ;  $I^2 = 0\%$ ). Subgroup analysis indicates that polysporin ointment (HIPPO Study *et al.*

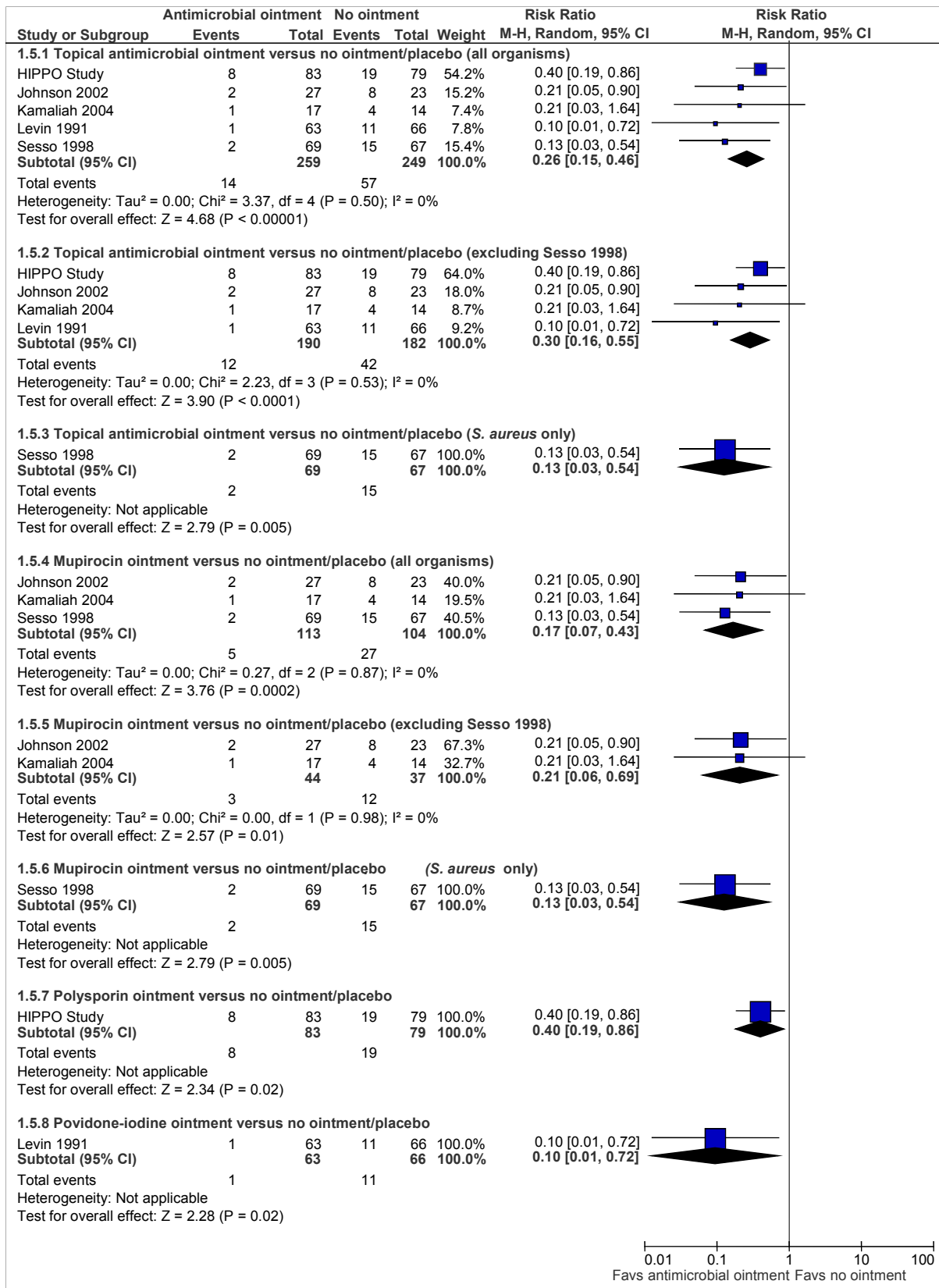
2003) significantly reduced the risk of CVC infection (figure 4.2, analysis 1.1.3, 1 study, 162 patients: RR 0.35, 95% CI 0.18 to 0.68) while mupirocin ointment had no significant effect on CVC infection (figure 4.2, analysis 1.1.2; 1 study, 31 patients: RR 0.16, 95% CI 0.02 to 1.25).

**Figure 4.2 Exit site & catheter-related bacteraemia: Topical antimicrobial ointment versus no ointment or placebo**



Topical antimicrobial ointments compared to no ointments or placebo significantly reduced the risk of exit site infection (4 studies, 346 patients: RR 0.20, 95% CI 0.09 to 0.45) and catheter-related bacteraemia (fig 4.3, analysis 1.5.1; 5 studies, 508 patients: RR 0.26, 95% CI 0.15 to 0.46), caused by all types of organisms. There was no significant heterogeneity across the relevant studies that investigated either exit site infection (Chi<sup>2</sup> = 0.69, P = 0.88; I<sup>2</sup> = 0%) or catheter-related bacteraemia (Chi<sup>2</sup> = 3.37, P = 0.50; I<sup>2</sup> = 0%). Sesso *et al.* (1998) only investigated infections caused by *S. aureus*. A subgroup analysis, excluding Sesso *et al.* (1998) found similar, significantly reduced risks for exit site infection (3 studies, 210 patients: RR 0.22, 95% CI 0.08 to 0.64) and catheter-related bacteraemia (figure 4.3, analysis 1.5.2; 4 studies, 372 patients: RR 0.30, 95% CI 0.16 to 0.55).

**Figure 4.3 Catheter-related bacteraemia: Topical antimicrobial ointment versus no ointment or placebo, subgroup analysis**





Analyses of individual topical antimicrobial ointments suggest that mupirocin, when compared to no ointment or placebo significantly reduced the risk of exit site infections caused by all types of organisms (3 studies, 217 patients: RR 0.17, 95% CI 0.06 to 0.48). Heterogeneity was not evident among the studies ( $\text{Chi}^2 = 0.40$ ,  $P = 0.82$ ;  $I^2 = 0\%$ ), but a subgroup analysis, excluding Sesso *et al.* (1998) found that mupirocin ointment did not significantly reduce the risk of exit site infection (2 studies, 81 patients: RR 0.14, 95% CI 0.02 to 1.14). Analysis of exit site infections caused only by *S. aureus* found that mupirocin significantly reduced the risk of this type of infection (1 study, 136 patients): RR 0.18, 95% CI 0.06 to 0.60).

Mupirocin ointment compared to no ointment or placebo significantly reduced the risk of catheter-related bacteraemia caused by all types of organisms (figure 4.3, analysis 1.5.4; 3 studies, 217 patients: RR 0.17, 95% CI 0.07 to 0.43). There was no evidence of heterogeneity among the studies ( $\text{Chi}^2 = 0.27$ ,  $P = 0.87$ ;  $I^2 = 0\%$ ). Analysis, excluding Sesso *et al.* (1998) indicated a similar, significantly reduced risk (fig 4.3, 1.5.5; 2 studies, 81 patients: RR 0.21, 95%CI 0.06 to 0.69). The risk of catheter-related bacteraemia caused by *S. aureus* was significantly reduced in patients using mupirocin ointment (figure 4.3, analysis 1.5.6; 1 study, 136 patients: RR 0.13, 95% CI 0.03 to 0.54).

When compared to no ointment or placebo, povidone-iodine ointment significantly reduced the risk of exit site infection (1 study, 129 patients: RR 0.26, 95% CI 0.08 to 0.88). The risk of catheter-related bacteraemia was significantly reduced by polysporin ointment (figure 4.3, analysis 1.5.7; 1 study, 162 patients: RR 0.40, 95% CI 0.19 to 0.86) and povidone-iodine ointment (fig 4.3, analysis 1.5.8; 1 study, 129 patients: RR 0.10, 95% CI 0.01 to 0.72).

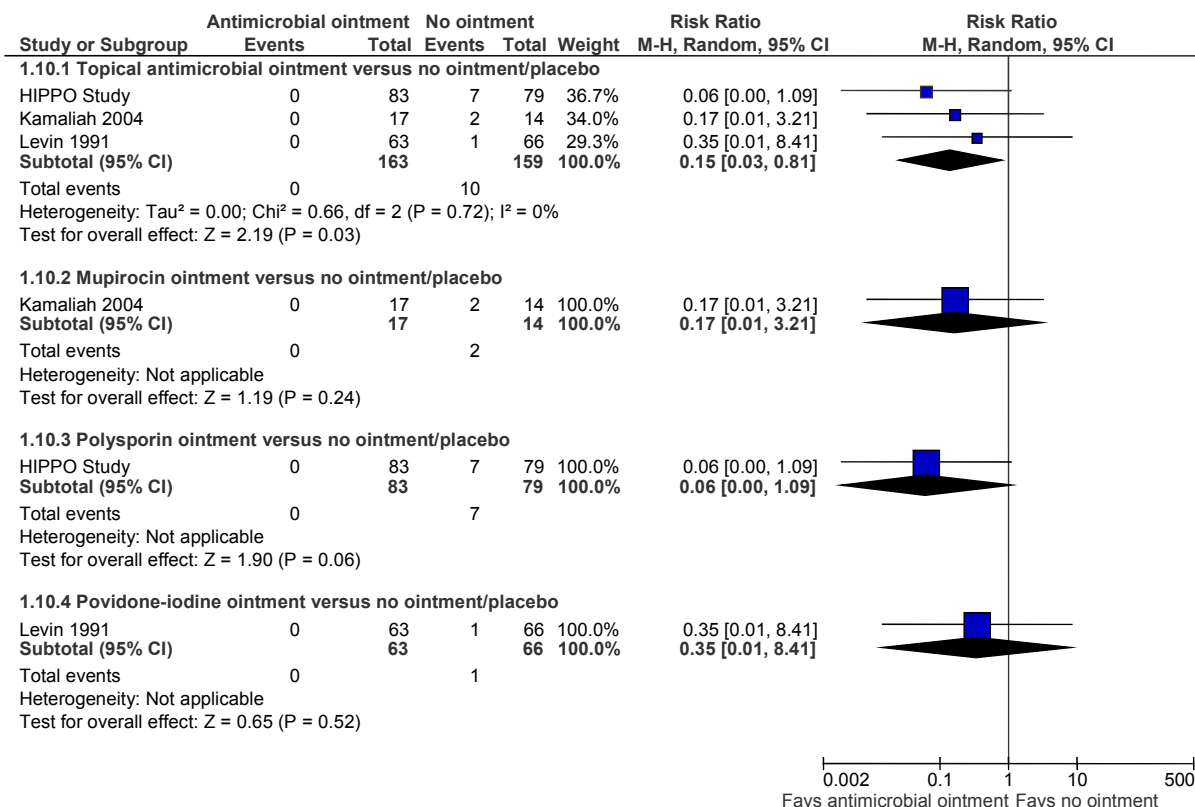
#### 4.5.1.2 Patient mortality

Topical antimicrobials compared to no ointment or placebo had no significant effect on all-cause mortality (3 studies, 322 patients: RR 0.36, 95% CI 0.12 to 1.07). Seven patients died in the topical antimicrobial group (163 patients) compared to 21 in the no ointment or placebo group (159 patients). There was some heterogeneity across studies ( $\text{Chi}^2 = 2.95$ ,  $P = 0.23$ ;  $I^2 = 32\%$ ). Subgroup analyses did not detect any effect of mupirocin (1 study, 31 patients: RR 0.12, 95% CI 0.01 to 2.13) or povidone-iodine ointment (1 study, 129

patients: RR 0.84, 95% CI 0.24 to 2.98) on all-cause mortality. Polysporin ointment showed a significant reduction with three patients dying in the ointment group (83 patients) versus 13 of 79 patients in the no ointment or placebo group (1 study, 162 patients: RR 0.22, 95% CI 0.07 to 0.74).

Topical antimicrobials significantly reduced mortality related to infection (figure 4.4, analysis 1.10.1; 3 studies, 322 patients: RR 0.15, 95% CI 0.03 to 0.81). There was no significant heterogeneity across these studies ( $\text{Chi}^2 = 0.66$ ,  $P = 0.72$ ;  $I^2 = 0\%$ ), but subgroup analysis by individual drugs (mupirocin, polysporin and povidone-iodine ointments) were not significant on their own for mortality related to infection (figure 4.4, analysis 1.10.2; analysis 1.10.3; analysis 1.10.4).

**Figure 4.4 Mortality related to infection: Topical antimicrobial ointment versus no ointment or placebo, subgroup analysis**



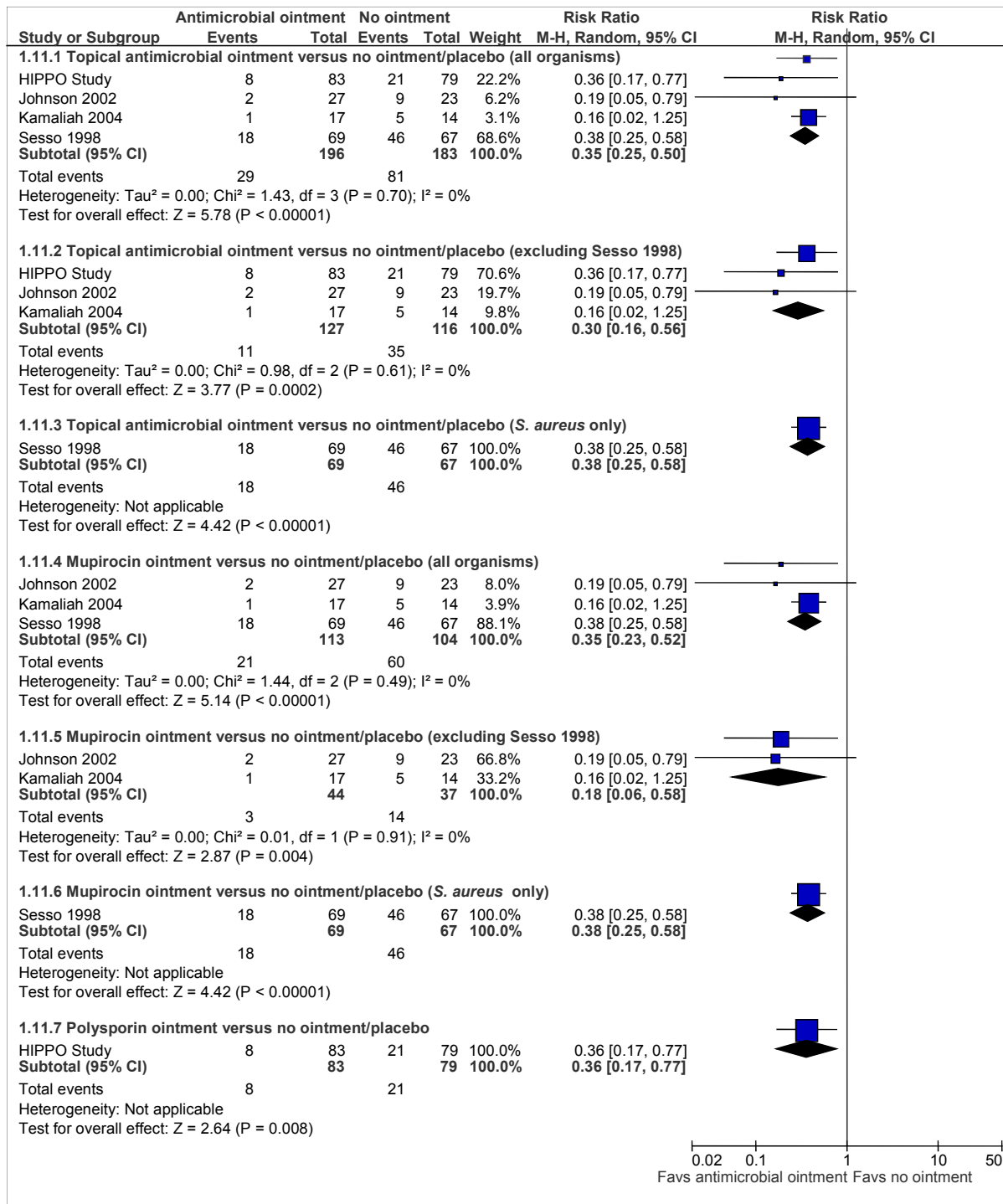
#### 4.5.1.3 Survival rate of CVC

Topical antimicrobial ointments compared to no ointment or placebo had a significant favourable effect on catheter removal due to infection caused by all types of organisms (figure 4.5, analysis 1.11.1: 4 studies, 379 patients: RR 0.35, 95% CI 0.25 to 0.50). No heterogeneity was evident ( $\text{Chi}^2 = 1.43$ ,  $P = 0.70$ ;  $I^2 = 0\%$ ). Subgroup analysis excluding Sesso *et al.* (1998) found a similar significant reduction in risk (figure 4.5, analysis 1.11.2: 3 studies, 243 patients: RR 0.30, 95% CI 0.16 to 0.56). Heterogeneity was not evident ( $\text{Chi}^2 = 0.98$ ,  $P = 0.61$ ;  $I^2 = 0\%$ ). Catheter removal due to *S. aureus* was significantly reduced by topical antimicrobial ointment (figure 4.5, analysis 1.11.3: 1 study, 136 patients: RR 0.38, 95% CI 0.25 to 0.58). Analysis of individual topical antimicrobial ointments compared to no ointment or placebo indicated that polysporin ointment had a significant effect on catheter removal due to infection (figure 4.5, analysis 1.11.7: 1 study, 162 patients: RR 0.36, 95% CI 0.17 to 0.77).

Mupirocin also had a significant effect on catheter removal due to infections caused by all types of organisms (figure 4.5, analysis 1.11.4: 3 studies, 217 patients: RR 0.35, 95% CI 0.23 to 0.52). This significant effect persisted when Sesso *et al.* (1998) was excluded from the meta-analysis (figure 4.5, analysis 1.11.5: 2 studies, 81 patients: RR 0.18, 95% CI 0.06 to 0.58). Heterogeneity was not evident ( $\text{Chi}^2 = 1.44$ ,  $P = 0.49$ ;  $I^2 = 0\%$ ). Mupirocin had a significant positive effect on catheter removal due to *S. aureus* infection (figure 4.5, analysis 1.11.6: 1 study, 136 patients: RR 0.38, 95% CI 0.25 to 0.58).

It was not possible to analyse the effect of topical antimicrobial ointments, when compared to no ointments or placebo, on survival time of CVC because of inconsistency in how survival time of catheters was reported (Table 4.3). Sesso *et al.* (1998), used median duration of catheter placement, range and number of cumulative days catheter was in place. Johnson *et al.* (2002), reported median catheter survival censored for end of treatment. Kamaliah *et al.* (2004), used mean duration and range of catheter placement.

**Figure 4.5 Catheter removal due to infection: Topical antimicrobial ointment versus no ointment or placebo, subgroup analysis**



**Table 4.3 Topical antimicrobial ointments: CVC Survival time**

Study	Description of Survival Time	Results as Reported by Study Author	
		Ointment	No Ointment /Placebo
Sesso <i>et al.</i> (1998) S. aureus only Mupirocin ointment	Median duration of catheter placement	37 days	20 days
	Range	4-142 days	3 to 135 days (P<0.01)
	Cumulative days catheter in place	2836	1682 (P<0.01)
Johnson <i>et al.</i> (2002) Mupirocin ointment	Median catheter survival censored for end of treatment	108 days	31 days
Kamaliah <i>et al.</i> (2004) Mupirocin ointment	Mean duration of catheter placement	48.53 days	25.90 days
	Range	6-154 days	3-60 days (P=0.05)

#### 4.5.1.4 Episodes of hospitalisation

When compared to no ointment or placebo, mupirocin ointment had no significant effect on frequency of hospitalisation (1 study, 136 patient: RR 0.85, 95% CI 0.72 to 1.01), but had a significant effect on episodes of hospitalisation due to *S. aureus* infection (1 study, 136 patients: RR 0.35, 95%CI 0.13 to 0.91). Polysporin had a significant effect on episodes of hospitalisation (1 study, 162 patients: RR 0.30, 95% CI 0.13 to 0.71).

#### 4.5.1.5 Time to development of infection

Only Johnson *et al.* (2002) and the HIPPO Study (2003) reported time to development of infection. It was not possible to analyse the effect of topical antimicrobial ointments because of inconsistency in how this was reported (Table 4.4). Johnson *et al.* (2002), noted median interval between catheter insertion and onset of catheter-associated bacteraemia and reported time to first exit site infection in patients receiving mupirocin ointment. Johnson *et al.* (2002), also reported the effect of nasal colonisation with *S. aureus* at baseline on time to first infection. The HIPPO Study (2003), analysed time to first infection and first bacteraemia using the log rank test.

**Table 4.4 Topical antimicrobial ointments: Time to infection**

Study	Description of Time to Development of Infection	Results as Reported by Study Author	
		Ointment	No ointment /placebo
Johnson <i>et al.</i> (2002) Mupirocin ointment	Median interval between catheter insertion and onset of catheter associated bacteraemia	108 days	55 days
	Time to first exit site infection		Significantly shorter for placebo group log rank 7.3, (P<0.01)
	Time to first infection	Significantly increased time to first infection (log rank score 6.3, p=0.001) if patients did not have nasal colonisation with <i>S. aureus</i> at baseline	
HIPPO Study (2003) Polysporin ointment	Time to first infection		Shorter for placebo group (P=0.0002, log rank test)
	Time to first bacteraemia		Significantly shorter in placebo group (P=0.0056, log rank test)

#### 4.5.1.6 Adverse reactions

Three studies reported no adverse reactions to mupirocin ointment (Sesso *et al.* 1998, Johnson *et al.* 2002, Kamaliah *et al.* 2004). Only Johnson *et al.* (2002) addressed mupirocin resistance, and reported that no mupirocin-resistant staphylococcal isolates were observed. Adverse reactions to povidone-iodine ointment were not detected in Levin *et al.* (1991), while the Lok *et al.* (2003) did not comment on adverse reactions to polysporin ointment.

## 4.5.2 Topical honey

### 4.5.2.1 Incidence & type of infections

The use of topical honey (Medihoney/Manuka) compared to topical antimicrobial ointments did not significantly reduce the risk of exit site infection (2 studies, 150 patients: RR 0.45, 95% CI 0.10 to 2.11) or catheter-related bacteraemia (2 studies, 150 patients: RR 0.80, 95% CI 0.37 to 1.73). There

was no evidence of heterogeneity across the studies investigating either exit site infection ( $\text{Chi}^2 = 0.0$ ,  $P = 1.00$ ;  $I^2 = 0\%$ ) or catheter-related bacteraemia ( $\text{Chi}^2 = 0.87$ ,  $P = 0.35$ ;  $I^2 = 0\%$ ). Subgroup analyses suggest that honey did not significantly reduce the risk of exit site infection or catheter-related bacteraemia when compared to topical mupirocin or povidone-iodine ointment. Johnson *et al.* (2005) reported the bacteraemia-free survival periods for Medihoney (Table 4.5).

**Table 4.5 Honey & bacteraemia-free survival period**

Study	Description of Bacteraemia-free Survival Period	Results as Reported by Study Author	
		Honey	Mupirocin ointment
Johnson <i>et al.</i> (2005)	Mean $\pm$ SE actuarial bacteraemia-free survival period	367 $\pm$ 42 days	334 $\pm$ 17 days (Log rank 0.01, $p=0.92$ )
	Honey or mupirocin were not significantly associated with bacteraemia free survival.		
	Unadjusted hazard ratio for honey	0.94, 95% CI, 0.27 to 3.24 ( $P=0.92$ )	

#### 4.5.2.2 Adverse reactions

No adverse reactions to topical honey were noted by Quadri & Huraib (1999). One case of transient, mild local skin discomfort was reported by Johnson *et al.* (2005), which resolved after a number of days despite continued administration of the agent. A similar reaction was noted in one patient who received mupirocin ointment. No systemic reaction to either honey or mupirocin was observed. Mupirocin resistant strains were not detected in any staphylococcal isolates from study patients with catheter-associated bacteraemia.

### 4.5.3 Non-medicated dressings

#### 4.5.3.1 Incidence & type of infections

The use of transparent semi-permeable polyurethane dressing compared to dry gauze dressing did not significantly reduce the risk of CVC infection (1 study, 58 patients: RR 0.33, 95% CI 0.04 to 3.02), exit site infection (1 study, 58 patients: RR 0.33, 95% CI 0.01 to 7.86) or catheter-related bacteraemia (study, 58 patients: RR 0.50, 95% CI 0.05 to 5.21).

#### 4.5.3.2 *Adverse reactions*

Erythema (two patients) and pruritus (six patients) was observed in patients whose CVC site was dressed with dry gauze, while nine patients who received a transparent dressing also experienced both erythema and pruritus (Le Corre *et al.* 2003). The majority of the transparent dressing local reactions were linked to insufficient time been given to drying of chlorhexidine cleansing solution before application of dressing.

### **4.5.4 Tunnelled CVC versus non-tunnelled CVC**

#### 4.5.4.1 *Incidence & type of infections*

Tunnelled CVC did not significantly reduce the risk of exit site infection (1 study, 29 patients: RR 1.07, 95%CI 0.17 to 6.61) or catheter-related bacteraemia (1 study, 29 patients: RR 0.98, 95%CI 0.68 to 1.43) when compared to non-tunnelled CVC.

### **4.5.5 Post insertion catheter care protocols (haemodialysis nurses using heparin 3 times/week versus intravenous team using heparin 3 times/day)**

#### 4.5.5.1 *Incidence & type of infections*

There was no significant difference in the risk of CVC infection (1 study, 40 patients: RR 0.50, 95% CI 0.14 to 1.73), exit site infection (1 study, 40 patients: RR 0.67, 95% CI 0.12 to 3.57) or catheter-related bacteraemia (1 study, 40 patients: RR 0.33, 95%CI 0.04 to 2.94) between haemodialysis nurses using heparin three times/week and an intravenous team using heparin three times/day.

#### 4.5.5.2 *Patient mortality*

When compared to the intravenous team, haemodialysis nurses did not significantly change all-cause mortality (1 study, 40 patients: RR 5.00, 95% CI 0.26 to 98.00). Two patients died in the haemodialysis nurses group (20 patients); while there was no deaths in the intravenous team group (20 patients).



## 4.5.6 Other outcomes

Catheter removal due to infection, survival time of CVC, time to development of infection, all-cause mortality, and mortality related to infection, frequency and episodes of hospitalisation and episodes of hospitalisations due to infection were seldom reported.

## 4.6 Discussion

### 4.6.1 Summary of main results

This review identified ten randomised controlled trials that investigated topical antimicrobials (mupirocin, polysporin, and povidone-iodine ointment), topical honey, non-medicated dressings, tunnelled versus non-tunnelled CVCs and different post insertion catheter care protocols. Findings from this systematic review are summarised as follows:

#### 4.6.1.1 Topical antimicrobial ointments

- Topical antimicrobial ointments, which include mupirocin, polysporin and povidone-iodine ointment, significantly reduced the risk of catheter-related infections, exit site infections and catheter-related bacteraemia while having a significant effect on mortality-related infection and catheter removal due to infection.
- Topical mupirocin ointment significantly reduced the risk of catheter-related bacteraemia and catheter removal due to infection. It did not significantly reduce the risk of exit site infection and had no significant effect on all-cause mortality, mortality related to infection or frequency of hospitalisation.
- Topical mupirocin ointment significantly reduced the risk of *S. aureus* exit site infection and catheter-related bacteraemia. The risk of catheter removal and episodes of hospitalisation due to *S. aureus* were also significantly reduced in those patients who used topical mupirocin ointment.
- Topical polysporin ointment significantly reduced the risk of catheter-related infection and catheter-related bacteraemia. It also significantly reduced the risk of catheter removal due to infection and episodes of hospitalisation. Polysporin ointment had a significant effect on all-cause mortality, but did not significantly reduce mortality related to infection.

- Topical povidone-iodine significantly reduced the risk of exit site infection and catheter-related bacteraemia, but had no significant effect on all-cause mortality or mortality related to infection.

#### 4.6.1.2 *Topical honey*

- The use of topical honey (Medihoney/Manuka honey) did not significantly reduce the risk of exit site infection or catheter-related bacteraemia when compared to mupirocin or povidone iodine ointment.

#### 4.6.1.3 *Non-medicated dressings*

- There was no significant difference in the incidence of CVC infection, exit site infection or catheter-related bacteraemia between transparent dressing and dry gauze dressing.

#### 4.6.1.4 *Other interventions*

- The review identified weak evidence from small, poor quality studies which showed that tunnelled CVC did not significantly reduce the risk of exit site infection or catheter-related infection when compared to non-tunnelled CVC. In addition, haemodialysis nurses using heparin three times per week did not significantly reduce the risk of CVC infection, exit site infection, or catheter-related bacteraemia when compared to an intravenous team using heparin three times per day.

### **4.6.2 Overall completeness & applicability of evidence**

#### 4.6.3.1 *Topical antimicrobial ointments*

Topical antimicrobial ointments are used as prophylactic agents against CVC infection and include mupirocin and povidone-iodine ointment. A third agent is polysporin triple ointment, an antibiotic ointment composed of bacitracin, gramicidin and polymyxin B. In our review, topical antimicrobial ointments, including mupirocin, polysporin and povidone-iodine ointment, significantly reduced the risk of catheter-related infections, exit site infection and catheter-related bacteraemia. Topical antimicrobials also had a significant effect on mortality related to infection and catheter removal due to infection.

Mupirocin ointment, like povidone-iodine and polysporin ointment, is normally applied topically to the exit site of the CVC each time the dressing is changed. It causes few side effects and high concentrations are achieved at the

application site. Mupirocin is not used systemically or to treat serious infections (Herwaldt & Supp 1998), but it is an important element of MRSA decolonisation protocols within healthcare settings, resulting in a cautious approach to its use. Within the dialysis patient population, mupirocin ointment can be applied to the skin (CVC exit site or peritoneal dialysis catheter exit site) or intranasally. It has a reported beneficial effect in peritoneal dialysis and haemodialysis patients by eradicating colonisation with *S. aureus* and significantly reducing the risk of *S. aureus* infections, including exit site infection and CVC-related bacteraemia (Laupland & Conly 2003, Tacconelli *et al.* 2003, Strippoli *et al.* 2004, Van Rijen *et al.* 2008). This review focused on topical catheter exit site application of mupirocin ointment. Studies describing intranasal application of mupirocin in haemodialysis patients were not considered and are included in another Cochrane Review on mupirocin ointment for preventing *S. aureus* infections in nasal carriers (Van Rijen *et al.* 2008).

Our review included three studies that investigated the effect of mupirocin ointment on CVC-related infections. One study, which included only 31 patients, did not report the method of randomisation or allocation concealment, and the type of dressing used in both study groups differed (Kamaliah *et al.* 2004). Another study focused exclusively on *S. aureus* CVC-related infections (Sesso *et al.* 1998). A meta-analysis, which excluded the *S. aureus* study, suggests that mupirocin ointment significantly reduces the risk of catheter-related bacteraemia, but does not significantly reduce the risk of exit site infections. This analysis also indicates that mupirocin ointment had a significant effect on catheter removal due to infection. Analysis of the study that focused on *S. aureus* infections (Sesso *et al.* 1998) indicates that mupirocin ointment had a significant effect on catheter-related infections caused by *S. aureus*, with a significant reduction in the risk of *S. aureus* exit site infection and catheter-related bacteraemia. In addition, mupirocin had a significant effect on catheter removal due to *S. aureus* infection. The researcher involved in this study reported that patients using mupirocin ointment had a 96.6% (95% CI, 92.1 to 100) cumulative probability of not having a *S. aureus* catheter-related bacteraemia after 15 days versus 82% (95%CI, 72.4 to 91.6;  $P < 0.001$ ) cumulative probability for patients with no treatment. This probability remained at 96.6% after 30 days (95% CI, 92.1 to 100) for the mupirocin group, but decreased to 75.7% (95% CI, 64.5 to 86.9;  $P < 0.001$ ) for those not using mupirocin. The hazard ratio of developing *S.*

*aureus* bacteraemia was 7.2 (95% CI -1.6 to 31.6) times greater in patients not receiving mupirocin. All three studies (Sesso *et al.* 1998, Johnson *et al.* 2002, Kamaliah *et al.* 2004) reported no adverse reactions to the use of mupirocin ointment.

Our review indicates a beneficial effect against *S. aureus* CVC infections, which is one of the leading causes of CVC infections in haemodialysis patients (Herwaldt & Supp 1998), but this is based on the findings of one high quality study (Sesso *et al.* 1998). Mupirocin resistance among *S. aureus* isolates is a concern that has been raised in the dialysis and the broader medical community (Cookson 1990, Tacconelli *et al.* 2003, Van Rijen *et al.* 2008). Our review found no case of mupirocin resistance in the one study (Johnson *et al.* 2002) that monitored this outcome; in this study patients were followed up until removal of the CVC, with only median survival times reported (31 and 108 days for the control and mupirocin groups). Staphylococcal isolates from exit swabs and blood cultures taken from patients with suspected CVC infection were routine screened for mupirocin resistance. Mupirocin resistance has been reported in other patient populations (Van Rijen *et al.* 2008) so there is a need for future studies to monitor mupirocin resistance in staphylococcal isolates. Concerns about mupirocin resistance are also reflected in the manner in which international guidelines differ in their recommendations and there is no evidence of an optimal strategy for its use. Dialysis facilities that routinely use mupirocin ointment should develop a strategy to monitor the impact of its use on antimicrobial resistance.

Povidone-iodine ointment, like mupirocin, is not used systemically or to treat serious infections. It has residual antibacterial effect at the site of application, but can cause allergic reactions and some local side effects (Herwaldt & Supp 1998). Our review noted no adverse reactions to the use of povidone-iodine ointment. Another Cochrane Review that investigated antimicrobial agents for preventing peritonitis in peritoneal dialysis patients noted that povidone-iodine ointment or povidone-iodine powder when applied to the peritoneal dialysis catheter exit site, did not significantly reduce the risk of peritonitis, exit site or tunnel infection when compared to no treatment or soap and water (Strippoli *et al.* 2004). In contrast, the review for this research project found that povidone-iodine ointment significantly reduced the risk of CVC exit site infection and catheter-related bacteraemia. However, these findings are based on one study (Levin *et al.* 1991), which lacked detailed information on allocation

concealment. Our review also found that the routine application of polysporin triple ointment to the CVC exit site significantly reduced the risk of catheter-related bacteraemia, catheter removal due to infection and episodes of hospitalisation. Again, these findings are based on one study. Adverse reaction to polysporin ointment was not reported.

Despite the lack of high level evidence supporting the routine use of povidone-iodine ointment and polysporin ointment and the reported concerns of mupirocin resistance, international guidelines continue to recommend the routine use of these three ointments for the prevention of CVC infection in haemodialysis patients. The Canadian Society of Nephrology (Jindal *et al.* 2006) recommends either povidone, mupirocin or polysporin ointments. These recommendations were informed by the findings of three studies included in this review (Levin *et al.* 1991, Sesso *et al.* 1998, Lok *et al.* 2003). Similarly, the UK Renal Association (2007) recommends that local protocols may incorporate infection prevention and control measures that RCTs have shown can lead to a reduction in catheter-related infection and suggest the use of topical mupirocin, Medihoney or an antiseptic at the catheter exit site. In contrast to these recommendations, the UK Epic 2 guidelines recommend that topical antimicrobial ointments should not be used in the prevention of CVC (Pratt *et al.* 2007). The CDC, using one study to inform the opinion, recommends the use of povidone-iodine ointment (CDC 2002). Finally, two international Nephrology Guideline groups make no recommendations on the use of topically antimicrobials ointments (NKF K/DOQI 2006a, Tordoir *et al.* 2007). While there is high level evidence supporting the routine use of mupirocin, concerns remain regarding the emergence of mupirocin resistance, but our review did not find any reports of mupirocin resistance in the included studies and therefore cannot confirm or refute this concern.

#### 4.6.2.2 Honey

Honey has been used in the treatment of wounds for centuries, but has only been subject to evaluation in RCTs in the last decade (Jull *et al.* 2008b). Honey is also reported to have antimicrobial properties that lend itself to its possible use as a prophylactic agent at temporary and permanent invasive device exit sites, such as CVC and peritoneal dialysis catheters. *In vitro* investigations have confirmed the susceptibility of pathogens to the antimicrobial actions of honey (French *et al.* 2005). An RCT comparing Manuka honey versus hydrogel dressing in chronic leg ulcers suggests that

Manuka honey was effective in eradicating MRSA from 70% of chronic venous ulcers (Gethin & Cowman 2008). A Cochrane Review on honey as a topical treatment for wounds noted that while honey dressings increased the likelihood a burn wound would remain sterile when compared to other treatments, it did not significantly decrease the infection rate in other types of wounds (Jull *et al.* 2008a).

In the review presented here, Medihoney and Manuka honey did not significantly reduce the risk of exit site infection or catheter-related bacteraemia when compared to mupirocin or povidone-iodine. No adverse reactions to honey were noted by Quadri & Huraib (1999) while Johnson *et al.* (2005) reported a local skin reaction in one patient. As there is no significant difference between the topical use of honey and mupirocin ointment in the prevention of CVC infection, possible benefits of honey as an alternative prophylactic agent cannot be ruled out and needs to be explored further.

#### 4.6.2.3 Dressings

The purpose of a CVC dressing is to protect the catheter insertion site from external contamination; anchor the catheter, so preventing trauma or CVC accidental dislodgement and provide a barrier permeable to water and bacteria, which deters bacterial proliferation at the insertion site (Treston-Aurand *et al.* 1997). Historically, two types of dressings have been used to protect the CVC site, a transparent semi-permeable polyurethane dressing or dry gauze type dressing. Transparent dressings are occlusive dressings, allowing inspection of the CVC insertion site readily, and are comfortable for patients who can bath and shower without saturating the dressing and require less frequent changes than dry gauze dressing (CDC 2002). Transparent dressings are considered more cost effective because they require less nursing time due to the smaller number of dressing changes needed and the reduced time it takes to change the dressing (Shivnan *et al.* 1991, Brandt *et al.* 1996).

The moisture vapour permeability of transparent dressings is sufficiently low to enable skin evaporative water loss through the dressing. However, if blood or serous fluid leakage occurs at the insertion site, its accumulation under a film type dressing may create an environment that is conducive to microbial growth (Wille *et al.* 1993). Indeed, concerns have been raised that the type of dressing applied to the CVC may influence the risk of catheter-related

infection, with some authors suggesting that transparent dressings are conducive to micro-organism growth (Conly *et al.* 1989, Richet *et al.* 1990). Conversely, RCTs on bone marrow transplant patients report no significant difference between transparent and dry dressing in the incidence of catheter-related infection (Shivnan *et al.* 1991, Brandt *et al.* 1996).

In our review, only one study compared the use of transparent and dry gauze dressing in a haemodialysis patient population. Local skin reactions were reported in six patients using dry dressings and nine patients using transparent dressings. Local skin reactions with transparent dressings developed as a result of not letting the chlorhexidine cleansing solution dry before applying the dressing. The study found no significant difference in the incidence of CVC infection, exit site infection or catheter-related bacteraemia when transparent dressing was compared to dry gauze dressing. As these findings were based on one study (Le Corre *et al.* 2003) with only 58 patients, it is not feasible to draw any firm conclusions regarding the risk of CVC infection with each dressing type. This lack of clarity on what is the best dressing to use is reinforced by a Cochrane Review on the use of gauze and tape and transparent polyurethane dressings for CVC in a variety of clinical settings (Gilles *et al.* 2003). That review noted that there was no evidence of any difference in the incidence of infectious complications between any dressing types and suggested that this lack of difference could be explained by the lack of adequate data because each comparison in the review was based on no more than two studies and all studies reported data from a small patient sample. The authors concluded that the choice of dressing for a CVC can be based on patient preference, cost or both. Recommendations by international guidelines differ on the type of dressings that should be used. Those guidelines that recommended the use of a dry dressing did so on the evidence of one RCT (UK Renal Association 2007) or an RCT that also included the additional intervention of topical antimicrobial ointment (Jindal *et al.* 2006). The CDC (2002) and NKF K/DOQI (2006a) express no preference and recommend either transparent or dry gauze dressing, but suggest that if the exit site is oozing, a dry gauze dressing should be used. In conclusion, there are too few good quality studies to evaluate the effects of different non-medicated dressing types on the incidence of CVC infection, exit site infection or catheter-related bacteraemia in haemodialysis patients.

#### 4.6.2.4 *Other interventions*

Other interventions included in our review were a comparison between tunnelled and non-tunnelled CVCs and different post insertion catheter care protocols. Our review suggests that there was no difference between tunnelled and non-tunnelled CVCs in the prevention of CVC infection in haemodialysis patients (Atapour & Shahidi 2006). Similarly, there was also no difference between different post insertion catheter care protocols. This protocol investigated the effect haemodialysis nurses using heparin three times per week had on CVC infections when compared to an intravenous team using heparin three times per day (Huraib *et al.* 1994). The findings from both these studies should be treated with caution as they are based on poor quality data from small sample sets. In particular, the studies that compared the two different post insertion catheter care protocols consisted of two different sets of health professional personnel using different dosages of heparin solution, so it is unclear which particular aspect of the intervention was being investigated; the different heparin locking dosages, the frequency of its delivery or the personnel who delivered the dosage.

#### 4.6.2.5 *Agreements & disagreements with other studies or reviews*

Most catheter-related infections are caused by micro-organisms that colonise the skin surrounding the catheter exit site, with increased density of micro-organism increasing the risk of catheter-related infection. Therefore, an integral component of CVC care and the prevention of catheter-related infection is cleaning the catheter exit site and surrounding skin with an antiseptic solution (UK Renal Association 2007). A meta-analysis of RCTs compared different strengths of chlorhexidine gluconate with povidone-iodine solution, within intensive care units and suggests that the incidence of catheter-related infections was significantly reduced in patients whose catheter exit site and surrounding skin was cleaned by a chlorhexidine gluconate solution. Thereby justifying the use of chlorhexidine gluconate as an cutaneous antiseptic agent (Chalyakunapruk *et al.* 2002). However, we found no RCTs on the use of skin cleansers and different cleansing solutions. In particular, there was no RCT on the use of chlorhexidine gluconate and the different strengths of this solution in haemodialysis patients with a CVC. The use of chlorhexidine gluconate, specifically 2% chlorhexidine gluconate in 70% isopropyl alcohol, as a cleansing agent for CVC is recommended in a number of international guidelines (NKF K/DOQI 2006a, Pratt *et al.* 2007). However, to the best of our knowledge no direct comparison has been performed between



2% chlorhexidine gluconate in 70% alcohol and other alcoholic or aqueous concentrations of chlorhexidine gluconate in the haemodialysis patient population.

The optimal strategy for the prevention of catheter-related infections in haemodialysis patients is not necessarily confined to the interventions included in this review. Other interventions include catheter locking solutions, which are the focus of a separate Cochrane Review. Catheter locking solutions such as cefazolin, cefotaxime, gentamicin, minocycline, EDTA, vancomycin and citrate have been the subject of other meta-analyses as well (Jaffer *et al.* 2008, James *et al.* 2008, Labriola *et al.* 2008, Yahav *et al.* 2008). These meta-analyses confirm that antibiotic catheter locking solutions have a significant effect in the reduction of catheter-related blood stream infection and catheter removal. Only one study reported a single case of gentamicin resistant *S. aureus*, but the development of resistance was not recorded in all studies. Analysis of studies that compared non-antibiotic locking solutions such as citrate showed no significantly effect. However, when these agents were used in conjunction with additional preventive measures such as topical povidone-iodine and nasal mupirocin, they were highly effective. International guidelines caution against the routine use of catheter antibiotic locking solutions because of the possible development of resistance (CDC 2002, NKF K/DOQI 2006a).

## **4.7 Implications for Practice**

### **4.7.1 Topical antimicrobial ointments & honey**

Our review indicates that mupirocin ointment is effective in reducing the risk of catheter-related bacteraemia and CVC infections caused by *S. aureus*. No case of mupirocin resistance was reported in the included studies and, so, our review is unable to conclude that mupirocin resistance is a real or proven threat. The clinical decision to use mupirocin ointment as a prophylactic agent in the prevention of CVC infections requires local knowledge of the prevalence of antibiotic sensitivity within that community. A lack of studies on the routine use of povidone-iodine ointment, polysporin ointment and topical honey in the haemodialysis patient population means that there is insufficient evidence to guide clinical practice in relation to these interventions. Clinical decisions on the use of these topical agents as part of a prophylactic strategy in the

prevention of CVC infection needs to be informed by larger high quality studies demonstrating evidence of effect.

#### **4.7.2 Dressings**

Based on our review, it is not feasible to determine which dressing is the most effective as there is insufficient good quality data to determine which dressing type has the lowest risk of catheter related infections. In addition, no conclusion can be made on the optimal frequency of dressing changes. However, CVC sites need to be dressed and, pending further evidence, those caring for haemodialysis patients with CVC may consider using either a dry gauze or transparent dressing. This choice may be informed by the presence of an oozing exit site, patient preference or cost.

#### **4.7.3 Other interventions**

Due to the poor quality of existing data, there is insufficient evidence to guide clinical practice in relation to the use of either tunnelled or non-tunnelled CVCs or the components of an effective post catheter insertion protocol.

### **4.8 Implications for Research**

#### **4.8.1 All interventions**

Our review highlights inconsistency in the manner in which studies were reported. There is a need to:

- State the methods used in randomisation, allocation sequence and concealment.
- Use a double blind approach where possible and, if not, blind assessors.
- Report completeness of follow-up and withdrawals.
- Indicate intention-to-treat analysis and outline how data from those lost to follow-up were analysed.
- Use standard valid outcome measures that will allow comparisons between RCTs in a meta-analysis (particularly in the incidence of catheter-related infection, time to development of infection and survival time).
- Include outcome measures such as mortality, quality of life measures and cost evaluation.

#### **4.8.2 Topical antimicrobial ointments & honey**

Objective evidence should be used to support and monitor for mupirocin resistance in future studies. Topical honey, povidone-iodine ointment and polysporin ointment are possible alternative prophylactic strategies and should be explored further. High quality RCTs should investigate their effectiveness in the prevention of catheter-related infections including catheter-related blood stream infections and the development of resistance. RCTs could explore the effectiveness of:

- Povidone-iodine ointment versus no treatment
- Polysporin ointment versus no treatment
- Povidone-iodine ointment versus polysporin ointment
- Honey versus no treatment
- Honey versus polysporin
- Honey versus povidone-iodine.

#### **4.8.3 Dressings**

Only one study, which had a small sample, investigated different types of dressings in a haemodialysis patient population. In order to increase the body of evidence in this area, it is important that larger more robust RCTs, investigating dry gauze and transparent dressing, be undertaken. Future studies need to consider the influence that the frequency of dressing changes may have on the incidence of catheter-related infections.

#### **4.8.4 Other Interventions**

No RCTs were found on antiseptic cleansing agents used for catheter hub and exit site care. To ensure that clinical decisions in the management of CVCs in haemodialysis patients are informed by high quality evidence, it is important that this area is the focus of future clinical studies. International guidelines currently recommend the use of 2% chlorhexidine gluconate (CHG) in 70% isopropyl alcohol, but we did not find any RCTs that directly compared aqueous and alcohol preparations of CHG. Future RCTs could compare 2% CHG in 70% isopropyl alcohol and other alcoholic or aqueous concentrations of CHG.

## **4.9 Conclusions**

The systematic review published in 2010 and reported in this chapter, identified a lack of randomised evidence to inform decisions about the effectiveness of antiseptic solutions as CVC hub and exit site cleansing agents in haemodialysis patients. The review recommended a randomised trial comparing the effectiveness of 2% CHG in 70% isopropyl alcohol to other alcoholic or aqueous concentrations of CHG. Recognising that the inclusion criteria for the systematic review was restricted to haemodialysis patients with CVCs it was important to critically analyse trial evidence on the use of CHG in other clinical settings. Chapter 5 will explore the literature on the use of CHG as a skin antiseptic in the maintenance and care of central venous catheters, providing further justification for the direction and focus of the randomised trial performed as part of this PhD research project.

## **CHAPTER 5: CHLORHEXIDINE GLUCONATE AS AN ANTISEPTIC CLEANSING AGENT FOR INTRAVASCULAR CATHETERS**

### **5.1 Introduction**

The Cochrane Review, in chapter 4, found no randomised controlled trials (RCTs) investigating the use of skin cleansers in the maintenance of central venous catheters (CVC) in the haemodialysis patient population. This chapter provides a more in-depth exploration of trials investigating the use of a chlorhexidine gluconate (CHG) antiseptic solution for the care and maintenance of intravascular catheters in the general patient population. A brief outline on the antiseptic activity of CHG is provided, followed by a critical analysis of the literature. Finally, the chapter identifies further gaps in the evidence, adding to the justification for the direction and focus of this randomised trial.

### **5.2 Chlorhexidine Gluconate as a Skin Antiseptic**

CHG, first manufactured in 1954, is a safe and effective broad spectrum germicide that is widely available across Europe (including Ireland). It is used for skin disinfection; hand washing; oral care; irrigation of surgical wounds, the urinary bladder and the vagina; and topical treatment of burn wounds (Maki *et al.* 1991, Denton 2001, Damani 2012). For the majority of dialysis facilities in Ireland (chapter 6, section 6.4.2.7), CHG is the routine established antiseptic agent for catheter exit site and hub cleansing.

CHG is a water soluble cationic biguanide, which binds to and changes the osmotic equilibrium of negatively charged bacterial cell walls. Cell membrane integrity is affected by low concentrations of CHG, while high concentrations cause cytoplasmic contents to precipitate, resulting in cell death. CHG has bactericidal or bacteriostatic actions against a wide range of gram positive and gram negative bacteria, but is not sporicidal. The microbial effect of CHG is not deactivated by blood, serum and other protein rich biomaterials and its antimicrobial suppressive activity is prolonged (McDonnell & Russell 1999, Milstone *et al.* 2008).

Chlorhexidine is commercially available in a variety of concentrations (0.05% to 4%) and formulations (with or without isopropyl alcohol or ethanol). Isopropyl alcohol is a fast acting bactericidal broad spectrum antiseptic that evaporates rapidly, so its action is not prolonged. Its antimicrobial activity is optimal at concentrations ranging between 60-90% and its mechanism of action is thought to be related to the denaturation of proteins and interference with metabolism and cell lysis (McDonnell & Russell 1999). Combining isopropyl alcohol and CHG results in the rapid killing of micro-organisms by isopropyl alcohol followed by the persistent antimicrobial effect of CHG, which prevents the rapid re-growth of micro-organisms (Milstone *et al.* 2008). The addition of isopropyl alcohol also acts as a preservative, eliminating the possibility of microbial contamination of CHG. When opened, containers of CHG in isopropyl alcohol solutions should be used within 7 days (Denton 2001).

### **5.3 Randomised Trials of CHG CVC Antiseptic Agents**

#### **5.3.1 Search strategy**

A search of the literature was undertaken to identify trials that focused on CHG as a CVC antiseptic agent. The search strategy was limited to papers for which at least an English-language abstract was available; no limits were placed on the year of publication. The following MeSH and non-MeSH keywords were used: chlorhexidine OR chlorhexidine gluconate OR chlorhexidine disinfectant OR alcohol OR hibitane AND central venous catheters OR central venous catheterisation OR intravascular catheters OR peripheral vascular catheters. The search yielded 100 citations from PubMed, 317 from Embase, 188 from The Cochrane Library (including 98 from the Cochrane Central Register of Clinical Trials) and 128 from CINAHL. Papers were excluded because they were RCTs investigating other interventions (CVC antimicrobial locks, CHG antimicrobial impregnated CVCs or CHG impregnated CVC dressings) or were not RCTs.

Eleven RCTs were identified that evaluated the effectiveness of CHG versus other solutions, as an intravascular catheter cleansing agent (Maki *et al.* 1991, Mimos *et al.* 1996, Legras *et al.* 1997, Humar *et al.* 2000, Langgartner *et al.* 2004, Mimos *et al.* 2007, Small *et al.* 2008, Valles *et al.* 2008, Garland *et*

*al.* 2009, Atahan *et al.* 2012, Bilir *et al.* 2013). The Legras *et al.* (1997) trial was published in French; but data could be extracted from its English abstract.

A meta-analysis (Chalyakunapruk *et al.* 2002) investigating CHG versus povidone iodine as an intravascular catheter antiseptic agent was also identified. This meta-analysis included eight trials in nine publications. Of the eight trials (Maki *et al.* 1991, Sheehan *et al.* 1993, Meffre *et al.* 1996, Mimos *et al.* 1996, Legras *et al.* 1997, Cobbett & LeBlanc 2000, Humar *et al.* 2000, Knasinski & Maki 2000, LeBlanc & Cobbett 2000) evaluated, four were not identified in the aforementioned search. One trial was published in two papers (Knasinski & Maki 2000, Maki *et al.* 2001), two trials were reported in conference abstracts and the fourth trial was a conference paper (Sheehan *et al.* 1993, Meffre *et al.* 1996, Cobbett & LeBlanc 2000, Knasinski & Maki 2000, LeBlanc & Cobbett 2000). An update of Knasinski & Maki (2000) paper was reported in a 2001 conference abstract (Maki *et al.* 2001), data presented in this abstract was included in the analysis of the literature.

Reference lists of pertinent literature were reviewed for relevant material not identified from the database search. This search yielded an additional two trials (Astle & Jensen 2005, Kelly *et al.* 2006). One of the trials (Astle & Jensen 2005) compared CHG with a chlorine-based solution (ExSept®), among haemodialysis patients with CVCs. This study was not identified in the literature search undertaken for the Cochrane Review (chapter 4). A highly sensitive search strategy developed for The Cochrane Collaboration for the identification of clinical trials was used for the Cochrane Review, but this does not negate against the possibility of missing clinical trials. Hopewell *et al.* (2007), in a Cochrane Review comparing hand searching and electronic searching for identifying clinical trials, found that the Cochrane Highly Sensitive Search Strategy (HSSS) identified 80% of the total number of reports of randomised trials found. One explanation for missing this particular trial is the possibility that it may not have been adequately indexed with the appropriate indexing term, given that the title of the trial made no reference to chlorhexidine.

A search of the grey literature also identified three further systematic reviews (Lee & Umscheid 2010, Rickard & Ray-Barruel 2010, Maiwald & Chan 2012). All six trials reviewed by Lee & Umscheid (2010) were identified in my literature search. Rickard & Ray-Barruel (2010), reviewed seven trials, five of

which were identified in my literature search and the two other trials focused on different preparations of povidone iodine and were not relevant to the discussion on CHG. Finally, Maiwald & Chan (2012) meta-analysis evaluated 10 trials, all of which were identified in my search and included in the critical analysis of the CHG literature.

Overall, my literature search identified 17 RCTs (appendix 5.1) of the effectiveness of CHG based antiseptic solutions, for the prevention of intravascular catheter-related infection. The trials had been done in Canada, France, Germany, the United States (US), the United Kingdom (UK), Spain and Turkey. To the best of my knowledge, as of March 2014, only one clinical trial investigated the effectiveness of CHG as a CVC antiseptic cleansing agent within the haemodialysis population (Aistle & Jensen 2005). One three-arm trial (Valles *et al.* 2008) compared 0.5% CHG in alcohol (strength of alcohol was not given) and 2% aqueous CHG to 10% povidone iodine. I found no published trials that compared 2% CHG in 70% isopropyl alcohol to other formulations or strengths of CHG.

### **5.3.2 Randomised trials of CHG as a CVC antiseptic agent**

One of the first RCTs to investigate the effectiveness of CHG was undertaken in the US by Maki *et al.* (1991). This compared 2% aqueous CHG ( $n=214$  catheters), 10% povidone iodine ( $n=227$  catheters) and 70% alcohol ( $n=227$  catheters) for the prevention of CVC and arterial catheter-related infections, among intensive care unit (ICU) patients. All three antiseptic solutions were used for catheter insertion and maintenance. Risk of bias is unclear, because allocation sequence generation and concealment were not reported. Microbiology staff were not aware of solution assignment. The CHG group had significantly fewer local catheter-related infections, also referred to as catheter colonisation, than the povidone iodine group (5/214 [2%] vs. 21/227 [9%];  $p=0.004$ ). This significant difference was also found when the CHG group was compared to both the povidone iodine and 70% alcohol groups ( $p=0.02$ ). The rate of catheter-related bacteraemia was lower in CHG treated participants (1/214, 0.5%), but was not significantly different than povidone iodine (6/227, 3%) or 70% alcohol (3/227, 1%;  $p=0.18$ ) treated participants. Investigating the effect of antiseptic solutions on CVCs only, the CHG group had significantly fewer catheter-related infections than the povidone iodine group (4/67 [6%] vs. 15/77 [19%];  $p=0.02$ ). Erythema was observed in 45% of the CHG group, compared to 28% and 39% in the povidone iodine and 70% alcohol groups,



but this difference was not significant. Acute local or systemic reaction associated with hypersensitivity was not observed in trial participants.

Sheehan *et al.* (1993), investigated the effectiveness of 2% aqueous CHG (94 patients, 169 catheters) versus 10% povidone iodine (95 patients, 177 catheters) in the prevention of catheter-related infections in ICU patients. The antiseptic solutions were used for catheter insertion and maintenance, types of catheters included arterial and CVCs. No details were provided on allocation sequence generation and allocation concealment. Participants treated with the CHG solution (3/169, 2%) had a significantly lower rate of catheter colonisations than participants in the povidone iodine group (12/177, 7%;  $p < 0.05$ ). Similar to Maki *et al.* (1991), there was no significant difference between the two groups in the frequency of catheter-related bloodstream infections (1/169 [1%] vs. 1/177 [1%]).

A French RCT (Legras *et al.* 1997) involving medical ICU patients, found no significant difference between participants assigned to 0.5% CHG in alcohol (0/88) and 10% povidone iodine solutions (4/102; 4%) in the rate of catheter-related bacteraemia ( $p = 0.13$ ). The strength of alcohol in the 0.5% CHG solution was not given, so it is unclear if the alcohol component of the CHG solution was within the aforementioned antimicrobial activity range (section 5.1). Antiseptic solutions were used for CVC and arterial catheter insertion and site care. Risk of bias was unclear as allocation sequence generation and concealment were not reported in the English abstract of this French publication. No reference was made to adverse reactions.

A Canadian multi-centred RCT (Humar *et al.* 2000) involving ICU patients at three teaching hospitals compared 10% povidone iodine ( $n = 181$  patients) and 0.5% tincture of CHG solution ( $n = 193$ ) for the prevention of catheter colonisation, catheter-related bacteraemia and exit site infections. Solutions were used for catheter (CVC and pulmonary) insertion and site maintenance. Randomisation was guided by a blinded block randomisation schedule; but no information is provided in the article on block size or allocation concealment. Staff and patients were not blinded to assigned solutions because of difference in solution colour. Overall, risk of bias was low. A total of 242 patients had a central line for more than 72 hours (117 vs. 125), and the primary analysis was based on this group of participants. Only 180 (74%) catheter tips were available for culture. The frequency of catheter colonisation

(24/88 [27%] vs. 31/92 [34%];  $p>0.05$ ) and exit site infections (4/117 [3%] vs. 0/125;  $p=0.053$ ) did not differ significantly between participants treated with 10% povidone iodine and CHG. Similar to Maki *et al.* (1991), Sheehan *et al.* (1993) and Legras *et al.* (1997) there was no significant difference between povidone iodine and CHG participants in the frequency of catheter-related bacteraemia (4/117 [3%] vs. 4/125 [3%];  $p>0.05$ ). Adverse reactions to either of the antiseptic solutions were not discussed.

Maki *et al.* (2001), compared 1% CHG in 75% alcohol ( $n=422$ ) to 10% povidone iodine ( $n=617$ ) for the prevention of catheter-related infections in patients with CVC, arterial, and peripheral inserted central lines. Participants were recruited from any hospital unit. Trial solutions were used for catheter insertion and maintenance. Allocation generation and concealment were not reported. This trial, reported in an abstract, was an update of a paper presented in 2000 (Knasinski & Maki 2000). Only data from the 2001 abstract is discussed. Participants in the CHG group had a significantly lower rate of catheter colonisation (43/422 [10%] vs. 192/617 [31%];  $p< 0.05$ ) and catheter-related bloodstream infections (4/422 [1%] vs. 23/617 [4%];  $p< 0.05$ ) than participants in the povidone iodine group.

Langgartner *et al.* (2004), in a University teaching hospital, investigated three antiseptic regimens and their effectiveness on preventing catheter colonisation. This German RCT, recruited patients from all ward settings, including the ICU, who required elective CVC insertions. The trial compared 10% povidone iodine ( $n=52$ ), 0.5% CHG in 70% propanol ( $n=45$ ) and 0.5% CHG in 70% propanol followed by a 10% povidone iodine solution ( $n=43$ ). Sealed and numbered envelopes were used for randomisation; but it is unclear if the envelopes were opaque. Blinding of participants, staff and outcome assessors was not reported. Participants treated with 0.5% CHG in 70% propanol followed by a 10% povidone iodine solution has a significantly lower frequency of catheter colonisation than participants treated with 0.5% CHG in 70% propanol (2/43 [5%] vs. 11/45 [24%];  $p=0.01$ ) and 10% povidone iodine (2/43 [5%] vs. 16/53 [31%];  $p=0.001$ ). There was no significant difference in the frequency of catheter colonisation between participants treated with 0.5% CHG in 70% propanol (11/45, 24%) and 10% povidone iodine (16/52, 31%;  $p=0.32$ ). No adverse reactions to CHG were observed.

In the only published study involving haemodialysis patients, Astle & Jensen (2005) compared ExSept® (chlorine based solution [ $n=57$ ]) to 0.5% CHG in 70% alcohol ( $n=64$ ), as a CVC skin and hub cleansing agent. Different strengths of ExSept® were used to cleanse the catheter exit site (10%) and hub (50%). The recruited population came from a convenience sample of haemodialysis patients. Inclusion criteria included new patients commencing haemodialysis and patients requiring new CVC insertions. The type of haemodialysis catheter was a dual lumen, tunnelled, permanent cuffed CVC. Patients under the age of 18 or who were allergic to the trial antiseptic solutions were excluded from the study. Of the 135 patients eligible for the trial, 121 gave their consent, a refusal rate of 11%. Reasons for refusal included length of study, transfer to peritoneal dialysis or booked for living donor transplantation. Solutions were applied to the skin and catheter hub at each dialysis session by the haemodialysis nurse. Polysporin antimicrobial ointment was applied to the CVC exit site at each dressing change. Packages, containing group assignment were selected prior to catheter insertion. It is unclear if an allocation sequence was used to guide the distribution of these packages, which were previously prepared and randomly organised. Information is not provided on strategies to prevent manipulation of this sequence. It is also unclear as to whether the assignment package was opaque. There was a high risk of bias because not enough information was provided on the allocation of patients to the intervention groups or on the methods used to conceal package assignment. No  $p$ -values were given for the trial outcomes; I entered trial data into The Cochrane Collaboration's Review Manager [RevMan] software. No significant difference between the two antiseptic solutions was found in relation to the proportion of participants with catheter-related bloodstream infections (1/57 [2%] vs. 1/64 [1%];  $p=0.93$ ) or exit site infections (5/57 [9%] vs. 5/64 [8%];  $p=0.85$ ). No adverse reactions to CHG or ExSept® solutions were observed. A potential weakness in the design of the study was the short follow-up period, with patients either participating in the trial for three months or until development of an infection. Additionally, the trialists commented on the potential influence of staff turnover and staff patient ratio on consistency in implementing the trial protocol. Another potential weakness was the use of different strengths of ExSept® for different aspects of CVC care.

Kelly *et al.* (2006) compared 2% CHG in 70% isopropyl alcohol (Chloraprep®) to 10% povidone iodine for skin asepsis for catheter (arterial and CVC) insertion and site care, in ICU patients. Allocation sequence generation, concealment and blinding were not reported so the risk of bias was unclear. Additionally, no information was provided on adverse reactions to either intervention. In this parallel trial, which was reported in an abstract, CHG in alcohol was superior to povidone iodine in preventing catheter-related infections (4/82 [5%] vs. 15/82 [18%]) and primary bloodstream infections (1/82 [1%] vs. 8/82 [10%]); however, no p-values were given. Using RevMan, I calculated p-values of 0.01 and 0.05 for the two types of infection, both of which are statistically significant.

A Spanish study (Valles *et al.* 2008) investigated the superiority of two CHG solutions (2% aqueous CHG and 0.5% CHG in alcohol [strength of alcohol was not recorded]) over a 10% aqueous povidone iodine solution. This single centre, three arm-trial was undertaken in a medical-surgical ICU and recruited patients requiring a CVC or arterial catheter insertion. The solutions were used for catheter insertion and site maintenance. Patients were randomised using a 'blinded block randomisation schedule', but no information was provided on block size and how the sequence was generated. Blinding of participants, staff or outcome assessors was not reported. It would be difficult to blind the intervention from the participants and staff as solutions differed in colour and odour. Risk of bias is unclear due to poor reporting. The 2% aqueous CHG ( $n=34/211$ , 16%;  $p=0.03$ ) and 0.5% CHG in alcohol groups ( $n=32/266$ , 14%;  $p=0.01$ ) had a significantly lower proportion of colonised catheters than the povidone iodine group ( $n=48/194$ , 24%). The proportion of colonised catheters was not significantly different between participants treated with 2% aqueous CHG and 0.5% CHG in alcohol solutions (34/211, 16% vs. 32/266, 14%;  $p=0.20$ ). There was no significant difference between all three groups in the frequency of catheter-related bacteraemia, with nine events occurring in each group. This finding is similar to Maki *et al.* (1991) and Sheehan *et al.* (1993) who used a 2% aqueous CHG solution and Legras *et al.* (1997) who used a 0.5% CHG solution in alcohol. No adverse reactions to CHG solutions were observed. Given the lack of information on the alcohol component of the 0.5% CHG solution, it is unclear if this antiseptic solution reached the necessary antimicrobial activity range, which may or may not have implications for the trial's findings.

Garland *et al.* (2009), compared 2% CHG in alcohol (strength not given) and 10% povidone iodine, for the prevention of peripheral inserted central catheter colonisation and catheter-associated bloodstream in neonates. This US multi-centre trial, undertaken in five neonatal ICUs, was also concerned with the frequency of contact dermatitis and CHG absorption rate. Although block randomisation was used, block size was not reported. Risk of bias was unclear as allocation sequence generation, allocation concealment and blinding were not reported. There was no significant difference between 2% CHG in alcohol and 10% povidone iodine treated participants in the frequency of catheter colonisation (3/24 [12%] vs. 1/24 [4%];  $p=0.61$ ) and catheter-associated bloodstream infections (1/24 [4%] vs. 1/24 [4%];  $p=0.99$ ). No episodes of catheter-related bloodstream infection or contact dermatitis were observed in either arm of the trial. These findings differ to the aforementioned study that used a similar CHG solution (Kelly *et al.* 2006).

Bilir *et al.* (2013), in a Turkish trial, investigated 4% CHG ( $n=19$ ), 10% povidone iodine ( $n=19$ ) and octenidine hydrochlorodine ( $n=19$ ) solutions for the prevention of catheter colonisation and catheter-related sepsis in ICU patients, with CVC and arterial catheters. The three solutions were used for catheter insertion and maintenance. A blinded randomisation schedule was used, but the generation of the allocation sequence was not discussed. Laboratory staff were blinded to allocation assignment. The CHG group had no catheter colonisation or catheter-related sepsis events. When compared to povidone iodine (26.3%), the 4% CHG (0%) and octenidine hydrochlorodine (21.5%) solutions had a significant effect on catheter colonisation ( $p=0.001$ ). Similarly, the 4% CHG (0%) and octenidine hydrochlorodine (10.5%) solutions had a significant effect on catheter-related sepsis when compared to a povidone iodine solution (10.5%;  $p=0.001$ ). No adverse events due to CHG were observed.

A number of RCTs compared the effectiveness of CHG based solutions (CHG combined with other antiseptic agents) to other antiseptic solutions including povidone iodine. Mimosz *et al.* (1996), compared an antiseptic solution composed of 0.25% CHG, 0.025% benzalkonium chloride and 4% benzyl alcohol to 10% povidone iodine. These solutions were used for the prevention of CVC and arterial catheter colonisation and catheter-related sepsis. This single centre French study, undertaken in an ICU, involved 162 patients with 315 catheter insertions. Analysis was based on catheter tips (170 vs. 145).

Patients were randomised by drawing envelopes from an urn, while this is considered as leading to a low risk for selection bias, no information was provided on the type of envelopes used (opaque or not) and systems used to prevent manipulation of this lottery method. Patients and staff were not blinded to the trial solutions because of differences in appearance; but, microbiology staff were not aware of solution assignment. Participants treated with the CHG based solutions had a significantly lower rate of colonisation (12/170 [7%] vs. 31/145 [21%];  $p=0.01$ ) and catheter-related sepsis (6/170 [3%] vs. 16/145 [11%];  $p=0.05$ ), per 1000 catheter days than participants treated with povidone iodine. Similar significant differences in frequency of colonisation (8/87 [9%] vs. 31/71 [44%];  $p=0.03$ ) and catheter-related sepsis (5/87 [6%] vs. 19/71 [27%];  $p=0.02$ ) were found when CVC tips were analysed separately. No difference between solutions was found in the rate of bacteraemic catheter-related sepsis, 3/170 (2%) vs. 4/145 (3%;  $p=0.40$ ) per 1000 catheter days. No adverse reactions to the CHG based solution were observed.

A second RCT involving the aforementioned 0.25% CHG based solution was undertaken by Mimoz *et al.* in 2007. This French study, compared this CHG based solution to 0.5% povidone iodine in 70% ethanol, in ICU patients with CVCs. The randomisation sequence was generated by a computer and stratified according to CVC insertion site and in blocks of eight. Allocation concealment was achieved through the use of sealed envelopes, with instructions guiding the selection process. Patients and staff were not blinded to the solutions, but laboratory staff and outcomes assessors were not aware of trial allocation. The 0.25% CHG based solution (28/242, 12%) has significantly fewer colonised catheters than 5% povidone iodine in 70% ethanol solution (53/239, 22%;  $p=0.02$ ). The frequency of catheter-related bloodstream infections did not differ between solutions (4/242, 2% vs. 10/239, 4%;  $p=0.09$ ). Adverse reactions to either of the solutions were not observed.

A small ( $n=50$ ) Turkish study (Atahan *et al.* 2012) involving a general patient population compared a 1.5% CHG based solution (15% cetrimide and ethanol, strength not given) to 10% povidone iodine. Trial solutions were used at time of CVC insertion and for site maintenance. Compared to participants treated with povidone iodine, the 1.5% combined CHG group had a significantly lower proportion of participants with catheter-related bloodstream infections (0/23 vs. 4/27 [15%];  $p=0.02$ ) and catheter colonisation (6/23 [26%] vs. 9/27 [33%])

$p=0.05$ ). Participants were randomised to two operating theatres, with one theatre using the experimental intervention and the second theatre using the control. No information was provided on how the randomisation sequence was generated. A description of theatres was not provided; as a result, differences in trial outcomes could potentially be attributed to difference between theatre environments as opposed to the antiseptic solutions. Blinding of trial solutions and adverse reactions to trial solutions were not reported.

The literature search also identified three RCTs (Meffre *et al.* 1996, Cobbett & LeBlanc 2000, LeBlanc & Cobbett 2000, Small *et al.* 2008) that focused on the prevention of peripheral vascular catheter (PVC)-related infections. Meffre *et al.* (1996), compared 10% povidone iodine ( $n=549$ ) to 0.5% CHG alcohol ( $n=568$ ) in the prevention of peripheral vascular catheter colonisation and infection. This French study was reported in an abstract. There was no difference between solutions in the rate of catheter-related infections (0.5 vs. 0.5), but significant difference was found in the rate of catheter colonisation (4% vs. 1.6%;  $p=0.002$ ). No information was provided on allocation sequence generation or allocation concealment.

In a three-arm trial, Cobbett and LeBlanc (Cobbett & LeBlanc 2000, LeBlanc & Cobbett 2000) compared 0.5% CHG in 70% isopropyl alcohol ( $n=83$ ) to an application of 70% alcohol followed by 10% povidone iodine ( $n=80$ ) and an application of 10% povidone iodine followed by 70% alcohol ( $n=81$ ). This Canadian study with 244 patients from different clinical settings in a regional hospital, collected data at time of PVC removal (baseline) and 72 hours post removal. In 131 cases, 72 hour follow-up was undertaken after participants were discharged home, using follow-up phone calls. The 0.5% CHG in 70% isopropyl alcohol group ( $n=1/83$ , 1%) had significantly fewer probable IV site infections than the alcohol/povidone iodine ( $n=10/80$ , 12%) and povidone/alcohol ( $n=8/81$ , 10%) groups ( $p=0.008$ ). However, these findings should be treated with caution because diagnoses of all 19 probable infections were informed by data collected by follow-up phone calls. There was no significant difference between comparison groups (5/83 [6%], 2/80 [2%], 3/81 [4%];  $p=0.62$ ) in the number of local catheter infections (colonisations). The risk of bias in this trial was unclear as no information was provided on allocation sequence generation or concealment. No reference was made to adverse reactions to trial solutions.

A third RCT (Small *et al.* 2008) involving PVCs, investigated 2% CHG in 70% isopropyl alcohol (Chloraprep®;  $n=91$ ) and 70% isopropyl alcohol wipes ( $n=79$ ) for the prevention of PVC colonisation in elective cardiology patients admitted for ablation or pacemaker insertion. There were no infections in either arm of the trial. The CHG group ( $n=18/91$ , 20%) had significantly fewer colonised PVC tips than the 70% isopropyl alcohol ( $n=39/70$ , 49%;  $p=0.001$ ). Participants did not exhibit any evidence of adverse reactions to trial solutions. Blinding of staff and participants was not feasible because of difference in the physical application of the solutions; and no information was provided on generation of the allocation sequence or its concealment.

Although the collection of studies described above were not identified using formal systematic review methods (such as with a pre-prepared protocol, trial quality assessment and data extraction by two independent parties), meta-analyses of their results may be informative (see appendix 5.2 for forest plots). Using RevMan, the relative risk for catheter colonisation and catheter-related bloodstream infections (CRBSI) were estimated using data from trials comparing CHG to povidone iodine (Maki *et al.* 1991, Sheehan *et al.* 1993, Legras *et al.* 1997, Humar *et al.* 2000, Maki *et al.* 2001, Langgartner *et al.* 2004, Kelly *et al.* 2006, Valles *et al.* 2008, Garland *et al.* 2009, Bilir *et al.* 2013).

CHG (any strength) compared to povidone iodine, significantly reduced the risk of catheter colonisation (9 trials, RR 0.51, 95% CI 0.34 to 0.77;  $p=0.001$ ) and catheter-related bacteraemia (9 trials, RR 0.52, 95% CI 0.32 to 0.84;  $p=0.008$ ). There was a high degree of heterogeneity across the studies that investigated catheter colonisation ( $\text{Chi}^2 = 35.88$ ,  $P=0.001$ ;  $I^2=75\%$ ).

When compared to povidone iodine, 2% aqueous CHG significantly reduced the risk of catheter colonisation (3 trials, RR 0.41, 95% CI 0.19 to 0.85;  $p=0.02$ ), but had no significant effect on CRBSI (3 trials, RR 0.71, 95% CI 0.30 to 1.70;  $p=0.44$ ). There was moderate degree of heterogeneity across the studies that investigated catheter colonisation ( $\text{Chi}^2 = 4.75$ ,  $P=0.09$ ;  $I^2 = 58\%$ ).

The risk of catheter colonisation (3 trials, RR 0.78, 95% CI 0.42 to 1.43;  $p=0.42$ ) and CRBSI (3 trials, RR 0.70, 95% CI 0.34 to 1.46;  $p=0.34$ ) was not significantly reduced by 0.5% CHG in alcohol when compared to povidone iodine. There was a high degree of heterogeneity across the studies that



investigated catheter colonisation ( $\text{Chi}^2=9.25$ ,  $P=0.01$ ;  $I^2=78\%$ ). CHG 2% in alcohol did not significantly reduce the risk of catheter colonisation (2 trials, RR 0.73, 95% CI 0.73 to 7.63;  $p=0.80$ ) or CRBSI (2 trials, RR 0.29, 95% CI 0.04 to 2.24;  $p=0.24$ ) as compared to povidone iodine. There was moderate to high degree of heterogeneity across the studies that investigated either catheter colonisation ( $\text{Chi}^2=3.80$ ,  $P=0.05$ ;  $I^2=75\%$ ). or CRBSI ( $\text{Chi}^2=1.48$ ,  $P=0.22$ ;  $I^2=32\%$ ).

CHG in an alcohol solution that was greater than 0.5% (1% and 2%) significantly reduced the risk of catheter colonisation (3 trials, RR 0.39, 95% CI 0.18 to 0.88;  $p=0.02$ ) and CRBSI (3 trials, RR 0.26, 95% CI 0.11 to 0.63;  $p=0.003$ ). There was moderate degree of heterogeneity across the studies that investigated catheter colonisation ( $\text{Chi}^2=4.05$ ,  $P=0.13$ ;  $I^2=51\%$ ).

## 5.4 Systematic Reviews on CVC Antiseptic Agents

The following section provides an overview of findings reported by four systematic reviews of antiseptic solutions used for the prevention of intravascular catheter-related infections. My critical analysis of the CHG literature includes all identified CHG trials, but none of the systematic reviews included all of the CHG trials discussed above and there is variation across the systematic reviews in relation to the CHG trials they included.

Chalyakunapruk *et al.* (2002), completed the first systematic review comparing CHG and povidone iodine solutions for the prevention of intravascular catheter-related infections. Their meta-analysis included eight trials (4143 catheters) that focused on various type of catheters (Maki *et al.* 1991, Sheehan *et al.* 1993, Meffre *et al.* 1996, Mimos *et al.* 1996, Legras *et al.* 1997, Humar *et al.* 2000, Knasinski & Maki 2000, LeBlanc & Cobbett 2000). Clinical settings varied, with five studies conducted in ICUs. Only one study was multi-centred. The trials used different formulations of alcoholic and aqueous CHG, but did not include a 2% CHG in 70% isopropyl alcohol solution. All studies used a 10% povidone iodine solution as the control. Catheter-related bloodstream infections were significantly fewer in CHG than povidone iodine treated participants (7 studies; RR 0.49, 95% CI 0.28 to 0.88). Catheter colonisation was also significantly lower in the CHG group than in the povidone iodine group (8 studies; RR 0.49, 95% CI 0.31 to 0.71), but there was significant evidence of heterogeneity across trials in this particular

comparison ( $p=0.001$ ). An analysis limited to CVCs also found CHG participants had significantly fewer catheter colonisations (RR 0.52, 95% CI 0.29 to 0.95) and catheter-related bloodstream infections (RR 0.51, 95% CI 0.27 to 0.97) than povidone iodine participants. No hypersensitivity reactions, to either solutions, were reported by studies included in Chalyakunapruk *et al.* (2002) review.

An Australian systematic review (Rickard & Ray-Barruel 2010) investigated the effectiveness of different antiseptic solutions (CHG, povidone iodine, alcohol and sodium hypochlorite) as skin antiseptic solutions prior to intravascular device insertion. Seven RCTs, focusing on various types of catheters (central and peripheral), were included in the meta-analysis. Clinical settings included ICU, in centre haemodialysis centre and general clinical areas. Astle & Jensen (2005) RCT involving haemodialysis patients was not included in the meta-analysis because it was rated at a high risk of bias. The meta-analysis included four comparisons.

The first comparison compared any strength of CHG to other solutions (Langgartner *et al.* 2004, Mimos *et al.* 2007, Small *et al.* 2008, Valles *et al.* 2008). CHG (any strength) did not significantly reduce the risk of catheter-related bloodstream infections (2 studies, 1112 participants; RR 0.66, 95% CI 0.34 to 1.26;  $p=0.21$ ) than other solutions. In contrast, CHG (any strength) had significantly fewer catheter colonisations than other antiseptic agents (4 studies, 1422 participants; RR 0.44, 95% CI 0.33 to 0.57;  $p=0.00001$ ). The second meta-analysis compared CHG (any strength) to povidone iodine (Langgartner *et al.* 2004, Mimos *et al.* 2007, Valles *et al.* 2008). There was no significant difference in the frequency of catheter-related bloodstream infection between CHG (any strength) versus povidone iodine participants (2 studies, 1112 participants; RR 0.66, 95% CI 0.34 to 1.26,  $p=0.21$ ). Catheter-colonisation was significantly lower in participants treated with CHG (any strength) than povidone iodine treated participants (3 studies, 1209 participants; RR 0.53, 95% CI 0.39 to 0.71;  $p=0.00001$ ). The third comparison involved 0.5% CHG alcohol versus 10% aqueous povidone iodine solutions (Langgartner *et al.* 2004, Valles *et al.* 2008). Catheter colonisation was significantly less in 0.5% CHG alcohol treated participants than participants treated with aqueous povidone iodine (2 studies, 517 participants; RR 0.55, 95% 0.35 to 0.84;  $p=0.007$ ). The final comparison was made between alcohol and aqueous based solutions. Two trials were included (Parianti *et al.*

2004, Valles *et al.* 2008); one compared different strengths of povidone iodine and was not included in the critical analysis of the CHG literature. There was no significant difference between these solutions in the frequency of catheter-related bloodstream infections (2 studies, 853 participants; RR 0.75, 95% CI 0.35 to 1.59;  $p=0.45$ ) and catheter colonisation (2 studies, 853 participants; RR 0.45, 95% CI 0.20 to 1.01;  $p=0.05$ ).

The Rickard & Ray-Barruel (2010) meta-analysis of seven trials found strong evidence that CHG based solutions, versus other antiseptic solutions, reduced device colonisation when used for skin preparation prior to intravascular device insertion. Compared to other antiseptic agents, evidence was lacking on the effectiveness of CHG based solutions in reducing catheter-related bloodstream infections, contradicting findings from Chalyakunapruk *et al.* (2002) meta-analysis.

The Rickard & Ray-Barruel (2010) systematic review did not include the eight RCTs included in Chalyakunapruk *et al.* (2002) meta-analysis because their literature search was limited to the years 2002 to 2009. This time limit was justified on methodological grounds and the possibility that bias control and execution of trials may have been less rigorous in trials published before 2002. However, there are various frameworks available to assess the quality of RCTs and excluding trials on this basis may in itself introduce bias into the review. Another reason put forward for the publication year limits was the limited usefulness of RCTs predating advances in intravascular catheter technology and changes to patient and care processes, and the application of trial findings to a modern healthcare setting. This is a flawed argument as many RCTs were primarily focused on skin asepsis prior to the insertion of intravascular catheters. Since the latter end of the 1980s, little or no change has occurred in the principles underpinning the practice of cleansing catheter exit sites. This is the time period when the oldest trial (Maki *et al.* 1991) included in Chalyakunapruk *et al.* (2002) meta-analysis was undertaken. This is a weakness of the Australian review and no strong conclusion can be drawn from its findings, given the large amount of potential data missing from their meta-analysis.

As part of the preparatory work for updating the 2002 CDC guidelines on the prevention of intravascular catheter infections, the University of Pennsylvania Healthcare System's Centre for Evidence-based practice at Penn Medicine (Lee & Umscheid 2010) was asked to undertake a review of the evidence on the use of CHG in the prevention of intravascular catheter-related infections. The review focused on CVCs and RCTs. No meta-analysis was undertaken. A total of six trials were identified that compared CHG with povidone iodine or 70% alcohol (Maki *et al.* 1991, Mimos *et al.* 1996, Humar *et al.* 2000, Langgartner *et al.* 2004, Mimos *et al.* 2007, Valles *et al.* 2008). There was only one study that directly compared two formulations of chlorhexidine, as part of a three arm trial (Valles *et al.* 2008). The review concluded that there was low quality evidence of no significant difference between 0.5% CHG in 70% isopropyl alcohol and 2% aqueous CHG solutions for the prevention of catheter-related bacteraemia and catheter colonisation in patients with central catheters.

The Maiwald & Chan (2012) systematic review identified 15 RCTs that investigated intravascular catheter antiseptic agents. The primary focus of this review was the alcohol component of antiseptic solutions and the contribution it made to their effectiveness in preventing catheter-related infections. Various types of catheters were included in the RCTs. A total of 11 RCTs compared CHG to povidone iodine. The meta-analysis made four comparisons, in the first comparison (Maki *et al.* 1991, Sheehan *et al.* 1993, Valles *et al.* 2008) participants receiving 2% aqueous CHG had a significantly lower risk of catheter colonisation than participants receiving 10% aqueous povidone iodine (3 studies, 1,192 patients; RR 0.41, 95% CI 0.18 to 0.95;  $p=0.04$ ). In the second comparison (Maki *et al.* 1991, Sheehan *et al.* 1993, Valles *et al.* 2008), this significant difference between these antiseptic agents was not evident for catheter-related bloodstream infections (RR 0.66, 95% CI 0.31 to 1.41). The third and fourth comparison focused on CHG (0.5%, 1% and 2%) in alcohol versus povidone iodine (Meffre *et al.* 1996, Legras *et al.* 1997, Humar *et al.* 2000, Maki *et al.* 2001, Langgartner *et al.* 2004, Kelly *et al.* 2006, Valles *et al.* 2008, Garland *et al.* 2009). There was a significantly lower risk of catheter colonisation in participants receiving CHG in alcohol (8 studies, 3,520 patients; RR 0.62, 95% CI 0.39 to 0.98;  $p=0.04$ ) than participants receiving povidone iodine. A similar significant lower risk for catheter-related bloodstream infections was also found in the CHG in alcohol group (7 studies; 3,619

patients; RR 0.44, 95% CI 0.26 to 0.73;  $p= 0.002$ ) when compared to povidone iodine.

These four systematic reviews draw attention to the evidence that CHG is more effective at preventing intravascular catheter-related infections when compared to povidone iodine and other antiseptic agents. Furthermore, they highlight the dearth of evidence on the effectiveness of alcohol CHG versus aqueous CHG antiseptic solutions in the prevention of such infections.

## **5.5 Guidelines when Randomised Trial was Designed**

In 2009, when the trial for this PhD study was designed, CHG was the antiseptic agent recommended by National and International guidelines for the prevention and control of intravascular catheter and haemodialysis catheter related-infection (CARI 2000, CDC 2002, NKF K/DOQI 2006a, Pratt *et al.* 2007, The UK Renal Association 2007, SARI 2009). Although all guidelines were unanimous in recommending a CHG solution, recommendations differed in its strength and formulation. Two guidelines did not specify the strength or formulation of CHG (CARI 2000, The UK Renal Association 2007). The remaining guidelines recommended the use of 2% CHG, with one guideline not stating its formulation (CDC 2002). All others recommended a 2% CHG in 70% isopropyl alcohol solution. The variation in these guideline recommendations reflects the lack of strong evidence on the most effective strength and formulation of CHG antiseptic solutions for the prevention of intravascular catheter-related infections.

## **5.6 Summary**

Following a rigorous search of the literature, 17 RCTs were identified comparing the effectiveness of CHG based solutions versus other antiseptic solutions for the prevention of intravascular catheter-related infection. Those trials that monitored for adverse reactions did not observe any events. The duration of RCTs ranged from three months (Astle & Jensen 2005) to three years. RCTs were primarily undertaken in the ICU ( $n=10$ ), with one trial, which was assessed as at a high risk for bias, conducted in a haemodialysis centre. Various catheter types were included in the trials, with three RCTs focusing exclusively on CVCs.

The superiority of CHG versus povidone iodine, as a cutaneous antiseptic solution for the prevention of intravascular catheter-related colonisation was confirmed by six RCTs (Maki *et al.* 1991, Sheehan *et al.* 1993, Maki *et al.* 2001, Kelly *et al.* 2006, Valles *et al.* 2008, Bilir *et al.* 2013). CHG solutions investigated in these studies included 4% CHG, 2% aqueous CHG, 2% CHG in 70% isopropyl alcohol, 1% CHG in 75% alcohol and 0.5% CHG in alcohol (no strength given). This finding was not observed in three RCTs (Humar *et al.* 2000, Langgartner *et al.* 2004, Garland *et al.* 2009), with no significant difference in frequency of catheter colonisation in 0.5% CHG alcohol and 2% CHG alcohol treated participants as compared to participants treated with povidone iodine. There is strong evidence from the three meta-analyses (Chalyakunapruk *et al.* 2002, Rickard & Ray-Barruel 2010, Maiwald & Chan 2012) that CHG antiseptic solutions (any strength) are more effective at reducing the risk for catheter colonisation than povidone iodine or 70% alcohol solutions.

There is conflicting evidence on the effectiveness of CHG as compared to povidone iodine for the prevention of catheter-related bacteraemia (catheter-related bloodstream infections). In three RCTs (Maki *et al.* 2001, Kelly *et al.* 2006, Bilir *et al.* 2013), the frequency of catheter-related bacteraemia was lower in CHG (1% CHG in 75% alcohol, 2% CHG in 70% alcohol and 4% CHG) than povidone iodine treated participants. This compares to findings from six RCTs (Maki *et al.* 1991, Sheehan *et al.* 1993, Legras *et al.* 1997, Humar *et al.* 2000, Valles *et al.* 2008, Garland *et al.* 2009) that report no significant difference in the frequency of catheter-related bacteraemia between participants assigned to CHG (0.5% CHG alcohol, 0.5% CHG tincture, 2% aqueous CHG & 2% CHG alcohol) and povidone iodine groups.

Of the six trials that found no significant difference in the frequency of catheter-related bacteraemia, four (Legras *et al.* 1997, Humar *et al.* 2000, Valles *et al.* 2008, Garland *et al.* 2009) lacked information on the alcohol concentration of the CHG solution, raising concerns about the alcohol's optimal range (60% to 90%) for antimicrobial activity. Five trials (Maki *et al.* 1991, Sheehan *et al.* 1993, Legras *et al.* 1997, Humar *et al.* 2000, Valles *et al.* 2008) had a lower CHG in alcohol solution (0.5% versus 1% and 2% CHG) or were in a lower aqueous based solution (2% versus 4%) when compared to those trials that report a significant effect on catheter-related bacteraemia rates (Maki *et al.* 2001, Kelly *et al.* 2006, Bilir *et al.* 2013). Although the sixth

trial used a 2% CHG in alcohol solution (Garland *et al.* 2009), its sample size was small (24/24), the alcohol concentration of the CHG was not provided and participants were recruited from neonatal units, a patient population that was particularly vulnerable to infection. All other CHG trials recruited participants over the age of 18 years. Given the difference between trials that had an effect versus those that did not, it could be hypothesised that a higher strength of CHG (4%) or a higher strength of CHG in alcohol (1-2% CHG in 70% isopropyl alcohol) could potentially have a more beneficial effect than 0.5% CHG in alcohol or 2% aqueous CHG.

Differences in trial findings are also mirrored by conflicting findings from the systematic reviews. None of the reviews included all 17 trials that are discussed individually in this chapter. These systematic reviews were guided by specific criteria that potentially limited trials that were identified as eligible for the meta-analysis. It is unclear what impact the exclusion of trials may have on the meta-analysis of trial data. In Chalyakunapruk *et al.* (2002) meta-analysis, CHG (0.5% & 1% in alcohol, 2% aqueous) solutions, as compared to povidone iodine solution, significantly reduced the risk of intravascular catheter (all types) and CVC catheter-related bloodstream infections. This is somewhat supported by Maiwald & Chan (2012), whereby participants treated with CHG (0.5%, 1% and 2%) in alcohol had a significantly lower risk of catheter-related bloodstream infections than participants treated with aqueous povidone iodine. However, there was no statistically significant difference between participants treated with 2% aqueous CHG and aqueous povidone iodine solution in the frequency of catheter-related bloodstream infections. Based on findings from two RCTs, Rickard & Ray-Barruel (2010) meta-analysis also estimated that there was no statistically significant differences in the frequency of catheter-related bloodstream infections between CHG (any strength) and povidone iodine treated participants. Conclusions made in the Rickard & Ray-Barruel (2010) meta-analysis need to be tempered given the exclusion from their meta-analysis of RCTs published before 2002.

## 5.7 Conclusion

There is strong evidence that CHG antiseptics solutions of any strength are more effective than other agents in reducing the risk of intravascular catheter colonisation. However, there is no clear evidence that aqueous and alcohol CHG antiseptic solutions are more effective than other antiseptic solutions in reducing the risk of catheter-related bloodstream infections.

National and international guidelines recommend the use of CHGs for the insertion and maintenance of CVCs, including haemodialysis catheters. However, only one RCT compared the effectiveness of different strengths of CHG for the prevention of catheter-related infections. This three arm trial found no significant difference in the frequency of catheter colonisation and catheter-related bloodstream infection in participants treated with 0.5% CHG in alcohol versus participants treated with a 2% aqueous CHG solution. A number of intravascular-catheter guidelines recommend a 2% CHG in 70% isopropyl alcohol solution, even though no RCTs were found that directly compared this solution to other strength/formulations of CHG. Such RCTs would provide the evidence justifying such a recommendation. A lack of evidence is the cause of continuing uncertainty as to which strength and formulation of CHG is the most effective in reducing the risk of CVC-related infections. This gap in the existing evidence provides further justification for the direction and focus of the randomised trial for this PhD research. The findings in this chapter, and from the Cochrane Review in chapter 4, highlight the need to explore the comparison through a pilot RCT testing the relative effectiveness of 2% CHG in 70% isopropyl alcohol versus other alcohol or aqueous strengths of CHG for the prevention of catheter-related infections in haemodialysis patients. There is also a need to explore the feasibility of undertaking a more powerful study, as a multi-national, multi-centre trial.

The review of CHG RCTs highlights a number of issues that have implications for the design of this randomised trial. Only three trials focused exclusively on CVCs, with one (Aistle & Jensen 2005) recruiting participants from an in-centre haemodialysis unit. The type of catheter used in that trial was a dual lumen, tunnelled, permanent cuffed catheter; similar to what is used for haemodialysis patients in Ireland (chapter 3 section 3.5). RCTs focused on CVC, including Aistle & Jensen (2005), recruited participants with newly inserted CVCs and trial solutions were used for catheter insertion, exit site and catheter hub care. It is not feasible to confine this pilot trial population to haemodialysis patients



with newly inserted CVCs, because there are insufficient numbers of such patients in Ireland (chapter 3 sections 3.3 and 3.4). It is important that at each dialysis session and dressing change, trial solutions are used by haemodialysis nursing staff for all aspects of participants' CVC exit site and catheter hub care. This includes the avoidance of topical antimicrobial ointments, limiting potential confounding variables in this trial.

As most of the RCTs were undertaken in ICUs, their inclusion and exclusion criteria are of relatively little help for planning the design of my trial, other than their decisions to require that patients be over the age of 18, able to give informed consent, have no allergies to the trial solutions, and with a standard CVC site e.g., internal jugular and subclavian vein and the use of CVCs for haemodialysis only. Astle & Jensen (2005) did not report the methods used to randomise haemodialysis patients to their assigned solution, but some of the other RCTs used randomised block allocation sequence that were blinded, with one study using a block size of 8. In general, no detail was provided on the method used to generate the randomisation sequence, except for one RCT that used a computer. For a majority of trials, staff and participants were not blinded to the assigned treatment because of the nature of the solutions being applied, but efforts were made to keep outcome assessors unaware of participant allocation. Drawing on these features of earlier trials, a computer generated randomised block sequence is an appropriate method for ensuring a low risk of selection bias in my trial and allocation concealment bias can be addressed through the use of a central randomisation centre.

Primary outcomes for many of the RCTs included colonisation, exit site infections and bloodstream infections related to the use of a catheter. Various case definitions were used in the trials, which impinges on comparability. The most clinically important primary outcomes for outpatient haemodialysis participants are bloodstream infections related to the use of the CVC and exit site infections (chapter 3, section 3.5.1). These two outcomes were taken into account when designing my trial. It is also important that adverse reactions to the trial solutions are monitored, recorded and reported in the CHG Trial. Another consideration for the design of my trial was the potential impact haemodialysis nursing staff turnover may have on the consistent implementation of the trial protocol, as highlighted by Astle & Jensen (2005). In order to overcome this potential limitation, the trial protocol included the

provision of in-service education to new haemodialysis nursing staff during the course of the trial.

## **SECTION 3**

### **PREPARATION FOR TRIAL: ASCERTAINING ROUTINE PRACTICE IN HAEMODIALYSIS UNITS**

#### **TRIAL DESIGN, METHODS & CONDUCT**

## **CHAPTER 6: ROUTINE PRACTICE IN HAEMODIALYSIS UNITS**

### **6.1 Introduction**

The prevention of central venous catheter (CVC)-related infections is achieved through various interventions that are part of routine practice. Chapters 4 and 5 clearly identify a gap in the evidence on the most effective strength and formulation of chlorhexidine gluconate (CHG), as an antiseptic skin cleansing agent, for the prevention of CVC-related infections. This PhD trial compares 2% CHG in 70% isopropyl alcohol against established routine CHG solutions. Trial design is underpinned by infection prevention and control routine practices. A large body of information exists on routine practices within different healthcare settings, but there is little discourse in the literature over the last four decades on what is meant by the term 'routine practice'. Within nursing and medical literature the term routine practice is used interchangeably with standard care. This chapter examines the literature with regard to the meaning of routine practice and standard care, and variations in routine practices, with a particular focus on infection prevention and control and the haemodialysis environment. The search of the literature highlights a lack of published literature on routine practices in Irish haemodialysis units. In order to place the clinical trial within the context of haemodialysis practices, a national survey of routine practices in haemodialysis units in Ireland was undertaken, with a particular emphasis on infection prevention and control and vascular access. The methodology and results of this survey are also discussed in this chapter.

### **6.2 Routine Practice**

Within the healthcare environment, the term 'routine practice' is used to describe the care and management that is normally provided to patients with a particular condition. This term is often used interchangeably with standard care, standard practice and standard treatment. The National Cancer Institute in the United States (US) (2012) notes that standard care is also synonymous with best practice, standard medical care and standard of care. These terms relate to the provision of interventions that experts agree are appropriate, accepted and widely used. In contrast to the lack of discourse on the concept

of routine practice, there is much deliberation on the concept of standard of care.

The legal definition of standard of care is the level at which practitioners serving a particular patient population should practice; for example, patients with similar conditions should receive similar management from practitioners (Sheil & Conrad 2008). A similar legal definition is used within the nursing profession, where there is an expectation that nurses adhere to the standard of care that is expected of them (Miola 2009). Both definitions do not include any criterion indicating the quality of care that should be provided.

Standard of care in clinical research, similar to the legal definition, is defined as the treatment that should be provided to research participants (Nuffield Council on Bioethics 2002, van der Graaf & van Delden 2009). In the context of clinical research there is much debate on what the standard of care comprises, especially among those organisations that make recommendations on ethical principles governing such research.

The Nuffield Council on Bioethics (2002, 2005) categorise standard of care as either universal or non-universal. Universal standard of care is the best treatment available anywhere in the world for a particular illness. It may not be feasible to deliver such a standard of care, due to the economical circumstance of participating countries or a lack of agreement among medical experts on a universal standard of care for that particular illness. Additionally, the means of delivering a universal standard may not exist for reasons other than economic; for example, the configuration of the healthcare service might not be suitable. Instead, a non-universal standard of care may be provided, which is the best treatment provided by the national public health system for that illness.

Other organisations provide an outline of what the standard of care should entail. For example, the Declaration of Helsinki (World Medical Association 2008) describes the standard of care as the best current proven intervention for that illness. Similar, the Council for International Organisations of Medical Sciences (CIOMS) (2002) defines standard of care as the established effective intervention.

Overall, there is general agreement that the standard of care is the treatment that should be provided to patients with a specific illness, similar to that expected from routine practice. Various terms are used in the literature to describe the standard of care, such as the provision of the best available, the best current, a proven or an established effective treatment. The terms 'best', 'proven' and 'established effective' indicate the quality of treatment provided, with the expectation that this treatment is based on the best evidence.

Within nursing there is also an expectation that routine nursing practice be evidence-based, using evidence from research, clinical guidelines (international, national or local), nursing and medical literature and literature relevant to specialist areas of practice (Davies *et al.* 2006, Gerrish *et al.* 2007, Knowles *et al.* 2010, Profetto-McGrath *et al.* 2010, Gerrish *et al.* 2011, Gerrish *et al.* 2012). The broader definition of 'evidence-based'; however, is not solely focused on the best evidence, but the integration of that evidence with clinical expertise, clinician and patient preferences and individual values (Sackett 2002). The Nursing and Midwifery Board of Ireland (2000) code of professional conduct advocate that nurses provide the highest standard of care. The UK Nursing & Midwifery professional code (2008) goes further and expects that this standard of practice and care is underpinned by the best available evidence or best practice.

Clinical practice that is rooted in the best evidence is considered essential in optimizing patient outcomes (Profetto-McGrath *et al.* 2010). A Cochrane Review (Thomas *et al.* 1999) investigating the effects of clinical practice guidelines concluded that there was some evidence that practice underpinned by practice guidelines were effective in changing the process and outcome of care provided by professions allied to medicine. The review included 18 studies, and 17 of these related to the nursing profession. Limitations include the inability of the review's authors to undertake a meta-analysis due to the substantial heterogeneity between studies and the methodological quality of the studies included in the review.

As outlined above, the term routine practice is synonymous with standard of care and will therefore be used throughout this thesis to describe the treatment provided to patients with a specific illness. One of the aims of integrating routine practice with clinical practice guidelines, which are based

on the best evidence, is to decrease inappropriate variations in practice (Thomas *et al.* 1999, Chalkidou 2009).

### **6.3 Variation in Routine Practice**

Variations in practice may involve under or excessive use of interventions or procedures. It exists between hospitals, professional groups, groups of doctors or between doctors who have similar expertise (Peveler 2002, Mercuri & Gafni 2011). Variation in practice can be warranted or unwarranted, with warranted variations occurring in response to differences in patient needs. In contrast, unwarranted variations are linked to practices that impact negatively on patient care and exist despite evidence from robust clinical research or agreement among professionals, as to what is best practice (Mercuri & Gafni 2011).

Unwarranted practices may occur due to lack of knowledge, professional attitudes or external/environmental factors. Professionals may not be familiar with guideline recommendations, may not agree with the expected patient outcomes in the guideline recommendations they do know of, or may opt not to adhere to guidelines based on the clinical experience they gained over a number of years. External factors include guidelines offering contradictory advice, being of poor quality, or so complex that professionals may have difficulty understanding them and integrating them into their practice. Environmental factors that impede implementation of evidence-based guidelines include time constraints, lack of resources and organisational resistance (Davis & Taylor-Vaisey 1997, Cabana *et al.* 1999, Bevans *et al.* 2009)

#### **6.3.1 Variation in infection prevention & control practices**

Inconsistencies in routine practice are apparent in infection prevention and control practices within ICUs, pre-operative preparation, paediatric care and haemodialysis units.

Investigating CVC infection prevention and control practices in 14 Australian ICUs, Richard *et al.* (2004) noted variation in the frequency of catheter dressing change, which was not in keeping with CDC guidelines. In addition, a wide variety of solutions were used to clean the CVC exit site. These include

tincture of iodine/iodophor, 70% alcohol, 0.5% CHG in 70% alcohol, saline and chlorhexidine sponges. No unit used a 2% CHG solution even though it was recommended at that time by the CDC guidelines. The inconsistency in practice when compared with CDC guidelines was linked to lack of knowledge of evidence-based practice or a lack of resources to enable the development of up-to-date evidence-based policies.

Variation in preoperative practices was reported among 63 surgeons in Northern Ireland, with more than half continuing to shave the preoperative site hours before surgery even though the evidence suggests this is not necessary (McGrath & McCrory 2005). This audit survey also reported a wide variation in the types of antiseptic solutions used in preoperative skin preparation.

Surveying five healthcare professional groups (n=146), Niedner (2010) investigated catheter-associated bloodstream infection (CABSI) surveillance practices in 16 American paediatric ICUs. There was wide variation in surveillance practices including inconsistencies in the methods used to calculate line days; surveillance methods, timing and resources used to identify possible cases of CABSI and a lack of written policies for classifying bloodstream infections (BSI). More than half of those surveyed did not fully adhere to written guidelines on obtaining blood cultures.

Inconsistency in infection prevention and control practices were also noted in haemodialysis settings. Kumwenda *et al.* (1996) surveyed nurse managers on vascular access practices across UK dialysis units. Practice varied between units, with 64% using one nurse to change the CVC dressing and 36% of units using two nurses. Dressings were changed at each dialysis session by most units (60%). The most common antiseptic skin solution used to cleanse the CVC exit site was betadine (65%).

An audit of infection prevention and control practices across 393 haemodialysis units in eight European countries suggests considerable variation between countries (De Vos *et al.* 2006). Differences in isolation procedures were apparent for patients who were hepatitis B positive, HIV positive and Methicillin Resistant *Staphylococcus Aureus* (MRSA) positive. Substantial disparity in relation to regular screening for MRSA existed between counties, with 50% of centres in Greece, Italy, Belgium and England



regularly screening for MRSA compared to 10% of centres in Slovakia, Scotland, Norway and the Czech Republic.

Higgins and Evans (2008) investigated nurses' knowledge and practice of vascular access infection prevention and control, among adult haemodialysis patients in Ireland. A questionnaire was posted to 190 nurses in nine haemodialysis units, and the response rate was 74% (n=140). A majority of units had written infection prevention and control policies; but, there was considerable variation in practices between respondents. Differences related to time spent on hand hygiene, with only 29% identifying the recommended minimum time of 15 seconds. Diversity also existed among respondents in the type of antiseptic solution used to clean the CVC, with 38% using 10% povidone iodine and 20% using a chlorhexidine based solution. Differences also existed in the length of time 10% povidone iodine and chlorhexidine antiseptic soaks were applied to the catheter hubs even though this was not recommended practice for a CHG solution. Indeed, CDC and NKF-K/DOQI guidelines at the time of the survey advocated the use of 2% CHG as the antiseptic solution for cleaning the CVC, yet 38% of respondents used a povidone iodine solution. Variation in practice was also evident in dressing of the CVC, with 51% reflecting guideline recommendations on frequency of CVC dressing change. It is important to note that the Higgins and Evans (2008) survey was completed before the publication of national guidelines on the prevention of intravascular catheter related infections (Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) 2009). A number of infection prevention and control interventions evaluated in the survey are now outdated

Finally, a survey of 320 Swedish haemodialysis nurses, investigated self-reported knowledge and actual knowledge of MRSA, and routine practices used to prevent its transmission. Findings indicated that 24% of those surveyed were not aware that gloves were inadequate in preventing MRSA transmission (Lindberg & Lindberg 2012). Nurses also lacked knowledge of routine practices in MRSA management, common sites of colonisation (53%), treatment of colonisation (42%) and the symptoms of MRSA infection (44%). Consistency in knowledge was evident in relation to hand washing procedure (96%) and the use of protective apron (95%).

### 6.3.2 Variation in renal care practices

Infection prevention and control is not the only area of renal care that experienced variation in routine practices. Practice variation was seen in nutritional care (Burrowes *et al.* 2005, Schatz *et al.* 2006, McKnight *et al.* 2010, Trudel *et al.* 2010, Hall-McMahon & Campbell 2012), peritoneal dialysis (Allen *et al.* 2011) and the management of anticoagulation therapy (Parker *et al.* 2012).

Bannister and Snelling (2006) in a retrospective study, investigated compliance to national anaemia management guidelines among 15 dialysis centres in Australia. The number of chronic haemodialysis patients achieving the haemoglobin target remained similar to that in 2001, 66% and 65% respectively. This study highlights an interesting dilemma within the field of nephrology where many practices are guided by evidence that is not supported by trial evidence because few trials are undertaken in nephrology (Lok & Moist 2007; McCann *et al.* 2012). Since Bannister and Snelling (2006) study, evidence from a randomised trial involving 1,432 patients (Singh *et al.* 2006), found that normalisation of haemoglobin using erythropoietin was dangerous in haemodialysis patients. A higher risk of death, myocardial infarction and stroke was observed. This contradicts guideline recommendations that were based on observational studies.

Routine practice in AVF creation also varied across renal care settings. Lopez-Vargas *et al.* (2011), using a mixed methods approach, investigated the barriers and enablers to AVF creation across nine nephrology centres in Australia and New Zealand. There was considerable variation in patients' attendance at pre-dialysis education sessions, which ranged from 25% to 97%. Similarly, non-attendance by patients at surgical review for AVF creation, while low, varied between centres. There was no difference for wait times for surgical review among centres; but this was not the case for those patients waiting for access creation. Centres also differed on the type of vascular access used by patients commencing haemodialysis, with incident AVF use ranging from 14% to 51%.

Variation in practice within the haemodialysis environment is apparent across a breadth of treatment strategies used in the management of patients with CKD. This is no more evident than in results published from the Dialysis Outcomes Practice Pattern Study (DOPPS). This international longitudinal

study of haemodialysis practice has, since 1996, reported on variation in dialysis practices in such areas as vascular access and associated risk of hospitalisations and mortality (Pisoni *et al.* 2002, Young *et al.* 2002, Mendelssohn *et al.* 2006, Pisoni *et al.* 2009, Ng *et al.* 2011); starting and withdrawal of haemodialysis (Lambie *et al.* 2006); mortality and hospitalisation in dialysis patients (Rayner *et al.* 2004); imbalance in calcium, phosphate and PTH concentrations and mortality risk (Tentori *et al.* 2008) and length of dialysis session and impact on patient survival (Tentori *et al.* 2012). There is no published literature on routine practices in haemodialysis units in Ireland and consequently it is not possible to be sure that practice variation exists among units, although given the worldwide evidence of variations in dialysis practices it would seem likely that such variations are present in Irish dialysis settings.

#### **6.4 Routine Practice in Haemodialysis Units in Ireland**

As outlined already in this chapter, the degree to which routine practices are underpinned by the best evidence varies across healthcare settings, including haemodialysis. Although national and international guidelines recommend the use of effective vascular access (VA) and infection prevention and control practices within the haemodialysis environment, there is little evidence to suggest that this is being achieved within Irish haemodialysis units. As discussed in chapter 3 (section 3.5.1) haemodialysis patients and, in particular, patients with CVCs, are at increased risk of healthcare-associated infections (HCAI) (National Renal Office 2012b). These infections have a profound impact on patient health, and can lead to death, serious illness, longer stays in hospital and long term disability (Health Information and Quality Authority 2009). To minimise HCAI, it is essential that infection prevention and control within the haemodialysis environment take an evidence-based approach (chapter 2, sections 2.3 and 2.5) (Health Information and Quality Authority 2009).

In order to ascertain the degree to which evidence-based practice underpins healthcare professionals' daily routine in Irish haemodialysis units and to identify practice variation among haemodialysis units, there is a need to evaluate routine practices using a survey approach. Given that there are no renal register data on VA use in Ireland, the survey also offers an ideal opportunity to capture VA use in dialysis units in Ireland. Finally, the survey

provides a contextual background to my trial reported in chapters 7-10 of this thesis.

## **6.4.1 Research methodology**

This first ever national survey aimed, firstly, to identify routine practice in haemodialysis units in Ireland, with a particular emphasis on VA and infection prevention and control. The second aim was to evaluate the impact that national and international guidelines, in particular the 'SARI Prevention of Intravascular Catheter-related Infection' (2009) guidelines, have had on routine practice.

### *6.4.1.1 Population*

One children's and all 19 adult outpatient haemodialysis units in the Republic of Ireland were surveyed (12 parent hospitals, three satellite and five contracted units).

### *6.4.1.2 Survey design*

The survey focused on routine practices in AVF formation, infection prevention and control, CVC insertion and maintenance and VA use. Questions were relevant to recommendations made in the SARI Prevention of Intravascular Catheter-related Infection' (2009) guidelines. The majority of questions were answered by tick boxes and completion of the survey took approximately ten minutes.

Experts in survey design and quantitative research, and healthcare professionals with clinical expertise in infection prevention and control, and haemodialysis reviewed the survey to ensure that it would capture the sought data appropriately. Amendments to the survey improved clarity, with additional questions capturing more in-depth data on infection prevention and control. The final survey consisted of 38 questions (appendix 6.1).

### *6.4.1.3 Survey implementation*

In November 2011, the National Renal Office emailed surveys to nurse managers in the 20 dialysis units, with a covering letter from me explaining the study. Completed surveys were returned to me by post.

#### 6.4.1.4 Data analysis

Data were analysed using IBM SPSS (statistical package for social science) version 20. Descriptive statistics were used to summarise data, with means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical data. Fisher's exact test (two tailed) was used to compare associations between size of dialysis units and implementation of guideline recommendations.

#### 6.4.1.5 Ethical considerations

The Faculty of Health Science, Trinity College Dublin research ethics committee granted ethical approval, with return of completed surveys implying informed consent.

### 6.4.2 Results

By March 2012, 19 completed surveys (18 adult units and the one paediatric unit) were returned from 12 parent hospital, five contracted and two satellite units (response rate of 95%). The number of patients attending each unit varied (Table 6.1), ranging from 11 to 185 patients. The mean number of patients per unit was 80 (SD 43.7).

**Table 6.1 Number of patients attending for haemodialysis**

Total number of patients	Parent hospital unit	Satellite unit	Contracted unit	Total
	N	N	N	N
<=30	1	0	0	1
31-60	0	2	2	4
61-90	8	0	0	8
91-120	1	0	1	2
>120	2	0	1	3
Total	12	2	4	18 <sup>1</sup>

<sup>1</sup>18 dialysis units provided complete data on the number of patients attending their unit

In general, survey responses indicated adherence to national guidelines, the main areas of practice variation and noncompliance were non-adherence to the recommendation not to administer intravenous prophylactic antimicrobials prior to CVC insertion and the use of CVC insertion checklists and

maintenance care bundles (Table 6.2). Other areas of variation included the creation of an arterio-venous fistula (AVF) when the eGFR was 17-12ml per hour, access to dedicated vascular surgical theatre time, undertaking root cause analysis for each episode of healthcare-associated catheter-related bloodstream infection (HCA CRBSI) and the use of impregnated permanent cuffed CVCs in patient population at high risk of CRBSI.

#### *6.4.2.1 Prevalence of vascular access*

Eighteen dialysis units provided data on the number of patients attending for haemodialysis (total of 1450 patients), and 17 units provided complete data in relation to VA use. VA prevalence was, therefore, based on the number of patients attending 17 dialysis units (n=1370) (Table 6.3). Nine dialysis units had no patients with an arterio-venous graft (AVG) and one unit used CVCs for all its 11 patients. Seven dialysis units had a CVC prevalence of greater than 50% (five parent and two contracted units).

#### *6.4.2.2 Timeline to formation of primary AVF*

Only three parent hospital dialysis units (n=12) routinely created a primary AVF, when the eGFR was between 17 and 12 mls/hr; each unit had > 60 patients. The AVF prevalence for these units was 42%, 49% and 50%.

Seven dialysis units did not routinely create early AVFs; one unit did not know and another did not respond to the question. Seven other units had alternative routine practices; for two units, pre-emptive creation of AVFs was dependent on available resources such as vascular support, theatre slots and hospital beds. Five units referred patients to a vascular surgeon from pre-dialysis clinics; but, these patients may not have had a primary AVF created prior to starting haemodialysis.

**Table 6.2 Compliance with guideline recommendations**

NKF K/DOQ/SARI Guideline Recommendation	Number of Dialysis Units that meet the Recommendation N (%)	
NKF-K/DOQI AVF prevalence >65%	0	One unit had an AVF prevalence of 65%, but not greater
NKF-K/DOQI CVC prevalence <10%	0	
Vascular Access		
Maintain records of VA <sup>1</sup> use	17 (89%)	
Create AVF <sup>2</sup> when eGFR <sup>3</sup> 17-12ml/hr	3 (16%)	
Access to dedicated vascular surgical theatre time	3 (16%)	Findings indicate a lack of adequate access to vascular surgical procedures
Infection Prevention and Control		
Undertake three monthly MRSA <sup>4</sup> screening	17 (89%)	
Review bacteraemia rates regularly, for patients with or without CVCs <sup>5</sup>	16 (84%)	Weekly n=1; monthly n=10; three monthly n=2; alternative times n=3
Obtain two sets of blood cultures in suspected cases of HCA CRBSI <sup>6</sup> prior to administration of antibiotics	13 (68%)	
Put in place a surveillance programmes for HCA CRBSI	12 (63%)	
Undertake root cause analysis for each episode of HCA CRBSI	9 (47%)	
CVC insertion		
Use interventional radiology department or operating theatre for insertion of CVC	18 (95%)	
Do not administer intravenous prophylactic antimicrobials prior to CVC insertion	7 (37%)	6 units did not know
Use impregnated permanent cuffed CVCs in patient population at high risk of CRBSI	3 (16%)	15 units did not use these CVCs on any of their patients
Use CVC check list at time of CVC insertion	2 (11%)	14 units did not know
CVC care and maintenance		
Have policies, protocols, guidelines for CVC care and maintenance	19 (100%)	
Do not use a topical antimicrobial ointment on the CVC exit site	19 (100%)	
Use 2% chlorhexidine gluconate in 70% isopropyl alcohol antiseptic solution to clean CVC exit site and catheter hubs	14 (74%)	
Use antimicrobial locks on patients with long term CVC e.g., haemodialysis patients	13 (68%)	
Use a transparent semi-permeable polyurethane dressings to cover CVC exit site	11 (58%)	
Use CVC care bundles	8 (42%)	

<sup>1</sup> VA, vascular access

<sup>2</sup> AVF, arterio-venous fistula

<sup>3</sup> eGFR, estimated glomerular filtration rate

<sup>4</sup> MRSA, methicillin resistant *Staphylococcus aureus*

<sup>5</sup> CVCs, central venous catheters

<sup>6</sup> HCA CRBSI, healthcare-associated catheter-related bloodstream infection

**Table 6.3 Vascular access use**

	AVF <sup>1</sup>	AVG <sup>2</sup>	CVC <sup>3</sup>	Total <sup>4</sup>
<b>Number</b>	668	18	683	1370
<b>Prevalence</b>	49%	1%	50%	100%
<b>Mean % (SD)</b>	46% (16.2)	1% (1.3)	53% (16)	-
<b>Range</b>	20%-65%	1%-4%	35%-100%	-

<sup>1</sup>AVF, arterio-venous fistula; <sup>2</sup>AVG, arterio-venous graft; <sup>3</sup> CVC, central venous catheter; <sup>4</sup>Based on completed data from 17 units

#### 6.4.2.3 Access to vascular surgeon for creation of AVF

Dialysis units used the services of vascular surgeons based at their own hospital ( $n=8$ , 42%) or at a variety of other hospitals. Of the dialysis units that used resources located at other hospitals ( $n=11$ , 58%), two used services located in Northern Ireland. Three contracted units reported that AVF formation took place in other hospitals, but did not provide the name of these hospitals.

#### 6.4.2.4 Dedicated theatre sessions for AVF formation

Only four (21%) dialysis units (three parent hospitals and one contracted) had access to dedicated theatre time for the creation of AVFs. The number of dedicated theatre sessions ranged from 1-2 hours or one hour every other week.

#### 6.4.2.5 Infection prevention and control

Seventeen dialysis units (89%) did three-monthly MRSA screening of patients attending their units. A majority of units ( $n=16$ , 84%) reviewed bacteraemia rates on a regular basis, including: monthly ( $n=10$ ); three monthly ( $n=2$ ) and at other intervals ( $n=4$ ). Two parent hospital units with more than 60 patients and one satellite unit (< 45 patients) never reviewed their bacteraemia rates. Of those units that reviewed bacteraemia rates, 15 reviewed all types of bacteraemias; the other unit confined its review to bacteraemias caused by a specific organism.



Less than half the units ( $n=9$ , 47%) did root cause analysis for each episode of bacteraemia (four parent hospital and five contracted units), with over half these units having 60 or more patients. Five parent hospitals (60-90 patients) and two satellite units (fewer than 45 patients) never undertook root cause analysis.

The majority of dialysis units ( $n=12$ , 63%) had a surveillance programme, monitoring the incidence of infection associated with CVC (seven parent hospitals and five contracted units). Three of these units (parent hospitals) had fewer than 60 patients. A majority of units ( $n=5$ ) that did not have a surveillance programme had more than 60 patients attending their unit. The units that had surveillance programmes used either the CDC dialysis events protocol ( $n=2$ ), *S. aureus* bacteraemia surveillance ( $n=2$ ), a combination of both ( $n=1$ ) or other tools ( $n=6$ ). There was no significant association between the size of dialysis units and having a surveillance programme in place ( $p=0.29$ ) and undertaking bacteraemia reviews ( $p=0.93$ ) and root cause analysis ( $p=0.17$ ).

In suspected cases of CVC-related infection, 13 (68%) dialysis units routinely obtained two sets of blood cultures either from the CVC, dialysis circuit or peripherally. This was not routine practice for four dialysis units (three of which were parent hospitals).

#### 6.4.2.6 CVC insertion

Two parent hospital units used CVC checklists at the time of CVC insertion, three did not. A majority of units ( $n=14$ , 74%) did not know if a CVC insertion checklist was used (seven parent hospital, two satellite and five contracted units).

In total, seven units (37%) adhered to the recommendation of not routinely administering intravenous prophylactic antimicrobials prior to CVC insertion; in contrast, six (32%) parent hospital units routinely administered these agents. Furthermore, six units (one parent hospital, four contracted and one satellite) did not know if such agents were used.

Antimicrobial/antiseptic impregnated cuffed catheters were used in a minority of units (two parent hospitals and one contracted).

#### 6.4.2.7 CVC care and maintenance

A majority of units ( $n=13$ , 68%) used trisodium citrate as an antimicrobial locking agent (nine parent hospitals, two satellite and two contracted units); two of these units also used urokinase. Six units (three parent hospitals and three contracted) used heparin to lock the CVC.

All 19 units had written CVC care and maintenance guidelines; however, over half of the dialysis units ( $n=11$ , 58%) did not use care bundles in CVC maintenance. Those units that used CVC care bundles were either parent hospitals ( $n=4$ ) or contracted sites ( $n=4$ ), with a majority ( $n=5$ ) having more than 60 patients. All 19 dialysis units routinely used CVC sterile connect and disconnect packs.

The majority of units ( $n=17$ , 89%) reported the use of one registered general nurse (RGN) to connect and disconnect patients to and from dialysis. One parent hospital unit used two RGNs and one contracted unit used one RGN and one healthcare assistant to connect and disconnect patients to and from dialysis.

Three quarters of dialysis units ( $n=14$ , 74%) used 2% CHG in 70% isopropyl alcohol antiseptic solution to decontaminate catheter hubs before CVC connection and disconnection from dialysis. The remaining units used 0.5% CHG in 70% isopropyl alcohol ( $n=3$ ), 2% aqueous CHG ( $n=1$ ) or 0.05% aqueous CHG ( $n=1$ ). Similarly, 13 units used 2% CHG in 70% isopropyl alcohol to clean the CVC exit site. The other six units used alternative strengths and formulation of CHG.

It was not routine practice to apply a topical antimicrobial ointment to the CVC exit site in any of the units following CVC dressing change. For 11 (58%) dialysis units, a transparent semi-permeable polyurethane dressing was used to cover the CVC site. These dressings were changed every seven days. Two units used dry gauze dressings that were changed at every dialysis session, three units used both dry gauze and transparent dressings and three units used a dressing impregnated with CHG, which was covered with a transparent dressing.

### 6.4.3 Survey implications

This survey found that AVF prevalence in Irish dialysis units is 49%. When compared to the 12 countries participating in the Dialysis Outcomes Practice Patterns Study (DOPPS 4), in 2010, the AVF prevalence in Irish dialysis units is the second lowest, and is lower than the seven participating European countries (2010). None of the Irish dialysis units that completed the survey met the NKF-K/DOQI or UK guideline recommending AVF prevalence above 65% and 85% respectively (2006a, The UK Renal Association 2011a). There are various explanations for such a high use of CVCs (chapter 3, section 3.4).

As discussed in chapter 3 (section 3.5.1), CVCs as a permanent vascular access are considered the last resort for patients due to increased mortality and morbidity risk. The CVC prevalence of 50% among the 1370 patients in 17 units who provided the necessary data would make Ireland the second highest users of CVCs, when compared to those countries participating in DOPPS 4 (2010), and the prevalence is much higher than the 10% maximum recommended by NKF-K/DOQI (2006a).

There is a general consensus that patients should have, where possible, a functional AVF at the initiation of haemodialysis. Many guidelines recommend creating an AVF during stage 4 CKD (eGFR 15-29ml/hr) (Jindal *et al.* 2006, Tordoir *et al.* 2007, The UK Renal Association 2011a). Irish guidelines (2009) recommend that patients should have an AVF created when the eGFR is between 17-12ml/hr (between stage 4 and 5 CKD). The survey shows that only three units achieved this recommendation. AVF creation was dependent on available resources such as vascular surgery support, hospital beds and dedicated theatre time, the latter having been identified as a potential barrier to AVF creation (Lopez-Vargas *et al.* 2011). Five units acknowledged that many patients, although referred to the vascular surgeon from pre-dialysis clinics, will not have a primary AVF created prior to starting dialysis. This would support findings from the National Renal Office 2012 census survey (chapter 3 section 3.4) and DOPPS assertion that pre-emptive AVF creation is not being achieved, with a higher proportion of patients commencing haemodialysis using a permanent cuffed CVC (Rayner & Pisoni 2010, National Renal Office 2012b).

Inadequate access to vascular surgeons is considered a leading cause for the high use of CVCs (Ethier *et al.* 2008). Irish guidelines (2009) recommend that all dialysis units should have 'adequate access' to vascular access procedures; but, the definition of 'adequate access' is unclear. Although all dialysis units in the study have access to a vascular surgeon, this access does not meet the needs of those patients in need of AVF creation. This may be due to a number of factors including the current economic difficulties in Ireland, which has resulted in a reduction in healthcare expenditure, leading, in some centres, to a decrease in elective surgical procedures and an increase in waiting lists for outpatient appointments. Another explanation could be that many dialysis units lack a formalised referral programme for AVF formation, given that patients attending seven units in the study did not have the opportunity for pre-emptive AVF creation. Indeed, a lack of policy on referral of patients for AVF creation has been identified as a barrier to access creation (Lopez-Vargas *et al.* 2011). An additional possibility could be that vascular surgeons do not perceive the creation of AVFs to be important, which may account for the lack of dedicated vascular surgical theatre time for AVF formation. Involving vascular surgeons who have a willingness and ability to provide access services is one of the 11 change concepts put forward by the Fistula First Breakthrough Initiative for increasing AVFs in the United States (US) (Goodkin *et al.* 2010).

It is difficult to identify barriers to pre-emptive creation and use of AVFs within an Irish dialysis setting without information on the following timelines: patients' referral to a nephrologist; their referral to a vascular surgeon and evaluation by the vascular team; admission for AVF creation and the time from AVF creation to cannulation. Using a mixed methods approach in the collection of this data would highlight any differences between perceived timelines and actual timelines. Lopez-Vargas *et al.* (2011) note that physicians perceived prolonged waiting times for surgical appointments and vascular access placement as barriers to AVF formation; yet actual waiting times suggest differently (Lopez-Vargas *et al.* 2011). Patient preference may also act as a barrier to the creation and use of AVFs and warrants further exploration.

Recent findings from DOPPS (Rayner & Pisoni 2010, Stack 2010) suggest that inadequate access to vascular surgeons may not be the only explanation for increased use of CVCs; with the possibility that facility preference influences patient's choice of VA. Given the current economic difficulties in

the Irish health services, it might be a premature assumption to associate the high prevalence of CVCs with facility preference; however this cannot be ruled out, without a full investigation of the issue.

An important aspect in infection prevention and control in the dialysis setting is the ongoing vigilance in relation to MRSA. As outlined in chapter 3 (section 3.5.1), the relative risk of MRSA bacteraemia is higher in haemodialysis patients with CVCs than in patients with AVFs or compared to the general patient population. Reducing the number of dialysis patients colonised with MRSA will have a positive impact on bloodstream infection rates (National Clinical Effectiveness Committee 2013). Unlike other guidelines (European Renal Association 2002, Yokoe *et al.* 2008), which restrict MRSA screening to high risk patient populations, Irish guidelines (SARI 2009, National Clinical Effectiveness Committee 2013) recommend three-monthly MRSA screening of dialysis patients. The survey found high adherence to this recommendation ( $n=17$ , 89%). Surveillance of MRSA is higher in Irish dialysis centres compared to those European countries that participated in a European Practice Database audit (De Vos *et al.* 2006).

Few renal guidelines make recommendations on surveillance, review of bacteraemia rates and root cause analysis. Renal guidelines suggest auditing *S. aureus* bacteraemias and recording all details regarding catheter-related bloodstream infection (CRBSI), irrespective of causative organisms, and undertaking root cause analysis in an outbreak of CRBSI (Vanholder *et al.* 2010, The UK Renal Association 2011a). Irish guidelines recommend that dialysis units review bacteraemia rates for patients with or without CVCs on a regular basis. While the expected frequency of these reviews is not stated, over half ( $n=10$ , 53%) of the units in our survey undertake monthly reviews. Most units reviewed all type of bacteraemias ( $n=15$ , 79%).

Surveillance is an essential component of infection prevention and control programmes, aimed at preventing and controlling HCA CRBSI (Donlon *et al.* 2011). In order to improve the quality and safety of patient care, local monitoring of these infections is advocated (Health Information and Quality Authority 2009). Dialysis units are expected to put in place surveillance programmes, to determine rates and trends of HCA CRBSI (SARI 2009). Twelve dialysis units had a surveillance programme monitoring infections associated with all types of VA. Five parent hospital units did not have any

surveillance programme in place, even though they have access to onsite infection prevention and control expertise.

The absence of a surveillance programme hinders the identification of gaps in infection prevention and control practices. This absence within dialysis units surveyed may be due to a number of factors including a lack of resources, lack of suitable personnel dedicated to surveillance in the dialysis unit and a lack of suitable surveillance software. An area that needs further exploration is the scope of surveillance programmes within dialysis units, identifying any deficits and resources needed to establish such programmes. Standardising surveillance methods and programmes across dialysis units will enable national and international comparisons to be made.

It is recommended that each episode of bacteraemia, within the dialysis population, should have a root cause analysis undertaken (SARI 2009). This is not reflected across routine practice, where more than a third of units are not undertaking such an analysis ( $n=7$ , 37%), a majority of which were parent hospital units and had more than 60 patients. Failing to identify possible sources of infection and gaps in practice may hinder improvements in infection prevention and control. The size of the dialysis unit was not associated with implementing guideline recommendations related to review of bacteraemia rates, the existence of a surveillance programme or the use of root cause analysis for episodes of bacteraemia.

For patients with suspected HCA CRBSI, national guidelines (SARI 2009) suggest obtaining two sets of blood cultures, from the CVC, peripheral veins or the dialysis circuit, before commencing antibiotic therapy. This is achieved by a majority of dialysis units ( $n=13$ , 68%).

Both the Infection Disease Society of American and Irish guidelines recommend the use of CVC insertion checklist (Yokoe *et al.* 2008, SARI 2009). Such checklists are used to facilitate adherence to infection prevention and control evidence-based practices at the time of CVC insertion. Only two dialysis units used an insertion checklist; 14 (74%) did not know, which may be due, in part at least, to patients presenting to the dialysis unit with their CVC line already in place.

Although not recommended, more than a third of the units surveyed administer intravenous prophylactic antimicrobials prior to catheter insertion (Pratt *et al.* 2007, Yokoe *et al.* 2008, SARI 2009, Centers for Disease Control and Prevention (CDC) 2011). Six dialysis units were not aware if this was routine practice, therefore, practices in a substantial number of Irish units might not be in keeping with existing guidelines.

Guidelines differ on the use of antimicrobial lock solutions. While Irish (SARI 2009) and renal specific guidelines (The UK Renal Association 2011a) recommend antimicrobial locks for patients who require long term CVCs, non-renal specific catheter guidelines confine their use to patients with a history of multiple CRBSI (Yokoe *et al.* 2008, CDC 2011a). Over two thirds of units in the study routinely use trisodium citrate as an antimicrobial locking agent ( $n=13$ , 68%).

As outlined in chapter 2 (section 2.5), the use of maintenance CVC care bundles is recommended in Irish and CDC guidelines (SARI 2009, CDC 2011a). Although the use of CVC care bundles in Irish haemodialysis units has been advocated since 2009 (SARI 2009), only 8 of 19 units (42%) surveyed incorporated this intervention into their routine practice. There is a need to explore potential barriers to the implementation of CVC care bundles in dialysis settings.

National guidelines make no recommendations on the number of healthcare personnel involved in connecting and disconnecting patients to and from dialysis, which is when contamination of the CVC is the most likely to occur. There is a lack of evidence to support the premise that having two healthcare staff involved in the process is more effective in preventing infection; but one international guideline recommends that two personnel should be involved when connecting patients to the dialysis machine, so maintaining an aseptic technique (The UK Renal Association 2011a). A prospective study (Reddy *et al.* 2010) exploring the benefits of changes in Irish dialysis nursing practices (having two nurses when connecting and disconnecting dialysis patients, changing CVC lock solution from unfractionated heparin to sodium citrate and the use of valve bungs), reports a lower bacteraemia rate than that reported in other literature. However, because the study introduced a variety of different changes, it is difficult to associate a lower infection rate to one specific intervention.

Another intervention used in the prevention of CVC infection is cleansing the CVC exit site and catheter hubs with an antiseptic solution. As outlined in chapter 5 (section 5.5) renal guidelines agree on the use of a CHG antiseptic solution, but differ on solution strength and formulation. SARI (2009), guidelines recommend the use of 2% CHG in 70% isopropyl alcohol, and most units ( $n=14$ , 74%) surveyed are compliant with this recommendation. Some units ( $n=5$ , 26%) use alternative strengths and formulations of CHG. As discussed in Chapter 5, this reflects uncertainty in the research literature about the most effective ways to cleanse the CVC exit site and catheter hubs.

SARI (2009) does not recommend the use of topical antimicrobial ointments at the CVC exit site. This is in contrast to the CDC (2011) and European Renal Practice Guidelines (2010). For all dialysis units surveyed, it was not routine practice to apply a topical antimicrobial ointment.

Guidelines differ on the type of dressing to be used to cover the CVC exit site. CDC (2011) and NKF K/DOQI (2006) guidelines recommend either sterile gauze or transparent semi-permeable polyurethane dressings. SARI (2009) and Epic 2 (2007) guidelines recommend transparent dressings, with the UK Renal Association (2011) and European Renal Best Practice (2010) guidelines advocating dry gauze dressings. A majority of dialysis units ( $n=11$ , 58%) used transparent dressings, two units used dry gauze dressings and three used both dry gauze and transparent dressings. These differences in routine practices reflect the lack of evidence supporting the use of any specific type of dressing (Webster *et al.* 2011).

Although there is no renal registry in Ireland, the National Renal Office (2014) is at present introducing the National Kidney Disease Clinical Patient Management System (KDCPMS) into dialysis units in Ireland. This system will facilitate the collation of data, in real time, on a wide variety of renal practices. As a result, auditing of dialysis practices can be undertaken, thus allowing the measurement of key performance indicators; for example, vascular access prevalence, infection prevention and control practices and CVC-related infection outcomes.

A limitation of this survey is that it collected data pertaining to the type of access being used at the time of survey completion and did not seek data on patients whose AVF was maturing. Future surveys of VA prevalence would



benefit from including patients with functioning AVF; functioning AVG; maturing AVF using CVC, CVC not suitable for AVF or not willing to consent for an AVF, CVC awaiting AVF and other temporary access (as is collected in a less structured fashion by the National Renal Office Annual ESKD Census). Another limitation is the possible difference in how units interpret 'review of bacteraemia rates' and 'root cause analysis' and the survey might not have captured this variability. These issues need to be explored in more depth in future studies, including issues relating to how bacteraemia rates are audited, details of the root cause analysis process and steps taken to decrease bacteraemia rates.

## **6.5 Conclusion**

This chapter explored the literature pertaining to routine practice, its meaning and how it varied across different healthcare settings; with a particular focus on haemodialysis and infection prevention and control. Although the concept of routine practice, per se, is not defined in the literature, it is synonymous with standard of care and given the detailed discourse in this chapter it can be argued that routine practice is the provision of care that is normally provided to patients with a particular condition and is rooted in the best available evidence. This evidence may be from research or clinical guidelines. Evidence-based practice guidelines have been developed with the view of harmonising patient care and ensuring patients with similar conditions receive the same care. However, a review of the literature illustrates that such harmonisation has not been achieved, with unwarranted variation in routine practice evident across infection prevention and control and renal care practices.

CVC infection prevention and control practices varied not just in ICUs, but also in haemodialysis settings. Variation in practice included types of dressings used to cover the CVC exit site and frequency of changing the dressing. In addition, there was substantial disparity in the type of antiseptic skin solutions used to cleanse the CVC exit site. Healthcare professions used a variety of antiseptic solutions such as tincture of iodine/iodophor, povidone iodine, 70% alcohol, 0.5% CHG in 70% isopropyl alcohol, saline and chlorhexidine

sponges, even though clinical guidelines at that time recommended the use of 2% CHG. Wide variation in CRBSI<sup>1</sup> surveillance practices was also apparent.

Given that there was no published literature on routine practices in haemodialysis units in Ireland it was unclear if vascular access and infection prevention and control practices varied between haemodialysis units and whether these variations mirrored those highlighted in the literature. Undertaking the first national survey of routine practices in haemodialysis units provided an opportunity to compare vascular access and infection prevention and control practice not only to national and international clinical guidelines, but also to international research.

The national survey shows that haemodialysis routine practices in VA and infection prevention and control are generally underpinned by the best available evidence. Although national guidelines on the prevention of intravascular catheter-related infection were published in 2009, the survey clearly highlights a number of areas where practice varies between units and differed from guideline recommendations. Variations in practice included undertaking root cause analysis for each episode of CRBSI, not administering prophylactic antimicrobials prior to CVC insertion, the use of antimicrobial locks on patients with long term CVCs and the use of CVC insertion checklists and maintenance care bundles. When compared to the literature a number of similar variations in practice were identified including waiting times for the creation of an AVF and the types of dressings to cover the CVC exit site. Contrary to the literature, all dialysis units surveyed used a CHG solution to cleanse the CVC exit site. This is the antiseptic solution recommended by national guidelines; however, a particular strength and formulation of chlorhexidine gluconate is recommended (2% CHG in 70% isopropyl alcohol) and this is not reflected in the routine practice of 26% ( $n=5$ ) of units surveyed. Dialysis units used various strengths and formulations of CHG including 0.05% aqueous CHG, 0.5% CHG in 70% isopropyl alcohol, 2% aqueous CHG and 2% CHG in 70% isopropyl alcohol.

A report of the survey findings has been submitted to the National Renal Office, Health Service Executive and presented to the Clinical Director HSE National Renal Office, Dr Liam Plant and Dr Fidelma Fitzpatrick, the National Clinical Lead for the Prevention of HCAI and Antimicrobial Resistance

---

<sup>1</sup> CRBSI, Catheter-related bloodstream infections

Programme (McCann *et al.* 2012). This report was also discussed at the national HCAI implementation group and the RCPI<sup>1</sup> clinical advisory group on HCAI and AMR<sup>2</sup>. The findings were disseminated at national conference and international conferences and published in a peer reviewed scientific journal (McCann *et al.* 2013)

National and international guidelines recommend that an evidence-based approach is required in order to prevent HCAI CRBSI. Recommended strategies include the use of a particular antiseptic skin cleansing solution (CHG). Findings from the national survey and a review of the CHG literature (chapter 5) would suggest variation in the use of CHG antiseptic solution in the prevention of CVC-related infections. As discussed in chapter 5 there is a dearth of evidence-based literature on the use of CHG for the prevention of CVC-related infections in haemodialysis patients. Given the lack of evidence, a clinical trial comparing different strengths and formulations of CHG for the prevention of CVC-related infections in haemodialysis patients would contribute to the evidence-base in this area.

---

<sup>1</sup> RCPI, Royal College of Physicians in Ireland

<sup>2</sup> AMR, Antimicrobial resistance

## CHAPTER 7: TRIAL DESIGN

### 7.1 Introduction

My study is a pilot multi-centre randomised trial investigating 2% chlorhexidine gluconate (CHG) in 70% isopropyl alcohol antiseptic solution as a skin, exit site and catheter hub cleansing agent for the prevention of central venous catheter (CVC)-related infections in haemodialysis patients. The effectiveness of this antiseptic solution is compared to established routine CHG agents (0.5% CHG in 70% isopropyl alcohol and 0.05% aqueous CHG). An important aspect of this study is exploring the feasibility of undertaking the trial as a multi-national, multi-centre study and testing the trial methods.

Every effort was made to ensure that reporting of the CHG Trial reflects the CONSORT (Consolidated Standard of Reporting Trials) statement. This chapter is concerned with trial design; chapter 8 explores the methods and conduct of the trial. Also outlined is my personal interest in the trial topic, and drawing on discussions from previous chapters briefly reiterates the scientific justification for this study. The rationale for the theoretical perspective underpinning trial design including the chosen research paradigm, and approach are also discussed.

### 7.2 Background & Significance

My personal interest in the research topic stemmed from my nursing background in haemodialysis and my role as educator on a post graduate diploma in renal nursing programme. I have a particular interest in haemodialysis vascular access (McCann *et al.* 2008, McCann *et al.* 2010) and interventions used to prevent CVC-related infections (McCann & Moore 2010).

Chapter 2 (section 2.4) and chapter 3 (section 3.5.1) outline how CVCs in haemodialysis patients places this patient group at an increased risk of healthcare-associated infections (HCAI), making them more likely to experience considerable morbidity and more likely to die as a consequence of their treatment. Given the high number of haemodialysis patients in Ireland using a CVC (chapter 6, section 6.4.2.1), it is essential that infection prevention and control focuses on practices that are based on the best

available evidence as recommended in standards 2.1 and 3.1 of the *National Standards for Safer Better Healthcare* (Health Information and Quality Authority 2012). One practice is the use of antiseptic solutions for CVC hub and exit site cleansing.

As outlined in chapter 4 and chapter 5, there is a paucity of randomised trial evidence on antiseptic cleansing solutions for CVC hub and exit site care in haemodialysis patients. Only one study was identified that compared 0.5% CHG in 70% alcohol ( $n=64$ ) to a chlorine-based solution (ExSept®;  $n=55$ ) for the prevention of CVC-related infection in haemodialysis patients (Astle & Jensen 2005). No significant difference was found between the two antiseptic solutions in relation to the proportion of participants with catheter-related bloodstream infections (1/64 [1%] vs. 1/57 [2%];  $p=0.93$ ) or exit-site infections (5/64 [8%] vs. 5/57 [9%];  $p=0.85$ ).

Chapter 5 confirms the superiority of CHG over other antiseptic solutions, such as povidone iodine, as a cutaneous antiseptic solution in the prevention of CVC-related infection. There is a consensus within the literature and national and international guidelines that CHG is the optimum antiseptic for CVC hub and exit site care. Only one trial (Valles *et al.* 2008), conducted in an intensive care unit (ICU), was found that compared CHG antiseptic solutions. Valles *et al.* (2008), three-arm trial, compared 2% aqueous CHG and 0.5% CHG in alcohol to a povidone iodine solution. No significant difference was found between the two CHG solutions in the prevention of catheter-related infections.

Although a number of guidelines recommend the use of a 2% CHG in 70% isopropyl alcohol solution for the maintenance of CVCs, none of the 17 CHG trials, discussed in chapter 5, directly compared 2% CHG in 70% isopropyl alcohol to other strengths or formulations of CHG. Given the dearth of trials comparing CHG solutions, it is reasonable to state that the most appropriate and effective solution of CHG is not known. Chapter 6 (section 6.4.2.7) highlights continuing uncertainty as to which formulation of CHG is the most effective in reducing the risk of catheter-related infections, with 26% of dialysis units in Ireland using different strengths and formulation of CHG.

My PhD study is in synergy with SARI's research recommendation that promotes the investigation of the effectiveness of strategies to prevent infection (SARI 2001). In keeping with this research recommendation and given the lack of direct evidence indicating that 2% CHG in 70% isopropyl alcohol is more effective than other preparations of CHG in reducing the risk of catheter-related infections, there was a need for a randomised trial to resolve this issue.

### **7.3 Research Question**

What are the effects of 2% CHG in 70% isopropyl alcohol, as a skin, exit site and catheter hub cleansing agent, on CVC-related infections in outpatient haemodialysis patients, when compared to routinely used forms of CHG (0.05% aqueous CHG and 0.5% CHG in 70% isopropyl alcohol), with a particular emphasis on determining the feasibility of a multi-national, multi-centre study?

### **7.4 Aim of Study**

The aims of this pilot multi-centre randomised trial are twofold:

- To test the trial methods in preparation for a study to evaluate the effectiveness of 2% CHG in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent in the reduction of CVC-related infections in outpatient haemodialysis patients, in comparison to the other forms of CHG that were in routine use at the time in dialysis centres in Ireland; and
- To evaluate the feasibility of undertaking a future multi-national, multi-centre study on this topic.

The study findings are likely to need cautious interpretation because of the small size of the trial, and although capable of detecting a large effect, its primary focus is to inform the feasibility of the main study.

## **7.5 Primary Objectives**

- To compare the effects of 2% CHG in 70% isopropyl alcohol versus routine CHG solutions, on the reduction of CVC-related infections (catheter-related bloodstream infection, catheter-associated bloodstream infections and local access infection) in haemodialysis patients; and
- To explore the feasibility of undertaking this study, as a multi-national, multi-centre study.

## **7.6 Secondary Objectives**

To compare the effects of 2% CHG in 70% isopropyl alcohol to routine CHG solutions on:

- Access-associated bacteraemia;
- Vascular access infection;
- All-cause mortality;
- Patient mortality secondary to catheter-related infection;
- Adverse reactions;
- Hospitalisation;
- Catheter removal;
- Intravenous antimicrobial starts;
- Positive blood cultures;
- Time to development of first CVC-related infection;
- Time to catheter removal;
- CVC-related infection rates according to causative organism; and
- Prevalence of vascular access use.

## **7.7 Methodology**

Methodology refers to the research strategy underpinning the study design and determines the methods used to gather and analyse data. The type of methodology and methods used in a study are ultimately determined by a theoretical perspective, selected on its ability to answer the research question (Gray 2009).

### **7.7.1 Theoretical perspectives**

A research study is underpinned by a theoretical perspective that has its own philosophical stance including ontology and epistemology assumptions. Ontological assumptions are concerned with the nature of reality and existences, which can differ from one person to another. Epistemology relates to understanding the nature and ways of gaining knowledge (Rawnsley 1998, Polit & Beck 2008).

There are a number of possible epistemological positions; all are linked to a specific research theoretical perspective. Two of these positions are objectivist, linked to the positive research theoretical perspective and constructivist epistemology, which is linked to interpretivist research. Both theoretical perspectives have their place within healthcare research. It is important; however, that the theoretical perspective underpinning the design of a study is congruent, from both an ontological and epistemological point of view, with not only the study's aim and research question, but also the chosen methodology and methods (Houghton *et al.* 2012).

So, which of these philosophical stances best fits this research question? Using a deductive approach, the effectiveness of CHG solutions in preventing CVC-related infections can only be truly determined through empirical experimentation. This measures outcomes through predefined observable and measureable indicators, thus reflecting a positivist theoretical perspective, underpinned by objectivist epistemology assumptions.

### **7.7.2 Research methodology**

Given the aims of my study and the fact that the trial design was underpinned by a positivist theoretical perspective, the research methodology that best fits this perspective was a quantitative research approach (Polit & Beck 2008, Kovesdy & Kalantar-Zadeh 2012).

Quantitative research approaches can be categorised into two groups, experimental and non-experimental research. In experimental research the independent variable is actively manipulated by introducing an intervention or treatment to research participants. In non-experimental research, data are collected on the concept being investigated without actively manipulating the independent variable (Polit & Beck 2008). As my trial involved manipulation of



an intervention, measuring the effect of this intervention on participant outcomes and controlling extraneous variables, an experimental research design was best suited to achieve these aims.

### **7.7.3 True experimental design**

True experimental designs, also known as randomised controlled trials (RCTs) or clinical trials, can conclusively determine through manipulation, control and randomisation a cause and effect relationship. Given these traits the RCT is considered the gold standard in evaluating health care interventions and was the best fit for the CHG research question (Torgerson & Torgerson 2008, Schulz *et al.* 2010, Kovesdy & Kalantar-Zadeh 2012).

In such designs, researchers actively manipulate the independent variable by introducing a treatment or intervention to one group of participants (interventional group) and observing its effect on the dependent variable (outcome). Study outcomes are accurately measured and a comparison of these outcomes is then made to a control group. This comparison will determine if the intervention caused changes in, or affected, the dependent variable. This is often referred to as testing causal relationships. In order to establish causality it is important that the relationship between the independent and dependent variables cannot be explained as being caused by some other variables.

Using a control group allows for the control of as many study and participant variables as possible, eliminating many of the biases associated with non-experimental and quasi-experimental research designs. As a result, differences between intervention and control groups are attributed to a causal relationship between the intervention and study outcomes. Control groups either do not receive the intervention or receive a placebo, some other treatment or routine care.

Randomisation involves assigning participants to either intervention or control groups using random allocation. This ensures that each participant has an equal chance of being assigned to either group, thus reducing bias and increasing the likelihood of producing comparable groups. Measured and unmeasured confounding variables would, usually, be equally distributed between both groups (Polit & Beck 2006, Greene 2009).

This type of design also has a number of limitations; for example, the sample size of an RCT will determine its power and ability to adequately estimate causal relationships (Greene 2009). Another limitation includes the feasibility of applying this design to all areas of healthcare. Other limitations include the practicality of using such a design in the real messy world of clinical practice and the feasibility of controlling all extraneous variables present in an environment that is the clinical setting. A potential problem with this design is the Hawthorne effect, whereby clinical staff may provide different nursing care to those participants in the experimental group. The CHG Trial design took into account these possible limitations and set out appropriate strategies that either eliminated or minimised their effect on trial validity.

There are a number of different types of RCT designs including pretest-posttest (before and after study), factorial, crossover and parallel group designs. The parallel group design is the most commonly used design in RCTs and involves making a comparison between two or more parallel groups of participants (Parahoo 2006). The number of groups in a parallel design is determined by the purpose of the trial, although the most classic design consists of two groups. The merits of this design lie in its ability to produce reliable evidence about cause and effects, and due to its control of known and unknown confounding variables has exceptional internal validity (Torgerson & Torgerson 2008, Moher *et al.* 2010). Given the strength of this design a decision was made to use a two parallel group design for the CHG trial.

This two parallel group design, introduced the new intervention (2% CHG in 70% isopropyl alcohol) to one group of study participants (intervention group) and observed its effect on the rate of CVC-related infections, while a second group (control group) was observed while receiving 'routine practice' (Polit & Beck 2006, Gerrish & Lacey 2010). The control group's response to routine care (0.5% CHG in 70% isopropyl alcohol or 0.05% aqueous CHG) was used to evaluate the performance of the intervention on the rate of CVC-related infections (dependent variable) (Polit & Beck 2006).

#### **7.7.4 Pragmatic versus explanatory approach**

Clinical trials fall somewhere on a spectrum between a pragmatic and an explanatory approach. A pragmatic trial investigates the effectiveness of an intervention, implemented as it would normally be applied, within a clinical setting i.e. does it work under real-life conditions, what patients does it work for and how much does it cost. On the other hand, an explanatory trial determines the efficacy of an intervention under ideal conditions that are highly controlled i.e. how does it work. Consequently, both approaches reflect different attitudes to trial design (Schwartz & Lellouch 1967, Alford 2007, Torgerson & Torgerson 2008, Thorpe *et al.* 2009). As outlined in chapter 2 (section 2.3) recommendations from the Council of Europe and the European Commission recommend evaluating the real-life effectiveness of interventions that prevent the occurrence of adverse events, highlighting the need for a pragmatic trial design (Council of Europe 2006, European Commission 2008a).

Pragmatic trials seek to enrol a wide variety of participants with the condition of interest, irrespective of their co-morbidities. Typical clinical settings are included as research sites; for example, hospital centre and contracted satellite outpatient haemodialysis units. As the inclusion criteria are less restrictive, participants reflect the 'real world patient' and may be more heterogeneous when compared to participants in explanatory trials. It is not the norm to include a placebo group in a pragmatic study design, instead the comparative intervention is typically 'routine practice or care'. As outlined in chapter 6 (sections 6.2 and 6.5) routine practice is the provision of care that is normally provided to patients with a particular condition and is rooted in the best available evidence.

The primary outcome of a pragmatic design is an objectively measured outcome, which is meaningful to study participants and those clinicians who make every day healthcare decisions. Consequently, the value of a pragmatic trial is that findings are usually more generalisable. Additionally, pragmatic trials seek to inform clinicians' decision-making directly in the messy world of health care through a comparison of routine care to alternative interventions (Alford 2007, Stel *et al.* 2009, Thorpe *et al.* 2009, Zwarenstein & Treweek 2009).

There is an inherent risk of incomplete compliance to the trial protocol in pragmatic trials. Intention-to-treat analysis is used to minimise bias associated with protocol violations such as non-compliance and patients who drop out or stop receiving trial interventions. The variability inherent within this design may also reduce power, which needs to be taken into consideration when calculating sample size for such designs (Friedman *et al.* 1998, Thorpe *et al.* 2009, Zwarenstein & Treweek 2009). My trial used a pragmatic design to evaluate the effects of healthcare interventions used in 'real world' clinical conditions, in typical settings and on typical patients.

## **7.8 Clinical Trial of a Medicinal Product for Human Use**

My trial compared different strengths and formulations of CHG, for cleansing the CVC exit site of patients on haemodialysis. As solutions were applied directly on to human skin it was important to determine if the study was a clinical trial of a medicinal product for human use, as set out in the EU Clinical Trials Directives (European Community 2001a, 2001b, 2004, 2005) and Government of Ireland Statutory Instrument SI. NO 190 of 2004, which govern clinical trials in Ireland.

A medicinal product was defined as

*'any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis'* (pg L136/36)

(European Community 2004)

Given the above definition and the fact that trial interventions would be used to prevent CVC-related infections it was clearly evident that they were medicinal products for human use. What was not clear was whether the trial should be classified as a clinical trial per EU Clinical Trial Directives or as a non-interventional clinical trial, which is a study where the medicinal products are used in accordance with the terms of their marketing authorisation (European Community 2001a). My view was that the trial interventions had marketing authorisations, were used as part of routine practices in haemodialysis units

throughout Ireland (McCann *et al.* 2013) and were prescribed and used in accordance with marketing authorisation; therefore, making my study a non-interventional clinical trial. In order to clarify this issue, in November 2009, I contacted the Irish Medicines Board (IMB), the National Competent Authority responsible for the regulation of medicinal products for human and veterinary use in Ireland.

Contrary to my personal view, the medical assessment manager at the IMB, using an algorithm (appendix 7.1), determined that my trial was a clinical trial of a medicinal product for human use and within the scope of the EU Clinical Trials Directive. When I compared the CHG trial to this algorithm it was clear how the IMB came to this conclusion. The interventions in the trial were used to prevent CVC infection, had a medicine function and had an active pharmaceutical. Although trial interventions were not blood, food or cosmetic products or medical devices they were used to compare clinical efficacy and safety. Finally, while trial interventions all had marketing authorisation and were used in accordance with that authorisation, the decision to prescribe them was determined by a randomisation process, set out in the trial protocol.

The EU Directive (European Community 2001a) defines a clinical trial as

*'any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal products(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy; ...An investigational medicinal product is the pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial.*

*(pg L121/36)*

## **7.9 Implications of EU Clinical Trial Directives**

As my study was a clinical trial of a medicinal product, the planning and implementation of the trial had to be in accordance with EU Clinical Trials Directives including 2001/20/EC, 2001/83/EC and 2004/27/EC, and Government of Ireland Statutory Instrument SI. NO 190 of 2004. These set out the laws, regulations and administrative provisions relating to trial design and the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

### **7.9.1 Trial sponsor, chief investigator & principal investigator**

EU and National clinical trial legislation directs that a clinical trial must have a sponsor and each research site must have a principal investigator; where the trial involves multiple research sites a chief investigator is also required (European Community 2001a, Government of Ireland 2004).

A sponsor is responsible for the initiation, management and/or financing of a clinical trial and can be a company, organisation, institution, or an individual. In contrast, the principal investigator is the authorised healthcare professional responsible for the conduct of the clinical trial at the research site. The chief investigator, also an authorised healthcare professional, takes primary responsibility for the conduct of the trial, whether the trial takes place at a single research site or multiple sites. Legislation specifies that an authorised healthcare professional can only be a medical practitioner or a dentist. Furthermore, the sponsor and chief investigator can be the same person (European Community 2001a, Government of Ireland 2004, European Community 2005).

As medical practitioners have a primary role in this type of research, planning and implementing a clinical trial of a medicinal product for human use is very challenging for nurse researchers. Even though I developed the concept and early design of the trial, as a registered general nurse, working in a university setting, I could not act as sponsor or principal investigator for my own study. It was important to identify a medical professional who was interested and had an expertise in the research topic and methodology, and would be both approachable and supportive throughout the course of the trial. I initiated discussions with Professor George Mellotte, Consultant Nephrologist and

Medical Director of the dialysis unit at The Adelaide and Meath Hospital Dublin, Incorporating the National Children's Hospital (AMNCH), who expressed an interest in being involved in my study, at an earlier meeting. Towards the end of November 2009, Professor Mellotte agreed to act as sponsor and chief investigator (appendix 7.2). As per clinical trial legislation, all tasks and duties relating to the trial were delegated to me (appendix 7.3) (European Community 2001a, Government of Ireland 2004). Trials such as mine, which are not sponsored by or involve the pharmaceutical industry are referred to as non-commercial clinical trials or investigator-led trials (European Community 2001a).

### **7.9.2 Good clinical practice & investigational product accountability**

There is an expectation that the design, conduct, recording and reporting of a clinical trial should be in accordance with the International Conference on Harmonisation (ICH) 'Good Clinical Practice' guidelines (ICH 1996, European Community 2001a). The principles of good clinical practice require that those involved in conducting a trial should be qualified through education, training and experience, in order to perform the necessary tasks required in a clinical trial. Appendix 7.4 provides information on the specific training I received prior to and during the trial, which ensured that the CHG Trial was designed and conducted according to the principles of good clinical practice.

Good clinical practice guidelines (ICH 1996, European Community 2001a) also stipulate that responsibility for investigational product accountability can be delegated to another appropriate individual under the supervision of the investigator. I was responsible for ordering trial interventions, maintaining records of their delivery to trial sites, applying clinical trial labels on the exterior of the products and where relevant organising the destruction of unused products.

As this was a non-commercial trial involving interventions with a marketing authorisation, the CHG Trial did not require particular manufacturing or packaging processes (European Community 2001a). In addition, as interventions were used on participants with the same indication specified in its marketing authorisation, labelling of trial interventions was subject to simplified provisions laid down in the good manufacturing practice guidelines

on investigational products (European Community 2001a). Section 32 of Annex 13 of the EU Good Manufacturing Practice guide (2010) stipulates that the following information should be included in the label: name of sponsor, trial reference code allowing identification of the trial site, investigator and trial subject.

Trial interventions (ChloraPrep® with tint and Sani-Cloth CHG 2% medical device wipes) were provided free of charge by CareFusion and PDI. EU clinical trial legislation recognises that non-commercial trials, such as mine, may receive support from industry through the provision of medicinal products that are either free or at reduced cost. The provision of such supplies should not be taken to imply that industry is participating in the trial and therefore should not disqualify the trial from being regarded as a non-commercial trial (European Commission 2009).

### **7.9.3 Safety monitoring & recording**

EU and National clinical trial legislation stipulate that every effort is made to monitor the safety of medicines administered in clinical trials involving medicinal products for human use (European Community 2001a, Government of Ireland 2004). This requires ongoing safety monitoring of participants, which is also referred to as pharmacovigilance.

My trial had a number of mechanisms in place that facilitated the monitoring of participant safety. Safety monitoring involves assessing participants for adverse events/adverse reactions, evaluating their seriousness and expectedness and determining if these events should be reported to the trial sponsor and/or the national competent authority (IMB) (European Community 2001a). A Standard Operating Procedure (SOP) was developed to guide safety monitoring and reporting within the trial. Another mechanism required the establishment of a Trial Monitoring Committee.

An important component of safety monitoring is to define key terms used in the monitoring process. These key terms are adverse events, adverse reactions, serious adverse event/reaction, expectedness versus unexpectedness and suspected unexpected serious adverse reactions (SUSARs).



An adverse event is any untoward medical occurrence, in a participant who is administered an investigational medicinal product (IMP). This event does not necessarily have a causal relationship with the IMP (European Community 2001a). These events can be any sign, symptom, or disease, which is temporally associated with the use of the IMP and yet may or may not be linked to the medicinal product (ICH 1994, European Commission 2008b).

In contrast, an adverse reaction is a response to an IMP, which is noxious and unintended. This type of reaction occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease. They can also occur when used for the restoration, correction or modification of physiological function (European Commission 2008b). There is a reasonable possibility that there is a causal relationship between an IMP and an adverse event (ICH 1994).

When determining the expectedness of an adverse event, consideration should be given to the underlying condition of the subject; for example, co-morbidity and/or concomitant medications, patient population and severity and frequency of the occurrence.

An unexpected adverse event or adverse reaction is an event that is not consistent with the applicable product information e.g., summary of product characteristics and meets one of the following criteria:

- Not attributed to the underlying condition of the subject being studied;
- Not attributed to the patient population being studied;
- Not anticipated on the basis of prior experience with the drug under investigation or with related drugs;
- Not identified in the product information;
- Not defined in the study protocol.

(ICH 1996, European Commission 2008b).

Adverse events and adverse reactions can also be classified as serious. It is important to make a distinction between the terms 'serious' and 'severe'. The term 'serious' is associated with events that may threaten the functioning or life of participants. Severity on the other hand is used to describe the intensity of an event e.g., mild, moderate or severe. The event itself may be severe, but ultimately has little medical significance. Reporting of adverse events and reactions to the sponsor and/or national component authority is guided by the seriousness of the event (ICH 1994).

A serious adverse event and adverse reaction is any untoward medical occurrence or effect that at any dose:

- Results in death;
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect.

(European Commission 2006, 2008b)

An expected serious adverse event/reaction is an event that may be expected during the lifetime of the trial, when one takes into account the nature and course of the disease or condition being studied; for example, renal failure and haemodialysis and their impact on cardiac function. Expected serious adverse events in this circumstance could be death due to cardiac failure. Furthermore, serious adverse events or reaction may also be expected as a result of the medication administered in the trial.

Finally, a SUSAR<sup>1</sup> is a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information and which requires expedited reporting to the sponsor and national competent authority (ICH 1994).

While it was not anticipated that any serious events/reactions would occur it was my responsibility, as the sponsor's delegate, to ensure that all relevant information relating to a SUSAR was recorded and reported to the:

- Sponsor/Chief Investigator and Principal Investigator;
- IMB, no later than day 2 for any fatal/life-threatening SUSARs and by day 7 for any other SUSARs. This would facilitate the IMB's review and assessment of the reports, allowing some time for follow-up/clarification as necessary, prior to the IMB's subsequent submission to the EudraVigilance Clinical Trial Module (EVCTM).
- Research Ethics Committee (REC), St James's Hospital and AMNCH.

---

<sup>1</sup> SUSAR is suspected unexpected serious adverse reaction

#### 7.9.4 Type of adverse reactions expected in CHG trial

The CVC exit site of haemodialysis patients are either covered with a dry gauze adhesive dressing or a transparent dressing. Patients can complain of itchiness under the dressing, which can be due to either heat, moisture, allergy to dressing material or the solution used to clean the CVC exit site.

As discussed in chapter 5 (section 5.4) no reports of hypersensitivity reactions to CHG were reported in a 2002 meta-analysis of eight studies (4143 catheters) comparing CHG and povidone iodine antiseptic solutions (Chalyakunapruk *et al.* 2002). A critical analysis of 17 trials comparing CHG to other antiseptic agents (chapter 5 section 5.3.2) found no adverse reactions to CHG in the nine trials (1346 patients) that monitored for such reactions. However, one study (Maki *et al.* 1991) observed erythema in 45% ( $n=96$ ) of participants treated with CHG. Primary bacterial resistance and acquired resistance to chlorhexidine is rare despite its use in a wide variety of settings over a long period of time (Maki *et al.* 1991).

When ChloroPrep® with Tint (CareFusion) is used repeatedly and/or applied in an overly enthusiastic manner, especially on fragile or sensitive skin, a local skin reaction may occur. This skin reaction includes erythema or inflammation, itchy skin, dry and or flaky skin and local application site pain. Allergic or irritation skin reactions are reported to be very low (<1/10,000) for chlorhexidine, isopropyl alcohol and Sunset Yellow (E110) (a colour agent used in ChloroPrep® with Tint). These allergic reactions are similar to those outlined above (CareFusion 2010).

For the purpose of this trial, adverse reactions known to occur with CHG have been separated into the following three categories:

- Skin Sensitivity: erythema, prickling, burning or tingling sensation, tightness in skin after exposure to agent, pain or pruritus;
- Contact Dermatitis: Not associated with initial exposure, but develops after repeated contact with agent; erythematous (uniform redness of skin that blanches with pressure), oedema, blisters;
- Hypersensitivity: anaphylaxis, acute systemic and very severe type 1 hypersensitive allergic reaction.

### **7.9.5 Safety reports**

Clinical trial legislation requires the submission of a Quarterly Safety Report to the relevant research ethics committee (REC) and an annual submission of a 'Development safety update report' to the IMB and REC (European Community 2001a, Government of Ireland 2004). Additionally, an end of trial declaration form should be submitted to the IMB and the REC.

### **7.9.6 Trial monitoring committee**

Good clinical practice guidelines recommend the use of an independent Trial Monitoring Committee, also known as a data monitoring committee. I organised the formation of the Trial Monitoring Committee. The function of the Committee was to undertake an independent review of trial data, assess the progress of the trial, and advise the Trial Steering Committee on the safety of trial participants and the validity and scientific merit of continuing the CHG trial (ICH 1996, Grant *et al.* 2005). A confidential written report was to be submitted to the Trial Steering Committee concerning the continuation of the trial and whether there were any ethical or safety reasons why the trial should not continue, without revealing the un-blinded interim results unless they deemed it necessary to do so.

It is recommended that membership of such committees are independent from the trial team and include experts in trial design and statistics. There is much debate in the literature as to the degree of independence required of committee members, with some arguing for members who have no role with the trial other than being on the committee. Alternatively, others suggest that persons from the same institution or academic school can be members of the committee, as long as they have no previous involvement with the trial or have no supervisor relationship (Grant *et al.* 2005, Dixon *et al.* 2006). The Trial Monitoring Committee (TMC) comprised of three experts including a Professor of Healthcare Statistics, from the same academic school that I attended; a clinical microbiologist, who was based at one of the research sites (OA) and an expert on clinical trials methodology. The experts in statistics and microbiology had no previous involvement in this trial and were independent from the trial's research team. It is recommended that the committee is established before the trial starts and meets periodically during the course of the trial. The CHG Trial Monitoring Committee was to meet three times during the course of the Trial.

### **7.9.7 Trial protocol & standard operating procedures**

The principles of good clinical practice state that a clinical trial should be scientifically sound and described in a clear and detailed trial protocol (ICH 1996). Such a document outlines the design of the trial including trial objectives, methodology, statistical plan and how the trial should be organised. The background and rationale for the trial can also be included in the protocol (ICH 1996, European Community 2005). As per EU clinical trials legislation the term protocol also refers to successive versions of the protocol and protocol amendments (European Community 2001a). One of the benefits associated with having a predetermined outline on how the trial should be conducted is the decreased risk of undeclared post hoc changes and selective reporting of trial outcomes (Moher *et al.* 2010). In a multi-centre trial such as my study, the protocol ensures that the trial is run consistently across the three research sites. The trial protocol was developed through ongoing discourse between members of the trial's steering committee, and once agreement was reached it was then submitted to the relevant authorities for approval.

The trial protocol must be approved by the IMB and an approved REC and implementation of the trial must be in compliance with the approved protocol. Only the IMB, REC or the trial sponsor can amend the protocol. After trial approval, the sponsor can amend the protocol, and such amendments can be substantial or non-substantial. Substantial amendments must be submitted to the IMB and REC for approval (European Community 2001a, Government of Ireland 2004).

Standard operating procedures (SOPs) are written instructions on particular functions relating to the conduct of the trial, ensuring uniformity when implementing these tasks (ICH 1996). SOPs ensure that methods used in the conduct of the trial are compliant with trial protocol; they also contribute to ensuring quality control in the conduct of the trial. In accordance with clinical trial legislation (Government of Ireland 2004) seven SOPs were developed for the following areas:

- SOP01 Safety reporting;
- SOP02 Trial master file;
- SOP03 Document control;
- SOP04 Archiving of essential documents;

- SOP05 Case report form completion;
- SOP06 Participant recruitment; and
- SOP07 Informed consent.

All SOPs were reviewed, approved and signed off by the sponsor and chief investigator Professor George Mellotte.

### **7.9.8 Clinical indemnity for CHG trial**

Prior to undertaking a clinical trial, provisions must be made for indemnity cover or insurance to cover the liability of the investigator and the sponsor (European Community 2001a). National clinical trial legislation stipulates that a contract of indemnity will cover the liability of the sponsor and investigator, to provide compensation to any trial participants who as a result of the clinical trial experienced an injury, loss or death (Government of Ireland 2004).

As my trial was a non-commercial investigator-led trial, insurance coverage for trial design and conduct was another challenge that had to be addressed. In Ireland, the Clinical Indemnity Scheme (CIS) is responsible for the indemnification and management of all clinical negligence claims made in public hospitals. The CIS, operated by the State Claims Agency, a business area of the National Treasury Management Agency, also covers clinical trials (State Claims Agency 2013a). However, this cover is subject to certain criteria:

- The trial has received approval from the relevant REC;
- The trial is designed by an enterprise or any of its employees, covered by the scheme;
- Where a trial is sponsored by external organisation such as pharmaceutical companies, the CIS cover extends to treatment only and does not cover product liability or claims arising from trial design or protocol.

Taking the criteria above, both the chief investigator at site OA and the principal investigator at site OV were employees of agencies covered by the CIS and as such the cover under this scheme would extend to claims arising from trial design and conduct at these sites (State Claims Agency 2013b). However, getting my trial covered by the CIS was not an easy task. Two of the research sites were situated in public hospitals; therefore, each hospital had to request their respective hospital insurance provider to organise cover

for the trial and its investigators under the CIS (appendix 7.5). The third site, a contracted unit operated by a private company, requested their hospital insurance provider to cover the design and conduct of the trial at their site (appendix 7.6). Investigators at this site were covered by their own Medical Protection Society and the CIS, as their involvement with the contracted unit was part of their national hospital work. My role in the trial was covered by Trinity College Dublin Professional Indemnity (appendix 7.7) and Public Liability insurance cover (appendix 7.8).

### **7.9.9 Trial management**

How a clinical trial is organised is very much dependent on whether it is a commercial trial funded by the pharmaceutical industry, a trial funded by a health agency such as the Health Research Board or if the trial is a non-commercial trial such as this one (Pocock 1983). Although my study was a multi-centre trial there was no co-ordinating centre 'per se'; however, as per the EU Clinical Trials Directive (European Community 2001a), its administrative structure included:

- Sponsor/Chief Investigator: Professor George Mellotte. Consultant Nephrologist, Tallaght Hospital;
- Principal Investigator for two of the research sites: Professor Alan Watson, Consultant Nephrologist, St Vincent's University Hospital; and
- Researcher to whom all tasks and duties related to the trial have been delegated to by the Sponsor: Margaret McCann, PhD student, Trinity College Dublin.

A number of committees guided various activities in the CHG Trial:

- Trial steering committee;
- Eligibility assessment committee;
- Trial monitoring committee; and
- Outcomes assessment panel.

### **7.9.10 Management of trial documentation**

All clinical trial information should be recorded, handled and stored in a way that allows for accurate reporting, interpretation and verification (ICH 1996). Consequently, trial management also includes the safe administration of trial documentation. As per EU clinical trial legislation, SOP02 (Trial Master File) and SOP03 (Document Control), I developed and maintained a trial master

file, sponsor file and a site file for each research site. The Trial's Master File and Sponsor File will be archived in accordance with SOP04. All essential documents for the conduct of the CHG Trial are filed in the Trials Master File. These documents, individually and collectively allow for the evaluation of the conduct of the trial and the quality of the data produced (European Community 2001a).

### **7.9.11 Trial approval**

Unlike other randomised trials, a clinical trial of a medicinal product for human use must be approved by the IMB and by an approved REC (European Community 2001a).

Part of the application process requires a unique European Union Drug Regulating Authorities Clinical Trials (EudraCT) number, which was required from the EudraCT website, in March 2010. This number must be used on all documents and correspondence relating to the trial. The EudraCT is the European Clinical Trials Database for all clinical trials commencing in the European Union. An online clinical trial authorisation application form must be completed, downloaded and submitted with electronic copies to the IMB.

As per clinical trial legislation, ethical approval can only be granted by a REC authorised by the Department of Health and Children (DoHC) (Government of Ireland 2004). In addition, an application for ethical approval should be submitted to only one approved ethics committee, irrespective of the number of research sites involved in the study. This application requires the submission of a site specific assessment form signed by the principal investigator and hospital Chief Executive Officer at each research site.

### **7.10 Pilot Study**

Pilot studies are concerned with addressing questions in relation to the design and conduct of a trial, identifying potential sources of variability and bias, and ultimately the feasibility of conducting such a trial as a larger study. Prescott *et al.* (1999), in a systematic review, investigated factors that limit the quality, progress and numbers of RCTs. The review highlighted the value of pilot studies, which identified problems with trial design prior to the implementation of more expensive and larger studies.



Pilot studies can be internal or external studies. My trial was an external pilot study evaluating the feasibility of conducting a larger multi-national, multi-centre trial. An external pilot study is conducted separately from the full scale trial and informs decisions on whether it is feasible to conduct a much larger trial and what if any changes need to be made to the trial protocol. Data from external studies are not merged into the larger trial (Ravani *et al.* 2007, Friedman 2013).

My pilot study identifies areas within the design that need to be refined for the larger trial; for example, eligibility criteria and assessment, recruitment potential and the defined period of time allocated to recruitment, the informed consent process and randomisation procedures. It provides an opportunity to evaluate the adequacy of data collection tools to collect all the necessary information needed for outcome assessment (Watson *et al.* 2007, Navaneethan *et al.* 2010). The pilot trial also explores whether there is any ambiguity in relation to case definitions used to diagnose primary outcomes. In relation to retention, it gives an indication of the number of patients that may be lost to follow-up or who withdraw from the trial and why these may have occurred. This information provides some direction as to how these challenges can be addressed in the larger study (Watson *et al.* 2007, Friedman 2013).

The pilot study provides preliminary data that will allow me to estimate more reliably the event rate for the population in the larger study, which will be used to calculate its sample size. There are, however, some who criticize the use of such findings when estimating the treatment effect for the larger study, due to bias related to the limited sample size (Thabane *et al.* 2010). A number of mechanisms can be used to optimise information from my trial when calculating the sample size for the larger study. Information obtained in the pilot study can be enhanced by additional information obtained through discussions with experts in nephrology on possible effect size. Also, a sample size table, which includes a range of various effect sizes, can be created. This acknowledges the uncertainty surrounding estimates of effect, reported in this trial (Kelly *et al.* 2010, Thabane *et al.* 2010). Furthermore, the trial will provide estimates in relation to the number of patients who are potentially not eligible for the trial and the number of eligible patients who refuse consent to participate. These estimates will also be taken into consideration when calculating the sample size for the larger study.

While there is limited published literature on catheter-related infection within Irish haemodialysis settings, the pilot study provides an opportunity to report data that has been gathered within a prospective randomised trial, as opposed to observational studies. My study provides further data on vascular access use and, in particular, the use of CVCs among haemodialysis patients in Ireland.

The pilot study supports statistical analyses that would be capable of detecting large differences between the cleansing agents on infection rates and differences on other outcomes. These are important to both the larger study and the implementation of any changes to routine practice.

Finally, my pilot study refines the resources needed for the larger study such as research staff, finances, product supply, auditing of trial and setting up data monitoring and outcomes arbitrator committees (Watson *et al.* 2007). All of which leads to the refinement of the trial protocol. To sum up, the pilot study assesses feasibility, providing data needed to expand the research into a multi-national, multi-centre study, should this be deemed appropriate after this pilot trial.

Although the trial itself was a pilot study, some of the methods used (recruitment, randomisation, administration of trial interventions, recording of compliance, data collection tools) were piloted at the first research site between October and November 2010. This was to identify any major impediment to recruitment, compliance and data collection.

## **7.11 Comparative Groups**

This is a 2-arm randomised trial. It compares 2% CHG in 70% isopropyl alcohol (Chloraprep® with Tint 3ml applicator and Sani-Cloth CHG 2% medical device wipe) versus the routine antiseptic solutions used to cleanse haemodialysis patients' CVCs. Patients whose routine care is 0.5% CHG in 70% isopropyl alcohol (research site OA and OB) will be randomised to receive either 2% CHG in 70% isopropyl alcohol or 0.5% CHG in 70% isopropyl alcohol. Patients whose routine care is 0.05% aqueous CHG (research site OV) will be randomised to receive either 2% CHG in 70% isopropyl alcohol or 0.05% aqueous CHG.

The overarching comparison was 2% CHG in 70% isopropyl alcohol versus routine antiseptic solutions. However, as routine care among the three sites consists of different compositions of CHG, the trial design and protocol included a number of sub-comparisons. Altman (1991) reports that it is acceptable for a small number of sub-comparisons to be undertaken as long as it is stipulated in the trial protocol.

The trial used a 1:1 randomisation ratio with block sizes and stratification to ensure balance within each of the sub-comparisons. This allows separate analyses to be done of 2% CHG in 70% isopropyl alcohol versus the different types of routine care. The sub-comparison groups are:

- 2% CHG in 70% isopropyl alcohol versus 0.5% CHG in 70% isopropyl alcohol (research site OA and OB); and
- 2% CHG in 70% isopropyl alcohol versus 0.05% aqueous CHG (research site OV).

Primary and secondary outcomes were analysed and reported for the overarching comparison and sub-comparisons. The pilot trial does not have adequate power to detect the minimum clinically significant difference between the cleansing agents and that analyses will need to await the main study. However, the pilot trial, and the sub-comparisons mentioned above will support statistical analyses capable of detecting large differences between the agents on infection rates and differences on other outcomes (such as feasibility), which would be important to both the main study and the implementation of any changes to routine practice.

## **7.12 Validity in Clinical Trials**

One of the important aspects of a clinical trial is the inferences that can be made about cause and effect relationships. Factors such as uncontrolled extraneous variables and biases can threaten the validity of inferences, thus diminishing the credibility, generalisability and impact of trials results. Participants in studies have different characteristics, which need to be controlled in order for findings to be interpreted. Controlling these extraneous variables in this trial was achieved through randomisation using a computer generated random allocation sequence that was based on blocking and

stratification, allocation concealment using a central telephone randomisation service and statistical analysis.

Potential threats to validity need to be anticipated and strategies that either eliminate or minimise their effects incorporated into the trial design. There are various types of validity such as statistical conclusion validity, internal validity, construct validity and external validity.

Statistical conclusion validity relates to the appropriate use of statistics and whether or not variables are related to one another. Threats include violating assumptions of statistical tests, fishing for results and reliability of intervention implementation (often referred to as intervention fidelity). For this trial, strategies minimising their effect included using the right statistical test and performing it correctly. Intervention fidelity was assured by providing dialysis nurses with instruction manuals and education sessions on the implementation of trial interventions; thus, ensuring standardisation across the research sites (Polit & Beck 2008).

Although both comparison groups are initially equivalent, attrition of participants can lead to loss of comparability, resulting in differential group composition. This may be the cause of group differences on study outcome (dependent variable) as opposed to the independent variable (intervention) (Polit & Beck 2008, Torgerson & Torgerson 2008). Given the long follow-up period in the trial (12 months) there was an increased risk of attrition. If attrition was random in that those remaining in the study were similar to those dropping out then there would be no bias. During the course of the trial it was important to document attrition rates including why participants withdrew from the trial. Intention-to-treat analysis minimised bias associated with attrition rates.

Instrumentation can threaten internal validity and relates to changes in the manner in which the dependent variable is measured during the course of the trial. In the trial, an instruction manual on how to complete data collection tools was developed and this guided collection of data related to the dependent variable. In addition, I was the only person responsible for collecting the data, which eliminated any bias associated with the use of multiple data collectors (Polit & Beck 2008).

Construct validity refers to the degree to which inferences can be made from the measurements in a study. This is linked to the adequacy of instruments that measure the dependent variable. In relation to my trial, instruments used to collect data were developed by the CDC and used extensively across dialysis settings in the United States and in a number of European countries (chapter 3, section 3.5.1). Outcome measures were determined using case definitions used in research studies exploring haemodialysis CVC-related infections (chapter 3, section 3.5.1 and 3.5.3).

Another threat to construct validity is the possibility that participants' behaviour and perception of how they should behave may be influenced by their participation in the trial; this is known as the Hawthorne effect (Polit & Beck 2008). It was anticipated that this bias would be minimised through staff education and monitoring and the recording of interventions and treatments administered to participants during the course of this trial in dialysis nursing notes, monitoring sheets and trial solution record sheets.

The final type of validity is external validity, which refers to the generalisability of causal relationships to and across a similar patient population and setting and to and across different patient groups and settings (Polit & Beck 2008). The study was a multi-centre trial, which included public hospital centre dialysis units and standalone satellite units. The inclusion of such sites, which reflects the main providers of dialysis, eliminated the threat of not being able to generalise study findings to different haemodialysis settings.

Detection bias can threaten both internal and external validity and is associated with difference between groups in how outcomes are assessed (Lok & Moist 2007). This was minimised through the use of clearly defined primary endpoints and an independent microbiology assessor.

### **7.13 Blinding**

Another mechanism that reduces bias in RCTs is the use of blinding, often referred to as masking. Blinding can be defined as the non-disclosure of group assignments to one or more parties of the trial, after completion of the allocation assignment process (ICH 1996). For example, one or more of the following people may not know which treatment participants are receiving: trial members, participants, healthcare staff or those who determine that

participants have achieved a primary outcome (Viera & Bangdiwala 2007). Masking of intervention and control treatments is achieved through the use of similar packaging, colour, smell, taste etc. (Pocock 1983).

Blinding prevents bias such as ascertainment bias also known as detection, observer or assessment bias. Outcome assessors who know the allocation treatments may be biased toward one particular intervention by having a preconceived idea as to what outcomes would be expected in that group. Masking of this group removes any subjectivity they may have and enhances their objective assessment of trial outcomes (Viera & Bangdiwala 2007).

In the trial, it was not feasible to blind participants, healthcare staff or myself to the allocated assignment as ChloroPrep® with Tint 3ml applicator and Sani-Cloth CHG 2% medical device wipes differed in their physical appearance to the other forms of CHG being assessed. Creating solutions or wipes that had similar appearances was also not feasible as this would require funding that was not available for the trial; however, this will be explored for the main study whose proposal will be submitted to various funding agencies such as the Health Research Board. Consequently, my trial was an open trial.

A decision on whether a dialysis event met the criteria of a primary outcome case definition, involved some degree of clinical judgement, increasing the risk of ascertainment bias. This form of bias was minimised by utilising an assessment panel, which reviewed the evidence and provisionally determined if there was sufficient evidence to suggest that participants had achieved a primary outcome. Recognising that members of the assessment panel were not independent of the trial and in order to further reduce the risk of ascertainment bias, the provisional decisions made at the initial assessment meetings were reviewed by an independent microbiologist blind to allocation assignment.

Another strategy that could have minimised bias was the blind assessment of outcomes through the use of a blinded outcome arbitration committee, which would confirm primary outcomes for participants. This strategy was not feasible as such a committee would require resources that were not available for this trial, but will be considered when planning the larger study. However, this weakness in the design of the trial was minimised by the use of the aforementioned independent consultant microbiologist.

## 7.14 Randomisation

An adequate randomisation process is key for high quality RCTs (Moher *et al.* 2010). Using a random allocation sequence, patients in my trial had an equal and known chance of being randomly assigned to either the intervention or control group. Known and unknown confounding variables would be balanced between both arms of the trial, leading to somewhat comparable groups that would be representative of the target population, so, allowing inferences to be made (Altman 1991, Altman & Bland 1999).

Although the overall comparison in the trial was between intervention and routine care solutions, a sub-comparison was also planned. In order to facilitate this process stratified randomisation was used. This technique involved dividing the target population into two strata or subgroups, research sites that used 0.5% CHG in 70% isopropyl alcohol solution and those that used 0.05% aqueous CHG. Using these subgroups, eligible patients were randomly assigned to either the intervention or to that subgroup's routine CHG solution.

Adequate randomisation was dependent on generating a randomised sequence allocation list that was not predictable and concealing the allocation of that sequence from all those involved in the trial until after participants had been enrolled into the study. Minimising selection bias required that both strategies were planned in the design phase of the trial and implemented appropriately (Schulz & Grimes 2002a, Moher *et al.* 2010).

### 7.14.1 Generating randomised allocation sequence

A number of methods can be used to generate an allocation sequence list including repeatedly tossing a coin, random numbers table and computerised random number generator software. The sequence allocation may consist of simple or blocked randomisation (Friedman *et al.* 1998, Schulz & Grimes 2002b).

A computer randomisation software (Saghaei 2004) was used to generate the allocation sequence list for the CHG Trial (<http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html>). A separate randomised allocation sequence list, using permuted blocks, was generated according to the type of routine CHG solution used. Two sites used a 0.5%

CHG in 70% isopropyl alcohol solution; one allocation sequence list was generated and used to randomise allocation assignments at both of these sites. A second allocation sequence list was generated for the research site that used a 0.05% aqueous CHG solution. No other variables were stratified, as addressing too many variables through stratification can impact on the quality of randomisation by producing numerous strata that have too few patients and subsequently little data (Friedman *et al.* 1998). As this was a small study, fixed block sizes of 10 were used when generating the stratified random allocation sequence lists.

Equal or unequal randomisation ratios can be used when allocating patients to intervention or control groups. Those in favour of an equal ratio believe that it reflects the core values of clinical equipoise where there is an indifference towards which group patients are assigned; this is not reflected in a randomisation system that uses an unequal ratio. Consequently, an equal randomisation ratio of 1:1 was used in the CHG Trial (Friedman *et al.* 1998).

#### **7.14.2 Allocation concealment**

Allocation concealment is the second key element of the randomisation process. Allocation concealment is concerned with preventing the disclosure of forthcoming assignments (Moher *et al.* 2010). It prevents selection bias and manipulation of allocation to intervention or control groups by not disclosing the allocation assignment until after patients have been enrolled into the trial (Friedman *et al.* 1998, Odgaard-Jensen *et al.* 2011). The revealing of the random allocations in the trial was done by a central telephone randomisation service. This service was provided by the Research Office in the School of Nursing and Midwifery, Trinity College Dublin. They provided information on the allocation after the patient had given their consent and relevant information had been recorded centrally.

#### **7.15 Clinical Trial Registration**

Trial registration is described by the World Health Organisation (2013) as the publication of an internationally agreed set of information about the design, conduct and administration of a clinical trial. This information is published on web-based clinical trial registries, that are accessible to the public and



managed according to standards set by the International Clinical Trials Platform of the World Health Organisation (De Angelis *et al.* 2004).

Registration of a clinical trial prior to recruitment of the first patients is reinforced by the Declaration of Helsinki (World Medical Association 2008). Consequently, there is a moral, ethical and scientific expectation that all clinical trials are registered including pilot studies such as this trial. My trial was registered on the Current Controlled Trial website (31<sup>st</sup> August 2010), which operates the ISRCTN register. The following ISRCTN was assigned to the trial 'ISRCTN2657745'.

## **7.16 Ethical Considerations**

Protecting the well-being of patients is to the forefront of research ethics (World Medical Association 2008). In this section I explore the following core ethical principles and how they governed the conduct of the trial: clinical equipoise, respect for persons, beneficence and justice. In addition, issues relating to informed consent, confidentiality and anonymity will also be discussed.

### **7.16.1 Clinical equipoise**

RCTs are said to be ethical when clinical equipoise is obtained. Clinical equipoise is uncertainty among the expert medical community, about the benefits and harms of the arms being compared in a trial. This uncertainty is present prior to conducting a RCT (Freedman 1987). Given this uncertainty, participants would not experience relative harm from being randomised to a particular treatment arm of a trial (Fries & Krishnan 2004). Clinical equipoise is not just confined to the wider medical community, it is also found in patients who are indifferent as to which arm of the trial they are randomly assigned to and physicians who are uncertain as to which treatment is most beneficial (Freedman 1987, Ashcroft 1999, Djulbegovic & Clarke 2001).

Clinical equipoise was the driving force for undertaking my trial. Chapters 4, 5 and 6 of this thesis show the uncertainty among the wider medical and nursing community as to which strength of CHG was the most beneficial for preventing catheter-related infections in haemodialysis patients; therefore, a state of 'clinical equipoise' existed, justifying the need for an RCT. Clinical

equipoise also informs the informed consent process, whereby there is an expectation that patients are informed, prior to giving consent, of any uncertainty within the medical community as to which comparative arm is more beneficial (Freedman 1987, Djulbegovic & Clarke 2001). This influenced the type of information provided to patients eligible to participate in the trial.

### **7.16.2 Respect for persons & informed consent**

Within the Belmont Report (1979), respect for persons refers to autonomy and a person's right to enter into a research study voluntarily. A person can only make an autonomous decision once they are fully informed and have an awareness of the consequences of their decisions (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research 1979, Polit & Beck 2008, World Medical Association 2008). In this trial, the right of each haemodialysis patient to make an informed voluntary decision on trial participation, without fear of coercion either through threats to treatment or inducement through the use of monetary rewards was respected (Council for International Organisation of Medical Sciences (CIOMS) 2002).

An important component of the informed consent process is full disclosure. Patients deemed eligible for the trial were provided with written and verbal information. Written information included a letter of invite (appendix 7.9), a patient information leaflet (appendix 7.10) and copies of the informed consent form (appendix 7.11). Oral explanations, which covered the content of the leaflet and the consent form, were also provided to patients.

Patients were given seven days to review the written information and every effort was made to address any queries they or their families had during this period. As per the Good Clinical Practice guidelines, those patients who agreed to participate in the trial had to confirm their willingness to take part voluntarily in the trial by signing and dating three informed consent forms, which I co-signed. Patients were given one copy of the consent form for their own records (ICH 1996). Patients' decisions not to participate did not affect their treatment or care in any way.

Respect for persons also acknowledges that not all patients have the capacity for self-determination due to illness or mental disability (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research 1979). Recognising this difficulty, one of the eligibility criteria of the CHG Trial

required that any patients who did not have the capacity to give informed consent were to be excluded from the trial.

### **7.16.3 Beneficence**

The ethical principle of beneficence obligates researchers to do no harm, maximise possible benefits and minimise possible harms to participants (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research 1979). Although there is an expectation that research may directly benefit patients it also benefits other patients and society as a whole (Polit & Beck 2008). Foreseeable harms and inconveniences should be weighed against anticipated benefits, not just for trial participants, but also for society.

When planning the trial, anticipated benefits and harms were assessed. In relation to benefits, there was no guarantee that trial intervention or control CHG solutions used in the trial would prevent CVC-related infections. However, findings from my study may help others by contributing to the knowledge base on the strength of CHG that is the most effective in preventing such infections. In relation to harms, allergic or irritation skin reactions have rarely been reported with CHG. The CHG product Chloraprep® with Tint (CareFusion) contains alcohol. Participants assigned to receive this product were at risk of developing an allergic or irritation skin reaction to the alcohol, again the chances of this occurring were rare (<1/10,000) (CareFusion 2010).

In order to minimise harm, trial designs should include strategies that address any anticipated harms or discomforts that may occur during the study. An important component of the CHG trial involved dialysis nurses assessing participants' skin around the CVC exit site every time the catheter dressing was changed. The skin was assessed for any signs of a reaction to the solution. If participants developed a skin reaction to CHG or alcohol, the solution was discontinued, their physician informed, an alternative antiseptic cleansing agent prescribed and the event recorded in an adverse reaction form and reported to the Sponsor.

Other strategies used in the trial to minimise harm include the establishment of an independent Trial Monitoring Committee and ongoing monitoring and reporting of adverse events to the sponsor, principal investigator, the IMB and the REC.

#### **7.16.4 Justice**

The third ethical principle documented in the Belmont Report (1979) is that of justice. This ethical principle is primarily concerned with the recruitment process and the fair and equitable treatment of potential participants. The Belmont Report (1979) separates justice into two areas, individual and social.

Within this trial and in accordance with the principles underpinning a pragmatic design, the eligibility criteria were broad and directly related to those patients relevant to the topic under study and excluded patients unable to give informed consent. This ensured social justice which differentiates between classes of patients and involves selecting those patients best suited to answering the research questions as opposed to recruiting patients solely based on their vulnerability or social standing. As my trial was focused on preventing CVC-related infections, individual justice was achieved by assessing, for trial eligibility, all haemodialysis patients with permanent tunnelled cuffed catheters. An eligibility assessment panel consistently evaluated all patients with a CVC against predetermined eligibility criteria, thus, ensuring a fair and equitable recruitment process (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research 1979).

#### **7.16.5 Confidentiality and privacy**

Although not directly referred to in the Belmont Report (1979), confidentiality and privacy are important ethical issues that need to be addressed in order to protect participant dignity (World Medical Association 2008). Patient confidentiality was achieved by assigning participants a trial identification number and using that number in all CHG trial documentation. Only three documents included participants' details; signed consent forms, trial register forms and the master randomisation list. Trial documentation was only accessible to myself, the sponsor and, if required, assessors from the IMB.

Copies of source data needed for primary outcome assessment (e.g., microbiology laboratory results) were anonymised by blacking out the text in the document that related to the participant's name and medical record number. The participant's study identification code was added to these source documents. Research site confidentiality was also maintained by assigning a unique study ID number to each research site, which was used on all data collection forms.

I collected and stored all data in accordance with the 2003 Data Protection (Amendment) Act (Trinity College Dublin 2004). All hard copies were kept in a locked cabinet in a locked office. Computerised data were password protected. Data will be kept for five years from the submission date of the final report to the IMB and archived as per EU and National legislation and SOP04 (European Community 2001a, Government of Ireland 2004). Information gained from this study will be used by the researcher at a later date to expand it to a multi-national study. After this period, data will be destroyed by shredding.

## **7.17 Summary**

Using a randomised controlled design, my trial, which was a pilot study, evaluated the effectiveness of 2% CHG in 70% isopropyl alcohol solution as a skin, exit site and catheter hub cleansing agent in the outpatient haemodialysis patients. This solution was compared to other strengths and formulations of CHG routinely used in outpatient haemodialysis units. The feasibility of undertaking this study as a multi-national, multi-centre study was also evaluated. Using a pragmatic design, the trial was classed as a clinical trial of a medicinal product for human use. Consequently, the planning and implementation of the trial had to be in accordance with National and EU Clinical trial legislation. The CHG Trial was guided by the approved trial protocol and various SOPs governing different trial activities.

Trial sponsor and principal investigator roles were undertaken by medical practitioners as per EU Clinical Trial Legislation. Trial approval was sought from the IMB and an approved REC. Clinical Indemnity for the trial was obtained at each of the research sites, each one involving a different approval process. The CHG Trial was registered on the Current Controlled Trial website.

The trial was managed by the sponsor, principal investigator and me, while trial activities were guided by a trial steering committee, eligibility assessment committee, outcome assessment panel and trial monitoring committee. Its conduct was governed by a number of ethical principles, which served to ensure that participants were respected and their wellbeing protected throughout the trial.

## **CHAPTER 8: TRIAL METHODS & CONDUCT**

### **8.1 Introduction**

The methods and trial conduct of the CHG Trial are reported in this chapter, the structure of which has been guided by the CONSORT (Consolidated Standard of Reporting Trials) statement. The chapter explores issues relating to research sites, trial approval, study population, sampling, sample size and randomisation. Other issues addressed include preparation of research sites, adherence and trial compliance, and trial deviations. Outcomes, data collection and management, quality control and data analysis are also discussed. Challenges encountered during trial conduct are discussed in the relevant section of this chapter.

### **8.2 Research Sites**

The primary focus during the initial planning phase of the study was to identify dialysis units interested in participating in my trial. From September 2009 to March 2010, I held 11 'expression of interest' meetings, with clinical nurse managers and consultant nephrologists from dialysis units across Ireland. These units used 0.05% aqueous CHG, 0.5% CHG in 70% isopropyl alcohol, 2% aqueous CHG and 2% CHG in 70% alcohol isopropyl solutions.

Following the 'expression of interest' meetings, a number of units declined to participate in this trial (n=4). These units used a 2% CHG in 70% isopropyl alcohol antiseptic solution for central venous catheters (CVC) care and noted a decrease in CVC-related infection rates since introducing this solution. They expressed reservations in reintroducing an antiseptic solution (0.5% CHG in 70% isopropyl alcohol or 0.05% aqueous CHG) that they believed had a weaker effect when compared to the solution they currently used. This may pose a significant challenge to the planning of the larger study, given that SARI (SARI 2009) and UK national guidelines (Pratt *et al.* 2007, The UK Renal Association 2011a) recommend the use of a 2% CHG in 70% isopropyl alcohol antiseptic solution. For the main study, there is a high probability that dialysis centres in Ireland, Northern Ireland and the United Kingdom may use this solution and therefore be unwilling to participate in such a trial.

### **8.2.1 Potential research sites**

Of the five dialysis units (four urban and one rural) interested in participating in the trial, three units used a routine CHG solution that had a marketing authorisation licence (0.5% CHG in 70% isopropyl alcohol and 0.05% aqueous CHG). The other two units (an urban and rural unit) used a 2% aqueous CHG solution, manufactured in the United Kingdom (UK) under special licence.

I did not explore with the research sites the possibility of comparing all routine antiseptic CHG solutions at each research site. The logistics of conducting such a trial from a service provider point of view could potentially act as a disincentive to participate in the trial. Also, having multiple comparators in one busy dialysis unit could lead to confusion and forgetfulness among dialysis nursing staff, resulting in ongoing violations of the trial protocol and threaten internal validity. Costs would also increase, making the trial more expensive to run.

It would have been simpler to compare the trial intervention to one solution; for example, the most common alternative solution used in Ireland (0.5% CHG in 70% isopropyl alcohol) or the most expensive solution (2% aqueous CHG) or the solution with the largest difference in composition (0.05% aqueous chlorhexidine gluconate). None of the dialysis units were willing to standardise their routinely used CHG solution, which would have facilitated a direct comparison between the intervention solution and a comparator solution that was used across all research sites. Each unit asked that their own routinely used CHG antiseptic agent be compared to 2% CHG in 70% isopropyl alcohol.

One of the potential trial comparators (2% aqueous CHG antiseptic solution) had no marketing authorisation licence. As part of the trial approval process this comparator would require the submission of an Investigational Medicinal Product Dossier (IMPD) to the National Competent Authority (Irish Medicines Board [IMB]) (European Community 2001a, Government of Ireland 2004). This dossier includes information on the quality, manufacturing, control, chemistry and stability of the IMP. Also included are data from non-clinical and clinical studies including risk benefit assessment (Irish Medicines Board 2006). Additionally, a specific batch of the product would have to be manufactured to the requirements of the appropriate directive and prepaid in advance. Taking into account the economic climate in Ireland at that time, especially within the Health Service Executive, the amount of money tied up in stock would be



significant. These costs impacted on the feasibility of including those sites ( $n=2$ ) that used 2% aqueous CHG solution.

### **8.2.2 Confirmed research sites**

At the end of the 'expression of interest' process, three urban dialysis units agreed to participate in the CHG Trial, making this study a multi-centre trial. Each research site was assigned a facility study identification (ID) number that was used on all data collection forms related to that particular research site. Two of the research sites (OA and OV) were hospital centre outpatient dialysis units, with the third a contracted standalone satellite outpatient dialysis unit (OB). As outlined in chapter 7 (section 7.9.1), each site required its own principal investigator. The medical director of the satellite unit (OB), a consultant nephrologist at site OV, agreed to act as principal investigator at site OB and OV. The trial sponsor acted as principal investigator for site OA. The trial was conducted according to a single trial protocol.

The pragmatic design of the trial took into account the varied ways that CHG was implemented in the real world of the research sites. The overarching comparison was 2% CHG in 70% isopropyl alcohol versus routinely used CHG solutions, with sub-comparison groups comparing 2% CHG in 70% isopropyl alcohol to 0.05% aqueous CHG and 0.5% CHG in 70% isopropyl alcohol.

Details on the dialysis environment of all three research sites are provided in appendix 8.1. As discussed in chapter 3 (section 3.3), haemodialysis build guidelines (Department of Health UK 2013) recommend a minimum space of 900mm between dialysis stations in order to prevent the risk of cross-infection. Only one site (OB) met this minimum requirement.

Routine CVC care practices at all three research sites are outlined in appendix 8.2. The standard CVC lock solution was Trisodium Citrate (Duralock, MedComp®); one site (OA) used a different concentration of this solution. Given the antimicrobial properties of Trisodium Citrate (Duralock, MedComp®), this was a variable that needed to be considered when undertaking data analysis and warranted inclusion in the baseline data collection form. The types of CVC catheters used across the three units are outlined in appendix 8.3.

### **8.3 Permission to Access Research Sites**

Permission to access the research sites was granted by relevant Consultant Nephrologists, Directors of Nursing and Clinical Nurse Managers (appendix 8.4). Only one consultant refused access to their patients attending site OB and, although a reason for not granting permission was sought, none was given.

### **8.4 Trial Approval**

Formal trial approval was sought and granted by the IMB on 2 July 2010 (appendix 8.5). Ethical approval was granted by the St James's Hospital and AMNCH Joint Research Ethics Committee (REC) on 2 July 2010 (appendix 8.6).

As per EU and National Clinical Trials legislation, I had to obtain local approval from the Chief Executive Officer at each research site. This process differed between sites. At one research site (OV) I had to submit an application for trial approval to the Hospital Executive Council. This application included submitting signed permissions from different hospital departments including the human resource department, drug therapeutics committee, the data management department, which required signing a data processing agreement form and from the Director of Finance, who signed the site specific declaration form. The period of time it took to get local approval varied from one to three months.

### **8.5 Study Population**

The target population were patients over the age of 18, with End Stage Kidney Disease (ESKD), who required long term haemodialysis using permanent cuffed tunnelled CVCs and who attended for dialysis on an outpatient basis.

It was not feasible to confine the target population to patients with newly inserted CVCs as there were an insufficient number of such patients. This decision was based on the approximate number of patients in Ireland who commenced haemodialysis in 2008 (n=330) and the probability that 50% of these patients have a CVC (n=165). These estimates are based on data from

the National Renal Office (National Renal Office 2009) and PhD fieldwork, as discussed in chapter 3 (section 3.4).

Patients who have newly inserted CVCs are at increased risk of infection that is related to the insertion procedure rather than catheter care management (Guerin *et al.* 2010). In order to eliminate this risk, only patients who had their CVC inserted four weeks prior to eligibility assessment were included in the target population.

Patients requiring short term dialysis were excluded as they would not receive dialysis for the required 12 months of trial participation. Patients with non-tunnelled CVC were also excluded as this catheter requires replacement every three weeks. Patients with a particular CVC or CVC dressing that were not routinely used at the research sites were also excluded from the target population; for example, patients using femoral catheters, antimicrobial impregnated catheters or CVC dressings impregnated with CHG.

As this was a pragmatic trial no attempt was made to exclude patients who had multiple catheter insertions, previous CVC-related infections or who were on immunosuppressive therapy, all variables that may increase patients' susceptibility to infections. Information relating to these variables was collected at baseline and taken into consideration during statistical analysis.

### **8.5.1 Eligibility criteria**

Given the pragmatic design of the trial, the eligibility criteria for this study were broad and included the following characteristics:

#### **Inclusion Criteria**

- Patients over the age of 18 who require haemodialysis for ESKD;
- Patients on long term haemodialysis using a permanent tunnelled cuffed CVC; and
- Patients whose permanent tunnelled cuffed CVC were inserted at least four weeks prior to entry into this study.

#### **Exclusion Criteria**

- Patients whose CVC is used for purposes other than access for haemodialysis;
- Patients with a known allergy to any component of the interventions;

- Patients whose CVC material is not compatible with the interventions;
- Patients who are using CVCs or dressings that are not standard practice for the unit; and
- Patients who are unable to give informed consent.

## 8.6 Sampling

It is not feasible to include all of the target population; therefore, a sample of this population was selected. Using a random selection process, patients in the target population had an equal and known chance of being included in the sample (LoBiondo-Wood & Haber 2006). There was also greater confidence that this sampling technique would lead to a more representative sample that had key characteristics of the target population. This allows for inferences to be made and trial external validity to be increased (Polit & Beck 2008).

### 8.6.1 Sample size calculation

During the design phase of the trial the following statistical package <http://www.sealedenvelope.com/power.php> was used to calculate the number of patients needed in a larger study. This power sample size calculator was designed for binary outcomes in parallel group superiority trials. The percentage of patients that met the primary outcome definition is compared between the two randomised groups. The two randomised groups in this study are 2% CHG in 70% Isopropyl alcohol versus routine CHG antiseptic solutions.

In the CHG study the primary outcome event was CVC-related infection. As discussed in Chapters 4 and 5, no published studies were found that investigated similar strengths of CHG. The event rate was estimated on previous prospective studies that reported CVC-related infection rates, of between 10% and 11% (Marr *et al.* 1998, Powe *et al.* 1999). The expected event rate was estimated to be 10% for the control group. This event rate was expected to be reduced by 50% in the intervention group, giving an event rate of 5%. Significance level (alpha) was set at 0.05 and power (1-beta) was set at 80%. This power sample calculator gave a total sample size of 870 ( $n=435$  in each group). A sample size that would have an 80% chance of detecting, as significant at the 5% level, a decrease in CVC-related infections from 10% in the control group to 5% in the intervention group.

This sample size was clearly not achievable in Ireland within a reasonable period of time, as indicated in chapter 3 (section 3.4). For example, in 2009, there were 683 haemodialysis patients with CVCs in 17 dialysis units that provided this information. This figure could be potentially smaller once the number of patients who may not be eligible or who did not wish to participate in this trial were taken into account. Given that the target population in Ireland was not large enough, a multi-national trial would be needed. Consequently, this pilot study was undertaken to assess the feasibility of conducting such a multi-national, multi-centre trial.

The CHG pilot multi-centre study provides some estimates on the effect size that will allow re-calculation of the sample size. It is acknowledged that pilot studies in themselves may provide imprecise estimates of the difference in the population due to their limited sample size. However, a number of mechanisms can be used to optimise information from this trial when calculating the sample size for the larger study (chapter 7 section 7.10).

### **8.6.2 Sample size for pilot study**

For the purpose of this pilot study, it was not necessary to undertake a sample size calculation. The number of potentially eligible patients at the three research sites was approximately 180. During the recruitment period, 105 patients consented to enter the trial. In order to reach the initial target of 180 participants, given the approximate refusal rate of 30% (chapter 9, section 9.2), I would have had to approach 104 more eligible patients for a further 80 to consent to participant in this trial. As I had already approached all eligible patients at the three research sites I would have had to wait for new patients to start haemodialysis, assuming that they were commencing haemodialysis with a CVC and not an arterio-venous fistula (AVF). The implications were that recruitment would have extended to January 2012. As each participant is followed for 12 months this would have pushed back the timeline for completion of data collection until at least January 2013, which would not have been feasible for the PhD and, given that the trial was a pilot study, I made the decision to stop recruitment in September 2011.

## 8.7 Recruitment

The recruitment process consisted of three stages; eligibility screening, enrolment including obtaining informed consent, and randomisation. Initial preparation work included establishing a local eligibility assessment panel, obtaining a list of potential patients who used a CVC for haemodialysis, gathering relevant patient information that informed the eligibility assessment process, and establishing trial register forms for patients with CVCs.

Eligibility assessment panels included local trial steering committee members and me. Using trial inclusion and exclusion criteria, the panel undertook a standardised approach to eligibility assessment, upholding patient safety by identifying patients not capable of giving an informed consent and patients with a known allergy to the routine CHG, making them ineligible for the trial. The panel also identified patients with sensory deficits, enabling me to put in place the necessary strategies required for recruiting such patients, if deemed eligible.

The outcome of this assessment process was documented in patients' trial register forms. Records were kept of patients not eligible and the reasons why they were deemed not suitable. In order to ensure patient confidentiality, only patients' initials and date of birth were recorded.

When a patient was deemed eligible, the process of enrolment commenced. Patients were recruited while they received dialysis. Trial information packs were circulated, the date and time of which was documented in patients' trial register forms. As an outsider to the dialysis unit, who patients did not know, it was important that I provided some background details on myself, so putting patients at ease. I gave an outline of what was included in the letter of invite, patient information leaflet and consent form (appendices 7.9, 7.10 and 7.11).

It was important to inform patients that their own consultant supported the trial, had given me permission to discuss it with them, and was willing to randomise patients as they also had uncertainty about the effectiveness of solutions used to cleanse patients' CVCs. This reflects the clinical equipoise underpinning the study, as discussed in chapter 7 (section 7.16.1). Assessing patients' understanding of the trial and clarifying any issues or questions they may have, were important measures that ensured patients were fully informed prior to signing the consent form. Patients were encouraged to discuss trial

documentation with family members and make contact with me if they had any queries or concerns.

After a cooling-off period of at least seven days, I revisited the dialysis facility so that patients could inform me of their decision to participate in the study. Patients who agreed to participate signed three consent forms in my presence. I also signed these forms, returning one copy to the patient for their records, placing the second copy into their medical chart and keeping the third copy for the Trial Master File.

A patient's decision to participate was documented in their trial register form, and following this I assigned a trial participation number to that patient. The date and time the informed consent form was signed was also recorded. I formally entered patients into the trial by inserting their name, date of birth and trial identification number into a master trial randomisation book. Following these steps, I telephoned the central randomisation service for the allocation.

In some circumstances patients required admission during the period between eligibility assessment and the circulation of the study information pack. Once discharged from hospital I reassessed their eligibility with a member of the assessment panel. Furthermore, there were instances when patients required admission after receiving the study information pack. On discharge, I revisited these patients in the dialysis facility, distributed a fresh information pack and returned seven days later for their decision.

For patients who were eligible but refused to participate, I attempted to elicit reasons for their non-participation. This information was documented in the trial register form and in a separate electronic file.

I commenced recruitment and enrolment at each site at different periods of time, so preventing 'trial fatigue' that may have a negative impact on recruitment rates (Prescott *et al.* 1999). I updated, on an ongoing basis, the Sponsor/Chief Investigator, Principal Investigator, other members of the trial steering committee and members of nursing staff in the dialysis unit, on the outcome of the recruitment process.

At the end of the recruitment process, 201 outpatient haemodialysis patients with CVCs had been assessed for trial eligibility, and 149 (74%) of these were deemed eligible. A total of 105 patients agreed to participate in this trial, 70% of those deemed eligible (chapter 9, section 9.2).

### **8.7.1 Recruitment period & follow-up**

Recruitment and enrolment was to take place over an eight month period from October 2010 to May 2011. One of the research sites (OV) was reluctant to confirm a trial commencement date, at one stage suggesting that they withdraw from the trial. This reluctance to commit was linked to a unit-wide introduction of Trisodium Citrate (Duralock, MedComp®), an antimicrobial CVC locking agent. The renal medical team were undertaking an observational prospective study evaluating the impact this change in practice had on the unit's CVC-related infection rate. Starting the CHG trial at the same time would have introduced a confounding variable into the observational study. I was anxious not to lose the site as this would have impacted on trial numbers and, following a meeting with Professor Alan Watson and the Nurse Manager, it was agreed that my trial would commence after the other study had finished. As a result, recruitment commenced in August 2011 and continued until the end of September 2011, when all eligible patients at that site, had been approached to participate in my trial.

All participants were followed up to trial completion (12 months), primary outcome or death. Trial duration of 12 months was considered sufficient to evaluate trial interventions and their impact on primary outcomes (Samuels & Molony 2012). Data capture was completed 12 months after the last patient was recruited (September 2012).

## **8.8 Randomisation Process**

In the trial, the block stratified randomised allocation sequence was generated by computer software. Patients were deemed eligible by an assessment panel; the primary decision-makers on patient eligibility were medical and dialysis nursing staff. I was responsible for enrolling patients into the trial. Allocation assignment was made by an independent central telephone randomisation service. Putting these processes in place ensured allocation sequence was concealed until after interventions were assigned.



The independent central telephone randomisation service was provided by the Research Office in the School of Nursing and Midwifery, Trinity College Dublin. Just prior to trial commencement, administrative concerns were raised in relation to the workload involved and the feasibility of the centre facilitating this process. Following negotiation with the Head of School and Head of Administration, agreement was reached that the research centre would continue to act as the randomisation centre for the trial. However, such an arrangement would not be feasible for the main study, which would require a more flexible system. An example of such a system is the TENALEA service, which is a secure, computer-based system accessed online or by telephone. Funding for the use of such a system would need to be included in the budget for the main study

For the purpose of randomisation, a dedicated administrator from the Research Office was assigned to the trial. Both the office and administrator were independent from the trial team; preventing any manipulation during the allocation assignment process (Friedman *et al.* 1998, Torgerson & Torgerson 2008).

For the duration of the recruitment period, the stratified random allocation sequence lists including instructions outlining the steps to be taken during the randomisation process were kept in sealed labelled envelopes. These were kept in a locked desk drawer under the control of the administrator at the central randomisation office. At no time did members of the trial team have access to these lists.

The actual process of randomisation started when patients were formally entered into the trial by logging the following details in the master trial randomisation log book: their name, date of birth and trial identification number. Once this step was completed, at a pre-arranged time, I telephoned the central randomisation centre. Randomisation was then completed as per the steps set out in the randomisation process protocol (appendix 8.7). These steps provided an audit trail of the randomisation process so ensuring the integrity of the allocation process (Forder *et al.* 2005).

After randomisation, I completed the participants' baseline information form and informed participants of the solution to which they were assigned; dialysis nursing staff were also informed. The outcome of the randomisation process

was documented in participants' medical charts and dialysis folders. A site-specific log of trial participants and assigned solutions was kept at each research site. After completing the randomisation process, at the next dialysis session participants were connected and disconnected to and from dialysis using the assigned antiseptic cleansing solution.

## **8.9 Issues Related to Blinding**

Attempts were made to blind laboratory staff responsible for analysis of samples. This was achieved by ensuring that no reference to the trial or cleansing solution was made on samples or investigation request documentation. In addition, data collected as part of the trial were obtained from routine investigations of suspected infection.

The outcome assessment panel (chapter 7, section 7.13) included me and the research site principal investigator. This panel met every four months and reviewed those participants flagged as having a possible primary outcome. We reviewed anonymised copies of participants' laboratory data and medical and dialysis notes. A joint decision was made at this initial outcome assessment meeting on whether the dialysis event met the criteria of the primary case definitions.

The microbiologist reviewed participants' anonymised copies of laboratory data and medical, nursing and dialysis notes and determined whether the initial outcome assessment, met the primary case definitions. If the microbiologist did not support the initial outcome assessment this was discussed with the relevant investigator and a consensus reached between both parties. This decision trail was recorded in the 'Independent Microbiologist Review Record Sheet' (appendix 8.8).

## **8.10 Preparation of Research Site and Staff**

The success of the trial was dependent on the active participation of clinical nurse managers and dialysis nurses, and maintaining their motivation and interest for its duration. Prescott *et al.* (1999) in their review of factors that limited the progress of RCTs identified lack of trained staff and insufficient support as barriers to RCT progression, underlining the importance of

preparing dialysis nurses prior to trial commencement. Given that measures for preventing CVC-related infection were multifaceted and not solely contributed to trial interventions every effort was made, through extensive staff education and training, to standardise procedures and CVC care practices across the three research sites. This minimised differences in care that may account for variation in primary outcomes between the research sites.

Before the start of the trial, I held initial introduction sessions with dialysis nursing staff and clinicians. Issues discussed included trial procedures including recruitment, randomisation, trial interventions and their administration and trial outcomes. Staff were informed that investigations of suspected catheter-related infections were as per routine practice.

As discussed in chapter 2 (section 2.4), the WHO (2006) *Clean Care is Safer Care* programme and *the National Standards for the Prevention and Control of Healthcare-Associated Infections* (standard 6 and 11) emphasise the importance of clean hands and practice (Health Information and Quality Authority 2009). Given recent audits on hand hygiene compliance within the healthcare system in Ireland (chapter 2, section 2.4) and the suboptimal knowledge and practice of dialysis nurses in relation to CVC infection prevention and control (chapter 2, section 2.6), in-service education provided to dialysis staff took into account recommendations made by these international and national bodies.

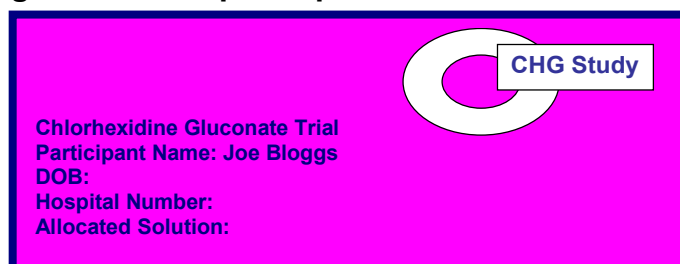
Following the initial information sessions, all dialysis nursing staff received in-service education, training and demonstrations on hand hygiene, aseptic technique, the administration of Chloraprep® with Tint 3ml applicator (CareFusion), Sani-Cloth-CHG 2% (PDI) medical device wipes and routine CHG solutions when connecting and disconnecting patients to and from dialysis and when cleaning the CVC exit site. At each research site, representatives from the company 'Iskus Health', on behalf of CareFusion, facilitated a number of workshops on Chloraprep® administration, reinforcing what was discussed in previous sessions. Where relevant, staff were also educated on the protocol governing the use of 200ml and 600ml bottles of 0.5% CHG in 70% Isopropyl alcohol. A staff manual outlining trial procedures and administration of intervention and comparator treatments was discussed and a copy provided to all dialysis nurses. These intense preparations were necessary, so minimising the occurrence of errors and differences in care that

may account for variation in primary outcomes between the research sites. Each research site was also given a CHG Trial site file (chapter 7, section 7.9.10).

Trial participants were informed that CVC dressings should only be changed by dialysis nurses. The active involvement of trial participants was important and assisted in maintaining staff awareness of the study by reminding them of the type of cleansing solution to be used for their CVCs. On completion of the overall study, participants will be informed of its findings through a patient newsletter.

Maintaining staff awareness of the trial and the solution assigned to trial participants was achieved by attaching a label to the front of participants medical/nursing and dialysis notes. This label indicated participants' assigned solution (Figure 8.1).

**Figure 8.1 Trial participant label**



Another strategy used to enhance staff awareness involved the recruitment of two members of nursing staff at each dialysis centre to act as trial advocates. Their role was to motivate and maintain an awareness of the trial among their nursing colleagues, update me on new staff joining the unit and any patients who had a CVC inserted. They were also asked to contact me with any queries that they, their colleagues or participants had in relation to the trial. As the trial was over a 20 month period, it was expected that new staff would start during that period. Newly recruited dialysis nurses were provided with the same education and training that was delivered to other members of staff. This avoided the potential influence staff turnover may have on consistency in implementing the trial protocol as witnessed in Astle & Jensen (2005) study. As discussed in chapter 5 (section, 5.3.2) their study compared 0.5% CHG in alcohol to a chlorine-based solution as CVC skin and hub cleansing agents for the prevention of CVC-related infections in haemodialysis patients.

From a trial management perspective, clear strategies were developed and communicated to dialysis nursing personnel on the management of patients admitted to their own parent hospital, admitted to a non-participating hospital or transferred permanently between research dialysis facilities.

Across the three sites there were 80 dialysis nurses involved in the trial, so it was not feasible for all of them to attend 'Good clinical practice' workshops. However, good clinical practice guidelines (ICH 1996, European Community 2001a) recommend that those delegated with the tasks and duties of the trial should explain the correct use of trial interventions to those responsible for its administration and should monitor at intervals that these instructions are being properly followed.

## **8.11 Trial Interventions**

The trial intervention was 2% CHG in 70% isopropyl alcohol. CVC care included cleansing the skin, catheter exit site and the catheter hubs when manipulating the CVC during dialysis connection and disconnection. It was, therefore, important to ensure that a 2% CHG in 70% isopropyl alcohol solution was used for all aspects of CVC care.

There were various 2% CHG in 70% isopropyl alcohol products on the market including a 200ml bottle, ChloroPrep® applicators (CareFusion) and alcoholic 2% Chlorhexidine Skin wipes; for example, clinell® (GAMA Healthcare, LTD) and Sani-Cloth CHG 2% (PDI) device wipes. Although some dialysis units in Ireland use these medical device wipes in CVC care, they do not have a marketing authorisation licence for use on human skin. The only products to have such a licence were ChloroPrep® and a 200ml bottle of 2% CHG in 70% isopropyl alcohol. In order to reduce the confounding factors associated with decanting from a 200ml bottle I made the decision to use ChloroPrep® as the trial intervention.

ChloroPrep® was available as a clear solution or a solution with an orange tint. Both solutions had marketing authorisation from the United Kingdom; however, neither had received authorisation from the IMB. At the time of trial design, ChloroPrep® with Tint was at the final stages of receiving IMB approval. EU and National clinical trial legislation (European Community 2001a, Government of Ireland 2004) permits the use of products that have

marketing authorisation in other EU countries. There was agreement between the three steering committees that ChloroPrep® with Tint would be used to clean the skin and exit site of the CVC. The ChloroPrep® applicator was not suitable for cleansing catheter material or hubs.

ChloroPrep® with Tint 3ml applicator (figure 8.2) is a pink solution, with an alcohol odour that is administered topically to cleanse participants' skin and CVC exit sites. Antimicrobial activity is maintained for at least 48 hours. The solution is an irritant to eyes and mucous membranes and should be kept away from these areas. It can cause an allergic or irritation skin reaction, but this is rare (CareFusion 2010).

**Figure 8.2 ChloroPrep® with Tint 3ml applicator**



It was important that a 2% CHG in 70% isopropyl alcohol solution was used on all aspects of CVC care. It was agreed by all three trial steering committees to use a Sani-Cloth CHG 2% medical device wipe (figure 8.3). This wipe was used for cleansing catheter hubs when connecting and disconnecting patients to and from dialysis.

**Figure 8.3 Sani-Cloth CHG 2% medical device wipes**



As outlined in chapter 7 (section 7.9.2) ChloroPrep® with tint and Sani-Cloth CHG 2% were provided free of charge. Neither company had any involvement in planning or conduct of the trial.

### 8.11.1 Control intervention

Patients in the control group received the CHG solution that was the routine antiseptic agent in their dialysis facility. These solutions were:

- 0.05% aqueous chlorhexidine gluconate (Sterets® Unisept solution Medlock Medical Ltd, 25ml individual sachet, figure 8.4).
- 0.5% chlorhexidine gluconate in 70% Isopropyl alcohol (Hydrex® Pink, ECOLAB). This solution is available in a 200ml (figure 8.5) or 600 ml bottle (figure 8.6).

**Figure 8.4 Sterets® Unisept**



**Figure 8.5 Hydrex® Pink 200ml**



**Figure 8.6 Hydrex® Pink 600ml**



All three solutions were administered topically and used to cleanse participants' skin and CVC exit sites; they were also used to cleanse catheter hubs and material.

Permission was given from pharmacy departments, clinical nurse managers or both, to use hospital supplies of the routine antiseptic solution. Supplies of control interventions were, therefore, obtained from the dialysis units stock of routine antiseptic solution.

## **8.11.2 Investigational product accountability**

### *8.11.2.1 Trial intervention*

Ordering products (ChloraPrep® with tint) that have marketing authorisation in other EU countries, but were not licensed by the IMB is problematic. An order declaration form requesting delivery of this unlicensed product to dialysis units had to be signed by the Sponsor/Chief Investigator, Professor Mellotte (appendix 8.10). Pharmacy, while not involved in ordering the product, were aware that deliveries of the product were to go directly to the dialysis unit (appendix 8.11). For each order of the product, I submitted a signed declaration order form to the Irish distributor (Medisource) of ChloraPrep®, who then shipped the product to the dialysis unit. Following IMB licensing in June 2011, ChloraPrep® with Tint 3ml applicators were ordered from Iskus Health Ltd. using a trial order form, which I developed for that purpose (appendix 8.12). I also developed a trial order form for ordering the Sani-Cloth CHG 2% medical device wipes from PDI (appendix 8.13).

A document was developed for recording receipt of trial interventions (appendix 8.14). Given that the trial was a pragmatic design, it was agreed that there was no need for special storage procedures for trial interventions beyond those outlined below:

- Trial interventions (ChloraPrep® with Tint 3ml applicator and Sani-Cloth CHG 2% medical device wipes) did not require temperature control and were isolated with regard to flammability by keeping them in a locked designated clinical trial press in the dialysis room (which is routine practice). This press was labelled 'Clinical Trials Press';
- Stock of trial interventions were stored in the clinical trials press in the dialysis unit rather than in general stores or pharmacy;
- I applied the clinical trial label to trial interventions on their arrival to the dialysis unit; and
- The control intervention was supplied by each research site's pharmacy.



Following discussions with the trial steering committees, a clinical trial label for trial interventions was developed (Figure 8.7 and 8.8). Chapter 7 (section 7.9.2) outlines the information that should be included in the label; however, it was not feasible to include all of this information on the clinical trial label.

Each box of ChloroPrep® with Tint contained 25 sterile, individual, single use, 3ml applicators. While each box of Sani-Cloth 2% CHG contained 100 individual, single use, medical device wipes. Given the volume and size of each box it was not feasible to label these per trial participant. Participants were not allowed to take these supplies home as there was a risk that the products would be stored incorrectly, the sterile packaging damaged or participants might forget to bring them to their next dialysis session. Additionally, it was not feasible to store individualised participant labelled boxes of each trial intervention, within the clinical trials press, due to the volume of box's that would result from such labelling. It was agreed that as trial interventions were individual single use products, a clinical trial label would be placed on the exterior of each box and the box contents would be used for all participants. As a result, there was no reference code to the participant on the clinical trial label.

**Figure 8.7 IMP trial label research site OA**

**For Clinical Trial Use Only**  
Chlorhexidine Gluconate Trial  
Sponsor/Principal Investigator: Prof. George Mellotte  
Researcher: Margaret McCann  
Trial Reference Code: EudraCT number 2010-019984-12;  
Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-  
2010/ SRCTN26577745

**Figure 8.8 IMP trial label research site OB & OV**

**For Clinical Trial Use Only**  
Chlorhexidine Gluconate Trial  
Sponsor/ Chief Investigator: Prof. George Mellotte  
Principal Investigator: Professor Alan Watson  
Researcher: Margaret McCann  
Trial Reference Code: EudraCT number 2010-019984-12;  
Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-  
2010/ SRCTN26577745

### 8.11.2.2 *Control intervention*

The control interventions also required labelling as indicated in Section 32 of Annex 13 of the EU Good Manufacturing Practice guide (2010). I or a delegated member of staff removed a quantity of products from the dialysis stock and applied the appropriate clinical trial label (figure 8.7 and 8.8). The quantity, batch numbers and expiration dates were recorded in documentation I developed for this purpose (appendix 8.15). Once recorded these products were then stored in the clinical trials cupboard.

### 8.11.3 **Administration of trial intervention**

Dialysis nurses cleansed participants' skin and CVC exit sites and catheter hubs using a ChloroPrep® with Tint 3ml applicator and Sani-Cloth CHG 2% medical device wipes as per the instructions set out in the staff trial manual (appendix 8.16). The frequency of cleansing CVC exit sites was patient dependent, but the norm would be three times a week if using a gauze dressing and once a week if a transparent semi-permeable polyurethane dressing was used.

During the course of the trial, two participants withdrew from the trial at research OA because ChloroPrep® with Tint stained their clothes. This problem was not anticipated and was not addressed in the summary of product characteristics. I contacted the marketing authorisation holders for ChloroPrep® with Tint to investigate if they had encountered this issue and they indicated that some patients following radiological procedures had made similar comments. The company stressed that the stain was easily removed. I was concerned that this issue might lead more participants to withdraw. I held a number of meetings with dialysis staff at research site OA and we agreed a strategy on how this issue could be addressed. This strategy was subsequently amalgamated into the information and training sessions, delivered to the two other research sites. After implementing this strategy, no further participants withdrew from the trial. However, while interviewing participants on their last day of the trial, a number did comment that the product stained their clothes, despite the preventive strategies that were put in place. The use of this product in the main study needs to be reconsidered, with the possibility of changing the trial intervention to a clear ChloroPrep® applicator. This issue could potentially be considered an adverse reaction given the distress it caused participants and was included in the analysis of CHG trial adverse reactions.

#### **8.11.4 Administration of control intervention**

At research site OV the control intervention was 0.05% aqueous CHG (Sterets® Unisept solution), which was a pink solution, available in single use individualised 25mls sterile sachets. At research sites OA and OB the control intervention was 0.5% CHG in 70% Isopropyl alcohol (Hydrex® Pink). This is a pink solution, available in a 200ml or 600 ml bottle. When planning the trial, I was faced with the challenge that while two research sites used 0.5% CHG in 70% Isopropyl alcohol (Hydrex® Pink) they both decanted this solution from different sized bottles.

Research site OA used a 200ml bottle of Hydrex® Pink and the routine practice was to leave a bottle of this solution at each dialysis station and replace when empty. This bottle was used on patients dialysed at that particular station. In order to minimise the risk associated with multiple openings on different participants, for the purpose of this trial, the research unit agreed to have one bottle assigned to each participant. It was not feasible to allow participants to bring this labelled bottle home due to the risk of contamination from participants or family members opening the bottle, young family members gaining access to the bottle and drinking its contents or participants forgetting to bring the bottle with them to the next dialysis session. In addition, making participants responsible for their own antiseptic solution bottle and having to carry it around with them could impact on their willingness to join this study. A protocol was developed for the individual use of Hydrex® Pink 200 ml bottles (appendix 8.17).

Research site (OB), used a 600ml bottle of Hydrex® Pink and it was not feasible to have an individualised bottle for each participant. Due to the costs involved, the research site was unable to change to a 200ml bottle. Recognising the infection risks associated with decanting from these bottles, every effort was made to minimise this risk by developing a protocol on their use (appendix 8.17).

Using control interventions, cleansing of participants' skin and CVC exit sites and catheter hubs were as per instructions set out in the staff trial manual (appendix 8.18). Frequency of CVC dressing changes were as outlined for the intervention group.

### **8.11.5 Standardised CVC care & maintenance**

CVC care provided to participants in intervention and control groups were in accordance with routine care, which was based on best practice guidelines. The principles of connecting/disconnecting participants to and from dialysis and caring for the exit site were similar across the three research sites (appendix 8.2). Every effort was made, through extensive staff education and training, to standardise procedures and CVC care practices across the three research sites. This minimised difference in care that may account for variation in primary outcomes between the research sites.

As discussed in chapter 2 (section 2.6) exit site care was provided by trained haemodialysis nurses, who assessed the exit site at each dressing change for signs of infection and sensitivity to trial interventions. This was then recorded in the trial solutions record sheet and the dialysis monitoring sheet, where relevant.

### **8.11.6 End of trial**

In research site OB, on trial completion, participants assigned to the intervention solution reverted back to the routine CHG antiseptic solutions used at that site (0.5% CHG in 70% isopropyl alcohol). CVC care practice remained unchanged 12 months post completion of this trial (Delos Santos 2014).

This was not the case at research site OA. When the study finished, the unit replaced the routine solution with the trial intervention. From a trial perspective, a decision had to be made as to how participants assigned to the intervention arm of the trial should be managed on trial completion. It was agreed that trial participants, with their permission, would continue to receive the trial intervention until the trial was finished at the research site. At that point, the trial intervention would become routine care for all patients attending the unit. When the study finished Sani-Cloth CHG 2% medical device wipes were introduced as the antiseptic agent for CVC exit site care and

maintenance. Since the introduction of the medical device wipe no adverse reactions were found. Although patients complained of an itchy sensation, the antiseptic agent was not discontinued. Twelve months after the completion of the trial, dialysis nurses had a continued awareness of antiseptic solutions, their correct use and enhanced problem solving in situations where patients' skin conditions did not tolerate alcohol-based antiseptic solutions. The clinical nurse manager stated that the trial re-energised nurses' interest in CVC care and maintenance and infection prevention and control. Furthermore, dialysis nursing staff were more open to monitoring infection rates within the unit (McCrohan 2014).

Research OV also changed their practice and introduced, at time of trial completion, ChloroPrep® and clinell® medical device wipes for all CVC exit site and maintenance. Since the unit-wide introduction of these solutions, one adverse reaction was observed. The unit initially used ChloroPrep® with Tint, but patients complained of the stains it left on their clothes. As a result, the unit changed over to a clear ChloroPrep® solution. This reinforces the need to use a similar solution in the main study. This change in practice initiated amendments to the CVC care and maintenance guidelines. The clinical nurse manager also commented, 12 months after the trial finished that knowledge gained from trial education sessions continued to inform dialysis nurses' CVC care practices (McQuaid 2014). Additionally, since the unit-wide introduction of 2% CHG in 70% isopropyl alcohol staff observed a noticeable decrease in the units' overall CVC-related infection rates. Prior to this change in practice, over a 19 month period, the mean number of CVC-related bloodstream infections was 2.1. Post change in practice and over a similar time period, the number of bloodstream infections associated with the use of a CVC decreased to a mean of 1.4 (Fitzgerald 2014).

## **8.12 Site-Visits**

I visited each research site twice a week during the course of the study, and more frequently during the recruitment phase. Given the trial's duration, it was important to keep staff motivated. I kept staff informed of trial progress by attending staff meetings, providing trial update sessions and, a trial update newsletter. I also sought staff feedback and any problems they or participants might have encountered. These weekly visits created a continuous awareness of the trial.

## 8.13 Compliance & Trial Deviations

Deviation from the protocol can result from participants, healthcare staff or team not adhering to procedures as outlined in the protocol. Any deviation from the intervention and/or evaluation is considered a protocol deviation. Deviations can be classified as minor or major, or a protocol violation. Minor deviations have no impact on the evaluation of the effectiveness of the intervention, a major deviation could not be prevented, while protocol violations could have been prevented and may affect study results (Pocock 1983).

A trial solutions record sheet was kept for each participant (appendix 8.19). Dialysis staff recorded the date of the dialysis session, the solution used to cleanse the CVC exit site and the solution used to connect and disconnect participants to and from dialysis. This was done for every dialysis session e.g., three times a week, for the 52 weeks that participants were on the trial.

During site visits I had the opportunity to engage with dialysis staff and monitor their compliance in completing this documentation. Dialysis nurses, who deviated from the protocol, were reminded of the importance of completing this documentation. This was achieved through face-to-face meetings and via written communication. A record was maintained of the number of dialysis sessions participants' interventions were not documented or not administered. The incidences of this type of deviation were low, making it a minor deviation that most likely did not affect the evaluation of the effectiveness of the interventions.

As noted above another type of protocol deviation that occurred related to the withdrawal of trial participants because their skin or clothes were stained as a result of the ChloroPrep® with Tint ( $n=3$ ). As part of the informed consent process participants were made aware that the solution would stain their skin, but staining of clothes was not anticipated when designing the trial. Recurrence of this type of deviation was preventable and, once highlighted was addressed (section 8.11.3). An unexpected deviation involved one participant simply requesting to come off the trial, no reason was given (participant was in the control group). All these participants were followed up to trial completion.

I kept a record of participants hospitalised or who were on holidays. It was expected that some participants would take holidays or be hospitalised during the lifetime of the trial. In these circumstances, I recorded the number of dialysis sessions participants missed. Participants who were hospitalised at non-participating sites for a considerable length of time were considered to have deviated from the trial protocol. When participants returned to the dialysis unit, their assigned solution was discontinued, but they were followed-up to trial completion.

Other participants were lost to follow-up because they transferred to another dialysis unit, were transplanted, changed their mode of renal replacement therapy to peritoneal dialysis or recovered their renal function.

As the trial was a pragmatic design, trial participants were included in the analysis of the results irrespective of their compliance to the trial protocol. This is referred to as 'analysis by intention to treat' (section 8.21.1).

## **8.14 Trial Outcomes**

As discussed in chapters 2 (section 2.4), 3 (section 3.5.1) and 5 (sections 5.3.2 and 5.6), the most clinically important outcomes for haemodialysis patients and patients in the general population with CVCs are CVC-bloodstream infections and exit site infections. In the literature these outcomes are collectively referred to as CVC-related infections, a primary outcome frequently used in studies involving patients with CVCs (Maki *et al.* 1991, Astle & Jensen 2005, Kelly *et al.* 2006, Mimosz *et al.* 2007).

The two most common and robust case definitions reported in the literature for CVC-bloodstream infections were catheter-related bloodstream infections (CRBSI) and catheter-associated bloodstream infections (CABSIs [chapter 3 section 3.5.1]). The strengths of these definitions were their clarity and lack of ambiguity (chapter 3 section 3.5.3). Taking these factors into consideration and given the recommendations made by SARI (2009) these internationally comparable case definitions were used as the trial's primary outcomes. Exit site infection case definitions vary. The most frequently used case definition within the outpatient haemodialysis population is 'local access infection' from the CDC/National Healthcare Safety Network (NHSN) dialysis event protocol (CDC/NHSN 2009).

The primary outcome set for this trial was, therefore, CVC-related infections, encompassing CRBSI, CABSIs and local access infections. It also had a number of secondary outcomes that are discussed later in this chapter.

### **8.14.1 Primary outcome case definitions**

The CONSORT guidelines stress the importance of describing case definitions underpinning the measurement of trial outcomes, indicating their origins and when they were published. Including such information improves the quality of measurement, and enables comparisons with similar studies (Lok & Moist 2007, Moher *et al.* 2010)

As discussed in chapter 3 (section 3.5.3), at the time of trial design in 2009 the most robust case definitions for catheter bloodstream infections was the Infectious Diseases Society of America 'CRBSI' (Mermel *et al.* 2009) and the CDC/NHSN 'CABSIs' (CDC/NHSN 2009). CRBSI and CABSIs case definitions are provided in tables 8.1 and 8.2. Table 8.3 outlines the case definition for local access infection as provided by the CDC/NHSN 2009 dialysis events protocol.

Using standardised case definitions ensured that I, the principal investigator, and the independent consultant microbiologist responsible for blindly assessing primary outcomes used the same definitions when classifying primary outcomes. In addition, standardised case definitions allowed me to benchmark findings from this trial against similar research that used the same case definitions.

During the course of the trial, issues emerged in relation to the suitability of the CDC/NHSN local access definition to Irish dialysis settings. The CDC/NHSN local access infection case definitions requires patients to be hospitalised or had initiation of an intravenous (IV) antimicrobial agent. Patients in Ireland with local access infection are not routinely admitted and normally receive oral antibiotics based on the culture and sensitivity of the CVC exit swab. So from a clinical perspective these patients would have a local access infection, but did not meet the CDC dialysis events specific outcomes measure. At the initial independent review of trial outcomes, the independent microbiologist suggested, that a subcategory be added to the case definition for local access infection. This subcategory would be 'Local access infection oral antimicrobial agent', with a case definition of 'pus, redness or swelling of the vascular



access site and access-associated bacteraemia was not present and patient was hospitalised or had initiation of an oral antimicrobial agent. The hierarchy of primary outcomes would not be affected by this subcategory. From an analysis perspective there would be two outcomes for local access infection; one per CDC/NHSN case definition and the second per the subcategory. In relation to a local access event, participants would only be entered into one or the other, but not both. This subcategory was analysed with the secondary outcomes.

**Table 8.1 Catheter-related bloodstream infections**

Case definition: Catheter-Related Bloodstream Infection (Mermel <i>et al.</i> 2009)
<p>For trial participants to be diagnosed with CRBSI, one of the following had to be present:</p> <ul style="list-style-type: none"> <li>• A positive result of semi-quantitative (&gt;15 CFU/catheter segment)<sup>1</sup> or quantitative (&gt;10<sup>2</sup> CFU /catheter segment)<sup>2</sup> catheter culture, whereby the same organism (species) is isolated from a catheter segment and a peripheral blood culture.</li> <li>• Simultaneous quantitative cultures of blood<sup>3</sup> with a ratio of &gt; 3:1 CFU/ml of blood (catheter vs. peripheral blood).</li> <li>• Differential time to positivity: Growth in a blood culture drawn through catheter hub is detected by an automated blood culture system at least 2 hours earlier than a simultaneously drawn, peripheral blood culture of equal volume.</li> </ul>

<sup>1</sup> Semi-quantitative catheter segment cultures involve the sterile removal of a 5cm segment of the catheter; in the laboratory the specimen is rolled across a blood agar plate and incubated. The criteria for positivity are measured in colony forming units (CFU).

<sup>2</sup> Quantitative catheter segment cultures involve the sterile removal of a segment of the catheter; in the laboratory the catheter is flushed with broth or sonicated in broth followed by serial dilutions, surface plating on blood agar and incubation. Criteria for positivity are similar to the semi-quantitative approach.

<sup>3</sup> Quantitative blood culture involves a comparison between the colony count of microbes grown from blood obtained through the catheter hub and the colony count of microbes grown from blood obtained from a peripheral sample (SARI 2009).

**Table 8.2 Catheter-associated bloodstream infections**

<b>Case Definition</b>
<b>Laboratory Confirmed Primary Bloodstream Infection (Primary BSI) Catheter-Associated Bloodstream Infection (CABSII)</b>
Laboratory confirmed primary bloodstream infection (LCBI criteria 1 and 2) may be used for patients of any age, including patients $\leq 1$ year of age.
A CABSII is a primary BSI in a patient that has a central line within the 48-hour period before the development of the bloodstream infection.
For participants in this trial to be diagnosed with a CABSII they must meet at least one of the following criteria:
<b>Criteria 1:</b> Patient has a recognised pathogen cultured from one or more blood cultures <b>and</b> Organism cultured from blood is not related to an infection at another site.
<b>Criteria 2:</b> Patient has at least one of the following signs or symptoms: fever ( $>38^{\circ}\text{C}$ ), chills, or hypotension <b>and</b> Signs and symptoms and positive laboratory results are not related to an infection at another site <b>and</b> Common skin contaminant (i.e., diphtheroids [ <i>Corynebacterium</i> spp], <i>Bacillus</i> [not <i>B anthracis</i> ] spp, <i>Propionibacterium</i> spp, coagulase negative staphylococci [including <i>S epidermidis</i> ], viridans group streptococci, <i>Aerococcus</i> spp, <i>Micrococcus</i> spp) is cultured from two or more blood cultures drawn on separate occasions.
<b>Notes</b> In criterion 1: <ul style="list-style-type: none"><li>• The phrase '1 or more blood cultures' means that at least 1 bottle from blood drawn is reported by the laboratory as having grown organisms (i.e., is a positive blood culture).</li><li>• The term 'recognised pathogen' does not include organisms considered common skin contaminants (see criteria 2 and 3 for a list of common skin contaminants).</li><li>• A few of the recognised pathogens are <i>Staphylococcus aureus</i>, <i>Enterococcus</i> spp, <i>Escherichia coli</i>, <i>Pseudomonas</i> spp, <i>Klebsiella</i> spp, <i>Candida</i> spp, and others.</li></ul> In criteria 2: <ul style="list-style-type: none"><li>• The phrase '2 or more blood cultures drawn on separate occasions' means (1) that blood from at least 2 blood draws were collected within 2 days of each other (e.g., blood draws on Monday and Tuesday or Monday and Wednesday would be acceptable for blood cultures drawn on separate occasions, but blood draws on Monday and Thursday would be too far apart in time to meet this criterion) and (2) that at least 1 bottle from each blood draw is reported by the laboratory as having grown the same common skin contaminant organism (i.e., is a positive blood culture).</li><li>• A blood culture may consist of a single bottle for a paediatric blood draw because of volume constraints. Therefore, to meet this part of the criterion, each bottle from 2 or more draws would have to be culture positive for the same skin contaminant.</li></ul>

**Table 8.3 Local access infection**

Case Definition
Local Access Infection (CDC/NHSN 2009)
For participants in this trial to be diagnosed with a local access infection they must meet the following criteria: <ul style="list-style-type: none"><li>• Pus, redness or swelling of the vascular access site and access-associated bacteraemia was not present <b>and</b> patient was hospitalised <b>or</b> had initiation of an IV antimicrobial agent.</li></ul>

### **8.14.2 Diagnostic methods used to assess CRBSI & CABS**

In pragmatic trials, primary outcomes are usually objectively measured and assessed under usual conditions, therefore data are collected on diagnostic tests that are normally conducted to diagnose CVC-related infections (Thorpe *et al.* 2009). In an ideal world it would be better to have all diagnostic tests done in one laboratory so avoiding any discrepancy that may arise using multiple laboratory departments (Pocock 1983). However, this a multi-centre pragmatic trial based in the real world of clinical practice where samples at each site were sent to their own respective laboratory. Research site laboratories have SOPs governing their practice, ensuring quality control over their procedures and guaranteeing satisfactory results in their laboratory. At time of trial design research site OV was CPA (Clinical Pathology Accreditation) accredited. Research site OA had no accreditation.

Clinical findings alone, due to their poor sensitivity<sup>1</sup> and specificity<sup>2</sup>, were not sufficient or reliable for diagnosing CRBSI (Mermel *et al.* 2009, SARI 2009). A diagnosis of CRBSI was dependent on a number of measures including culturing the tip of the CVC and blood cultures (chapter 3, section 3.5.3). The semi-quantitative CVC tip culture was the method used to diagnose CRBSI at research sites laboratories. The routine use of the quantitative culture method was not recommended by laboratory SOPs, as it was labour-intensive and time consuming.

Blood cultures are used to diagnose both CABS and CRBSI (chapter 3, section 3.5.3). The blood culture method used at each research site laboratory was a qualitative blood culture method<sup>3</sup>, using samples obtained via the CVC

---

<sup>1</sup> Sensitivity is the ability to correctly identify those who have the condition.

<sup>2</sup> Specificity is the ability to correctly identify those who do not have the condition.

<sup>3</sup> Qualitative blood culture through the device requires that one or more conventional blood cultures are drawn through the device and criteria for positivity is any growth.

and/or dialysis circuit. This method, while appropriate for the diagnosis of CABSIs did not meet the requirements of the case definition for CRBSI.

Within the literature, the terms CABSIs and CRBSIs are frequently used interchangeably, even though their meanings differ. It was important therefore that their meanings were clearly differentiated. Given that quantitative and differential time to positivity blood cultures were not conducted at the research site laboratories, a definitive diagnosis of CRBSI could only be made when the CVC was removed and the tip sent for appropriate culturing. A CVC may be the participant's only form of vascular access for haemodialysis and every effort was made to avoid removing it. As a result, in a number of cases, trial participants were diagnosed with a CABSIs, but a diagnosis of CRBSI could not be made as the catheter was not removed and the necessary CVC tip diagnostic methods could not be undertaken.

### **8.14.3 Secondary outcomes**

Secondary outcomes included CDC/NHSN access-associated bacteraemia and vascular access infection, CDC/NHSN dialysis events (hospitalisations, IV antimicrobial starts and positive blood cultures), mortality all-cause, infection-related and catheter infection-related, adverse reactions (chapter 7, section 7.9.4), catheter removal, time to CVC-related infection, time to CVC-removal, CVC-related infection rates according to causative organism and prevalence of vascular access. While these outcomes are not as important as the primary outcome set they are meaningful to participants, resulting in considerable morbidity and may have a negative impact on quality of life.

The CDC/NHSN (CDC/NHSN 2009) was the only organisation to develop case definitions associated with dialysis events related to vascular access use, including CVC use (Table 8.4). These events were specific to patients attending outpatient haemodialysis settings. When compared to inpatients, those attending for outpatient haemodialysis are exposed to fewer diagnostic tests and clinical assessments are less detailed. The dialysis events protocol was therefore designed in such a manner to ensure ease of use, requiring no extensive training of clinical personnel.

**Table 8.4 CDC/NHSN dialysis events outcomes & events**

<b>Case Definition</b>
<b>CDC/NHSN Dialysis Events Outcomes and Dialysis Events (CDC/NHSN 2009)</b>
<p><b>Access-associated bacteraemia</b></p> <ul style="list-style-type: none"><li>• Positive blood culture with source identified as the vascular access site or unknown.</li></ul>
<p><b>Vascular access infection</b></p> <ul style="list-style-type: none"><li>• Either local infection or access-associated bacteraemia.</li></ul>
<p><b>Hospitalisation</b></p> <ul style="list-style-type: none"><li>• The patient stayed overnight in a hospital, regardless of cause. Each time a patient was hospitalised (no matter how soon after the last hospitalisation), it was considered a new event.</li></ul>
<p><b>IV antimicrobial starts</b></p> <ul style="list-style-type: none"><li>• Includes all IV antimicrobial starts not in use for the previous 3 weeks. If the patient was given IV antimicrobial agents in the dialysis unit for any reason, not just those with vancomycin or for a vascular access problem. If IV antimicrobials were stopped for less than 21 days and then restarted, this is NOT considered a new event. However, if IV antimicrobials are stopped for ≥ 21 days and then restarted, this is considered a new event.</li></ul>
<p><b>Positive blood culture</b></p> <ul style="list-style-type: none"><li>• Includes all patients with a positive blood culture occurring 21 days or more after a previous positive blood culture, even if they did not have an associated hospitalisation or in-unit IV antimicrobial start.</li></ul>

#### **8.14.4 Outcome reporting requirements**

Numerator and denominator data were required in order to report primary and secondary outcome events. Numerator data are the number of participants with the condition being measured and denominator data are the number of the total population from which the numerator data are being collected.

CRBSI and CABSIs are normally associated with line days for denominator data (CDC/NHSN 2009, Mermel *et al.* 2009). This requires counting the number of patients with a CVC at the same time each day, for the duration of the study. As discussed in chapter 3 (sections 3.5.3 and 3.8) the collection of such data is not suited for an outpatient haemodialysis setting as patients attend the unit on alternative days. It would require the presence of a data collector, every day, at each research site for the duration of the trial. It would also result in the collection of a vast amount of data. A less labour-intensive method, that best suits the use of such rigorous case definitions, within a robust randomised trial such as this one, is the reporting of CRBSI and CABSIs event rates per 100 patient-months.

Primary and secondary event rates were reported per 100 patient-months. The CDC/NHSN (2009) has specific numerator and denominator data requirements for outpatient haemodialysis patients. A modified version of the CDC/NHSN 'Denominators for Outpatient Dialysis Census Form' was used to collect data on the number of chronic haemodialysis patients, according to vascular access type, who received dialysis at each research site (appendix 8.20). These data were collected during the first two working days of the month and used to estimate the number of patient-months. Only chronic haemodialysis outpatients were included. Throughout the course of the trial, participants' dialysis events were recorded in a modified version of the CDC/NHSN dialysis events form (appendix 8.21).

Event rate per 100 patient-months was calculated by dividing the number of events by the number of patients-months and multiplying the result by 100 (CDC/NHSN 2009). Normally, these rates would be stratified by vascular access type and compared to the mean rate reported from other centres. However, as this trial focused on participants with CVCs, primary and secondary event rates were only reported as they pertained to CVC access.

#### **8.14.5 Monitoring for primary & secondary outcomes**

Assessment of outcomes was undertaken throughout the course of the trial. When a CABSIs was suspected, blood cultures were obtained by healthcare staff as per hospital policy and sent to the local laboratory for analysis. This was noted in the dialysis monitoring sheet, the trial solution record sheet or the nursing notes section of the dialysis software and/or medical and nursing notes. The site from which the blood culture was taken was also recorded (peripheral, central venous catheter, or dialysis circuit).

At each CVC dressing change the dialysis nursing staff assessed the CVC exit site for signs of infection in accordance with CDC/NHSN (CDC/NHSN 2009) dialysis events outcomes measures for local access infection. An abnormal exit site appearance was documented in the relevant documentation. If an exit site infection was suspected, exit site swabs were obtained and sent to the local laboratory for analysis. This was also recorded.

Dialysis nursing staff, as part of their routine pre-dialysis patient assessment, recorded the following information: participants' visits to their general practitioner (GP), other medical visits and any medications prescribed to them e.g., antibiotics. On each site-visit I monitored trial participants' dialysis monitoring sheets, trial solutions record sheets, nursing notes, medical notes and pharmacy order forms for any events that may be associated with CVC-related infections.

I monitored laboratory, radiology and admissions databases monthly in order to identify episodes of infection and hospitalisation that would be relevant to trial outcomes. When an event was flagged, data relating to that event was collected using the modified version of the CDC/NHSN Dialysis Event Form (CDC/NHSN 2009). In the case of a suspected primary outcome, I photocopied and anonymised relevant laboratory data and medical, dialysis and nursing notes relating to the suspected outcome.

## **8.15 Data Collection**

Data collection tools used in the trial included:

- Trial register form (appendix 8.22), completed for all patients with a CVC. The outcome of the eligibility, recruitment and randomisation process, where relevant, was recorded in this document;
- Baseline assessment form (appendix 8.23), completed for participants post randomisation. This document collected information on co-morbidities associated with the increased risk or susceptibility for infection;
- Case report forms, recorded all of the protocol required information that had to be reported to the trial sponsor (ICH 1996). For the purpose of this trial, this was in paper format;
- CDC/NHSN modified dialysis event forms;
- Adverse event form (appendix 8.24);
- Adverse reaction form (appendix 8.25); and
- CDC/NHSN modified denominator for outpatient dialysis census form;
- Trial solutions record sheets.

### **8.15.1 Development & completion of data collection forms**

It is acknowledged that well designed collection forms decrease errors and variability. Every effort was made to either use existing forms proven to be effective in the haemodialysis environment or develop data collection forms that were short, simple and consisted of a logical sequence of questions, which required little 'write in' answers, relying instead on box's being ticked (Hosking *et al.* 1995, Friedman *et al.* 1998). Good clinical practice guidelines informed the development of a trial eligibility register form, consent form, case report form and adverse event and adverse reaction forms (ICH 1996). All data collection forms were pretested during the first two months of trial commencement, at research site OA.

In order to capture data relevant to the primary and secondary outcomes, I modified the CDC dialysis events data collection form and data collector's instruction manual. The following information was added subclavian insertion site, sources of positive blood culture, stop date for IV antibiotics and types of adverse reactions. This form was further modified following feedback from the IMB. Prior to trial commencement, the dialysis events form was successfully pretested in a surveillance project involving a large Dublin outpatient haemodialysis unit (Bajwa *et al.* 2012). For the purpose of the main trial, I would modify the layout of the form, adding tick boxes for access-associated bacteraemia and vascular access infection outcomes.

The baseline assessment form took into consideration variables that may increase participants' susceptibility to infections, which may influence the effects of trial solutions (chapter 3, section 3.5.1 and 3.5.2). Age is reported as the year of participants' age when they entered this study, no matter how many months they are into that year. Development of this form was guided by reviewing literature on the subject matter, as discussed in Chapter 3. In addition, feedback on the appropriateness of this form was sought from both principal investigators and academic professors with research expertise in clinical trials.

Every effort was made to obtain complete baseline data, but some participants' renal medical history went back a number of decades. Information relating to the aetiology of renal disease was not available for some participants and was recorded as unknown. For a small number of participants, the year they started haemodialysis was documented, but not the



exact commencement date. In these circumstances, the year dialysis commenced was recorded. Information on the exact number of CVC insertions and previous CVC infections was not available for a small number of participants; again these events were recorded as unknown. I experienced no difficulty in completing the baseline data collection form. However, in hindsight I would question the usefulness of collecting data on the type of dressing used to cover the CVC exit site and recommend that this be removed for the main trial.

In consultation with dialysis nurse managers, I developed a trial solutions record sheet. This form was completed by dialysis nurses at every dialysis session. Dialysis nurses recorded the solution they used to connect and disconnect participants to and from dialysis, and the solution used to cleanse the CVC exit site. The form also collected data on the CVC locking agent, if blood cultures were taken, blood culture site, the appearance of the CVC exit site (normal or abnormal) and if IV or oral antibiotics were prescribed. This form was pretested at research site OB before the start of the trial.

In relation to research site OA, the daily dialysis monitoring sheet was modified to include all of the above information. Nurse Managers' believed that documenting this information was important in monitoring quality of dialysis care. Agreement on the layout of this form was reached in August 2010. This new dialysis monitoring sheet was piloted by the unit and approval for its use was sought from the hospitals documentation committee. Two months after the trial started (December 2010); this committee recommended the removal of information relating to trial solutions; as this was not standard care provided by the unit. Given these changes to the dialysis monitoring sheet, I developed a new trials solutions record sheet for this site, similar to that used at research site OB and OV. I provided dialysis nurses with information and instructions on how to complete this new trial solutions record form before introducing this document into the unit.

Reflecting back on this experience, when initially planning the verification process for administration of trial solutions, I was anxious not to cause any extra workload for dialysis nurses, believing that this might cause a negative attitude to this trial. Although the dialysis monitoring sheet at research site OA was only used for the first three months of this trial, using this approach created extra workload for me, in that I had to transfer data from the dialysis

monitoring sheets into a trials solutions record folder. Looking back on the process of developing this verification form, I believe I lost sight of what was important for the smooth running of the trial. The lesson learned from this experience, which will inform my planning of the main trial, is the need to develop a standardised trial solutions record sheet that can be used across multiple sites.

### 8.15.2 Data collection interval

Table 8.5 and 8.6 outline the intervals for data collection.

**Table 8.5 Data collection intervals per research site**

Data Collection Interval (Per Research Site)			
	Baseline	Monthly	End of Study
Denominator for outpatient dialysis census form	√	√	√

**Table 8.6 Data collection intervals per trial participants**

Data Collection Interval (Participant)				
	Baseline	Weekly	Monthly	End of Study
Study register form	√			
Baseline information form	√			
Case report form	√		√	√
Dialysis event form		√	√	√
Adverse events form			√	√
Trials solution record sheet		√		

### **8.15.3 Quality control in data collection**

The following quality assurance strategies, aimed at ensuring the collection of high quality data and minimising potential problems in data collection, were implemented in the CHG Trial:

- The trial protocol clearly defined entry criteria, outcomes criteria and trial methodology so minimising problems in data collection.
- A site file was given to each research site. This provided clinical staff with information on trial procedures including IMPs and their administration. Instructions on performing hub and catheter exit site care; obtaining exit site swabs and blood cultures was guided by local policy;
- Well-designed data collection forms were used.
- An instruction manual guided the completion of data collection forms;
- SOPs guided particular trial activities, ensuring uniformity in their implementation.
- Verification of IMP administration was achieved through the use of trial solutions record sheets, which were monitored on a weekly basis.
- I provided education and training to dialysis nurses on hand hygiene, aseptic technique, and the administration of IMPs and the completion of trial solutions record sheets. This promoted the adoption of standard procedures and minimised errors.
- I met with microbiology laboratory staff at each of the research sites to discuss this study and outcome event measurement and assessment, stressing the importance of keeping the laboratory staff blinded to each patient's allocation.
- I piloted the administration of the IMPs, data collection forms, recruitment and randomisation process at one research site, to pre-test the procedures before this study started at the other research sites.
- The participant's date of birth was included in data collection forms as a means of acting as an independent verification of the identification process, at the time of data entry.
- Exit site swabs and blood cultures were noted in the trial solutions record sheet and or the dialysis monitoring sheet.

## 8.16 Data Management

The purpose of data management is to ensure all data are collected, checked and organised. This guarantees that all data collection forms are ready for statistical analysis (Pocock 1983). Data management was broken down into a number of activities including:

- Predetermining who was responsible for data collection and completion of data collection forms.
- Developing an instructors' manual, guiding completion of these forms.
- Establishing a Trial Master File and developing a specific SOP guiding its use.
- Distribution of a sufficient volume of trial solution record sheets at each research site.
- General checks that ensured correct forms had been completed for each trial participant.
- Checking all completed data collection forms for any missing data.
- Logical checks for any data that was inconsistent; for example, date of birth, date of CVC insertion;
- Ensuring that all data collection forms for each participant were kept in readily accessible order.
- Maintaining a Microsoft Excel file, which was used to track the flow of participants through this study;
- Inputting of data into IBM SPSS on a continuous basis; and
- Maintaining accurate records of patients deemed not eligible for this trial and patients deemed eligible, but refused to participate.

As this study was a small multi-centre trial, all responsibilities in relation to data collection and handling were delegated to me. Each participant's data collection forms were kept together in files that were part of the Trial Master File (TMF). These were organised according to participant trial number and arranged in chronological order. Data was entered manually into IBM SPSS Version 20, on a continuous basis, by me and a post graduate student.

## **8.17 Ethical Issues during the Conduct of the Trial**

The trial commenced at research site OA in October 2010. On 28 October of that year, a nurse manager in the dialysis unit brought to my attention a hospital memo emailed to all hospital departments, from the Nurse Practice Development Department and the infection prevention and control team. This informed clinical staff that Sani-Cloth CHG 2% medical device wipes were being introduced across the hospital from the 1 November, for all CVC care and maintenance. This product would replace the routine solution of Hydrex® Pink (ECOLAB; 0.5% CHG in 70% isopropyl alcohol). Introducing such a change in practice into the dialysis unit would have had major implications for the feasibility of continuing the trial at this research site, as Sani-Cloth CHG 2% was an intervention product, while Hydrex® Pink was the comparator solution.

Before starting the trial, I met Dr Fennell Consultant Microbiologist, who was very supportive of my trial and no mention was made of this change in practice during our discussion. I also emailed each infection prevention and control nurse outlining the trial, asking if I could meet with them, but I received no reply. Following circulation of the memo, I contacted Professor Mellotte who recommended that I make contact with the nurse practice development coordinator; unfortunately she was not contactable. I sought the advice from Dr Fennell Consultant Microbiologist, who informed me that he and Professor Murphy, head of the infection prevention and control team had both agreed at their infection prevention and control meeting that my trial could go ahead. I was informed by Dr Fennell that Practice Development and the Director of Nursing were aware that the trial had been given the go ahead, but they had ethical reservations about it.

Given the ethical reservations raised by the Director of Nursing and Practice Development, the trial was referred back to the Joint St James's hospital and AMNCH REC. Dr Fennell made contact with the REC secretary seeking her advice on how we should proceed. The secretary met with the Vice Chair of the committee who sought clarification on why the change of practice was being implemented and who was responsible for that decision. He also suggested that the trial be suspended temporarily, and that patients already recruited should be given the routine treatment.

I believed that suspending the trial would be damaging, as patients would lose trust in it, with a high probability that they would refuse to participate on trial recommencement. Letters justifying the continuation of this trial and appealing the decision to suspend it were sent to the Vice Chair. In a compromise, I agreed to suspend recruitment until a formal decision had been made at the next REC meeting. The Chair of the REC reapproved the trial on 9 December 2010 and recruitment began again on 2 January 2011.

Although the trial was reapproved, Dr Fennell contacted me in February 2011 with a number of issues raised by the Department of Nursing. The department requested information on whether my ethical application had *'any plan in place if there was any institutional change in policy; if the AMNCH site could be used as the 2% intervention arm of this trial and what information I gave to patients regarding both products to make sure that they are fully informed prior to consent'*.

My reply outlined that there was no plan in place for institutional change in practice. The approved application was for a comparison between 2% CHG in 70% alcohol and other forms of CHG, which are in routine use in dialysis facilities. The experimental group would receive 2% CHG in 70% alcohol while the comparator group would use the routine CHG solution used in their dialysis facility. In relation to the issue of using the AMNCH site as the intervention arm, I outlined that this was not feasible because the trial had Ethics and IMB approval based on a protocol for an RCT that compared the experimental intervention and routinely used CHG solutions. To do anything different would have a detrimental effect on the trial and its robustness. Furthermore, a design in which an intervention in one hospital is compared with another intervention in a different hospital is much weaker than a trial in which both interventions are used, with random allocation, inside the same hospital because of confounding. A comparison between hospitals would be too weak to answer my research question. I also confirmed that patients were fully informed of the different solutions used at the research sites and the recommendations made by National guidelines.

Given the ongoing difficulties that Practice Development had with not being able to introduce the change of practice into the dialysis units, I was concerned that further issues would be raised that would lead to the closure of the trial. By the end of February, I had approached all eligible patients and

from that point onwards recruitment would focus on patients with newly inserted CVCs. I made the decision to discontinue recruitment at this site (February 2011); therefore the trial finished in AMNCH in February 2012.

### **8.18 Amendments to Trial Protocol**

Only one amendment was submitted to the IMB post approval. This amendment related to the IMB agreeing to enter suspected unexpected serious adverse reactions (SUSAR) onto the Eudravigilance database.

### **8.19 Trial Management Issues**

Leadership was provided by Professor George Mellotte who offered me support and guidance when dealing with clinical and scientific issues that occurred during the trial. Both Professor Mellotte and Professor Watson, as principal investigators were involved in different phases of the trial, while I managed day to day trial activities. I maintained contact with Professor Mellotte and Professor Watson on an ongoing basis via email, telephone and face-to-face meetings. Emails relevant to trial decisions are kept in the Trial Master File.

I established a trial steering committee at each research site, meetings were held initially once or twice a month. Minutes of these meetings are also filed in the Trial Master File. Members of the committee included the principal investigator, renal nurse managers and other healthcare personnel, as deemed necessary.

### **8.20 Safety Monitoring & Reporting During Trial**

Any participant who developed an adverse reaction as described in chapter 7 (section 7.9.4) had their assigned solution discontinued, their physician informed and an alternative antiseptic agent prescribed. This event was recorded in the adverse reaction form. No serious adverse reactions were anticipated, but a process was in place to report such reactions to the sponsor.

Two types of complaints were made by trial participants. The first related to itchiness under the dressing, which did not resolve following implementation of an action plan (appendix 8.26). Participants with this type of complaint were deemed to have skin sensitivity related to their assigned solution. The second complaint related to itchiness under the dressing, which resolved following implementation of the action plan and was not considered as skin sensitivity to the assigned solution.

### **8.20.1 Recording/reporting of adverse events & reactions**

During my weekly visits to the research sites, I monitored each participant for any adverse events that might have occurred since my previous visit. Dialysis nursing staff were encouraged from the onset of this study to contact me if an adverse event occurred. However, this rarely happened except in those instances where participants died. Such incidents were recorded and reported to the Sponsor/Chief Investigator and site investigator. Adverse events were recorded in the participant's Case Report Form.

I met with Professor George Mellotte (Sponsor/Chief Investigator) and Professor Alan Watson (principal investigator) every four months to review and confirm the classification of adverse events (expected and unexpected). The seriousness of these events was also discussed and their relationship with this trial's medicinal products determined. No events required reporting to the IMB or REC (European Commission 2008b).

### **8.20.2 Trial monitoring committee**

The Trial Monitoring Committee held its first meeting in September 2010, before the trial started. This meeting was by telephone conference and focused on reviewing the study protocol. I took part, answering any questions committee members had in relation to the trial design. This meeting also discussed terms of reference, with agreement being reached on which member of the committee would act as chair.

The second meeting took place after the trial commenced in all three research sites and after recruitment was completed. I was not involved in this meeting. The meeting focused on the interim results. The Trial Monitoring Committee agreed that there was no particular ethical or scientific reason to stop the trial and that the trial should continue to completion (appendix 8.24).



During the course of the trial, an issue emerged in relation to the independence of the membership of the committee. Following submission of the interim report, the Chair of the Committee telephoned me and indicated that the microbiologist was interested in following up those participants with a CVC-related infection, who were based at his hospital. I informed the Chair that the sharing of this information was not feasible, not only from an ethical perspective, but also given the purpose of the committee and its terms of reference. Disclosing such information was not part of the consent process with patients and doing so would breach that process. Following my reply, I did not receive any further communication on this request. This query did not impact on the independence of the decisions made by the Committee. However, it could have impacted on the running of the trial at the site where the microbiologist worked, but for the fact that the trial was finished at that site. When reflecting back on this incident, it highlighted to me the need to review the membership of the Trial Monitoring Committee. Even though the literature suggests committee members can come from the same institution, membership of the committee for the main study should consist of personnel independent from the trial, clinical settings and academic institutions. Such a committee would require funding, which needs to be considered when planning the budget for the main study.

## **8.21 Data Analysis**

As per the intention-to-treat analysis, all participants were followed up to trial completion (12 months), primary outcome or death and were analysed in accordance with their original assigned groups. A rigorous statistical review of the trial protocol was undertaken by a statistician at the Centre for Support and Training in Analysis and Research (CSTAR), University College Dublin. Statistical tests were two-tailed, with a p-value below 0.05 considered statistically significant.

### **8.21.1 Intention-to-treat analysis**

On CHG trial completion, the data set of some participants was incomplete due to non-adherence to the trial protocol. This was linked to either early stopping of the assigned treatment or participants not receiving the full 52 weeks of the intervention due to an episode of hospitalisation, being away from the dialysis unit, or dialysis nurses non-adherence to the trial protocol. As

these participants deviated from the trial protocol there is a school of thought that they should be excluded from the data analysis process. This is known as per-protocol analysis. This approach can introduce possible bias associated with attrition (chapter 7, section 7.12), eliminating the benefits of randomisation and leading to groups that are no longer comparable (Moher *et al.* 2010, Sedgwick 2013). An alternative school of thought, called intention-to-treat, believes that all participants should be followed and analysed in their original assigned groups, irrespective of whether they continued or discontinued their assigned treatment. Intention-to-treat maintains the balance between randomised groups, it estimates the treatment effect within the real world of clinical practice; consequently, it is the preferred data analysis method in pragmatic trials such as this one (Friedman *et al.* 1998, Polit & Beck 2008, Sainani 2010).

In my trial, 17 participants stopped using their assigned treatment; nine in the intervention group and eight in the control group (chapter 9, section 9.2.2). As per intention-to-treat analysis all participants were followed up to trial completion or death and analysed as per their assigned group. In the real world of clinical trials, some participants may be lost to follow-up. Difficulties then arise in how data from these participants should be treated. The trial did not involve repeated measures, relying instead on monitoring participants for the primary outcome. Participants lost to follow-up could not be assessed in relation to that outcome. A total of 16 participants were lost to follow-up (nine in the intervention group and seven in the control group). The reasons for lost to follow-up reflect the nature of End Stage Kidney Disease and haemodialysis (chapter 9, section 9.2.1). Although, there is little difference in the number of participants lost to follow-up between the two arms of the trial, the possibility of bias cannot be ruled out. Participants lost from each group may differ in their prognosis and in relation to the likelihood that they will develop the primary outcome (Friedman *et al.* 1998).

There is no agreement in the literature on how missing data from participants lost to follow-up should be handled. Different approaches are available, each suited to different circumstances (Hollis & Campbell 1999). This trial undertook a sensitivity analysis that included recommendations by Altman (1991) and Alshurafa *et al.* (2012). This sensitivity analysis kept participants in their assigned groups and imputed the most pessimistic outcome (CABS1) for all participants lost to follow-up. Additionally, a worst and best case

scenario was undertaken, whereby participants were analysed, as per their assigned groups, with those lost to follow-up in the intervention arm assumed to have the worst outcome (CABSI), while those lost to follow-up in the control arm had the best outcome (no CABSI) and vice versa. Findings from this analysis assessed the potential impact of lost participants on the primary outcome analysis (chapter 9, section 9.4).

### **8.21.2 Data entry & cleaning**

IBM SPSS Version 20 was used for statistical analysis. The data analysis plan involved single entry of coded data from data collection forms and verifying entries and correcting mistakes. As this trial was a small study, double entry of data was not considered, but its feasibility will be explored for the main study.

Data were cleaned using frequency distributions for categorical data and descriptive statistics for continuous data. Both were checked for outliers, which are data outside the normal range of values. All outliers were then checked for accuracy and whether they were due to wrong coding. Additionally, recorded dates were checked as statistical tests on survival time were planned (Altman 1991, Pallant 2005, Polit & Beck 2008).

### **8.21.3 Categorical data**

Categorical data (baseline, and primary/secondary outcomes) were analysed by counting the frequencies (number and percentages) of participants with an event as opposed to counting the number of episodes for each event. Differences between groups at baseline or in the proportion of participants who developed a categorical outcome were analysed using a Chi-square test or Fisher's Exact test. The purpose of these tests is to assess for evidence of difference at baseline or in treatment effectiveness that was not due to chance alone (Pocock 1983). In the Chi-square test, a larger value indicates that there is less probability that the difference between trial arms occurred by chance alone, providing strong evidence of baseline or treatment differences. The probability value  $P$  in this instance would be small. The Fisher's Exact test is said to be more precise especially when trial numbers are small, but it is argued that this test is more conservative especially with fewer events (Campbell & Swinscow 2009).

One of the assumptions associated with the use of the Chi-square test was not met in this trial; a number of cells had expected cell counts of less than five because of the small number of events (Altman 1991, Field 2009). This less conservative test was of interest as it gave some indication of the direction of the significance of the effect. Differences in group proportions were, therefore, reported using Chi-square test and Fisher's exact test, where appropriate. The Chi-Square test statistic was reported as  $\chi^2$  and includes information on the degrees of freedom (df) and the significance value ( $\chi^2$  (df) =test result, p-value).

Finally, the relative risk and absolute risk reduction for primary and secondary outcomes and their 95% confidence interval were also calculated

#### **8.21.4 Continuous data**

Baseline and secondary outcome continuous variables were reported using mean, median, standard deviations and interquartile range, where appropriate. A comparison of the mean difference between the intervention and comparator groups, due to treatment effect rather than chance, was achieved through the parametric two-sample independent *t*-test (Pocock 1983). In this test, the larger the *t* value the smaller the probability that the difference in means between trial arms was due to chance alone. The independent *t*-test was reported as *t*(df)=test result, p-value. Assumptions associated with this test include a normal distribution, variances in populations that are roughly equal and scores that are independent because they come from different people.

In the trial, assumptions relating to variance and normality were not met. Variance was reported as *F*, two different degrees of freedom and a significance level e.g. *F* (df1, df2)= test result, p-value (Field 2009). For the following continuous outcomes, variances between groups were significantly different: positive blood cultures *F*(1,103)=10.20, *p*=0.002 and hospitalisations due to catheter-related infection *F*(1,103) =6.36, *p*=0.013. The independent *t*-test makes adjustments when variances are not equal, providing *t*-test statistics labelled *Equal variances not assumed*, these were reported for the variables that violated this assumption (Field 2009).

Normality of distribution was tested using the Kolmogorov-Smirnov (K-S) test, with a non-significant result indicating that the sample is not significantly different from a normal distribution. The test statistic for the K-S test was reported as  $D$ , degrees of freedom (df) and significance value e.g.,  $D$  (df)=test result,  $p$ -value. Kolmogorov-Smirnov test of normality was not normal for age ( $D$  [105] = 0.12,  $p=0.000$ ), serum albumin level ( $D$ [105]=0.14,  $p=0.000$ ), duration of haemodialysis ( $D$ [105]=0.15,  $p=0.000$ ), duration of CVCs ( $D$ [105]=0.17,  $p=0.000$ ) and number of previous CVC insertions ( $D$ [105]=0.29,  $p=0.000$ ).

A non-parametric test (Mann-Whitney) was therefore run for comparison and its  $p$ -values were mostly in agreement with  $t$ -test results. The Mann-Whitney was reported as  $U$  and includes  $z$  score, significance level and the effect size ( $r$ ); for example,  $U=$  test result,  $z =$ result,  $p=$ value,  $r=$ result (Field 2009). Providing findings from the  $t$ -test and the Mann-Whitney test gives a more complete picture of trial results rather than reporting just one test.

#### **8.21.5 Survival analysis**

Survival analysis explored time to development of CRBSI, CABSIs, local access infection, CVC removal and CVC removal because of infection, from trial entry. The date to infection was the date the blood culture was drawn. Over half of participants did not develop these events, thus median time to events could not be estimated (chapter 9, section 9.7). Using Kaplan-Meier survival analysis, the proportion of participants that did not experience an event was estimated from the survival curves at six and 12 months. Differences between survival curves was evaluated using the logrank test (Altman 1991).

#### **8.21.6 Logistic regression analysis**

Differences between trial arms were explored and their impact on primary outcomes assessed through logistic regression analysis. Primary outcomes were categorical; thus meeting one of the assumptions associated with logistic regression analysis. A binary logistic regression analysis was used as the dependent outcome had only two categories, that is CABSIs or no CABSIs (Pallant 2005, Field 2009). CABSIs, a clinically significant bloodstream infection, was selected because it had a higher event rate than CRBSIs. The logistic regression model assesses the predictive impact of multiple

independent variables (continuous, categorical or both) on the likelihood that participants would develop a CABS I (dependent variable) (Tabachnick & Fidell 2007). Although there are no rules governing the number of variables that can be included in a logistic regression model, Altman (1991) suggest a guide of  $n/10$  variables where  $n$  is the sample size. As the trial has 105 participants, the following 11 predictor variables were included in the model: research centre, age, sex, diabetes, immunosuppressive therapy in the last 12 month, previous CVCs, previous CVC infection, duration of CVC, antibiotics, CVC locking solution and serum albumin level.

Multicollinearity refers to the inter-correlation between predictor variables and is another assumption associated with logistic regression analysis. There was an expectation that variables would not be strongly related to each other, but rather related to the trial outcome. This was assessed using the collinearity diagnostics within IBM SPSS (chapter 9, section 9.8), which provides tolerance values for each predictor variable. None of the predictor variables had tolerance levels less than 0.1 or even 0.2; values that are associated with serious collinearity. The variance inflation factor for all predictor variables was near to one and none were substantially greater than one, suggesting that collinearity between predictor variables was not an issue (Field 2009).

Logistic regression methods include the forced entry (direct model) and stepwise approach. The forced entry method requires that all predictor variables are placed into the model at the same time and tested in one block. All are assessed for their predictive ability. In contrast, a stepwise regression (forward and backward method) is dependent on statistical software selecting predictor variables using mathematical criterion. The forward approach selects predictors with the highest correlation with the dependent variable and at the same time removes the least useful predictors from the model (Tabachnick & Fidell 2007, Field 2009).

As discussed in chapter 9 (section 9.8), using a forced entry logistic regression model, no estimate could be made on the predictability of the independent variables on the likelihood that participants would develop a CABS I. A similar outcome arose when the stepwise approach was used. Despite collinearity diagnostics suggesting that multicollinearity was not an issue, the standard errors logistic regression coefficients for both models could not be estimated and no inferences were made.

## 8.22 Conclusion

This chapter provides information on the methods and conduct of the trial. Trial approval was granted by the IMB and the St James's hospital and AMNCH joint REC. Permission was also sought from Directors of Nursing and Consultant Nephrologists.

The study population were outpatient haemodialysis patients with CVCs. Using broad inclusion criteria, trial eligibility was assessed by an assessment panel, at each research site. Computer randomisation software was used to generate the allocation sequence, which was stratified according to different types of routine CHG solution and consisted of permuted blocks of ten. Allocation concealment was achieved through the use of an independent central telephone randomisation service. Eligible participants were recruited and randomised to their assigned solution using a 1:1 randomisation ratio.

The intervention products consisted of Chloraprep® with Tint 3ml applicator and Sani-Cloth CHG 2% medical device wipes. Participants in the control arm received the dialysis unit's routine CHG solution (Sterets® Unisept or Hydrex® Pink). EU Clinical Trial legislation directed the manner in which both the intervention and control products were ordered, labelled and stored. All records in relation to ordering, receipt of supplies including batch numbers and expiry dates were kept in the Trial Master File. Blinding of intervention and control treatments was not feasible, but an independent microbiologist reviewed and confirmed primary outcomes of trial participants.

During on-site visits, I monitored trial participants for occurrence of primary and secondary outcome and, dialysis nurses for compliance to the trial protocol. Primary outcomes were CVC-related infections (CRBSI, CABSI, local access infection). Case definitions from the CDC/NHSN and the IDSA were used to diagnosis these infections. A modified version of the CDC/NHSN dialysis events form was used to collect data relevant to trial outcomes.

A SOP guided safety monitoring and reporting and participants were monitored for adverse events and adverse reactions. A Trial Monitoring Committee assessed trial progress, reviewed trial interim data and reported that there was no ethical or scientific reason why the trial should be stopped. Finally, the data analysis strategy was outlined.

**SECTION 4**

**RESULTS**  
**&**  
**DISCUSSION OF FINDINGS**



## CHAPTER 9: RESULTS

### 9.1 Introduction

This chapter presents findings of the CHG trial that are based on an 'intention to treat' analysis. All participants were followed up to trial completion (12 months), primary outcome or death and analysed in accordance with their original assigned groups. Findings are presented for the main comparison of 2% chlorhexidine gluconate (CHG) in 70% isopropyl alcohol (intervention group) versus routine antiseptic solution (comparator group). Results for sub-comparison 1 (0.5% CHG in 70% isopropyl alcohol) and sub-comparison 2 (0.05% aqueous CHG) are also discussed. CONSORT (Moher *et al.* 2010) guidelines for reporting parallel group randomised trials guided this presentation of the findings.

Statistical tests were two tailed, with a p-value below 0.05 considered statistically significant. Frequencies (numbers and percentages) are reported for categorical data, differences in group proportions were analysed using Chi-square and Fisher's Exact tests, where appropriate (chapter 8, section 8.21.3). Relative risk and absolute risk reduction were also calculated for categorical data. Continuous data are presented as means and standard deviations; and, where relevant, median and interquartile ranges are also provided. Two sample independent *t* test and the Mann-Whitney test were used to estimate differences in group means (chapter 8, section 8.21.4). The incidence rates, per 100 patient-months, for primary and secondary outcomes (categorical and continuous, chapter 7 sections 7.5 and 7.6) are also reported. Kaplan-Meier survival analysis was used to evaluate time to infection-related events, while the log rank test was used to analyse differences between groups. Confidence intervals are reported for statistical tests, where appropriate.

Results of recruitment and randomisation are discussed first, followed by findings relating to baseline characteristics, primary outcomes, secondary categorical and continuous outcomes, survival analysis, logistic regression, causative organisms and vascular prevalence.

## 9.2 Recruitment & Randomisation

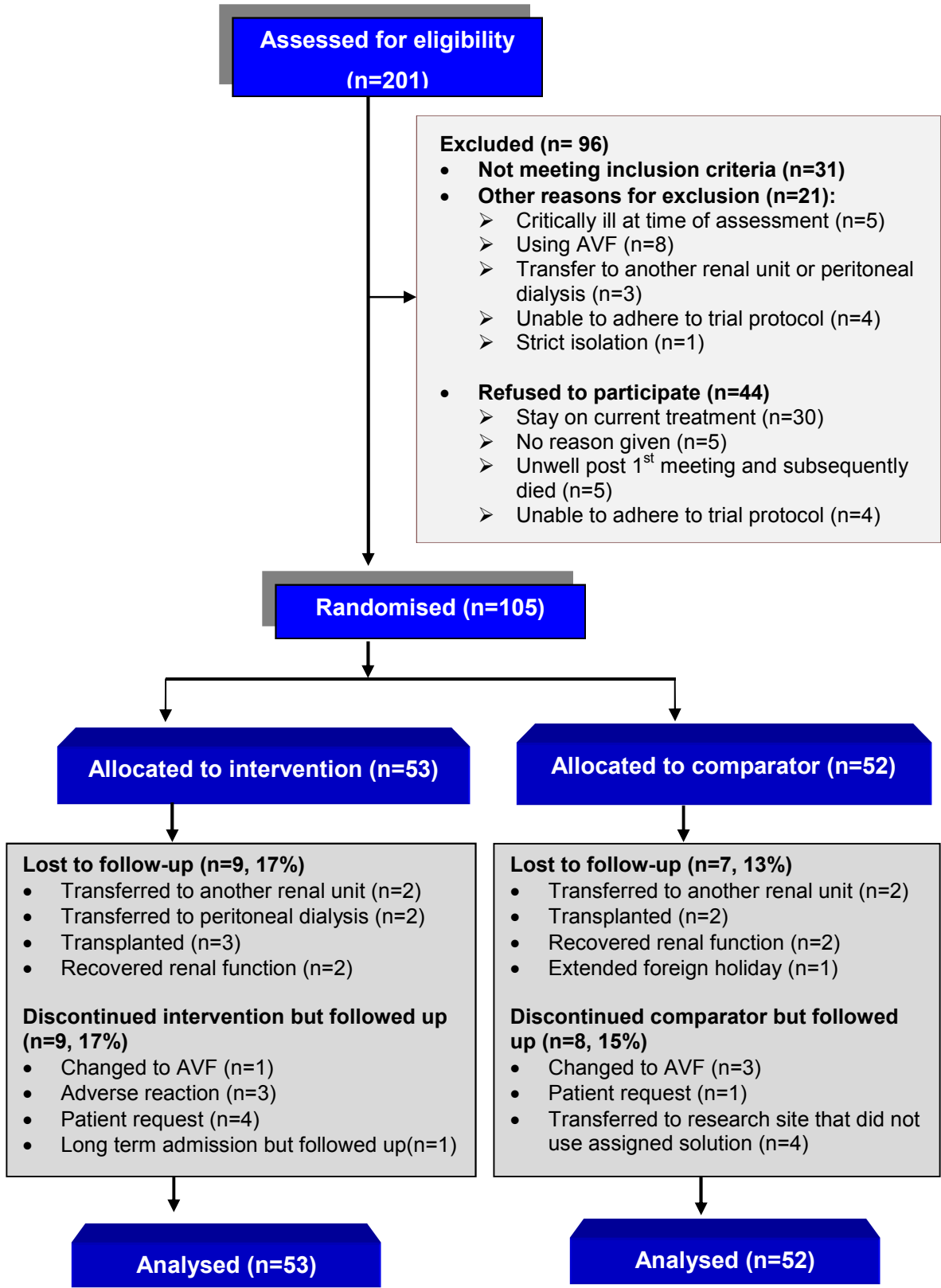
Figure 9.1 provides the CONSORT flow diagram for the trial. A total of 201 patients with central venous catheters (CVC) were assessed for trial eligibility, between October 2010 and September 2011; 65 (32%) from site OA, 92 (46%) from site OB and 44 (22%) from site OV (appendix 9.1). These differences are not unexpected, because, for example, site OB is the largest dialysis facility with the largest pool of patients; it also had the longest recruitment period (eight months), compared to site OA (three months) and OV (two months). Differences in recruitment periods were due to problems with accessing the research sites (chapter 8, section 8.7.1).

Following eligibility assessment, 52 (26%) patients were excluded; 31 did not meet the inclusion criteria and 21 were excluded for other reasons. Of those patients who did not meet the inclusion criteria, 17 were unable to give informed consent, 10 were allergic to the routine CHG solution (0.5% CHG in 70% isopropyl alcohol [ $n=9$ ] or to 0.05% aqueous CHG [ $n=1$ ]), three did not use a standard CVC and one was under the age of 18. Some patients who otherwise met the inclusion criteria, were excluded because they were critically ill at the time of assessment ( $n=5$ ), used an arterio-venous fistula (AVF) ( $n=8$ ), were scheduled to transfer to another haemodialysis unit or transfer to peritoneal dialysis ( $n=3$ ), were unable to adhere to the trial protocol ( $n=4$ ) or required strict isolation ( $n=1$ ).

In total, 149 (74%) patients were deemed eligible; 105 patients gave their consent and entered the trial, 70% of eligible patients. Forty-four patients (30%) declined to participate because they either wanted to stay on their current treatment ( $n=30$ ), gave no reason ( $n=5$ ), were unwell post first recruitment meeting and subsequently died ( $n=5$ ), or could not adhere to the trial protocol ( $n=4$ ). Site OA had the highest proportion of eligible patients who refused trial participation (42%).

Following randomisation, 53 participants were assigned to the intervention group and 52 to the comparator group (Table 9.1). Of the 52 participants assigned to the comparator group, 42 were in sub-comparison 1 and 10 in sub-comparison 2.

# CHG Randomised Trial Participant Flow Diagram



**Figure 9.1 CONSORT flow diagram: CHG randomised trial**

**Table 9.1 Outcome of randomisation process**

Main Comparison 2% CHG in 70% alcohol vs. Comparator		
Research Site (N)	Intervention ( <i>n</i> =53) N (%)	Comparator ( <i>n</i> =52) N (%)
OA (29)	15 (52%)	14 (48%) <sup>1</sup>
OB (55)	27 (49%)	28 (51%) <sup>1</sup>
OV (21)	11 (52%)	10 (48%) <sup>2</sup>
Total (105)	53	52

<sup>1</sup>Participants in sub-comparison 1, assigned to 0.5% CHG in 70% isopropyl alcohol;

<sup>2</sup>Participants in sub-comparison 2, assigned to 0.05% aqueous CHG.

### 9.2.1 Lost to follow-up

A total of 16 participants were lost to follow-up, 15% of the randomised participants; 17% (*n*=9/53) in the intervention group and 13% (*n*=7/52) in the comparator group (appendix 9.2). Group difference is not statistically significant ( $p=0.62$ ). In the comparator group, 14% (*n*=6/42) of participants were lost from sub-comparison 1 (0.5% CHG in 70% isopropyl alcohol) and 10% (*n*=1/10) from sub-comparison 2 (0.05% aqueous CHG). Loss to follow-up occurred because participants transferred to another haemodialysis unit (*n*=4), changed to peritoneal dialysis (*n*=2), were transplanted (*n*=5), or their renal function returned (*n*=4). In one case, a participant went on an unexpected extended holiday outside Ireland, lasting three months.

### 9.2.2 Early discontinuation of solution

During the course of the trial, 17 participants were discontinued from their assigned solutions, but were followed up and analysed according to their group assignment (appendix 9.3). Nine (17%) participants in the intervention group were discontinued. Reasons included adverse reactions to the 2% CHG in 70% isopropyl alcohol solution (*n*=3), in response to the participant's request because the solution either stained their clothes (*n*=2) or stained their skin (*n*=1). In one case, a participant experienced a generalised

dermatological condition (not related to the trial) and asked for their assigned solution to be discontinued. Another reason included the use of AVF ( $n=1$ ) and, lastly, one participant was admitted to hospital for 5 weeks and did not receive the assigned solution in that time, but was followed up during their hospitalisation and up to trial completion. Eight (15%) participants in the comparator group were discontinued from their assigned solution, seven (17%) in sub-comparison 1 and one (10%) in sub-comparison 2. Reasons for discontinuation included use of AVF ( $n=3$ ), participant request ( $n=1$ ) with no reason given or participants were transferred to another trial research site whose routine solution was not the participant's assigned solution ( $n=4$ ).

### 9.3 Baseline Characteristics

Overall, the mean age of trial participants ( $n=105$ ) was 65 (SD 15.28), ranging from 23 to 95 years. The majority of participants were over the age of 64 ( $n=61$ , 58%), with 46% ( $n=48$ ) in the 70-95 age group. Median (interquartile range [IQR]) duration on haemodialysis was 20 months (37 months [3.1 years]) and varied from one month to 153 months (12.8 years). Central venous catheter (CVC) duration time spanned from one month to 69 months (5.8 years), with a median duration of 9 months (IQR of 17 months).

Baseline characteristics for the main comparison groups are shown in Table 9.2. The mean age of participants in both the intervention and the comparator groups was 65 (SD 14.45 and 16.23, respectively), and the median age was also the same in both groups (69 years). The proportion of males in the intervention ( $n=27$ , 51%) and comparator groups ( $n=26$ , 50%) were similar. Both groups had comparable mean serum albumin levels, 37.2 g/l (SD 4.0) and 36.6 g/l (SD 4.52,  $p=0.42$ ), respectively. The mean duration of haemodialysis for intervention participants was 33 months (SD 27.4; median 28 and IQR 39 months) and 26 months (SD 29.61; median 15 and IQR 34 months) for participants in the comparator group. Differences between groups were not significant ( $t[103]=1.28$ ,  $p=0.20$ ; Mann-Whitney test ( $U=1090$ ,  $z=1.843$ ,  $p=0.06$ ,  $r=0.18$ ).

**Table 9.2 Baseline characteristics main comparison**

Main Comparison 2% CHG in 70% alcohol vs. Comparator N (%)				
	2% CHG in 70% alcohol (n=53)	Comparator (n=52)	<i>P</i> <sup>1</sup>	Overall Total Mean (SD)
Female	26 (49.1)	26 (50)		52
Male	27 (50.9)	26 (50)	0.92	53
Mean Age (SD)	65.09 (14.45)	64.92 (16.23)	0.95 (0.88) <sup>#</sup>	65.01 (15.28)
Mean Serum albumin (g/l) (SD)	37.23 (3.99)	36.56 (4.52)	0.42 (0.55) <sup>#</sup>	36.9 (4.25)
Mean duration of HD in months (SD)	32.63 (27.36)	25.53 (29.62)	0.20 (0.06) <sup>#</sup>	29.11 (28.5)
<b>Renal Aetiology</b>				
Diabetes	11 (20.8)	10 (19.2)		21
Glomerulonephritis	1 (1.9)	4 (7.7)		5
Hypertension	9 (17.0)	5 (9.6)		14
Polycystic adult kidney disease	4 (7.5)	6 (11.5)		10
Unknown	8 (15.1)	7 (13.5)		15
Other	20 (37.7)	20 (38.5)		40
Total	53 (100)	52 (100)	0.63	105
<b>Co-Morbidities</b>				
Diabetes	16 (30.2)	15 (28.8)	0.88	31
Immunosuppressive therapy	12 (22.6)	11 (21.2)	0.85	23
Malignancy	5 (9.4)	2 (3.8)	0.25	7
Previous immunosuppression in the last 12 months	16 (30.2)	16 (30.8)	0.95	32
<b>CVC History</b>				
Previous CVC	29 (54.7)	20 (38.5)	0.09	
Mean number of previous CVC (SD)	0.91 (1.18)	0.65 (1.05)	0.25 (0.14) <sup>#</sup>	0.78 (1.11)
Mean duration of CVC in months (SD)	14.59 (15.59)	11.23 (11.71)	0.21 (0.32) <sup>#</sup>	12.92 (13.84)
Previous CVC infection	11 (20.8)	18 (34.6)	0.19	
Right jugular CVC	34 (64.2)	45 (86.5)	0.01*	79
Left jugular CVC	16 (30.2)	6 (11.5)	0.02 (0.03)	22
Right subclavian CVC	2 (3.8)	1 (1.9)	0.57	3
Left subclavian CVC	1 (1.9)	0	0.32	1
<b>CVC locking Solution</b>				
Heparin	11 (20.8)	3 (5.8)		
Trisodium Citrate	39 (73.6)	48 (92.3)	0.01 (0.02)	
Other	3 (5.7)	0		
Heparin and Trisodium Citrate	0	1 (1.9)		
Total	53 (100)	52 (100)	0.02 (0.01)	

*P*<sup>1</sup>, *p*-value chi-square test (Fisher's Exact test); <sup>#</sup> *p*-value independent two-sample *t*-test (Mann-Whitney Test);\*same *p*-value for  $X^2$  and Fisher's Exact test.

Common renal aetiologies in the intervention group were diabetes ( $n=11$ , 21%) and hypertension ( $n=9$ , 17%), whilst diabetes ( $n=10$ , 19%) and adult polycystic kidney disease ( $n=6$ , 12%) were the most common aetiologies in the comparator group. The proportion of participants with co-morbidities such as diabetes, immunosuppressive therapy and immunosuppression therapy within the last 12 months were similar between groups.

More than half ( $n= 29$ , 55%) of the participants in the 2% CHG in 70% isopropyl alcohol group had a CVC previously inserted; the mean number of insertions was 0.91 (SD 1.18; median 1). The number of participants in the comparator group with previous CVC insertions was smaller ( $n=20$ , 39%); differences were not statistically significant ( $p=0.09$ ). Comparator participants ( $n=45$ , 87%) had a significantly higher use of right internal jugular CVCs than participants assigned to the intervention group ( $n=34$ , 64%;  $\chi^2 (1) = 7.1$ ,  $p= 0.01$ ). Conversely, left internal jugular CVC use was significantly higher in the intervention group ( $n=16$ , 30%) than the comparator group ( $n=6$ , 11%;  $\chi^2 (1) = 5.5$ ,  $p= 0.02$ ). A minority of intervention ( $n=11$ , 21%) and comparator ( $n=18$ , 35%) participants had previous CVC infections. The groups differed significantly in the use of Trisodium Citrate (Duralock, Medcomp®) antimicrobial CVC locking solution; 39 (74%) and 48 (92%;  $\chi^2 (1) = 6.5$ ,  $p= 0.01$ ), respectively. This might influence the infection rate in the comparator group.

In general, there were no significant differences between the main comparison groups with respect to baseline characteristics except for right and left internal jugular CVC use and usage of Trisodium Citrate (Duralock, Medcomp®) CVC antimicrobial locking solution.

Basic characteristics for sub-comparison 1 (2% CHG in 70% isopropyl alcohol [ $n=42$ ] versus 0.5% CHG in 70% isopropyl alcohol [ $n=42$ ]) and sub-comparison 2 (2% CHG in 70% isopropyl alcohol [ $n=11$ ] versus 0.05% aqueous CHG [ $n=10$ ]) are shown in Table 9.3.

**Table 9.3 Baseline characteristics sub-comparison 1 & 2**

Characteristic	Sub comparison 1			Sub comparison 2		
	2% CHG in alcohol (n=42)	N (%) 0.5% CHG in alcohol (n=42)	<i>P</i> <sup>1</sup>	2 % CHG in 70% alcohol (n=11)	N (%) 0.05% aqueous CHG (n=10)	<i>p</i>
Female	18 (42.9)	17 (40.5)	0.82 (1.0)	8 (27.3)	9 (90)	0.31 (0.59)
Male	24 (57.1)	25 (59.5)		3 (72.7)	1 (10)	
Mean Age (SD)	64.95 (13.57)	64.29 (15.48)	0.83 (0.96) <sup>#</sup>	65.64 (18.15)	67.60 (19.77)	0.81 (0.78) <sup>#</sup>
Mean Serum albumin (g/l) (SD)	38.19 (3.55)	37.86 (3.12)	0.65 (0.50) <sup>#</sup>	33.55 (3.53)	31.10 (5.51)	0.24 (0.11) <sup>#</sup>
Mean duration of HD in months (SD)	27.92 (22.80)	24.24 (30)	0.53 (0.16) <sup>#</sup>	50.60 (36.22)	30.96 (28.78)	0.19 (0.14) <sup>#</sup>
Diabetes	9 (21.4)	6 (14.3)		2 (18.2)	4 (40)	
Glomerulonephritis	1 (2.4)	2 (4.8)		0	2 (20)	
Hypertension	7 (16.7)	4 (9.5)		2 (18.2)	1 (10)	
Polycystic adult kidney disease	3 (7.1)	6 (14.3)		1 (9.1)	0	
Unknown	6 (14.3)	5 (11.9)		2 (18.2)	2 (20)	
Other	16 (38.1)	19 (45.2)		4 (36.4)	1 (10)	
Total	42 (100)	42 100.0)	0.68 (0.71)	11	10 (100)	0.33 (0.40)
Diabetes	12 (28.6)	10 (23.8)	0.62 (0.80)	4 (36.4)	5 (50)	0.53 (0.70)
Immunosuppressive therapy	10 (23.8)	9 (21.4)	0.79 (1.0)	2 (18.2)	2 (20)	0.92 (1.0)
Malignancy	5 (11.9)	2 (4.8)	0.24 (0.43)	0	0	0.86 (1.0)
Previous immunosuppression in the last 12 months	12 (28.6)	12 (28.6)	1.00 (1.0)	4 (36.4)	4 (40)	
Previous CVC	21 (50)	16 (38.1)	0.27 (0.38)	8 (72.7)	4 (40)	0.13 (0.20)
Mean number of previous CVC (SD)	0.76 (1.05)	0.60 (0.96)	0.45 (0.32) <sup>#</sup>	1.45 (1.51)	0.9 (1.37)	0.40 (0.27) <sup>#</sup>
Mean duration of CVC in months (SD)	14.21 (16.23)	10.54 (11.42)	0.23 (0.36) <sup>#</sup>	16.03 (13.42)	14.11(13.09)	0.74 (0.79) <sup>#</sup>
Previous CVC infection	6 (14.3)	13 (31.0)	0.13 (0.12)	5 (45.5)	5 (50)	0.83 (1.0)
Right jugular CVC	27 (64.3)	35 (83.3)	0.05 (0.08)	7 (63.6)	10 (100)	0.03 (0.09)
Left jugular CVC	12 (28.6)	6 (14.3)	0.11 (0.18)	4 (36.4)	0	0.03 (0.09)
Right subclavian CVC	2 (4.8)	1 (2.4)	0.56 (1.0)	0	0	
Left subclavian CVC	1 (2.4)	0	0.31 (1.0)	0	0	
Heparin	9 (21.4)	3 (7.1)		2 (18.2)	0	
Trisodium Citrate	30 (71.4)	39 (92.9)	0.01 (0.02)	9 (81.8)	9 (90)	0.60 (1.0)
Other	3 (7.1)	0		0	0	
Heparin and Trisodium Citrate	0	0		0	1 (10)	
Total	42	42 (100)	0.03 (0.02)	11	10 (100)	0.23 (0.48)

*P*<sup>1</sup>, *p*-value chi-square test (Fisher's Exact test); <sup>#</sup> *p*-value independent two-sample *t*-test (Mann-Whitney Test).



In sub-comparison 1, a statistically significant higher proportion of participants ( $n=35$ , 83%) treated with 0.5% CHG in 70% isopropyl alcohol had a right internal jugular CVCs as compared to participants ( $n=27$ , 64%) in the intervention group ( $\chi^2 (1)= 3.94$ ,  $p= 0.05$ ). This was not statistically different by Fisher's Exact test ( $p=0.08$ ). Participants ( $n=39$ , 93%) in the 0.5% CHG in 70% isopropyl alcohol group had a statistically significant higher use of Trisodium Citrate (Duralock, Medcomp®) antimicrobial lock solution than participants ( $n=30$ , 71%) in the intervention group ( $\chi^2 (1)= 6.57$ ,  $p= 0.01$ ; Fisher's Exact test  $p=0.02$ ).

Differences in the use of right and left internal jugular CVCs was found in sub-comparison 2. A significant difference in use of right internal jugular CVCs was found between participants ( $n=10$ , 100%) treated with 0.05% aqueous CHG as compared to participants ( $n=7$ , 64%) treated with the intervention ( $\chi^2 (1)= 4.5$ ,  $p= 0.03$ ), but this difference was not statistically significant by Fisher's Exact test ( $p=0.1$ ). Likewise, a higher proportion of participants ( $n=4$ , 36%;  $p= 0.03$ ) in the intervention group had a left internal jugular CVC, compared to zero participants in the 0.05% aqueous CHG group ( $\chi^2 (1)= 4.5$ ,  $p= 0.03$ ; Fisher's Exact test:  $p=0.09$ ).

A Cochrane Review (Ge *et al.* 2012) found a similar risk for catheter-related infectious complications between subclavian and internal jugular catheter insertion sites (2 studies, 470 cancer patients). Randomised trials focusing on catheter-related infections and stratified by internal jugular sites are lacking. As discussed in chapter 4 (section 4.6.2.5), meta-analyses of CVC antimicrobial and non-antibiotic lock solutions showed no significant effect in the reduction of catheter-related infection in patients using Trisodium Citrate. Furthermore, the robust randomisation methods used in my trial (including computer generated randomised allocation sequence list and the use of a central telephone randomisation centre) ensured that these imbalances were not due to manipulation of the assignments. Rather, they are simply what can happen by chance through randomisation.

## 9.4 Primary Outcomes

Overall, catheter-related infections were fewer in the intervention group ( $n=5/53$ , 9%) than the comparator group ( $n=10/52$ , 19%; relative risk [RR] 0.49, 95% CI 0.18 to 1.34%). Differences between groups was not statistically significant ( $p=0.15$ ; Table 9.4).

Catheter-related bloodstream infections occurred with similar frequency in participants treated with the intervention ( $n=1/53$ , 2%) and comparator solutions ( $n=2/52$ , 4%). The 2% CHG in 70% isopropyl alcohol solution did not significantly reduce the risk of CRBSI (RR 0.49, 95% CI 0.05 to 5.25;  $p=0.55$ ). The CRBSI rate was 0.03 (95% CI 0.03 to 0.04) episodes per 100 patient-months in the 2% CHG in 70% isopropyl group as compared to 0.07 (95% CI 0.06 to 0.08) episodes per 100 patient-months in the comparator group (appendix 9.4). Incidence density rates were not statistically different between groups ( $p=0.62$ ).

Catheter-associated bloodstream infections were higher in the comparator group ( $n=4$ , 8%) than in the 2% CHG in 70% isopropyl alcohol group ( $n=1$ , 2%), but the differences in proportion and risk were not statistically significant (RR, 0.25 95% CI 0.03 to 2.12,  $p=0.16$ ). In the intervention and comparator groups, the rate of CABSIs was 0.03 (95% CI 0.03 to 0.04) and 0.13 (95% CI 0.12 to 0.15) episodes per 100 patient-months, respectively ( $p=0.22$ ).

Participants in the intervention group developed three (6%) local access infections, which was similar for the comparator group ( $n=4$ , 8%; RR: 0.74, 95% CI 0.17 to 3.13;  $p=0.68$ ). Local access infection rates did not differ between groups ( $p=0.73$ ), with 0.1 (95% CI 0.09 to 0.11) episodes per 100 patient-months and 0.13 (95% CI 0.12 to 0.15) episodes per 100 patient-months for 2% CHG in 70% isopropyl alcohol and comparator treated participants.

A sensitivity analysis was undertaken to assess the potential impact of participants ( $n=16$ ) lost to follow-up on the primary outcomes analysis (appendix 9.5). Using the most pessimistic scenario, it was assumed that all participants lost to follow-up experienced a CABSIs at their last observed date. Additionally, an 'Intervention worst, comparator best' scenario assumed participants in the intervention group who were lost to follow-up experienced a CABSIs while those in the comparator group did not, and vice versa for

‘intervention best, comparator worst’. The analysis suggests that the main results are robust to participants lost to follow-up in the intervention group, because the results are not sensitive to a large increase in the number of events in the intervention group. However, if the worst case scenario was correct for the comparator group, this group would fare significantly worse than the intervention group. However, it is highly unlikely that this scenario could be true.

**Table 9.4 Primary outcomes main comparison**

Main Comparison 2% CHG in 70% alcohol vs. Comparator						
	2% CHG (n=53)	Comparator (n=52)	P <sup>4</sup>	Relative Risk (95% CI)	Absolute Risk Reduction (95% CI)	Total (n=105)
	N (%)	N (%)				N (%)
CRI <sup>1</sup>	5 (9)	10 (19)	0.15 (0.17)	0.49 (0.18 to 1.34)	0.09 (-0.04 to 0.23)	15 (14)
CRBSI <sup>2</sup>	1 (2)	2 (4)	0.55 (0.62)	0.49 (0.05 to 5.25)	0.02 (-0.07 to 0.11)	3 (3)
CABSI <sup>3</sup>	1 (2)	4 (8)	0.16 (0.21)	0.25 (0.03 to 2.12)	0.06 (-0.03 to 0.17)	5 (5)
Local access infection	3 (6)	4 (8)	0.68 (0.72)	0.74 (0.17 to 3.13)	0.02 (-0.09 to 0.13)	7 (7)

<sup>1</sup>CRI, Catheter-related infection; <sup>2</sup>CRBSI, Catheter-Related Bloodstream Infection; <sup>3</sup>CABSI, Catheter-Associated Bloodstream Infection; <sup>4</sup>p-value chi-square (Fisher’s Exact test)

#### 9.4.1 Primary outcomes sub-comparison 1

There were four (9%) catheter-related infections in the intervention group (n=42) and eight (19%) in the 0.5% CHG in 70% isopropyl alcohol (sub-comparison 1) group (n=42; RR 0.50, 95% CI 0.16 to 1.53) difference between groups was not statistically significant (p=0.21; Tables 9.5). The frequency of CRBSI in the 42 participants treated with 0.5% CHG in 70% isopropyl alcohol (sub-comparison 1) was two (5%), an incidence rate of 0.09 episodes per 100 patient-months (appendix 9.6). Of the 42 participants treated with 2% CHG in 70% isopropyl alcohol, none developed a CRBSI. The difference in proportion and risk were not statistically significant (RR 0.2, 95% CI 0.01 to 4.04; p=0.15).

Two (5%) participants in the 0.5% CHG in 70% isopropyl alcohol group developed a CABSIs as compared to one (2%) participant in the intervention group. When compared to the sub-comparison 1 solution, 2% CHG in 70% isopropyl alcohol did not significantly reduce the risk of CABSIs (RR 0.5 95% CI 0.05 to 5.31;  $p=0.56$ ). The CABSIs incidence density rate in participants treated with 2% CHG in 70% isopropyl alcohol and 0.5% CHG in 70% isopropyl group was 0.04 and 0.09 episodes per 100 patient-months ( $p=0.62$ ), respectively.

Overall, three (7%) participants treated with 2% CHG in 70% isopropyl alcohol developed a local access infection, which was similar to participants ( $n=4$ , 10%) treated with 0.5% CHG in 70% isopropyl alcohol. The differences between the intervention and 0.5% CHG in 70% isopropyl alcohol groups, in proportion and risk, were not significant (RR 0.75, 95% CI 0.18 to 3.15;  $p=0.70$ ). Incidence density rates for local access infection were not significantly different, with 0.13 and 0.17 episodes per 100 patient-months for patients treated with the intervention and sub-comparison 1 solutions ( $p=0.73$ ).

#### **9.4.2 Primary outcomes sub-comparison 2**

There was one (9%) catheter-related infection in the intervention group ( $n=11$ ) compared to two events (20%) in the 0.05% aqueous CHG solution (sub-comparison 2) group ( $n=10$ ; RR 0.45, 95% CI 0.05 to 4.28;  $p=0.47$ ). Of the ten patients treated with a 0.05% aqueous CHG solution, none developed a CRBSI, as compared to one (9%) of the 11 patients treated with 2% CHG in 70% isopropyl alcohol. When compared to the sub-comparison 2 solution, 2% CHG in 70% isopropyl alcohol did not significantly reduce the risk of CRBSI (RR 2.75, 95% CI 0.12 to 60.70;  $p=0.33$ ).

The frequency of CABSIs was higher in 0.05% aqueous CHG group ( $n=2$ , 20%) than the 2% CHG in 70% isopropyl alcohol group ( $n=0$ ). Difference in proportion and risk was not statistically significant (RR 0.18, 95% CI 0.01 to 3.41;  $p=0.12$ ). The incidence rate of CABSIs in participants treated with a 0.05% aqueous CHG solution was 0.28 episodes per 100 patient-months ( $p=0.25$ ; appendix 9.7). There were no episodes of local access infection in participants treated with either a 0.05% aqueous CHG or a 2% CHG in 70% isopropyl alcohol solution.

**Table 9.5 Primary outcomes sub-comparison 1 & 2**

	Sub comparison 1 2% CHG in 70% alcohol versus 0.5% CHG in 70% alcohol N (%)					Sub comparison 2 2% CHG in 70% alcohol versus 0.05% aqueous CHG N (%)				
	2% CHG (n=42) N (%)	0.5% CHG (n=42) N (%)	<i>P</i> <sup>4</sup>	Relative Risk (95% CI)	Absolute Risk Reduction (95% CI)	2% CHG (n=11) N (%)	0.05% CHG (n=10) N (%)	<i>p</i>	Relative Risk (95% CI)	Absolute Risk Reduction (95% CI)
CRI <sup>1</sup>	4 (9)	8 (19)	0.21 (0.35)	0.50 (0.16 to 1.53)	0.09 (-0.06 to 0.25)	1 (9)	2 (20)	0.47 (0.59)	0.45 (0.05 to 4.28)	0.11 (-0.21 to 0.43)
CRBSI <sup>2</sup>	0	2 (5)	0.15 (0.50)	0.20 (0.01 to 4.04)	0.05 (-0.04 to 0.16)	1 (9)	0	0.33 (1.0)	2.75 (0.12 to 60.70)	-0.09 (-0.40 to 0.20)
CABSI <sup>3</sup>	1 (2)	2 (5)	0.56 (1.0)	0.50 (0.05 to 5.31)	0.02 (-0.08 to 0.13)	0	2 (20)	0.12 (2.14)	0.18 (0.01 to 3.41)	0.20 (-0.09 to 0.51)
Local access infection	3 (7)	4 (10)	0.70 (1.0)	0.75 (0.18 to 3.15)	0.02 (-0.11 to 0.16)	0	0	NA <sup>5</sup>	NA	NA

<sup>1</sup>CRI, Catheter-related infection; <sup>2</sup>CRBSI, Catheter-Related Bloodstream Infection; <sup>3</sup>CABSI, Catheter-Associated Bloodstream Infection; <sup>4</sup>p-value chi-square (Fisher's Exact test), <sup>5</sup>NA, Not Applicable

## 9.5 Secondary Categorical Outcomes

Two (4%) intervention participants experienced an access-associated bacteraemia as compared to eight (15%) in the comparator group (RR 0.25, 95% CI 0.06 to 1.10; Table 9.6). Although the chi-square test found a significant difference between the groups ( $\chi^2 (1) = 4.10$   $p=0.04$ ), this was not confirmed by the Fisher's Exact test ( $p=0.05$ ). The incidence rate of access-associated bacteraemia was 0.07 (95% CI 0.06 to 0.08) episodes per 100 patient-months for patients treated with 2% CHG in 70% isopropyl alcohol solution and 0.27 (95% CI 0.25 to 0.28) episodes per 100 patient-months for participants in the comparator group ( $p=0.06$ ; appendix 9.8).

In the comparator group, 12 (23%) participants developed a vascular access infection, a rate of 0.40 (95% CI 0.38 to 0.42) episodes per 100 patient-months. Participants treated with 2% CHG in 70% isopropyl alcohol solution had a lower frequency of vascular access infections ( $n=5$ , 9%), but this difference was not statistically significant (RR 0.55, 95% CI 0.2 to 1.52;  $p=0.06$ ). The vascular access infection rate in the intervention group rate was 0.17 (95% CI 0.15 to 0.18) episodes per 100 patient-months ( $p=0.10$ ).

The 2% CHG in 70% isopropyl alcohol solution did not reduce the risk of local access infections (oral antibiotics) (RR 0.25, 95% CI 0.03 to 2.12). Participants in the comparator group had a higher number of local access infections (oral antibiotics, [ $n=4$ , 8%]) than participants treated with 2% CHG in 70% isopropyl alcohol solution ( $n=1$ , 2%;  $\chi^2 (1) = 1.95$ ,  $p=0.16$ ). The rate of local access infection (oral antibiotics) was 0.03 (95% CI 0.03 to 0.04) episodes per 100 patient-months for participants treated with 2% CHG in 70% isopropyl alcohol as compared to 0.13 (95% CI 0.12 to 0.15) episodes per 100 patient-months for comparator participants ( $p=0.22$ ).

There were five (9%) deaths in the 2% CHG in 70% isopropyl alcohol group, an incidence rate of 0.17 (95% CI, 0.15 to 0.18) episodes per 100 patient-months. This compared to nine (17%) deaths in the comparator group (0.30 [95% CI 0.28 to 0.32] episodes per 100 patient-months; RR 0.58, 95% CI 0.21 to 1.60;  $p=0.23$ ). None of the deaths were caused by catheter-related infections. Of the 14 deaths, causes related to infection ( $n=5$ ), cardio-vascular disease ( $n=4$ ) and withdrawal from dialysis ( $n=2$ ). The remaining three cases related to liver failure secondary to alcohol, renal cancer and calciphylaxis.

**Table 9.6 Secondary categorical outcomes<sup>1</sup> main comparison**

	Main Comparison					
	2% CHG in 70% alcohol vs. Comparator					
	2% CHG	Comparator	<i>P</i> <sup>2</sup>	Relative Risk (95% CI)	Absolute Risk Reduction (95% CI)	Total
	( <i>n</i> =53)	( <i>n</i> =52)				( <i>n</i> =105)
N (%)	N (%)				N (%)	
Access associated bacteraemia	2 (4)	8 (15)	0.04 (0.05)	0.25 (0.06 to 1.10)	0.12 (0.00 to 0.24)	10 (10)
Vascular access infection	5 (9)	12 (23)	0.06 (0.07)	0.55 (0.2 to 1.52)	0.14 (-0.00 to 0.28)	17 (16)
Local access infection PO Antibiotics	1 (2)	4 (8)	0.16 (0.20)	0.25 (0.03 to 2.12)	0.06 (-0.03 to 0.17)	5 (5)
Mortality at 12 months	5 (9)	9 (17)	0.23 (0.26)	0.58 (0.21 to 1.60)	0.08 (-0.06 to 0.22)	14 (13)
Adverse reaction	4 (7)	0	0.04 (0.12)	NA <sup>3</sup>	-0.07 (-0.18 to -0.00)	4 (4)
Hospitalisation	37 (70)	42 (81)	0.19 (0.26)	0.86 (0.69 to 1.01)	0.11 (-0.06 to 0.27)	79 (75)
Vascular access hospitalisation	4 (7)	5 (10)	0.70 (0.74)	0.79 (0.22 to 2.76)	0.02 (-0.10 to 0.14)	9 (9)
Infection related hospitalisation	12 (23)	11 (21)	0.85 (1.0)	1.07 (0.52 to 2.21)	-0.01 (-0.17 to 0.15)	23 (22)
Catheter infection related hospitalisation	3 (6)	6 (11)	0.28 (0.32)	0.49 (0.13 to 1.86)	0.06 (-0.06 to 0.18)	9 (9)
CVC removal	10 (19)	15 (29)	0.23 (0.26)	0.65 (0.32 to 1.32)	0.10 (-0.06 to 0.26)	25 (24)
CVC removal dysfunction	6 (11)	4 (8)	0.53 (0.74)	1.47 (0.44 to 4.92)	-0.04 (-0.16 to 0.09)	10 (10)
CVC removal infection	3 (6)	6 (12)	0.28 (0.32)	0.49 (0.13 to 1.86)	0.06 (-0.06 to 0.18)	9 (9)

<sup>1</sup>at least one episode; <sup>2</sup>*p*-value chi-square (Fisher's Exact test); <sup>3</sup>NA, Not Applicable.

Participants treated with the comparator solutions experienced no adverse events. In contrast, four (7%) participants in the intervention group experienced a skin sensitivity reaction to 2% CHG in 70% isopropyl alcohol solution (0.13 [95% CI 0.12 to 0.15] episodes per 100 patient-months;  $\chi^2$  (1) =4.08,  $p=0.04$ ; Fisher's Exact test:  $p=0.12$ ). Three participants in the intervention group complained that the 2% CHG in 70% isopropyl alcohol solution stained their clothes or skin. This was not anticipated when the trial was designed and caused great annoyance and inconvenience to these participants, so much so they asked to withdraw from the trial. Classifying this event as an adverse reaction, increased the total number of adverse reactions to seven, a statistically significant difference between both groups ( $\chi^2$  (1) =7.36,  $p=0.01$ ; Fisher's Exact test:  $p=0.01$ ).

Over two thirds of participants ( $n=37$ , 70%) treated with a 2% CHG in 70% isopropyl alcohol solution experienced at least one episode of hospitalisation (1.23 [95% CI 1.19 to 1.27] episodes per 100 patient-months). This compared to 81% ( $n=42$ ) of participants in the comparator groups (1.39 [95% CI 1.35 to 1.44] episodes per 100 patient-months;  $p=0.58$ ). When compared to the comparator solution, the 2% CHG in 70% isopropyl alcohol solution had no statistically significant effect on the frequency of hospitalisation (RR, 0.86, CI 0.69 to 1.01;  $p=0.19$ ).

A number of hospitalisations occurred because of problems with vascular access, four (7%) in the 2% CHG in 70% isopropyl alcohol group and five (10%) in the comparator group (RR 0.79, 95% CI 0.22 to 2.76;  $p=0.70$ ). Overall infection (excluding catheter-related infection) accounted for 23% ( $n=12$ ) of hospitalisations in the 2% CHG in 70% isopropyl alcohol group, similar to the comparator group ( $n=11$ , 21%). The 2% CHG in 70% isopropyl alcohol solution did not significantly reduce the risk of infection-related hospitalisation (RR 1.07, 95% CI 0.52 to 2.21;  $p=0.85$ ). Catheter-infection related hospitalisations were higher in the comparator group ( $n=6$ , 11%) than the intervention group ( $n=3$ , 6%); but this difference was not statistically significantly (RR 0.49, 95% CI 0.13 to 1.86;  $p=0.28$ ).



Ten (19%) participants in the 2% CHG in 70% isopropyl alcohol group had their CVC removed; a rate of 0.33 (95% CI 0.31 to 0.35) episodes per 100 patient-months. The rate of catheter removal in the comparator group ( $n=15$ , 29%) was higher at 0.50 (95% CI 0.47 to 0.52) episodes per 100 patients months; but differences in group proportions and risk were not statistically significant (RR 0.65, 95% CI 0.32 to 1.32;  $p=0.23$ ).

Catheter dysfunction accounted for 11% ( $n=6$ ) of catheter removals in the 2% CHG in 70% isopropyl alcohol group and 8% ( $n=4$ ) in the comparator group, rates were 0.20 (95% CI 0.18 to 0.22) episodes per 100 patient-months and 0.13 (95% CI 0.12 to 0.15;  $p=0.55$ ) episodes per 100 patient months, respectively. There was no significant difference in group proportions or risk (RR 1.47, 0.44 to 4.92;  $p=0.53$ ).

Removal of a CVC because of catheter-related infection was higher in the comparator group ( $n=6$ , 12%) than in the 2% CHG in 70% isopropyl alcohol group ( $n=3$ , 6%). When compared to the comparator solution, the intervention solution did not have a statistically significant favourable effect on catheter removal due to infection (RR 0.49, 95% CI 0.13 to 1.86;  $p=0.28$ ). The rate of catheter removal because of infection was 0.1 episodes (95% CI 0.09 to 0.11) per 100 patient-months in the intervention group and 0.2 (95% CI 0.18 to 0.22) episodes per 100 patient-months in the comparator group;  $p=0.34$ ).

### **9.5.1 Secondary categorical outcomes sub-comparison 1**

In sub-comparison 1, there was no statistically significant differences in group proportions or risk between participants treated with 2% CHG in 70% isopropyl alcohol solution ( $n=42$ ) and 0.5% in 70% isopropyl alcohol solution ( $n=42$ ; appendix 9.9) in relation to access-associated bacteraemia (1 [2%] vs. 5 [12%]; RR 0.20, 0.02 to 1.64;  $p=0.09$ ); vascular access infection (4 [9%] vs. 9 [21%]; RR 0.44, 0.15 to 1.33;  $p=0.13$ ) and local access infection (oral antibiotics; 1 [2%] vs. 3 [7%]; RR 0.33, 0.04 to 3.08;  $p=0.31$ ). The rate of access-associated bacteraemia was 0.04 and 0.22 episodes per 100 patient-months ( $p=0.12$ ) for participants assigned to the intervention and 0.5% in 70% isopropyl alcohol solutions (appendix 9.10). There was no significant difference in the incidence of vascular access infection in participants treated with the intervention solution (0.17 episodes per 100 patient-months) as compared to participants treated with 0.5% in 70% isopropyl alcohol solution

(0.40 episodes per 100 patient-months;  $p=0.18$ ). The incidence density rate for local access infection (oral antibiotics) did not differ between the intervention (0.04 episodes per 100 patient-months) and sub-comparison 1 solutions (0.13 episodes per 100 patient-months;  $p=0.37$ ).

In relation to the other secondary categorical outcomes, participants assigned to 0.5% in 70% isopropyl alcohol solution did not differ significantly from participants treated with the 2% CHG in 70% isopropyl alcohol solution; see appendix 9.9 and 9.10.

### **9.5.2 Secondary categorical outcomes sub-comparison 2**

In sub-comparison 2, the proportion of participants with access-associated bacteraemia did not differ significantly between 2% CHG in 70% isopropyl alcohol and 0.05% aqueous CHG treated participants ( $n=1$ , 9% vs.  $n=3$ , 30%;  $\chi^2(1) = 1.48$ ,  $p=0.22$ ; RR 0.30, 95% CI 0.04 to 2.46; appendix 9.11). The rate of access-associated bacteraemia in participants assigned to the 2% CHG in 70% isopropyl alcohol and 0.05% aqueous CHG groups was 0.14 and 0.42 episodes per 100 patient-months ( $p=0.37$ ), respectively (appendix 9.12).

In relation to vascular access infection (1 [9%] vs. 3 [30%]; RR 0.30, 95% CI 0.04 to 2.46) and local access infection (oral antibiotics) (Nil vs. 1 [10%]; RR 0.18, 95% CI 0.01 to 3.41), there was no statistically significant difference between 2% CHG in 70% isopropyl alcohol treated and 0.05% aqueous CHG treated participants ( $p=0.22$  and  $p=0.28$ ). Incidence density rates for vascular access infection and local access infection (oral antibiotics) did not differ significantly between intervention and sub-comparison 2 groups ( $p=0.37$  and 0.50).

For the remaining secondary outcomes, no statistically significant differences were found between 0.05% aqueous CHG and 2% CHG in 70% isopropyl alcohol groups in proportions and risk of developing at least one secondary outcome; see appendix 9.11 and 9.12.

## 9.6 Secondary Continuous Outcomes

Secondary continuous outcome distributions were assumed normal and independent *t*-tests were run. A normality test (Kolmogorov-Smirnov) on the sample was performed and deviations from normality were detected. Non-parametric tests (Mann-Whitney) were therefore run for comparison, and *p*-values were mostly in agreement with the *t*-test results. Results from both the *t*-test and Mann-Whitney test are presented, giving a more complete picture of the results, as opposed to reporting just one set of tests.

### 9.6.1 Secondary continuous outcomes main comparison

There was no significant difference between the 2% CHG in 70% isopropyl alcohol group and the comparator group (Table 9.7) with regard to intravenous (IV) antimicrobial starts ( $t [103]=1.20, p=0.23; U= 1216.5, z= -1.085, p=0.28, r=0.11$ ). Mean intravenous antimicrobial starts were 1.09 (SD 1.39; median 1, IQR 2) and 1.44 (SD 1.58; median 1, IQR 2), respectively. The incidence density rate of IV antimicrobial starts was 1.93 (95% CI 1.88 to 1.98) episodes per 100 patient-months for the intervention group as compared to 2.50 (95% CI 2.43 to 2.55) episodes per 100 patient-months for the comparator group ( $p=0.16$ ; appendix 9.13).

Participants in the 2% CHG in 70% isopropyl alcohol group had a lower mean number of positive blood cultures (0.15, SD 0.46; median zero) than the comparator group (0.35, SD 0.79; median zero); however, differences between groups were not significant ( $t [81]=1.55, p=0.12; U=1259, z= -1.221, p=0.22, r=0.12$ ). Rates of positive blood cultures were not significantly different, with 0.27 (95% CI 0.25 to 0.28) episodes per 100 patient-months for intervention participants and 0.60 (95% CI 0.57 to 0.63) episodes per 100 patient-months for participants treated with the comparator solution ( $p=0.05$ ). There was no significant difference between groups ( $p=0.28$ ) and research sites ( $p=0.57$ ) in the mean number of blood cultures taken from trial participants.

**Table 9.7 Secondary continuous outcomes main comparison**

Main Comparison 2% CHG in 70% alcohol vs. Comparator			
	Mean (SD) 2% CHG (n=53)	Comparator (n=52)	<i>p</i> <sup>1</sup>
IV antimicrobial starts	1.09 (1.39)	1.44 (1.58)	0.23 (0.28)
Positive blood cultures	0.15 (0.46)	0.35 (0.79)	0.12 (0.22)
Hospitalisation	1.70 (1.61)	2.12 (2.10)	0.26 (0.38)
Vascular access-related hospitalisation	0.09 (0.35)	0.12 (0.38)	0.77 (0.71)
Infection-related hospitalisation	0.30 (0.64)	0.44 (1.06)	0.41 (0.99)
Catheter infection-related hospitalisation	0.06 (0.23)	0.13 (0.40)	0.22 (0.28)

<sup>1</sup>*p*-value independent two sample *t*-test (Mann-Whitney)

The mean number of all cause-hospitalisations were 1.70 (SD 1.61; median 1, IQR 3) and 2.12 (SD 2.10; median 2, IQR 2) for participants treated with 2% CHG in 70% isopropyl alcohol solution and the comparator solution, respectively ( $t [103]=1.14$ ,  $p=0.26$ ;  $U=1243$ ,  $z=-0.884$ ,  $p=0.38$ ,  $r=0.09$ ). All cause-hospitalisation rates were 2.99 (CI 2.93 to 3.05) episodes per 100 patient-months for the intervention group and 3.65 (95% CI 3.58 to 3.72) episodes per 100 patient-months for the comparator group ( $p=0.16$ ).

Intervention and comparator participants were hospitalised because of vascular access problems, with mean hospitalisations of 0.09 (SD 0.35; median zero) and 0.12 (SD 0.38; median zero); differences were not significant ( $t [103]=0.29$ ,  $p=0.77$ ;  $U=1350$ ,  $z=-0.370$ ,  $p=0.71$ ,  $r=0.04$ ). Participants were also hospitalised for infection (other than catheter-related infections). The mean number of infection-related hospitalisations was 0.30 (SD 0.64; median zero) and 0.44 (SD 1.06; median zero), respectively. No differences between groups were found ( $t [103]=0.82$ ,  $p=0.41$ ;  $U=1376.5$ ,  $z=-0.013$ ,  $p=0.99$ ,  $r=0.001$ ). Participants in both groups had a comparable mean number of hospitalisations due to catheter-related infection, which were not significantly different (0.06, SD 0.23, median zero vs. 0.13, SD 0.40, median zero;  $t [82]=1.22$ ,  $p=0.22$ ;  $U=1295.5$ ,  $z=-1.09$ ,  $p=0.28$ ,  $r=0.11$ ).

## **9.6.2 Secondary continuous outcomes sub-comparison**

### **1 & 2**

There was no significant difference between 2% CHG in 70% isopropyl alcohol and 0.5% CHG in 70% isopropyl alcohol (sub-comparison 1) or 0.05% aqueous CHG (sub-comparison 2) solutions in the mean number of participants with intravenous antimicrobial starts, episodes of positive blood cultures, hospitalisation, vascular access-related hospitalisation, infection-related hospitalisation and catheter infection-related hospitalisation (see appendix 9.14, 9.15 and 9.16). In sub-comparison 1, incidence density rates for positive blood cultures differed significantly between participants treated with 2% CHG in 70% isopropyl alcohol (0.13 episodes per 100 patient-months) and 0.5% CHG in 70% isopropyl alcohol solutions (0.52 episodes per 100 patient-months;  $p=0.02$ ).

## **9.7 Survival Outcomes**

Using Kaplan-Meier survival analysis, the proportion of participants not experiencing a CRBSI, CABSIs, local access infection, CVC removal and CVC removal due to infection are estimated from the survival curves at six and 12 months. As the numbers of events were small, median time to an event could not be estimated, because the survival curve did not cross the probability of half the participants experiencing the event. Estimating the mean survival time is not appropriate given the large proportion of censored observations (Altman 1991). The log rank test was used to test the statistical significance of any differences between the survival curves (Table 9.8).

**Table 9.8 Proportion surviving CVC-related events**

		Main Comparison 2% CHG in 70% alcohol vs. Comparator								
		2% CHG in 70% alcohol N=53				Comparator N=52				
Time Interval		Cumulative Proportion Surviving at the Time		Cumulative Events N	Remaining Cases N (%)	Cumulative Proportion Surviving at the Time		Cumulative Events N	Remaining Cases N (%)	Log Rank Test
		Estimate	Std. Error			Estimate	Std. Error			
CRBSI <sup>1</sup>	6 months	0.98	0.02	1	37 (70)	0.97	0.03	1	35 (67)	$X^2=0.37$ , $df^3=1$ , $p=0.54$
	12 months	0.98	0.02	1		0.94	0.04	2		
CABSI <sup>2</sup>	6 months	0.98	0.02	1	36 (68)	0.93	0.04	3	33 (63)	$X^2=2.04$ , $df=1$ , $p=0.15$
	12 months	0.98	0.02	1		0.90	0.05	4		
Local access infection	6 months	0.95	0.03	2	36 (68)	0.96	0.03	2	36 (69)	$X^2=0.16$ , $df=1$ , $p=0.70$
	12 months	0.92	0.04	3		0.90	0.05	4		
CVC removal	6 months	0.90	0.45	5	36 (68)	0.86	0.05	6	35 (70) <sup>4</sup>	$X^2=0.54$ , $df=1$ , $p=0.46$
	12 months	0.76	0.07	10		0.68	0.07	13		
CVC removal infection	6 months	0.96	0.03	2	38 (72)	0.93	0.04	3	35 (67) <sup>5</sup>	$X^2=0.66$ , $df=1$ , $p=0.41$
	12 months	0.93	0.04	3		0.87	0.06	5		

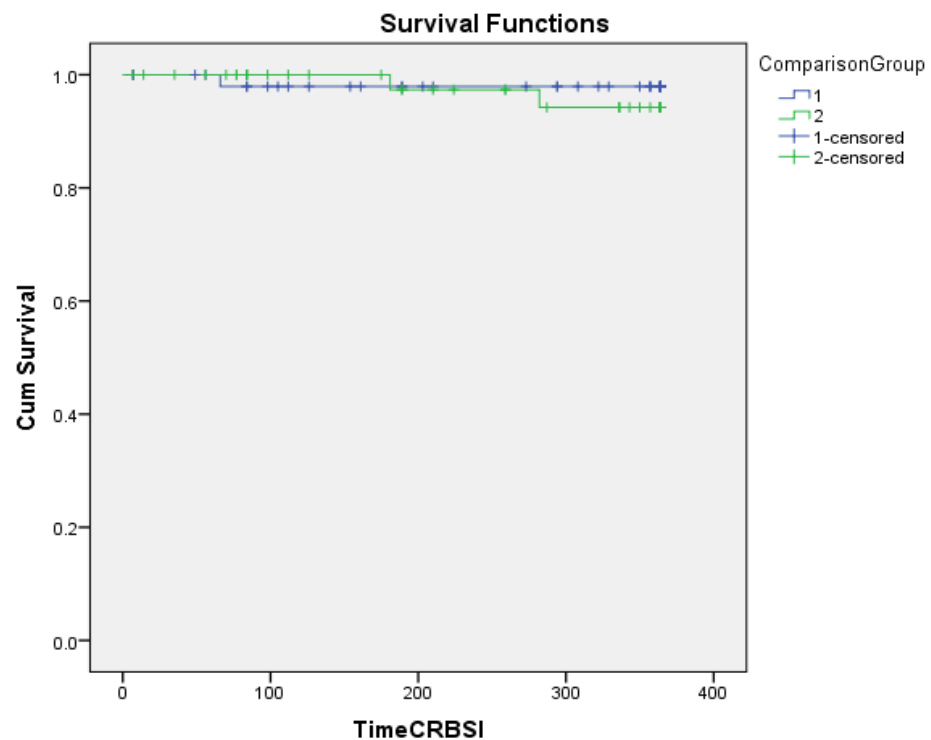
<sup>1</sup>CRBSI, Catheter-related bloodstream infection; <sup>2</sup>CABSI, Catheter-associated bloodstream infection; <sup>3</sup>df; Degrees of freedom; <sup>4</sup>data are estimated on 50 participants with known dates for catheter removal; <sup>5</sup>data are estimated on 51 participants with known dates for catheter removal.

### 9.7.1 Time to catheter-related events main comparison

The cumulative number of CRBSIs at six months and 12 months, in the 2% CHG in 70% isopropyl alcohol group, was one; this compares to one and two in the comparator group. The proportion of intervention participants who were infection free at six and 12 months was 98% (SE 0.02), compared to 97% (SE 0.03) and 94% (SE 0.04) participants in the comparator group for the same intervals. The difference between survival curves (figure 9.2) was not significant ( $p=0.54$ ).

**Figure 9.2 Kaplan-Meier curve: Time to CRBSI**

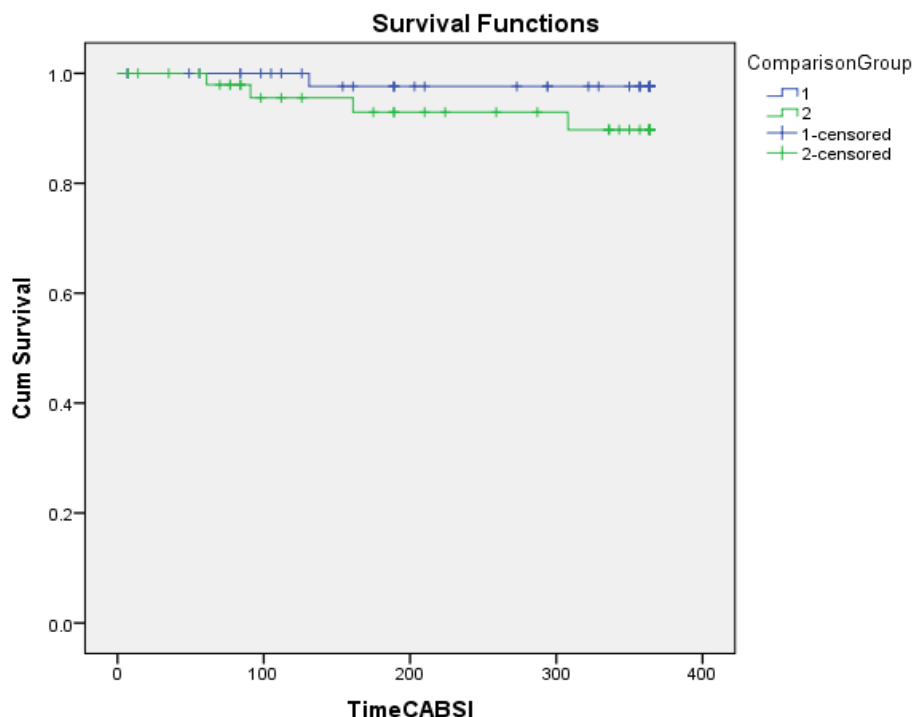
2% CHG in 70% isopropyl alcohol (blue line) versus Comparator solution (green line)



The proportion of the 53 participants who were allocated to 2% CHG in 70% isopropyl alcohol participants who had not developed a CABSIs was 98% at both six and 12 months (SE 0.02). A lower proportion of comparator participants were free from CABSIs at the same time intervals, 93% (SE 0.04) and 90% (SE 0.05), respectively ( $p=0.15$ ; figure 9.3). The accumulated CABSIs events, at six and 12 months, were one for the intervention group. For the same time intervals, the comparator CABSIs accumulated events were three and four.

### Figure 9.3 Kaplan-Meier curve: time to CABS

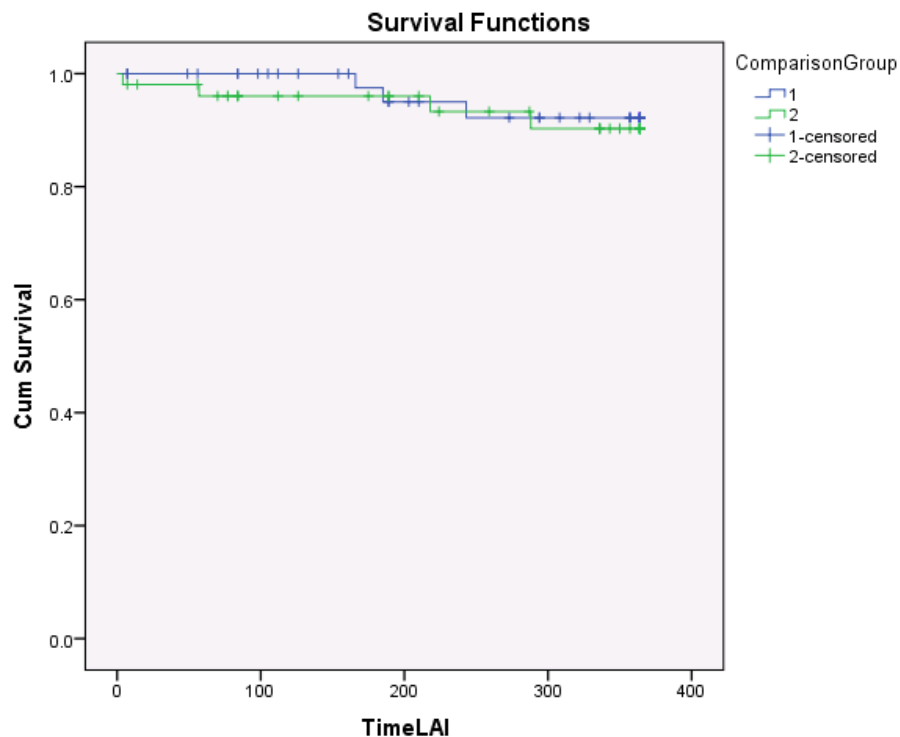
2% CHG in 70% isopropyl alcohol (blue line) versus Comparator solution (green line)



The proportion of participants in the intervention group who were free from local exit site infection at six and 12 months was 95% (SE 0.03) and 92% (SE 0.04), respectively. There were two infections by six months and three by 12 months. The comparator group had the same number of local access infections at six months ( $n=2$ ), with an estimated proportion of 96% (SE 0.03) participants who were infection free. At 12 months, the number of accumulated local access infections was four, the proportion infection free on the last day of the trial was lower than in the intervention group (90%, SE 0.05;  $p=0.70$ ; figure 9.4).



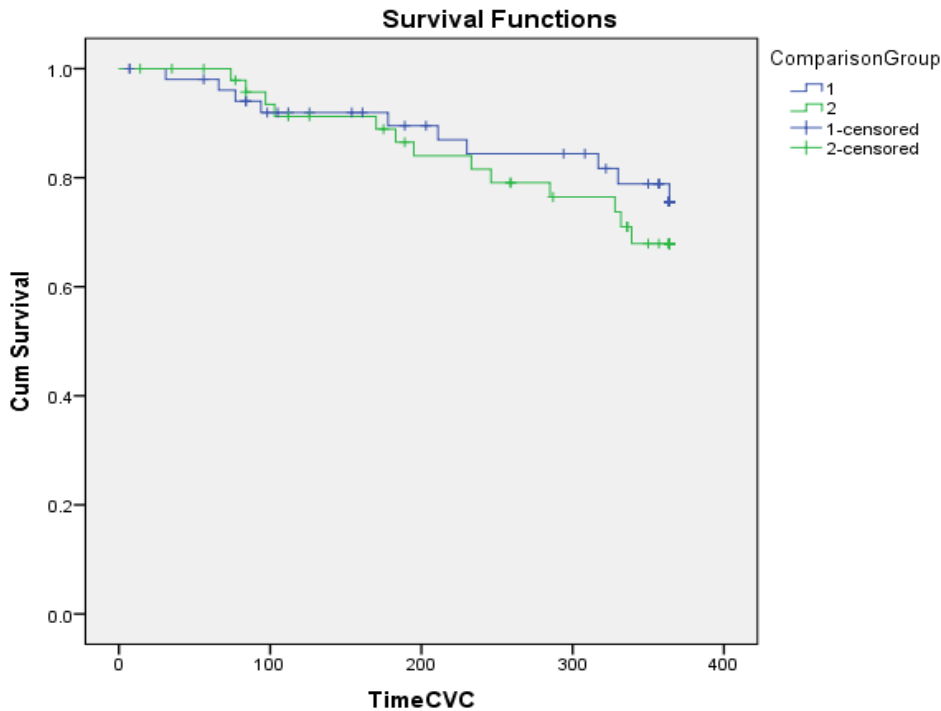
**Figure 9.4 Kaplan-Meier curve: time to Local access infection**  
 2% CHG in 70% isopropyl alcohol (blue line) versus Comparator solution  
 (green line)



Catheter removal dates for two comparator participants were unknown; so the analysis for this group was based on 50 participants. Catheter survival at six and 12 months was 90% (SE 0.45) and 76% (SE 0.07) for participants treated with 2% CHG in 70% isopropyl alcohol. This compares to 86% (SE 0.05) and 68% (SE 0.07) for comparator participants. The accumulated number of catheter removals by six and 12 months for intervention and comparator participants was five and ten versus six and 13. Survival curves for intervention and comparator groups did not differ significantly ( $p=0.46$ ; figure 9.5).

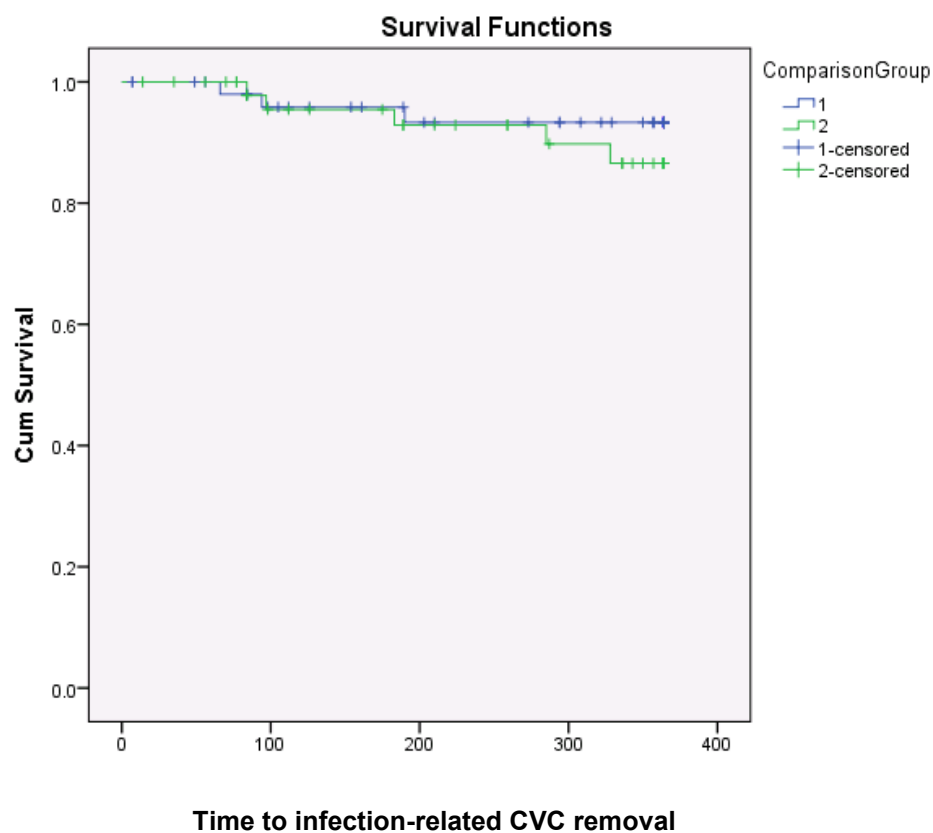
### Figure 9.5 Kaplan-Meier curve: catheter survival

2% CHG in 70% isopropyl alcohol (blue line) versus Comparator solution (green line)



One participant in the comparator group had their CVC removed because of an infection, but the date of removal was unknown. This event was not included in the survival analysis for the comparator group. A similar proportion of intervention and comparator participants had not had their catheter removed because of infection at the six month time point (96% [SE 0.03] vs. 93% [SE 0.04]). However, the comparator group (87%, SE 0.06) had a lower proportion of participants without this event as compared to the intervention group (93%, SE 0.04;  $p=0.41$ ; figure 9.6). Accumulated events at six and 12 months were two and three for the intervention group, and three and five in the comparator group.

**Figure 9.6 Kaplan-Meier curve: infection-related CVC removal**  
 2% CHG in 70% isopropyl alcohol (blue line) versus Comparator solution  
 (green line)



### 9.7.2 Time to catheter-related events sub-comparison 1 & 2

Survival analysis for sub-comparison 1 and 2 are provided in appendix 9.17 and 9.18. In sub-comparison 1 (2% CHG in 70% isopropyl alcohol [ $n=42$ ] versus 0.5% CHG in 70% isopropyl alcohol [ $n=42$ ]), there was no significant difference between survival curves for CRBSI ( $p=0.15$ ), CABSIs ( $p=0.55$ ) and local access infection ( $p=0.73$ ). In the comparator group, two participants were excluded from the survival analysis for catheter removal and one participant was excluded from the analysis of catheter removal due to infection. There was no significant difference between survival curves for CVC removal ( $p=0.32$ ) and removal due to infection ( $p=0.23$ ).

In sub-comparison 2 (2% CHG in 70% isopropyl alcohol [ $n=11$ ] versus 0.05% aqueous CHG [ $n=10$ ]), there was no significant difference between survival curves for CRBSI ( $p=0.34$ ), CABSIs ( $p=0.10$ ), CVC removal ( $p=0.58$ ) and CVC removal because of infection ( $p=0.34$ ). There were no local access infection events in sub-comparison 2.

## 9.8 Logistic Regression

As outlined in chapter 8 (section 8.21.6), the forced entry (appendix 9.19) and the stepwise logistic regression model (appendix 9.20) could not estimate the predictability of the independent variables on the likelihood that participants would develop a CABSIs. Even after selecting a subset of variables, the model could not be estimated (appendix 9.21). Despite collinearity diagnostics (appendix 9.22) suggesting that multicollinearity was not an issue, the standard errors logistic regression coefficients for both models could not be estimated and no inferences made. There are two possible explanations, the small CABSIs event rate and the possibility of quasi-complete separation. Both of these scenarios can result in coefficients that have unreasonably large standard errors.

## 9.9 Causative Organism

There was no statistically significant difference in the type of organisms that caused CRBSIs and CABSIs between the 2% CHG in 70% isopropyl alcohol and comparator groups (Table 9.9). However, it would not have been possible to detect differences given the limited amount of data available on the causative organism.

**Table 9.9 CRBSI<sup>1</sup> & CABS<sup>2</sup> causative organism main comparison**

Main Comparison 2% CHG in 70% alcohol vs. Comparator						
	CRBSI			CABS		
	2% CHG	Comparator	P <sup>3</sup>	2% CHG	Comparator	P
Coagulase negative staphylococci				0	1	
Enterococcus faecalis				0	1	
MRSA <sup>4</sup>	0	1		1	0	
MSSA <sup>5</sup>	1	1		0	2	
Total	1	2	0.39 (1)	1	4	0.17 (1)

<sup>1</sup>CRBSI, catheter-related bloodstream infection; <sup>2</sup>CABS, catheter-associated bloodstream infection; <sup>3</sup>P, p-value chi-square (Fisher's Exact test); <sup>4</sup>MRSA, methicillin resistant *staphylococcus aureus*; <sup>5</sup>MSSA. Methicillin sensitive *S. aureus*

## 9.10 Vascular Access Prevalence

During the 24 month period of the trial, the prevalence of vascular access for arterio-venous fistula (AVF) was 38%, arterio-venous graft (AVG) 1% and CVC 61% (table 9.10).

**Table 9.10 Vascular access prevalence**

Vascular Access	Research Site OA	Research Site OB	Research Site OV	Total
	N (%)	N (%)	N (%)	N (%)
AVF	694 (31)	1161 (44)	481 (40)	2336 (38)
AVG	0	48 (2)	0	48 (1)
CVC	1536 (69)	1438 (54)	718 (60)	3692 (61)
<b>Total</b>	2230	2647	1199	6076

## 9.11 Summary

In total, 105 patients gave their consent and entered the CHG trial. Randomisation assigned 53 to the intervention group (2% CHG in 70% isopropyl alcohol group) and 52 to the comparator group. Comparator participants were treated with a 0.5% in 70% isopropyl alcohol solution ( $n=42$ , sub-comparison 1) or a 0.05% aqueous CHG solution ( $n=10$ , sub-comparison 2). The number of participants in the main comparison groups lost to follow-up was similar (nine *versus* seven).

In general, participant baseline characteristics were similar between the main comparison groups, with the exception of insertion CVC site and use of trisodium citrate (Duralock, Medcomp®) CVC antimicrobial locking solution. Although there is a similar risk for catheter-related infections between subclavian and internal jugular catheter insertion sites, trial evidence on difference in risk between left and right internal insertion sites is lacking. Additionally, meta-analyses of CVC antimicrobial and non-antimicrobial locks solutions showed no significant effect in the reduction of catheter-related infection when patients were treated with trisodium citrate (Duralock Medcomp®). Given the robust methods used for allocation sequence generation and concealment these difference between groups are by chance through randomisation. However, it could be argued that using the antimicrobial lock, reduced the infection event rate in the comparator arm of the trial and thereby influenced the equivalent results between both two groups.

The intervention solution, 2% CHG in 70% isopropyl alcohol, did not significantly reduce the risk of CRBSI (RR 0.49, 95% CI 0.05 to 5.25,  $p=0.55$ ), CABSIs (RR 0.25, 95% CI 0.03 to 2.12,  $p=0.16$ ) and local access infection (RR 0.74, 95% CI 0.17 to 3.13,  $p=0.68$ ) when compared to the comparator solution. A sensitivity analysis was undertaken to assess the potential impact of participants lost to follow-up. Overall, the analysis indicates that the main results for the intervention group are robust to participants lost to follow, but in the highly unlikely worst case scenario the comparator group would fare worse than the intervention group.

When compared to the 0.5% in 70% isopropyl alcohol solution (sub-comparison 1) or 0.05% aqueous CHG (sub-comparison 2), the intervention solution did not significantly reduce the risk of CRBSI, CABSIs and local access infection.

The 2% CHG in 70% isopropyl alcohol solution did not significantly reduce the risk of access-associated bacteraemia, vascular access infection and local access infection (oral antibiotics) when compared to the comparator solution. There were no statistically significant differences between participants treated with 2% CHG in 70% isopropyl alcohol and the comparator solution in relation to all-cause mortality, all cause-hospitalisation, vascular access-related hospitalisation, overall infection (excluding catheter-related infection) hospitalisation, catheter infection-related hospitalisations, CVC removal rate and CVC removal because of catheter-related infection or dysfunction. In sub-comparison 1, incidence rates for positive blood cultures differed significantly between participants treated with 2% CHG in 70% isopropyl alcohol and 0.5% CHG in 70% isopropyl alcohol solutions. Although there was no significant difference in the mean number of positive blood cultures observed in both groups.

Four participants in the intervention group experienced an adverse reaction to 2% CHG in 70% isopropyl alcohol solution; a skin sensitivity reaction to the intervention solution. This compared to no adverse reactions in the comparator group. A number of participants withdrew from the trial because the intervention stained their clothes, an outcome that had not been anticipated. Including these participants in the total adverse reactions led to a statistically significant differences between groups ( $p=0.01$ ).

Secondary categorical outcomes did not significantly differ between 2% CHG in 70% isopropyl alcohol treated and 0.5% CHG in 70% isopropyl alcohol solution (sub-comparison 1) or 0.05% aqueous CHG (sub-comparison 2) treated participants.

For continuous data secondary outcomes, there were no significant differences between participants treated with 2% CHG in 70% isopropyl alcohol and the comparator solutions in relation to the mean number of IV antimicrobial starts, positive blood cultures, mean number of hospitalisations, infection-related hospitalisations and hospitalisations due to vascular access

problem and catheter-related infection. There was no significant difference in continuous secondary outcomes between the intervention group and sub-comparison 1 or sub-comparison 2.

Median time to CVC-related events could not be estimated due to the low number of events. The proportion of participants not experiencing the event was estimated from survival curves at six and 12 months. The proportion of participants in the intervention group free from CRBSI and CABSIs at six and 12 months was 98% (SE 0.02). This compares to 97% (SE 0.03) and 94% (SE 0.04,  $p=0.54$ ) for the same time intervals for comparator participants. The proportion of comparator participants free from CABSIs was lower at six (93%, SE 0.04) and 12 months (90%, SE 0.05), when compared to participants in the intervention group (98%, SE 0.02; at six and 12 months;  $p=0.15$ ). There was no significant difference between survival curves for local access infection ( $p=0.70$ ). A lower proportion of participants in the comparator group retained their CVC at six (86%, SE 0.05) and 12 months (68%, SE 0.07) when compared to participants in the intervention group, 90% (SE 0.05) and 76% (SE 0.07), respectively. There was no significant difference between survival curves for catheter removal due to infection ( $p=0.41$ )

The forced entry and the stepwise logistic regression model could not estimate the predictability of the independent variables on the likelihood that participants would develop a CABSIs. Even after selecting a subset of variables, the model could not be estimated.

## **9.12 Conclusion: Impact on the Design of the Main Study**

This pilot multi-centre trial was focused on the feasibility of undertaking such a study as a multi-national, multi-centre trial, with an emphasis on the future design of the main study. The outcome of the randomisation process and trial findings have important implications for the design of the study.

A total of 201 patients with CVCs were assessed for trial eligibility, and 52% ( $n=105$ ) of these entered the trial. The high number of patients who were not eligible ( $n=52$ ), refused to participate ( $n=44$ ) and were lost to follow-up ( $n=16$ ) has important implications for the main study. The sample size calculation for



the main study needs to incorporate a 15% increase to account for losses due to follow-up. Additionally, the design of the main study may need to be modified so that more of the eligible participants will be included.

Significant differences were noted in a minority of baseline characteristics between the 2% CHG in 70% isopropyl alcohol and comparator groups. Given the large number of tests performed caution should be exercised in their interpretation, as type 1 error rates are likely to be larger than 0.05. No explicit correction for multiple testing was made.

In relation to the trial's primary outcomes, the analyses indicate that 2% CHG in 70% isopropyl alcohol solution did not significantly reduce the risk of CRBSI, CABSIs and local access infection compared to participants in the comparator group as a whole or participants treated with 0.5% CHG in 70% isopropyl alcohol or 0.05% aqueous CHG solution.

No participants in the comparator groups experienced an adverse reaction. In contrast, four participants experienced a skin sensitivity reaction to 2% CHG in 70% isopropyl alcohol solution. A further three participants asked for the intervention solution to be discontinued as it either stained their clothes or skin. These events were not identified in the trial protocol as an adverse reaction to 2% CHG in 70% isopropyl alcohol. This particular issue related to a specific dye in the Chloraprep® applicator and could be avoided in the main study by using a clear Chloraprep® solution.

Overall, the number of primary events in the CHG trial were low, which may have contributed to the inability of the logistic regression models to estimate the predictability of independent variables on the likelihood that participants would develop a CABSIs. The use of a large sample number, may result in a potentially larger event rate in the main study; thus, eliminating this issue. The independent predictor variables included in the logistic regression models also need to be reviewed and refined for the main study. Finally, the low proportion of patients who had an event meant that it was not possible to estimate the median time to events, highlighting that this way of presenting the results of the analyses is not feasible in this setting.

## **CHAPTER 10: DISCUSSION & FEASIBILITY OF STUDY**

### **10.1 Introduction**

This final chapter discusses the trial's findings in the context of national and international literature and explores the feasibility of a main study. The structure and flow of the chapter is guided by the trial's aims and objectives. As no other study directly compared the antiseptic solutions tested in this trial, the findings from each arm of the trial are discussed in the context of literature that had similar trial arms. The aims of my trial were two fold. The first was to test the trial methods in preparation for a study to evaluate the effectiveness of 2% CHG in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent in the reduction of CVC-related infection in haemodialysis patients, in comparison to the other formulations of CHG that were in routine use in Ireland. The second was to evaluate the feasibility of undertaking such a study as a multi-national, multi-centre study.

### **10.2 Catheter-Related Infections**

My trial is the first to explore the effectiveness of cutaneous antiseptic 2% CHG in 70% isopropyl alcohol solution versus other CHG solutions for the prevention of catheter-related infections. It shows that 2% CHG in alcohol does not have an advantage over other alcohol (0.5% CHG) or aqueous (0.05%) based CHG solutions when used in CVC skin, exit site and catheter hub care and maintenance. However, although not statistically significant, more trial participants treated with 2% CHG in alcohol were free from catheter related-bloodstream infection (CRBSI), catheter-associated bloodstream infection (CABS) or local access infection at six and 12 months than participants in the comparator arm. The number of catheter-related infections, including CRBSI, CABS and local access infection, among haemodialysis patients assigned to this intervention solution, were similar to the number of events in comparator arm participants but, given the small sample size and low event rate, these findings are not unexpected.

Also, although not statistically significant, the relative risk ratio for all catheter-related infections in the main comparison are below one and although their confidence intervals are wide, lie consistently in one direction. They favour 2% CHG in alcohol over routinely used CHG solutions. This is most pronounced in sub-comparison 1, favouring 2% CHG in alcohol over 0.5% CHG in 70% isopropyl alcohol. In sub-comparison 2, the relative risk ratio is above one for CRBSI, but there was only one event among the 11 participants in the intervention group and no events in the 10 participants in the 0.05% aqueous group. In contrast, the relative risk for CABSIs is below one, favouring 2% CHG in alcohol, but is also not statistically significant. Therefore, uncertainty remains as to the relative effects of the different interventions and the main study would have to be adequately powered to ensure there were sufficient events to detect a statistically significant difference if there truly is one.

Findings from the intervention and comparator arms of my trial are discussed in the context of similar arms in other CHG studies (Table 10.1). Case definitions (Table 10.2) for catheter-related bloodstream infections used in previously published CHG studies are similar to that used in my trial, with the exception of Astle & Jensen (2005). CRBSI diagnosis is generally based on a CVC tip and blood culture that is positive for the same micro-organism. However, conclusions drawn from these comparisons are tempered by difference in study design and population. All CHG studies compared CHG to povidone iodine, with the exception of Astle & Jensen (2005), which compared CHG to a sodium hypochlorite solution in an outpatient haemodialysis setting.

**Table 10.1 ‘CHG trial’ compared to studies with similar trial arms**

2% CHG in alcohol		0.5% CHG in alcohol	
Study	CRBSI N (%)	Study	CRBSI N (%)
Kelly <i>et al.</i> (2006)	1/81 (1)	Legras <i>et al.</i> (1997)	0/88 (0)
		Humar <i>et al.</i> (2000)	4/125 (3)
Garland <i>et al.</i> (2009)	0/24 (0)	Astle & Jensen (2005)	1/64 (1)
		Valles <i>et al.</i> (2008)	9/226 (4)
‘The CHG Trial’	1/53 (2)	‘The CHG Trial’	2/42 (5)

**Table 10.2 Comparison of CRBSI case definitions**

Study	Case Definitions for Catheter-Related Bloodstream Infection
Kelly <i>et al.</i> (2006)	None provided.
Garland <i>et al.</i> (2009)	Concordance between organisms grown from the blood and catheter tip.
Legras <i>et al.</i> (1997)	Culture of catheter and at least a positive blood culture with the same micro-organism.
Humar <i>et al.</i> (2000)	Single positive blood culture, with no other source of bacteraemia, in the presence of a culture of a catheter segment from which the same organism was isolated.
Astle & Jensen (2005)	Two or more positive blood cultures with no evidence for source other than the catheter or Single positive blood culture and positive culture of catheter segment with identical organism or Single positive blood culture and positive culture from discharge from exit site with identical organism.
Valles <i>et al.</i> (2008)	Same organism (i.e. the same species with the same antibiotic susceptibility profile) was recovered from the catheter-tip culture and from a blood culture.
'The CHG Trial'	A positive result of semi-quantitative (>15 CFU/catheter segment) or quantitative (>10 <sup>2</sup> CFU /catheter segment) catheter culture, whereby the same organism (species) is isolated from a catheter segment and a peripheral blood culture.

### 10.2.1 2% CHG in alcohol & CRBSI

Participants in studies, whose intervention arm consisted of 2% CHG in alcohol, experienced CRBSI events of zero (0/24, Garland *et al.* 2009) and 1% (1/82, Kelly *et al.* 2006). This compares to a marginally higher proportion of participants in the intervention arm of my trial (2%;  $n=1/53$ ). Garland *et al.* (2009), recruited participants from neonatal units, while Kelly *et al.*'s (2006) study included patients from intensive care units (ICU). Taking these differences into account, the CRBSI event rate in the 2% CHG in alcohol arm of my trial was comparable to that reported in the only study that included adult ICU patients (Kelly *et al.* 2006).

### 10.2.2 0.5% CHG in alcohol & CRBSI

It is not feasible to compare the number of events in the comparator arm of my trial as a whole to other CHG studies because it consisted of two routinely used solutions; 0.5% CHG in 70% isopropyl alcohol (sub-comparison 1) and 0.05% aqueous CHG (sub-comparison 2). A tentative comparison is made

between 0.5% CHG in alcohol and 0.05% aqueous CHG arms of sub-comparison 1 and 2, to CHG studies with similar trial arms.

The frequency of CRBSI in ICU patients treated with 0.5% in alcohol, in two studies, was zero (0/88, Legras *et al.* 1997) and 3% (4/125, Humar *et al.* 2000). In contrast, a 5% ( $n=2/42$ ) event rate was detected in trial participants assigned to the same solution, 1.5 times higher than Humar *et al.* (2000). This trend for higher CRBSI in my trial was also found when it was compared to a study from Spain (Valles *et al.* 2008), which compared two different CHG solutions to povidone iodine. The proportion of participants shown to have a catheter-related bacteraemia was 4% (9/226) in ICU participants assigned to 0.5% CHG in alcohol (no strength given), similar to that observed in my trial (5%).

Given the acuity of patients in an ICU setting, it is anticipated that they would experience a higher number of CRBSI events than patients attending an outpatient haemodialysis centre. Yet, the proportion of trial participants with CRBSI, who were treated with 0.5% CHG in alcohol, was 1 to 5 times higher than ICU participants. The CDC (CDC 2011b) in a review of CABSIs in healthcare settings across the United States (US), estimated that a substantial number of CABSIs occur in outpatient haemodialysis centres compared to ICU or inpatient wards. Findings from my trial reaffirm the continued burden such infections have on the outpatient haemodialysis patient population. Difference in event numbers between haemodialysis and ICU patient groups may be attributed to the use of the CVC for dialysis vascular access. The haemodialysis CVC is a permanent fixture that patients live with on a day to day basis and is present in all of their activities of daily living. This is in contrast to the short term use of central catheters in ICU patients. The mean duration of CVCs for participants in my trial was 13 months, demonstrating their long term use in haemodialysis patients. Due to renal failure, patients are immunosuppressed, increasing their susceptibility to infection. Given this immunocompromised state, patients are also exposed to regular manipulation of the haemodialysis CVC; a minimum of twice a day, three times a week. This increases the risk of extra-luminal and intra-luminal contamination from their own skin flora and haemodialysis nurses' hands (Crnich & Maki 2002b, 2002a, Casey *et al.* 2003).

Only one study was found that involved outpatient haemodialysis patients (Astle & Jensen 2005) and the frequency of bacteraemia for participants treated with 0.5% CHG in alcohol was 1% (1/64), lower than the event rate in trial participants treated with a similar solution. The difference may be linked to the three month follow-up period used by Astle & Jensen (2005) compared to the 12 month period used in my trial.

### **10.2.3 0.05% aqueous CHG & CRBSI**

No CHG study evaluated the effectiveness of 0.05% aqueous CHG in the prevention of catheter infections. A prospective observational study (Ishizuka *et al.* 2009) compared 0.05% CHG and 10% povidone iodine in colorectal surgery, or post-operative chemotherapy patients requiring CVC insertion. The frequency of CRBSI for participants treated with 0.05% aqueous CHG was 5% (14/286), compared to zero events in my trial's participants. The difference may be due to Ishizuka *et al.*'s (2009) use of a CRBSI case definition that was much broader than that used in my trial. They diagnosed CRBSI on positivity of blood cultures or catheter tips. On the other hand, participants in my trial presenting with positive blood cultures (including pre-determined clinical signs) were diagnosed with CABSI, the event rate of which was 20%, five times higher than the frequency of CRBSI in the Ishizuka *et al.* (2009) prospective study. Since the completion of my trial, the research site (OV) that used 0.05% aqueous CHG introduced, unit-wide, 2% CHG in alcohol for CVC exit site and catheter hub care. A noticeable decrease in catheter-related infections was observed by staff since this change in practice. Prior to this change, over a 19 month period, the mean number of CVC-related bloodstream infections was 2.1. Following this change in practice and over a similar time period, the number of bloodstream infections associated with the use of a CVC decreased to a mean of 1.4 (Fitzgerald 2014).

### **10.2.4 CHG solutions & exit site infections**

Three trial participants, treated with 2% CHG in alcohol, experienced a local access infection. Although none of the other 2% CHG in alcohol studies measured exit site infections, an observational study detected a positive association between 2% CHG and exit site infections (Harwood *et al.* 2008), but no information was provided on the formulation of the CHG solution used in that study.

Two 0.5% CHG in alcohol studies (Humar *et al.* 2000, Astle & Jensen 2005) monitored for exit site infections, but the case definitions were not comparable to that used in my trial where diagnosis was dependent on clinical signs of infection and the administration of intravenous (IV) antibiotics or hospitalisation. A positive exit swab culture was not a requirement. The definitions used in the two other CHG studies had fewer criteria, with diagnoses based on clinical signs and/or a positive exit site culture. Taking into account the use of different case definitions, the frequency for such infections in trial participants treated with 0.5% CHG (10%, 4/42) was higher than Humar *et al.* (2000) ( $n=0$ ). It was similar to Astle & Jensen (2005, [8%, 5/64]), the only study that included haemodialysis patients. The higher event number in my trial may relate to the inclusion of cases linked to hospitalisation and IV antibiotic starts.

### **10.2.5 CHG solutions & CRBSI/CABSI causative organisms**

Given the limited amount of available data it was not feasible to detect significant difference in CRBSI and CABSI causative organisms in my trial. Out of the eight bloodstream infections, four (50%) were caused by methicillin sensitive *Staphylococcus aureus* (MSSA), two (25%) were due to methicillin resistant *S. aureus* (MRSA) and the remaining infections were caused by coagulase negative staphylococci and *Enterococcus faecalis*. The trial's trend for higher episodes of MSSA compared with MRSA bloodstream infections reflects a national trend. In 2013 (to the end of quarter four), the number of *S. aureus* bloodstream infections in hospitals in Ireland increased by 3% from 1060 to 1094 episodes (Health Protection Surveillance Centre 2014). At least 80% ( $n=872$ ) of these episodes were MSSA, a 7% increase since 2012, but in the same time period there was an 8% reduction in episodes of MRSA bloodstream infections from 242 to 222 (20.3%).

Trial episodes for *S. aureus* are comparable (Table 10.3) to that observed in CDC/National Healthcare Safety Network (NHSN) studies (Tokars *et al.* 2002, Klevens *et al.* 2005, Klevens *et al.* 2008), with episodes of *S. aureus* bacteraemia ranging from 20% to 32%. In comparison to other studies from Ireland, the frequency of MSSA in my trial is similar to Bajwa *et al.* (2012, [57%]), but lower than Reddy *et al.* (2010, [85%]). Although Little *et al.* (2001) observed an *S. aureus* event rate of 69%, this also included 19 MRSA isolates, increasing the possibility that the MSSA rate would be somewhat similar to that shown in this trial. The frequency of MRSA in my trial was lower

than that reported in the 2011 United Kingdom (UK) Renal Registry Report (61%), but higher than Reddy *et al.* (2010, [7%]).

**Table 10.3 CVC bloodstream infections episodes of *S. aureus***

CVC Bloodstream Infection Episodes of <i>S. aureus</i>			
Study	<i>S. aureus</i> % (N) <sup>1</sup>	MSSA <sup>2</sup>	MRSA <sup>3</sup>
Little <i>et al.</i> (2001)	69%	N/S <sup>4</sup>	N/S
Tokars <i>et al.</i> (2002)	32%	N/S	N/S
Klevens <i>et al.</i> (2005)	29%(1538/5275)	N/S	N/S
Klevens <i>et al.</i> (2008)	20% (91/461)	N/S	N/S
Reddy <i>et al.</i> (2010)	92%	85%	7%
UK Renal Registry Report (2011)	N/S	N/S	61%
Bajwa <i>et al.</i> (2012)	57% (4/7)	57% (4/7)	Nil
HPSC <sup>5</sup> (2014)	N/A <sup>6</sup>	80% (872/1094)	20.3% (222/1094)
'The CHG Trial'	75%(6/8)	50% (4/8)	25% (2/8)

<sup>1</sup>(N), episodes of *S. aureus*/episodes of positive blood cultures, where data are provided on this breakdown; <sup>2</sup>MSSA, Methicillin sensitive *S. aureus*; <sup>3</sup>MRSA, methicillin resistant *S. aureus*; <sup>4</sup> N/S, not stated; <sup>5</sup>HPSC, Health Protection Surveillance Centre; <sup>6</sup>N/A, not applicable.

### 10.2.6 Overview of trial primary objectives

Overall, the frequency of CRBSI and CABSIs in trial participants treated with 2% CHG in alcohol is lower than that detected in comparator participants. This difference was not statistically significant.

Looking at the results for the 2% CHG in alcohol trial arms of CHG studies (including my trial) and comparing these to trial arms of 0.5% CHG in alcohol studies (including my trial), it could be argued that the frequency of CRBSI appeared to be higher in 0.5% CHG in alcohol treated participants than participants treated with 2% CHG in alcohol. This warrants further exploration either through a systematic meta-analysis of the evidence, in which my trial's findings would make an important contribution, or through a larger comparator trial comparing the two solutions.

My trial provides an opportunity to present a picture of the overall infection rate among trial participants in three large outpatient dialysis facilities in Ireland.



Previous reports from Ireland focused on outcomes from a single dialysis facility (Little *et al.* 2001, Reddy *et al.* 2010, Smyth *et al.* 2010, Fitzgerald *et al.* 2011). In total, 14% (15/105) of the participants in my trial experienced a catheter-related infection, 3% ( $n=3$ ) CRBSI and 5% ( $n=5$ ) CABSIs. When compared to US haemodialysis patients (3.32 episodes per 100 patient-months) (CDC 2011b), the incidence rate of CABSIs was considerably lower at 0.17 episodes per 100 patient-months. The CABSIs incidence rate was also lower than that observed by Reddy *et al.* (2010), 1.94 episodes per 100 patient-months. Case definitions in both studies differed, which may explain the difference in episodes of infection.

The local access infection event rate among the participants in my trial was 7% ( $n=7$ ), an incidence rate of 0.23 episodes per 100 patient-months. This incidence rate is considerably lower than that observed by Reddy *et al.* (2010) (5.49 per 100 patient-months) and may relate to that unit's use of a solution that is 10 times weaker than 0.5% CHG in alcohol and 40 times weaker than 2% CHG in alcohol solution. The trial event rate of 7% for local access infection is higher than that reported in a Saudi Arabian surveillance study (El-Saed *et al.* 2011), which used the same CDC case definition for local access infection ( $n=10$ , 4%).

Since my trial was designed in 2009, a number of renal and international guidelines have been updated. The 2011 CDC guidelines recommend the use of a CHG solution that is greater than 0.5% and based in a 70% isopropyl alcohol solution; a change from the 2002 guidelines, which recommended a 2% CHG solution. The UK Renal Association guidelines (The UK Renal Association 2011) recommend a 2% CHG-based solution, but no guidance is given on its formulation. Similar to SARI (SARI 2009) and NKF K/DOQI (2006) guidelines, the 2014 epic 3 guidelines (Loveday *et al.* 2014) recommend the use of 2% CHG in 70% isopropyl alcohol for skin, exit site and catheter hub care. However, there are no trials demonstrating that 2% CHG in alcohol is more effective than other CHG-based solutions. This continuing variation across the guidelines reflects the lack of evidence on the most effective CHG solution for the prevention of catheter-related infections.

Case definitions used to diagnose CABSIs and local access infections have also been updated since the design and implementation of my trial. In general, no changes were made to the criteria for CABSIs, (CDC/NHSN 2014a)

with the exception that there must not be a gap of more than one calendar day between two adjacent elements. Applying this amendment to my trial did not alter the number of CABSIs events, as all positive blood cultures were obtained within one day of each other. Changes to the CDC/NHSN dialysis event protocol (CDC/NHSN 2014b) included the removal of inpatient dialysis from the denominator data. Potentially, this change could have decreased the number of patient-months, which in turn would have increased the incidence rates of catheter-related infections and dialysis events. Changes were also made to the case definition for local access infection, which removed the criteria for hospitalisation and IV antimicrobials and is now defined as pus, redness, or increased swelling of the vascular access site and access-related bloodstream infection is not present. As a result, trial participants classified in the subcategory 'local access infection (oral antibiotics)' could be reclassified as local access infection. This change might increase the local access infection event rate from 6% (n=3) to 7.5% (n=4) in the intervention arm of the trial and from 8% (n=4) to 15% (n=8) in the comparator arm. This revised event rate could be even higher, as trial participants with exit sites that were red, inflamed or had increased swelling, but were not prescribed an antibiotic, were excluded from the diagnosis process for this trial outcome.

### **10.3 Dialysis Event Outcomes**

The most clinically significant event is patient mortality. The overall mortality event rate in my trial (13%) is comparable to Australia and US studies, with mortality of 15.2% and 25% (Pastan *et al.* 2002, Polkinghorne *et al.* 2004), but higher than that reported for patients with AVFs, which varied from 7.3% to 11.7% (Pastan *et al.* 2002, Astor *et al.* 2005). The leading cause of death in my trial was infection (36% of deaths). None of the infection-related deaths were directly linked to catheter-related infection. The second highest cause of death related to cardiovascular disease (29%).

My trial provides important information on the burden of CVC-related infections on the dialysis patient population in Ireland. It provides further insight into the importance of effective infection prevention and control strategies and the use of effective cutaneous CHG antiseptic agents. The findings also contribute to the knowledge base established by the Bajwa *et al.* (2012) feasibility study on the implementation of the CDC/NHSN dialysis event protocol in Ireland, which collected data from one large haemodialysis unit

over a six week surveillance period. In contrast, my trial collected dialysis event data from three dialysis units over 15 to 17 months and estimated incidence rates for a variety of dialysis events. An attempt is made to compare my dialysis event findings to CDC/NHSN reports and studies that used the CDC/NHSN protocol. A caveat to the conclusions drawn from this comparison is that my analysis for catheter-related infections was restricted to at least one episode per patient. Conversely, CDC/NHSN reports and studies (from this point onwards referred to as NHSN studies), may include more than one event when analysing dialysis event incidences.

NHSN studies (George *et al.* 2006, Klevens *et al.* 2008, El-Saed *et al.* 2011) detected an incidence rate for CVC access-associated bacteraemia from 2.0 to 9.8 episodes per 100 patient-months. This was noticeably higher than the incidence rate observed in my trial (0.33 episodes per 100 patient-months), which had an overall event rate of 10% ( $n=10$ ). The UK vascular audit report also had a higher incidence rate (8 episodes per 100 patient-months) than my trial (The NHS Information Centre 2011b). Differences between the aforementioned studies and my trial, suggest that the higher incidence may result from the inclusion of more than one event for each patient.

Vascular access infection is a broad term used in the CDC/NHSN dialysis events protocol that encapsulates both local access infection and access-associated bacteraemia (CDC/NHSN 2009). Similar to access-associated bacteraemia, the overall incidence rate for vascular access infections in my trial (0.56 episodes per 100 patient-months) was considerably lower than NHSN studies (Tokars *et al.* 2002, Klevens *et al.* 2005, Klevens *et al.* 2008, El-Saed *et al.* 2011), which varied from 4.8 to 10.4 episodes per 100 patient-months. This substantial disparity may relate to the inclusion of more than one event, when estimating the incidence density for vascular access infections. Furthermore, my incidence rates were higher than those observed in patients with AVFs (0.4 and 0.7 episodes per 100 patient-months) (Klevens *et al.* 2005, El-Saed *et al.* 2011).

Unlike CVC-related infection incidence rates, my estimates for hospitalisation, IV antimicrobial starts, positive blood cultures and catheter removals were based on more than one event per patient. Bajwa *et al.* (2012), observed incidence rates for all-cause hospitalisation (23.81 episodes per 100 patient-months) and IV antimicrobial starts (16.19 episodes per 100 patient-months)

that were higher than my trial, 6.64 and 4.42 episodes per 100 patient-months, respectively. Possible explanations for the differences compared to Bajwa *et al.* (2012) may relate to differences in patient case mix and protocols guiding antimicrobial stewardship. Hospitalisation due to CVC-related infection (0.33 episodes per 100 patient-months) was four times lower in my trial than in the UK Hammersmith hospital (1.4 episodes per 100 patient-months) (George *et al.* 2006).

The incidence rate for positive blood cultures also differed between my trial and Bajwa *et al.* (2012); 0.86 versus 6.67 episodes per 100 patient-months, respectively, which might be due to different patient case mix and guidelines on obtaining blood cultures. NHSN studies also had a high rate of positive blood cultures, varying from 4.2 to 10.8 episodes per 100 patient-months (Tokars *et al.* 2002, Klevens *et al.* 2005, El-Saed *et al.* 2011). These rates were far greater than that seen in patients with AVFs, with a rate of zero and 0.9 episodes per 100 patient-months (El-Saed *et al.* 2011, Bajwa *et al.* 2012). This is a further demonstration of the burden that CVC usage has for haemodialysis patients.

CVC-related infections have a negative impact on catheter survival, with removal rates of 32% and 55% for permanent cuffed tunnelled CVCs (Weijmere *et al.* 2004, Alomari & Falk 2007). Removal rates in my trial are lower, with a quarter ( $n=25$ , 24%) of all participants having their CVC removed. Reasons for removal include catheter dysfunction (10%), which is substantially lower than the 36% rate observed by Little *et al.* (2001). Difference in the number of catheters removed may be linked to advances in catheter technology and interventions used to minimise the loss of CVCs, which may be the only access that patients have for dialysis. A total of 9% ( $n=9$ ) of CVCs in my trial were removed for suspected catheter-related infection, much lower than that reported by Smyth *et al.* (2010) and Little *et al.* (2001): 16.4% and 23% loss of CVCs due to infection, respectively.

## 10.4 Adverse Reactions

A critical review of the CHG trial literature found no evidence of adverse reactions; for example, hypersensitivity to CHG-based solution in studies that monitored for such reactions. Conversely, 7% of participants in my trial experienced an adverse reaction to the 2% CHG in alcohol solution; for

example, skin sensitivity that presented as redness and/or severe itching. It is worth noting that Maki *et al.* (1991) observed erythema in 45% of participants treated with CHG. It is suggested that many of these events could be avoided by gently cleansing the skin and allowing the antiseptic to dry before applying the CVC dressing (CareFusion 2010). However, participants in my trial who initially complained of redness and/or itchy skin and whose condition resolved following implementation of an agreed action plan (appendix 8.26) were deemed not to have a sensitivity reaction to the CHG in alcohol solution. This ruled out any issues related to CVC care technique as a possible cause of the reaction to the CHG solution. As a food dye was added to the 2% CHG in alcohol solution (ChloraPrep® with Tint); the possibility that participants reacted to the dye as opposed to the trial intervention cannot be ruled out.

No adverse reactions were observed in participants assigned to the comparator solutions. As the trial eligibility criteria included no known allergy to the trial solution, it is not surprising that comparator participants did not develop an allergy to this routine solution, because they had used it before the trial. The number of assessed patients who were deemed ineligible for my trial because of a known allergy to the routine CHG solution was 5% (10/201), which is not dissimilar to the event rate of adverse reactions seen in this trial's intervention arm.

Another issue to emerge was staining of clothes by ChloraPrep® with Tint. Two participants withdrew because of the annoyance and inconvenience this caused them. This was not anticipated in the trial protocol and was not included in the ChloraPrep® with Tint summary of product characteristics. A strategy aimed at minimising the recurrence of these complaints was implemented by dialysis nurses during the course of the trial. However, during interviews with participants on their last day in the trial, a number commented on the solution staining their clothes while on the trial. This issue was also encountered when one of the research sites (OV) introduced, unit-wide, ChloraPrep® with Tint solution for the cleaning of all vascular access. The level of complaints from patients was so high that the unit had to change over to a ChloraPrep® clear solution. Ironically, staff commented that they preferred the tint solution as they could visualise the area that was being cleaned, which was no longer possible with the clear solution.

## 10.5 Vascular Access Prevalence

The prevalence of CVCs across the three sites in my trial was 61%, higher (53%) than that reported in the national survey of haemodialysis units (McCann *et al.* 2013), and 2.5 times higher than that seen in prevalent patients in the UK (22%) (The UK Renal Registry 2012). In contrast, the prevalence of AVF was 38%, lower than the national survey prevalence of 46%. Possible explanations for difference in vascular access between participants in my trial and those in the UK include patient case mix, patients not suited for the creation of an AVF, patients not willing to have an AVF created and patients awaiting AVF creation or maturation. The research sites in my trial did not meet the recommended UK (85%) or US (65%) guidelines on AVF prevalence use or the NKF K/DOQI (2006) recommendation that CVCs should be in use for less than 10% of prevalent patients.

## 10.6 Feasibility

One of the objectives of my trial was to evaluate the feasibility of undertaking a multi-national, multi-centre study to resolve the uncertainty about these antiseptics in the haemodialysis setting. Evaluating feasibility through an external pilot study design ensured a comprehensive exploration of the pragmatic and scientific features of the planned study including what, if any, changes would need to be made to the trial protocol. This pilot study also provided an opportunity to identify problems that were not anticipated and only emerged during the course of this trial (Prescott *et al.* 1999). The following issues need to be considered when determining feasibility and design of the main study:

1. Availability of appropriate outpatient haemodialysis facilities to act as research sites;
2. Ability to standardise trial methodology and CVC care and maintenance practices across nations so controlling for any confounders that may explain differences between groups other than the trial intervention;
3. Methodological issues for the design of the main study; and
4. Appropriate funding to finance the planning and implementation of a multi-national, multi-centre study.

### **10.6.1 Research sites for main study**

At the time of planning this pilot study, haemodialysis facilities using a 2% CHG in 70% isopropyl alcohol solution for CVC care and maintenance could not be persuaded to take part in this trial. Since the national survey (McCann *et al.* 2013) and trial completion, four dialysis units changed their practice to a 2% CHG in 70% isopropyl alcohol solution, leaving only one unit in Ireland using a 0.5% CHG in alcohol solution.

SARI (2009), and UK national guidelines (The UK Renal Association 2011, Loveday *et al.* 2014) recommend the use of a 2% CHG in 70% isopropyl alcohol solution for CVC care and maintenance. It is possibility that a majority of dialysis facilities in Northern Ireland and elsewhere in the United Kingdom use this solution. Similar to Ireland, there is a high probability that these units would be unwilling to participate in the main study and alternative European countries would need to be sourced. A scoping exercise needs to be undertaking to identify units in the UK interested in participating in the main study.

Following personal communication with representatives from the European Dialysis and Transplant Nurses Association/European Renal Care Association it would appear that CHG is not universally used across European haemodialysis facilities. Alternative antiseptic solutions used for CVC care and maintenance include Octenidine dihydrochloride without alcohol (Octenisept® [German dialysis units, Reichardt 2014]) and Benzalkonium Chloride and Isopropanol (Cutasept spray® [Portuguese dialysis units, Saraiva 2014]). Dialyses units in Italy (Pegorana 2014) use 2% CHG in alcohol and may also have a similar attitude to trial participation as seen in units in Ireland. As haemodialysis facilities in Sweden (Nilsson 2014) and Iceland (Einarsdottir 2014) use 0.5% CHG in alcohol, it is feasible to undertake the main study in dialysis units based in these countries.

### **10.6.2 Standardisation of trial methodology & CVC care practices**

Conducting a randomised trial across multiple nations is challenging, particularly with regard to applying this design to haemodialysis facilities that are governed by different Departments of Health and policy decision-makers. Other issues include the practicality of using such a design in the real world of

haemodialysis facilities that may have policies, guidelines and nursing practices that vary with regard to CVC care and maintenance and dialysis connecting and disconnecting procedures (Greene 2009). These issues highlight the difficulties in controlling extraneous variables present in these geographically dispersed haemodialysis settings.

A challenge facing the main study is standardising not just trial methodology, but also infection prevention and control practices given that practices in other areas of renal care are not standardised (chapter 6, section 6.3.2). Any variability in practice could be balanced through the use of randomisation that is stratified according to centres. As part of a scoping exercise to identify interested units, CVC care and maintenance practices including policies and guidelines need to be identified. Additionally, this exercise could explore the possibility of standardising practice across units, where appropriate.

In multi-centre trials, EU Clinical Trial Directives and Good Clinical Practice guidelines requires that the trial be conducted according to a single protocol, at more than one site by more than one investigator (ICH 1996, European Community 2001). The protocol for the main study would provide a framework to guide the standardisation of methodology across all sites. Trial management structures are an important component in monitoring and enforcing correct implementation of the trial protocol and associated trial procedures (Prescott *et al.* 1999).

Proposed trial management structures for the main study include:

- Sponsor, who is responsible for initiation, management and or financing of a clinical trial. The sponsor and chief investigator can be the same person;
- Trial steering committee with overall responsibility for the conduct of the trial;
- National steering committee whose members will include principal investigators, local co-ordinator and trialists;
- A co-ordinating centre in each country/region to handle materials, data collection and communication with trialists;
- An overall trial co-ordinator and a local co-ordinator to run the co-ordinating centre;



- Chief investigator with primary responsibility for the conduct of the whole trial; where there is more than one country involved in the trial it may be necessary to have a chief investigator for each country;
- Principal investigator who is responsible for the conduct of the trial at their research site and must be an authorised healthcare professional;
- Trialists covering a number of research sites in the same region or research agreement contracts with research sites to undertake study at that site;
- Pharmacists responsible for investigational product accountability and entering relevant trial data into the EudraVigilance Clinical Trial Module;
- Trial monitoring committee or independent Data Monitoring Committee;
- Outcome arbitration committee; and
- Independent auditing of the clinical trial.

### **10.6.3 Methodological issues for main study**

As aforementioned, haemodialysis units in Sweden and Iceland use a 0.5% CHG in alcohol solution for cleansing the CVC exit and catheter hub. A study involving these two nations would allow a direct comparison between 2% CHG in 70% isopropyl alcohol and 0.5% CHG in 70% isopropyl alcohol. Undertaking the study in these two or more countries would require an alternative research question to that used in this pilot study, such as *‘What are the effects of 2% CHG in 70% isopropyl alcohol, as a skin, exit site and catheter hub cleansing agent on CVC-related infections in haemodialysis patients when compared to a 0.5% CHG in 70% isopropyl alcohol solution?’*

Opting for this alternative research question is prudent given the difference in strength between 0.05% aqueous CHG (0.05%) and 0.5% CHG in alcohol solutions. Not only does this research question evaluate a solution (2% CHG in alcohol) recommended by national and international guidelines, but it also provides the evidence that either accepts or refutes the CDC’s (2011) recommendation for using a CHG alcohol-based solution that is greater than 0.5%.

Although Iceland is not in the European Union (EU), it is a member of the European Economic Area (EEA) and the European Clinical Trials Database. Approval for clinical trials in Iceland is as per EU member states. In

accordance with the EU Clinical Trials Directives (European Community 2001), approval and conduct for the multi-national, multi-centre study would be similar to what was undertaken for this pilot study (chapter 7, sections 7.8 and 7.9), but there are some areas of difference between the pilot trial and the main study. The main study needs to be approved by each participant nation's national competent authority and approved research ethics committee, no matter how many countries are participating in the trial. The process can be facilitated by the Clinical Trial Facilitation Group in the European Medicine Agency, who assess the application prior to its submission to the relevant national competent authority. This is only available for studies involving two or more countries (Irish Medicines Board 2014). It is also expected that those involved in the main trial would adhere to the principles of 'Good clinical practice' guidelines for conducting clinical trials (ICH 1996).

Trial intervention solutions used in the pilot study have a marketing authorisation by the Medicines Products Agency in Sweden, but do not have a similar marketing authorisation by the Icelandic Medicines Agency. However, EU Clinical Trial legislation permits the use of medicinal products that have marketing authorisation in other EU/EEA member states. Individual countries may have their own regulations for the ordering of such products and these need to be incorporated into the protocol for the main study.

Safety monitoring in a clinical trial requires pharmacovigilance and the submission of Suspected Unexpected Serious Adverse Reactions to the EudraVigilance Clinical Trial Module. This was facilitated by the Irish Medicines Board for my pilot study, but was only agreed on the basis that such events would rarely if ever occur with the trial interventions. Given that the main study would have a large sample size, this activity needs to be completed by a designated pharmacist or medical scientist.

A trial monitoring committee or independent data monitoring committee needs to be established and terms of reference agreed. Due to the potential conflict of interest experienced in this pilot study (chapter 8 section 8.20.2), membership of the committee needs to be completely independent of persons and institutions participating in the main study. The monitoring committee should include experts in clinical microbiology, a statistician and an expert in clinical trial methodology. Resources required include remuneration fees for

travel expenses and the holding of three committee meetings through the trial, that might be face to face or via conference calls.

An important aspect of reducing bias in clinical trials is blinding. Creating solutions, wipes or applicators that have similar appearance needs to be explored for the main study, but has important implications for trial funding. It is important that the solutions do not include a food dye similar to what was used in the pilot trial, as it caused severe annoyance among trial participants. Masked investigational products would have to be manufactured for the sole purpose of the trial. Creating solutions, wipes or applicators also has implications for trial approval and manufacturing and labelling of trial products.

To reduce the risk of bias, the main study could include the use of an outcome arbitration committee, which would undertake a blinded assessment of the main study outcomes and confirm primary outcomes for participants. Committee members need to be independent of trial members and participating institutions, with no conflict of interests and consist of senior clinical practitioners that are experts in haemodialysis, microbiology and infection prevention and control. Terms of reference need to be established and committee meetings can be face to face or via conference calls, every four months for the duration of the trial. Resources include remuneration fees for travel expenses and the administration of committee meetings.

Generation of a random allocation sequence for the main study will be through computer randomisation software. As the main study focuses on a direct comparison of two solutions, stratification for randomisation may be determined by dialysis centre. Varying block sizes can be also used. Allocation concealment for the main study can be achieved using a central randomisation centre such as that provided by the TENALEA service.

A number of issues emerged during eligibility assessment in the pilot trial, suggesting the need for modifications to the main study's inclusion and exclusion criteria. The exclusion criteria need to include the use or maturation of an arterio-venous fistula, planned transfer to another haemodialysis unit or modality of treatment and adherence to trial protocol.

The sample size calculation for the main study takes into account the event rate for catheter-associated bloodstream infections (CABSI) that were observed in the intervention (2%) and control arm (5%) of sub-comparison 1 (2% CHG in alcohol versus 0.5% CHG in 70% isopropyl alcohol). Event rates from sub-comparison 1 are used because the comparator in this group was 0.5% CHG in alcohol, which is the solution proposed for the main study. Using the statistical package <http://www.sealedenvelope.com/power.php> the number of patients needed for the main study is 590 per trial arm. Significance level (alpha) was set at 0.05 and power (1-beta) was set at 80%. This sample size needs to be increased by 15% in order to take account of potential loss to follow-up, as witnessed in the pilot study. Strategies also have to be put in place to ensure more eligible patients are enrolled into the main study, as there was a 30% refusal rate in my trial. However, this refusal rate is not uncommon in renal patients. Another modification to the recruitment strategy is the need to increase the recruitment time period from eight to 12 months, given the sample size required for the main study. Similar to the pilot study, participants in the main study would be followed up to trial completion (12 months), primary outcome or death.

Unlike the pilot study, the main study will be undertaken in countries where English is not the first language. All documentation relating to the trial needs to be translated into the language of the participating nations, which has implications for trial funding. Data collection tools also need to be refined, with the possibility of using electronic based software, where feasible. The format used in the pilot study for the preparation of site staff can be replicated in the main study, with modifications made where necessary to suit local organisational structure and culture.

The pilot trial used outcome case definitions linked to the Infectious Diseases Society of America (CRBSI) and the CDC/NSHN (CABSI, local access infection and dialysis events). Events relating to CRBSI were low (2% vs. 4%) and required removal and culturing of the catheter tip, an event that is avoided in haemodialysis patients whose CVC is their lifeline to dialysis. It is proposed that this outcome be removed from the main study and the primary outcome for the main study could be catheter-related infection encompassing CABSI and local access infection.

Overall, the data analysis plan for the pilot study was appropriate and would be suitable for the main study, with the exception of time to survival and logistic regression. It was not possible to calculate the median time to survival for catheter-related infection and catheter survival because less than half of the participants experienced the event. Estimating time to survival especially in relation to catheter-related infections may not be feasible for the main study given the low number of participants in my trial and other CHG studies that experienced such events. Instead the proportion of participants not experiencing the event can be estimated from the survival curves at six and 12 months. The logistic regression model could not estimate the predictability of the independent variables on the likelihood that participants would develop a CABS. This may be due to the small number of CABS or the possibility of quasi-complete separation. As the main study will have a large sample size, it is anticipated that this issue will not recur. The number of predictor variables used in this pilot study needs to be stream-lined for the main study.

#### **10.6.4 Funding for main study**

Funding is required for the following trial activities:

- Scoping exercise to identify and prepare research sites;
- Trial steering committee;
- National steering committee;
- A co-ordinating centre in each country/region;
- Trial co-ordinator and a local co-ordinator to run the co-ordinating centre;
- Chief investigator;
- Principal investigator;
- Trialists;
- Pharmacists/medical scientist;
- Trial monitoring committee or Independent Data Monitoring Committee;
- Outcome arbitration committee;
- Independent auditors of clinical trial;
- Fees associated with national competent authority and research ethics approval application;
- Masking of investigational medical products (manufacturing, labelling, importing etc.);
- Translation services; and

- Central telephone randomisation service.

The success of the main study would be dependent on sourcing funding from agencies at national or European level.

## **10.7 Limitations of Pilot Study**

The pilot trial had a number of limitations, the most obvious being sample size, which was not large enough to demonstrate differences in catheter-related infections between the intervention and control solutions. It was acknowledged from the outset that while this trial would be able to detect large differences, it was not large enough to detect small, but clinically significant, differences. The small sample size and event rate also had implications for determining the predictability of baseline characteristics including the CVC lock solution and research sites on the likelihood that participants would develop CABS. Another implication of the small sample size was the inability to calculate the median time to survival.

The pilot study could not be blinded as trial solutions differed in colour, package and delivery mechanism. Additionally, there was insufficient funding to mask the solutions. However, the strength of this trial was the use of strictly defined end points and the involvement of an independent microbiologist assessor, all of which minimised ascertainment bias.

The pilot study restricted categorical primary outcomes and secondary categorical outcomes to the occurrence of at least one event. This limited the ability to compare the findings with CDC/NHSN studies that had included more than one event when estimating events relating to access-associated bacteraemia and vascular access infection.

The pilot trial did not use a centralised laboratory, relying instead on local laboratories and results from routine investigations that were obtained as part of the management of CVC-related infections. Not all research site laboratories were accredited; although, all had standard operational procedures that guided microbiological testing.

Differences in blood cultures taking could be a potential limitation, with the possibility that participants from a particular site or group may have had more blood cultures taken compared to other sites or patient groups. This could influence the trial outcomes as the more a variable is tested the more likely a positive result will be found. However, as discussed in chapter 10 (section 9.6.1) there was no significant difference between trial arms and research sites in the mean number of blood cultures obtained. Another potential limitation is the difference between units in their antibiotic starts whereby some units may treat all patients with a suspected infection while others may watch and wait. However, as discussed in chapter 9 (section 9.6.1) this was not found in my trial.

There was no guarantee that trial participants would adhere to the trial protocol and not interfere with the CVC dressing or open the CVC catheter between dialysis sessions. This is a risk that clinical trials are exposed to when recruiting patients from an outpatient setting. However, randomisation should minimise this confounding variable between the intervention groups.

## **10.8 Summary**

Haemodialysis patients are at increased risk of CVC-related infections due to the high use of this invasive medical device in this patient group. Preventing catheter-related infections is an important component to keeping patients safe. Infection prevention and control is dependent on the utilisation of strategies that are evidence-based. While CHG antiseptic solutions are more effective at preventing CVC-related infection than other antiseptic solutions, the most effective and appropriate strength of this formulation is not known. The aims of this trial were to test the trial methods in preparation for a study to evaluate the effectiveness of 2% CHG in alcohol in comparison to other routinely used CHG solutions for the prevention of CVC-related infections in haemodialysis patients. The second aim was to evaluate the feasibility of undertaking a multi-national, multi-centre study of this topic.

The trial demonstrated that 2% CHG in 70% isopropyl alcohol solution was no more effective than other alcohol (0.5% CHG in 70% isopropyl alcohol) or aqueous based CHG solutions (0.05% aqueous CHG) when used for CVC care and maintenance. The frequency of catheter-related infections including CRBSI, CABSIs and local access infection in participants treated with the

intervention solutions was not dissimilar to that found in participants treated with the comparator solution. For all catheter-related infections, although not statistically significant, relative risk ratios are below one and consistently favour the 2% CHG in 70% isopropyl alcohol solution over the comparator solutions. These conclusions are tempered by the small sample size and low event numbers. The catheter-related infection incidence rate is lower than that found in other studies from Ireland and may be explained by confining the analysis to at least one event per patient.

The leading cause of death among trial participants was infection and cardiovascular disease. Dialysis event outcomes relating to access-associated bacteraemia, vascular access infection, hospitalisation and catheter removal illustrates the significant burden catheter-related infections have on haemodialysis patients and trial participants. These events were lower in trial participants when compared to the only other study from Ireland that used the CDC/NHSN dialysis events protocol. Adverse reactions to the trial intervention were observed in 7% of participants, but a number of participants withdrew from the study because the intervention stained their clothes. This has major implications for patient acceptability of this particular product in CVC care and maintenance. Vascular access prevalence in this trial differed from that reported in a national survey of routine practices in haemodialysis units, with higher use of CVCs observed.

Finally, the pilot study confirms that the main study is feasible, but is dependent on availability of appropriate research sites; for example, in Sweden and Iceland and standardising trial methodology. Methodological issues for the design of the main study, such as changing the research question to reflect the routine solution used in countries that agree to participate in the study need also to be addressed and appropriate funding to finance the planning and implementation of a multi-national, multi-centre study would be required.



## **10.9 Conclusion, Implications & Recommendations**

An important aspect of any research activity is exploring the implications and recommendations for practice and research that emerge from the study's findings. Implications and recommendations made in this chapter are based on trial findings and previous sections of my thesis.

### **10.9.1 Implications for practice**

Providing optimal care to haemodialysis patients with CVCs is dependent on having the requisite knowledge, but dialysis nurses knowledge and practice of infection prevention and control is suboptimal (chapter 2). This highlights the need for ongoing in-service education in an area that is of clinical importance to patients and their healthcare providers.

Findings from the Cochrane Review, in chapter 4, found that the application of mupirocin ointment at the CVC exit site is effective in reducing the risk of catheter-related bacteraemia and CVC infections caused by *S. aureus*. However, the review was unable to determine if mupirocin resistance is a real or proven threat. There is insufficient evidence to guide dialysis nursing practice on the routine use of povidone-iodine ointment, polysporin ointment and topical honey in the prevention of CVC-related infections in the haemodialysis patient population. It was also not possible to determine which CVC dressing (dry gauze or transparent) has the lowest risk of catheter-related infections or the optimal frequency of dressing changes.

The critical analysis of the CHG literature in chapter 5 endorses CHG as the most optimal antiseptic solution for CVC care and maintenance. Dialysis nurses need to ensure that CVC guidelines in their respective units recommend this solution for CVC vascular access care.

Although national guidelines recommend a functional arterio-venous fistula (AVF) at the initiation of haemodialysis, the national survey (chapter 6) found that this was not the case. A formalised referral programme for AVF formation could overcome this problem. Standardisation of infection prevention and control surveillance programmes across dialysis units will allow for national and international comparisons.

Chapters 3, 6 and my trial findings demonstrate the chronicity of CVC use within the haemodialysis patient population when compared to other patient populations. Marginal improvements in CVC-related infections, through the use of effective infection prevention and control practices, would have long term benefits for the haemodialysis population because of increased duration of CVC use. Remaining infection free would reduce the burden of CVC infections on haemodialysis patients by decreasing episodes of hospitalisation, catheter removal and re-insertions, and bloodstream infections that harm patients.

Based on my trial findings, using a tinted Chloraprep® antiseptic solution in the care and maintenance of haemodialysis CVCs may not be acceptable to patients because it stains their clothes. Alternatively, a clear Chloraprep® applicator can be used. My trial was inconclusive and recommendations on the most effective CHG solution for the prevention of CVC-related infections should await findings from the main study.

### **10.9.2 Implications for research**

The impact CVC-related infections have on dialysis nurses' workload is outlined in chapter 2; however, there is scant evidence examining this issue and the possible effect a dialysis nurse's workload has on catheter-related infections.

Chapter 4 highlights the lack of monitoring of mupirocin resistance in previous randomised trials. Future studies need to provide the objective evidence on whether mupirocin resistance is a real threat. Possible alternative prophylactic strategies that include topical honey, povidone-iodine ointment and polysporin ointment need to be explored further using robust randomised trials. These trials should also monitor the development of resistance. In relation to CVC dressings, only one trial investigated different types of dressings in a haemodialysis patient population. A larger more robust randomised trial is needed.

As outlined in chapter 6, the formation of pre-emptive AVFs is not evident in renal units in Ireland; barriers to their creation need to be identified. A surveillance programme is an important component of an effective infection prevention and control programme, as is the use of CVC insertion and maintenance care bundles, the absence of these initiatives in dialysis units in

Ireland warrants attention. The use of two healthcare staff in connecting and disconnecting patients to and from dialysis is recommended in one guideline, but the evidence supporting this initiative is lacking. This chapter also highlights the lack of randomised trial evidence underpinning nephrology practice guidelines and highlights the need for more RCTs in nephrology patient care. The introduction of the National Kidney Disease Clinical Patient Management System (KDCPMS) will permit auditing of dialysis practices.

My trial found that a large multinational, multi-centre trial evaluating the effectiveness of 2% CHG in alcohol compared to other CHG solutions in the prevention of catheter-related infections is feasible. It is unclear what difference, if any, CVC antimicrobial lock solutions have in the prevention of CVC-related infections; this is an area of practice that would benefit from further investigation.

### **10.9.3 Recommendations for practice**

- Ongoing in-service education on infection prevention and control practices in the area of CVC care and maintenance is required (chapter 2);
- The use of mupirocin ointment in haemodialysis patients with CVCs should be guided by local knowledge of the prevalence of antibiotic sensitivity (chapter 4);
- The clinical decision on the use of topical antimicrobial ointments such as povidone-iodine, polysporin ointment and topical honey agents may be guided by national recommendations (chapter 4);
- Those caring for haemodialysis patients with CVCs may consider using either dry gauze or transparent dressings. This choice may be informed by the presence of an oozing exit site, patient preference or cost (chapter 4);
- Develop a formalised referral programme for AVF formation, that is led by pre-dialysis renal nurse specialists (chapter 6);
- Dialysis nurses need to liaise with the infection prevention and control team and establish an effective infection prevention and control surveillance programme that is comparable to international standards (chapter 6); and
- Avoid tinted antiseptic solutions for CVC skin and exit site cleansing (The CHG Trial).

#### 10.9.4 Recommendations for research

- Explore the impact catheter-related infections have on dialysis nursing workload and vice versa (chapter 2);
- RCTs on the effectiveness of:
  - Povidone-iodine ointment versus no treatment;
  - Polysporin ointment versus no treatment;
  - Povidone-iodine ointment versus polysporin ointment
  - Honey versus no treatment;
  - Honey versus polysporin,
  - Honey versus povidone-iodine (chapter 4);
- A RCT investigating dry gauze and transparent dressings in the prevention of CVC-related infections in haemodialysis patients including the influence that the frequency of dressing changes may have on the incidence of catheter-related infections (chapter 4);
- A systematic meta-analysis of the evidence from randomised trials investigating the use of CHG in CVC care and maintenance, in which my trial's findings would make an important contribution (chapter 5);
- Using a mixed methods approach investigate barriers and timelines to pre-emptive creation and use of AVFs (chapter 6);
- Investigate the scope of surveillance programmes within dialysis units in Ireland, including the utilisation of root cause analysis, CVC insertion and maintenance care bundles (chapter 6);
- Investigate the effect a two person connect and disconnect approach to dialysis has on the prevention of catheter-related infection (chapter 6);
- Investigate vascular access use, infection prevention and control practices and infections rates in Ireland using data from the National Kidney Disease Clinical Patient Management System (KDCPMS) (chapter 6);
- There is a need to use randomised controlled designs when investigating different aspects of renal nursing practices, where appropriate (chapter 6);
- Baseline characteristics between my trial groups differ in the use of CVC-antimicrobial lock solutions; it is unclear what effect this difference may have on reducing catheter-related infections. A randomised trial design could be used in a large comparator study

comparing trisodium citrate and heparin in the prevention of CVC-related infections in haemodialysis patients (The CHG Trial); and

- A multi-national, multi-centre trial evaluating the effectiveness of 2% CHG in 70% isopropyl alcohol, as CVC skin, exit site and catheter hub cleansing agents on CVC-related prevention of CVC-related infections in haemodialysis patients when compared to a 0.5% CHG in 70% isopropyl alcohol solution (The CHG Trial).

### **10.9.5 Conclusion**

This trial, investigating the effectiveness of 2% CHG in 70% isopropyl alcohol antiseptic solution versus other routinely used CHG solutions (0.5% CHG in 70% isopropyl alcohol and 0.05% aqueous CHG) in the prevention of CVC-related infections, is unique. This solution has been available for a number of years, but this trial is the first in the haemodialysis patient population. My trial is highly relevant to dialysis nurses, focusing on a topic that is an important component of everyday dialysis nursing practice. It contributes to the knowledge base that will help dialysis nurses choose between the solutions. My thesis also contributes to improvements in infection prevention and control practices in the haemodialysis setting, better patient safety and more efficient use of resources by identify areas of practice that warrant further development and research.

The aims of my trial were to test the trial methods and evaluate the feasibility of undertaking that study as a multi-national, multi-centre trial. Methods used in my trial were appropriate for evaluating the effectiveness of 2% CHG in alcohol. The trial did not show a significant difference between 2% CHG in alcohol and the comparator solutions in the prevention of CVC-related infections. For all catheter-related infections, although not statistically significant, relative risk ratios are below one and consistently favour the 2% CHG in 70% isopropyl alcohol solution over the comparator solutions. These conclusions are tempered by the small sample size and low event numbers. No conclusions for changes in practice can be drawn, but findings from my trial add to the evidence and can be used in a future meta-analysis of the evidence-based literature. Finally, this unique pilot multi-centre trial confirms that a larger multi-national, multi-centre study is feasible.

## REFERENCES

- Abdelsatir S. (2013) Evaluation of nurses awareness and practice of hemodialysis access care in Khartoum State, Sudan. *Arab Journal of Nephrology and Transplantation* **6**(2), 119-121.
- Adams D., Quayum M., Worthington T., Lambert P. & Elliott T. (2005) Evaluation of a 2% chlorhexidine gluconate in 70% isopropyl alcohol skin disinfectant. *Journal of Hospital Infection* **61**, 287-290.
- Al-Solaiman Y., Estrada E. & Allon M. (2011) The spectrum of infections in catheter-dependent hemodialysis patients. *Clinical Journal of the American Society of Nephrology* **6**(9), 2247-2252.
- Alford L. (2007) On difference between explanatory and pragmatic clinical trials. *New Zealand Journal of Physiotherapy* **35**(1), 12-16.
- Allen N., Schwartz D., Sood A., Mendelssohn D., Verrelli M., Tanna G., Schiff J., Komenda P., Rigatto C. & Sood M. (2011) Perceived barriers to guidelines in peritoneal dialysis. *Nephrology Dialysis Transplantation* **26**(5), 1683-1689.
- Allon M. (2009) Treatment guidelines for dialysis catheter-related bacteraemia: An update. *American Journal of Kidney Diseases* **54**(1), 13-17.
- Allon M., Daugirdas J., Depner T., Greene T., Omt D. & Schwab S. (2006) Effect of change in vascular access on patient mortality in hemodialysis patients. *American Journal of Kidney Diseases* **47**(3), 469-477.
- Allon M., Depner T., Radeva M., Bailey J., Beddhu S., Butterly D., Coyne D., Gassman J., Kaufman A., Kaysen G., Lewis J. & Schwab S. (2003) Impact of dialysis dose and membrane on infection related hospitalisation and death: Results of the HEMO study. *Journal of the American Society of Nephrology* **14**(7), 1863-1870.
- Alomari A. & Falk A. (2007) The natural history of tunnelled hemodialysis catheters removed or exchanged: A single institution experience. *Journal of Vascular Intervention Radiology* **18**(2), 227-235.
- Alshurafa M., Briel M., Akl E., Haines T., Moayyedi P., Gentles S., Rios L., Bhatnager N., Lamontagne F., Walter S. & Guyatt G. (2012) Inconsistent definitions for intention-to-treat in relation to missing outcome data: Systematic review of the methods literature. *PLoS One* **7**(11), e49163.
- Altman D. (1991) *Practical Statistics for Medical Research*. Chapman & Hall/CRC, Boca Raton.
- Altman D. & Bland J. (1999) Treatment allocation in controlled trials: why randomise? *British Medical Journal* **318**(7192), 1209.
- Amerling R. (2012) Con: On cardiovascular outcomes and the arteriovenous fistula: lesser of evils. *Nephrology Dialysis Transplantation* **27**(10), 3756-3757.

An Bord Altranais (2000) *The Code of Professional Conduct for Each Nurse and Midwife*. An Bord Altranais, Dublin.

Apisarnthanarak A., Thongphubeth K., Yuekyen C., Warren D. & Fraser V. (2010) Effectiveness of a catheter-associated bloodstream infection bundle in a Thai tertiary care center: a 3-year study. *American Journal of Infection Control* **38**(6), 449-455.

Aranaz-Andrés J., Aibar-Remón C., Vitaller-Burillo J., Requena-Puche J., Terol-García E., Kelley E., Gea-Velazquez de Castro M. & the ENEAS work group (2009) Impact and preventability of adverse events in Spanish public hospitals: results of the Spanish National Study of Adverse Events (ENEAS). *International Journal for Quality in Health Care* **21**(6), 408-414.

Aranaz-Andrés J., Aibar-Remón C., Vitaller-Murillo J., Ruiz-López P., Limón-Ramírez R., Terol-García E. & the ENEAS work group (2008) Incidence of adverse events related to health care in Spain: results of the Spanish National Study of Adverse Events. *Journal of Epidemiology and Community Health* **62**(12), 1022-1029.

Archibald L. (2012) Applied epidemiology and biostatistics in healthcare epidemiology and infection control. In *Hospital Epidemiology and Infection Control*, 4 edn. (Mayhall C., ed), Lippincott Williams and Wilkins, Philadelphia, pp. 1-19.

Arechabala M., Catoni M., Claro J., Rojas N., Rubio M., Calvo M. & Letelier L. (2013) Antimicrobial lock solutions for preventing catheter-related infections in haemodialysis (Protocol). *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: CD010597. DOI: 10.1002/14651858.CD010597.

Ashcroft R. (1999) Equipoise, knowledge and ethics in clinical research and practice. *Bioethics* **13**(3/4), 314-326.

Ashley C. (2009) *The Renal Drug Handbook*. 3 edn. Radcliffe Publishing, Oxford.

Association for Professionals in Infection Control and Epidemiology (2009) *Guide to the Elimination of Catheter-Related Bloodstream Infections*. Association for Professions in Infection Control and Epidemiology, Washington.

Astle C. & Jensen L. (2005) A trial of ExSept® for hemodialysis central venous catheters. *Nephrology Nursing Journal* **32**(4), 517-525.

Astor B., Eustace J., Powe N., Klag M., Fink N. & Coresh J. (2005) Type of vascular access and survival among incident hemodialysis patients: the Choices for Healthy Outcome in Caring for ESRD (CHOICE) Study. *Journal of the American Society of Nephrology* **16**(5), 1449-1455.

- Atahan K., Cokmez A., Bekoglu M., Durak E., Tavusbay C. & Tarcan E. (2012) The effect of antiseptic solution in central venous catheter care. *Bratisl Lek Listy* **113**(9), 548-551.
- Atapour A. & Shahidi S. (2006) Does tunneling the temporary vascular access extend its lifetime? *Journal of Research in Medical Sciences* **11**(1), 41-47.
- Bagdasarian N., Heung M. & Malani P.N. (2012) Infectious complications of dialysis access devices. *Infectious Disease Clinics of North America* **26**(1), 127-141.
- Bajwa R., Casey A., Collier C., O'Kelly P., Conlon P. & Fitzpatrick F. (2012) Can the NHSN dialysis event protocol be implemented in an Irish dialysis unit. *International Journal of Infection Control* **8**(3), 1-6.
- Baker G., Norton P., Flintoft V., Blais R., Brown A., Cox J., Etchells E., Ghali W., Hébert P., Majumdar S., O'Beirne M., Palacios-Derflinger L., Reid R., Sheps S. & Tamblyn R. (2004) The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *Canadian Medical Association Journal* **170**(11), 1678-1686.
- Bannister K. & Snelling P. (2006) National haemodialysis guidelines: an assessment of compliance from 2001-2003. *Nephrology* **11**(2), 90-96.
- Bednarski D. (2009) The value of nursing. *Nephrology Nursing Journal* **36**(2), 115-117.
- Berthoux F., Jones E., Gellert R., Mendel S., Saker L. & Briggs D. (1999) Epidemiological data of treated end stage renal failure in the European Union (EU) during the year 1995: report of the European Renal Association Registry and the National Registries. *Nephrology Dialysis Transplantation* **14**(10), 2332-2342.
- Bevans M., Tierney D., Bruch C., Burgunder M., Castro K., Ford R., Miller M., Rome S. & Schmit-Pokorny K. (2009) Hematopoietic stem cell transplantation cursing: A practice variation study. *Oncology Nursing Forum* **36**(6), E317-E325.
- Bilir A., Yelken B. & Erkan A. (2013) Chlorhexidine, octenidine or povidone iodine for catheter related infections: A randomized controlled trial. *Journal of Research in Medical Sciences* **18**(6), 510-512.
- Blot F., Schmidt E., Nitenberg G., Tancrede C., Leclercq B., Laplanche A. & Andremont A. (1998) Earlier positivity of central-venous- versus peripheral-blood cultures is highly predictive of catheter-related sepsis. *Journal of Clinical Microbiology* **36**(1), 105-109.
- Bouza E., Alvarado N., Alcalá L., Sánchez-Conde M., Perez M., Muñoz P., Martín-Rabadán P. & Rodríguez-Créixems M. (2005) A prospective,



randomized, and comparative study of 3 different methods for the diagnosis of intravascular catheter colonization. *Clinical Infectious Diseases* **40**(8), 1096-1100.

Bradbury B., Chen F., Furniss A., Pisoni R., Keen M., Mapes D. & Krishnan M. (2009) Conversion of vascular access type among incident hemodialysis patients: descriptions and association with mortality. *American Journal of Kidney Diseases* **53**(5), 804-814.

Brady A., Redmond R., Curtis E., Keenan P., Malone A. & Sheerin F. (2009) Adverse events in health care: a literature review. *Journal of Nursing Management* **17**(2), 155-164.

Brandt T., Irwin M., Shogan J. & Lucke J. (1996) Comparison of central venous catheter dressings in bone marrow transplant recipients. *Oncology Nursing Forum* **23**, 829-836.

Bray B., Boyd J., Daly C., Donaldson K., Doyle A., Fox J., Innes A., Khan I., Peel R., Severn A., Shilliday I., Simpson K., Stewart G., Traynor J. & Metcalfe W. (2012) Vascular access type and risk of mortality in a national prospective cohort of haemodialysis patients. *Quarterly Journal of Medicine* **105**(11), 1097-1103.

Bray B., Boyd J., Daly C., Doyle A., Donaldson K., Fox J., Innes A., Khan I., Mackinnon B., Peel R., Shilliday I., Simpson K., Stewart G., Traynor J., Metcalfe W. & on behalf of the Scottish Renal Registry (2014) How safe is renal replacement therapy? A national study of mortality and adverse events contributing to the death of renal replacement therapy recipients. *Nephrology Dialysis Transplantation* **29**(3), 681-687.

Brennan T., Leape L., Laird N., Hebert L., Localio A., Lawthers A., Newhouse J., Weiler P. & Hiatt H. (1991) Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *New England Journal of Medicine* **324**(6), 370-376.

Burrowes J., Russell G. & Rocco M. (2005) Multiple factors affect renal dietitians' use of the NKF-K/DOQI adult nutrition guidelines. *Journal of Renal Nutrition* **15**(4), 407-426.

Butterly D. & Schwab S. (2001) Catheter access for hemodialysis: an overview. *Seminars in Dialysis* **14**(6), 411-415.

Cabana M., Rand C., Powe N., Wu A., Wilson M., Abboud P. & Rubin H. (1999) Why don't physicians follow clinical practice guidelines?: A framework for improvement. *JAMA: The Journal of the American Medical Association* **282**(15), 1458-1465.

Campbell M. & Swinscow D. (2009) *Statistics at Square One*. 9 edn. Wiley-Blackwell, Chichester.

Canadian Institute for Health Information (2014) *Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2003 to 2012*. Canadian Institute for Health Information, Ottawa. Retrieved from

[https://secure.cihi.ca/free\\_products/2014\\_CORR\\_Annual\\_Report\\_EN.pdf](https://secure.cihi.ca/free_products/2014_CORR_Annual_Report_EN.pdf) on 25th April 2014.

CareFusion (2010) *ChloraPrep with Tint Summary of Product Characteristics*. CareFusion, Reigate. Retrieved from <http://www.enturia.co.uk/> on 21st February 2013.

CARI (2000) *Dialysis Vascular Access Guidelines*. CARI. Retrieved from [http://www.cari.org.au/guidelines\\_archives.php](http://www.cari.org.au/guidelines_archives.php) on 30th July 2012.

Casey A., Worthington T., Lambert P., Quinn D., Faroqui M. & Elliott T. (2003) A randomized, prospective clinical trial to assess the potential infection risk associated with the PosiFlow® needleless connector. *Journal of Hospital Infection* **54**(4), 288-293.

CDC (2002) Guidelines for the prevention of intravascular catheter-related infections. *CDC Morbidity and Mortality Weekly Report (MMWR)* **51**(No. RR-10).

CDC (2011a) *Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011*. CDC, Atlanta. Retrieved from <http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf> on 25th May 2014.

CDC (2011b) Vital signs: central line-associated blood stream infections--United States, 2001, 2008, and 2009. *CDC Morbidity and Mortality Weekly Report (MMWR)* **60**(8), 243-248.

CDC/NHSN (2009) *The National Healthcare Safety Network (NHSN) Manual, Patient Safety Component Protocol*. Division of Healthcare Quality Promotion, National Centre for Preparedness, Detection and Control of Infectious Diseases, Atlanta. Retrieved from <http://www.cdc.gov/nhsn/psc.html> on 31st January 2011.

CDC/NHSN (2014a) *The National Healthcare Safety Network (NHSN) Manual, Patient Safety Component Manual*. Division of Healthcare Quality Promotion, National Centre for Preparedness, Detection and Control of Infectious Diseases, Atlanta. Retrieved from [http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC\\_CLABSCurrent.pdf](http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABSCurrent.pdf) on 17th May 2014.

CDC/NHSN (2014b) *The National Healthcare Safety Network (NHSN) Manual, Patient Safety Component Manual: Dialysis Event Protocol*. Division of Healthcare Quality Promotion, National Centre for Preparedness, Detection and Control of Infectious Diseases, Atlanta. Retrieved from <http://www.cdc.gov/nhsn/PDFs/pscManual/8pscDialysisEventcurrent.pdf> on 17th May 2014..

Chalkidou K. (2009) Comparative effectiveness review within the U.K. National Institute for Health and Clinical Excellence. *Issue brief (Commonwealth Fund)* **59**, 1-12.

Chalyakunapruk N., Veenstra D., Lipsky B. & Saint S. (2002) Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: A meta-analysis. *Annals of Internal Medicine* **136**(11), 792-801.

Chatzinikolaou I., Finkel K., Hanna H., Boktour M., Foringer J., Ho T., & Raad I. (2003) Antibiotic-coated hemodialysis catheters for the prevention of vascular catheter-related infections: A prospective, randomized study. *American Journal of Medicine* **115**(5), 352-357.

Cobbett S. & LeBlanc A. (2000) Minimising IV site infection while saving time and money. *Healthcare Infection* **5**(2), 8-14.

Collins A., Foley R., Gilbertson D. & Chen S. (2009) The state of Chronic Kidney Disease, ESRD, and morbidity and mortality in the first year of dialysis. *Clinical Journal of the American Society of Nephrology* **4**(Supplement 1), S5-S11.

Conklin A., Vilamovska A., de Vries H. & Hatziandreu E. (2008) *Technical Report for EU Commission on 'Improving Patient Safety in the EU: Assessing the expected effects of three policy areas for future action'* RAND Corporation, Santa Monica, CA.

Conly J., Grieves K. & Peters B. (1989) A prospective, randomized study comparing transparent and dry gauze dressings for central venous catheters. *Journal of Infectious Diseases* **159**(2), 310-319.

Cookson B. (1990) Mupirocin resistance in staphylococci. *Journal of Antimicrobial Chemotherapy* **25**(4), 497-503.

Council for International Organisation of Medical Sciences (CIOMS) (2002) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Council for International Organisation of Medical Sciences, Geneva. Retrieved from [http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf) on 16th October 2012.

Council of Europe (2006) *Recommendation of the Committee of Ministers to Member States on the Management of Patient Safety and Prevention of Adverse Events in Health Care*. Council of Europe, Strasbourg.

Council of the European Union (2006) Council conclusion on common values and principles in European Union health systems. *Official Journal of the European Union* (C146/1-3).

Council of the European Union (2009) Council recommendation on patient safety, including the prevention and control of healthcare-associated infections. *Official Journal of the European Union* **52**(C151/01-06).

Couser W., Remuzzi G., Mendis S. & Tonelli M. (2011) The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney International* **80**(12), 1258-1270.

Crnich C. & Maki D. (2002a) The promise of novel technology for the prevention of intravascular device-related bloodstream infection II. Long-term devices. *Clinical Infectious Diseases* **34**(10), 1362-1368.

Crnich C. & Maki D. (2002b) The promise of novel technology for the prevention of intravascular device-related bloodstream infection I. Pathogenesis and short-term devices. *Clinical Infectious Diseases* **34**(9), 1232-1242.

Damani N. (2012) *Manual of Infection Prevention and Control*. Oxford University Press, Oxford.

Davies B., Edwards N., Ploeg J., Virani T. & Skelly J. & Dobbins M. (2006) *Determinants of sustained use of research evidence in nursing*. Canadian Health Services Research Foundation and Canadian Institutes for Health Research, Ottawa. Retrieved from

[http://www.chsrf.ca/Migrated/PDF/ResearchReports/OGC/davies\\_final\\_e.pdf](http://www.chsrf.ca/Migrated/PDF/ResearchReports/OGC/davies_final_e.pdf)

on 12th October 2012.

Davis D. & Taylor-Vaisey A. (1997) Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *Canadian Medical Association Journal* **157**(4), 408-416.

Davis P., Lay-Yee R., Briant R., Ali W., Scott A. & Schug S. (2002) Adverse events in New Zealand public hospitals I: occurrence and impact. *New England Journal of Medicine* **115**(1167), U271.

Davis P., Lay-Yee R., Briant R., Ali W., Scott A. & Schug S. (2003) Adverse events in New Zealand public hospitals II: preventability and clinical context. *New England Journal of Medicine* **116**(1183), U624.

De Angelis C., Drazen J., Frizelle F., Haug C., Hoey J., Horton R., Kotzin S., Laine C., Marusic A., Overbeke A., Schroeder T., Sox H. & Van Der Weyden M. (2004) Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *New England Journal of Medicine* **351**(12), 1250-1251.

Delos Santos F. (2014) Personal Communication.

De Palo V., McNicoll L., Cornell M., Rocha J., Adams L. & Pronovost P. (2010) The Rhode Island ICU collaborative: a model for reducing central line-associated bloodstream infection and ventilator-associated pneumonia statewide. *Quality and Safety in Health Care* **19**(6), 555-561.

De Vos J., Elseviers M., Harrington M., Zampieron A., Vlamincck H., Ormandy P. & Kafkia T. (2006) Infection control practice across Europe: Results of EPD. *EDTNA/ERCA Journal* **32**(1), 38-40.

Denton G. (2001) Chlorhexidine. In *Disinfection, Sterilization and Preservation*, 5 edn. (Block S., ed), Lippincott Willimans and Wilkins, Philadelphia.

Department of Health & Children (2001) *Quality and Fairness. A Health System for You*. Stationary Office, Dublin.

Department of Health & Children (2012a) *Annual Report 2011*. Department of Health & Children, Dublin.

Department of Health & Children (2012b) *Future Health A Strategic Framework for Reform of the Health Service 2012-2015*. Department of Health & Children, Dublin.

Department of Health & Children (2012c) *Statement of Strategy 2011-2014*. Department of Health & Children, Dublin.

Department of Health & Children (2013) *Healthy Ireland, A Framework for Improved Health and Wellbeing*. Department of Health & Children, Dublin.

Department of Health UK (2000) *An Organisation with a Memory: Report of an expert group on learning from adverse events in the NHS*. Stationary Office, London.

Department of Health UK (2007) *Saving Lives: reducing infection, delivering clean and safe care*. Department of Health, London.

Department of Health UK (2013) *Renal Care Health Building Note 07-01: Satellite Dialysis Unit*. Stationary Office, London.

Develter W., De Cubber A., Van Biesen W., Vanholder R. & Lameire N. (2005) Survival and complications of indwelling venous catheters for permanent use in hemodialysis patients. *Artificial Organs* **29**(5), 399-405.

Dhingra R., Young E., Hulbert-Shearon T., Leavey S. & Port F. (2001) Type of vascular access and mortality in US hemodialysis patients. *Kidney International* **60**(4), 1443-1451.

Dialysis Outcomes Practice Pattern Study (2010) *2010 Annual Report of the Dialysis Outcomes and Practice Patterns Study: Hemodialysis Data 1999-2010*. Arbor Research Collaborative for Health, Ann Arbor, MI. Retrieved from <http://www.dopps.org/annualreport/index.htm> on 17th August 2012.

Dixon D., Freedman R., Herson J., Hughes M., KyungMarin K., Silverman M. & Tangen C. (2006) Guidelines for data and safety monitoring for clinical trials not requiring traditional data monitoring committees. *Clinical Trials* **3**(3), 314-319.

Djulgovic B. & Clarke M. (2001) Scientific and ethical issues in equivalence trials. *Journal of the American Medical Association* **285**(9), 1206-1208.

Donlon S., Redmond A., McCann M. & Einarsdottir H. (2011) Prevention of infection in patients with chronic kidney disease part III: Surveillance and auditing in a renal care environment. *Journal of Renal Care* **37**(3), 167-173.

Duffly A. (2012) *An Analysis of the Culture in Ireland on Open Disclosure following Adverse Events in Healthcare*. Unpublished Masters Theses, University College Dublin, Dublin.

ECDC (2008) *Annual Epidemiological Report on Communicable Diseases in Europe 2008*. European Centre for Disease Prevention and Control, Stockholm.

ECDC (2012) *Point Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use in European Acute Care Hospitals*. European Centre for Disease Prevention and Control, Stockholm. Retrieved from [http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC\\_DispForm.aspx?ID=878](http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=878) on 13th March 2013.

ECDC (2013) *Point Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use in European Acute Care Hospitals*. European Centre for Disease Prevention and Control, Stockholm.

Eggers P. (2011) Has the incidence of end-stage renal disease in the USA and other countries stabilized? *Current Opinion in Nephrology and Hypertension* **20**(3), 241-245.

Eguare E., Tierney S., Maher R., Creamer M., Grace P., Cronin C. & Burke P. (2006) Demands for vascular access in a renal dialysis unit: implications for a regional vascular unit. *Irish Journal of Medical Science* **175**(1), 24-28.

Einarsdottir H. (2014) Personal Communication.

El-Saed A., Sayyari A., Hejaili F., Sallah M., Dagunton N. & Balkhy H. (2011) Higher access-associated bacteremia but less hospitalization among Saudi compared with US hemodialysis outpatients. *Seminars in Dialysis* **24**(4), 460-465.

Engemann J., Friedman J., Reed S., Griffiths R., Szczech L., Kaye K., Stryjewski M., Reller L., Schulman K., Corey G. & Fowler V. (2005) Clinical outcomes and costs due to staphylococcus aureus bacteremia among patients receiving long term hemodialysis. *Infection Control and Hospital Epidemiology* **26**(6), 534-539.

ERA-EDTA (2002) European best practice guidelines in haemodialysis (part 1). *Nephrology Dialysis Transplant* **17**(Supplement 7), 1-111.

Ethier J., Mendelssohn D., Elder S., Hasegawa T., Akizawa T., Akiba T., Canaud B. & Pisoni R. (2008) Vascular access use and outcome: an international perspective from the Dialysis Outcomes and Practice Patterns Study. *Nephrology Dialysis Transplant* **23**, 3219-3226.

European Commission (2005) *Patient Safety - Making it Happen! Luxembourg Declaration on Patient Safety*. European Commission, Brussels.

European Commission (2006) *Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medical Products for Human Use*. European Commission, Brussels.

European Commission (2007) *White Paper Together for Health: A Strategic Approach for the EU 2008-2012*. European Commission, Brussels.

European Commission (2008a) *Report on the Open Consultation on Patient Safety in the European Union*. European Commission, Brussels.

European Commission (2008b) *Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use*. European Union, Brussels. Retrieved from [http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a\\_09-2008\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf) on 24th March 2013.

European Commission (2009) *The Rules Governing Medicinal Products in the European Union, Volume 10 - Guidance Documents Applying to Clinical Trials, Questions and Answers, Version 4*. European Commission, Brussels.

European Commission (2010) *The Rules Governing Medicinal Products in the European Union, Volume 4 - EU Guidelines to Good Manufacturing Practices Medicinal Products for Human and Veterinary Use Annex 13 Investigational Medicinal Product*. European Commission, Brussels.

European Community (2001a) Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Communities* (L121/34-44).

European Community (2001b) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. *Official Journal of the European Communities* (L311/67-128).

European Community (2004) Directive 2004/27/EC of the European Parliament and of the Council of 31st March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal of the European Union* (L136/34-57).

European Community (2005) Commission Directive 2005/28/EC of 8th April 2005 Laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirement for authorisation of the manufacturing or importation of such products. *Official Journal of the European Union* (L91/13-19).

European Renal Association (2002) European best practice guidelines on haemodialysis part 1. *Nephrology Dialysis Transplantation* **17**(Suppl 7), 1-109.

European Union (2011) Directive 2011/24/EU of the European Parliament and of The Council of 9th March 2011 on the application of patient rights in cross border health care. *Official Journal of the European Union* (L88/45-65).

Field A. (2009) *Discovering Statistics Using SPSS*. 3 edn. Sage Publications Ltd, London.

Fitzgerald S. (2014) Personal Communication.

Fitzgerald S., O’Gorman J., Morris-Downes M., Crowley R., Donlon S., Bajwa R., Smyth E., Fitzpatrick F., Conlon P. & Humphreys H. (2011) A 12-year review of *Staphylococcus aureus* bloodstream infections in haemodialysis patients: more work to be done. *Journal of Hospital Infection* **79**(3), 218-221.

Fitzgibbons L., Puls D., Mackay K. & Forrest G. (2011) Management of gram-positive coccal bacteremia and hemodialysis. *American Journal of Kidney Diseases* **57**(4), 624-640.



- Fitzpatrick F. (2013) *Overview of National Programme: Prevention of Healthcare-Associated Infection and Antimicrobial Resistance*. Health Service Executive, Dublin. Retrieved from <http://www.hse.ie/eng/about/Who/qualityandpatientsafety/safepatientcare/HCAI Programme/HCAI Programme Presentation March 2013.pdf> on 9th December 2013.
- Forder P., Gebiski V. & Keech A. (2005) Allocation concealment and blinding: when ignorance is bliss. *Medical Journal of Australia* **182**(2), 87-89.
- Freedman B. (1987) Equipoise and the ethics of clinical research. *New England Journal of Medicine* **317**(3), 141-145.
- French V., Cooper R. & Molan P. (2005) The antibacterial activity of honey against coagulase-negative staphylococci. *Journal of Antimicrobial Chemotherapy* **56**(1), 228-231.
- Friedman L. (2013) Commentary: Why we should report results from clinical trial pilot studies. *Trials* **14**(1), 14.
- Friedman L., Furberg C. & DeMets D. (1998) *Fundamentals of Clinical Trials*. 3 edn. Springer, New York
- Fries J. & Krishnan E. (2004) Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. *Arthritis Research and Therapy* **6**(3), R250-R255.
- Garland J., Alex C., Uhing M., Peterside I., Rentz A. & Harris M. (2009) Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antiseptics for central venous catheter placement in neonates. *Journal of Perinatology* **29**(12), 808-813.
- Garrick R., Klinger A. & Stefanchik B. (2012) Patient and facility safety in hemodialysis: opportunities and strategies to develop a culture of safety. *Clinical Journal of the American Society of Nephrology* **7**(4), 680-688.
- George A., Tokars J., Clutterbuck E., Bamford K., Pusey C. & Holmes A. (2006) Reducing dialysis associated bacteraemia, and recommendations for surveillance in the United Kingdom: prospective study. *British Medical Journal* **332**(7555), 1435-1440.
- Gerrish K., Guillaume L., Kirshbaum M., McDonnell A., Nolan M. & Read S. (2007) *Empowering from line staff to deliver evidence-based care: The contribution of nurses in advanced practice roles*. Sheffield Hallam University. Retrieved from <http://research.shu.ac.uk/hwb/ncimpact/hsc-EmpoweringFrontlineStaffExecSum.pdf> on 12th October 2012.
- Gerrish K. & Lacey A., eds. (2010) *The Research Process in Nursing*, 6 edn. Wiley-Blackwell, Oxford.

- Gerrish K., McDonnell A., Nolan M., Guillaume L., Kirshbaum M. & Tod A. (2011) The role of advanced practice nurses in knowledge brokering as a means of promoting evidence-based practice among clinical nurses. *Journal of Advanced Nursing* **67**(9), 2004-2014.
- Gerrish K., Nolan M., McDonnell A., Tod A., Kirshbaum M. & Guillaume L. (2012) Factors influencing advanced practice nurses' ability to promote evidence-based practice among frontline nurses. *Worldviews on Evidence-Based Nursing* **9**(1), 30-39.
- Gethin G. & Cowman S. (2008) Bacteriological changes in sloughy venous leg ulcers treated with manuka honey or hydrogel: an RCT. *Journal of Wound Care* **17**(6), 241-244, 246-247.
- Gilles D., Carr D., Frost J., O'Riordan R. & O'Brien I. (2003) Gauze and tape and transparent polyurethane for central venous catheters. *Cochrane Database of Systematic Reviews 2003 Issue 3*. Art No: CD003837. DOI: 10.1002/14651858.CD003827.
- Goodkin D., Pisoni R., Locatelli F., Port F. & Saran R. (2010) Hemodialysis vascular access training and practices are key to improved access outcomes. *American Journal of Kidney Diseases* **56**(6), 1032-1042.
- Government of Ireland (2004) *S.I. No. 190 of 2004, European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004*. Stationery Office, Dublin.
- Grant A., Altman D., Babiker A., Campbell M., Clemens F., Darbyshire J., Elbourne D., McLeer S., Parmar M., Pocock S., Spiegelhalter D., Sydes M., Walker A., Wallace S. & the DAMOCLES study group (2005) Issues in data monitoring and interim analysis of trials. *Health Technology Assessment* **9**(7), 1-238.
- Gray D. (2009) *Doing Research in the Real World, 2nd ed.* Sage Publications, London
- Greene T. (2009) Randomized and observational studies in nephrology: How strong is the evidence? *American Journal of Kidney Diseases* **53**(3), 377-388.
- Grubbs V., Wasse H., Vittinghoff E., Grimes B. & Johansen K. (2014) Health status as a potential mediator of the association between hemodialysis vascular access and mortality. *Nephrology Dialysis Transplantation* **29**(4), 892-898.
- Guerin K., Wagner J., Rains K. & Bessesen M. (2010) Reduction in central line-associated bloodstream infections by implementation of a postinsertion care bundle. *American Journal of Infection Control* **38**(6), 430-433.

Hall-McMahon E. & Campbell K. (2012) Have renal dietitians successfully implemented evidence-based guidelines into practice? A survey of dietitians across Australia and New Zealand. *Journal of Renal Nutrition* **22**(6), 584-591.

Harbarth S., Sax H. & Gastmeier P. (2003) The preventable proportion of nosocomial infections: an overview of published reports. *Journal of Hospital Infection* **54**(4), 258-266.

Harwood L., Wilson B., Thompson B., Brown E. & Young D. (2008) Predictors of hemodialysis central venous catheter exit-site infections. *Canadian Association of Nephrology Nurses and Technologists Journal* **18**(2), 26-35.

Health Information and Quality Authority (2009) *National Standards for the Prevention and Control of Healthcare-Associated Infections*. Health Information and Quality Authority, Dublin.

Health Information and Quality Authority (2012a) *Guide: Monitoring Programme for National Standards for the Prevention and Control of Healthcare-Associated Infections*. Health Information and Quality Authority, Dublin.

Health Information and Quality Authority (2012b) *National Standards For Safer Better Healthcare*. Health Information and Quality Authority, Dublin.

Health Information and Quality Authority (2013a) *Report on the Unannounced Monitoring Assessment of St James Hospital, Monitoring Programme for the National Standards for the Prevention and Control of Healthcare-Associated Infections*. Health Information and Quality Authority, Dublin.

Health Information and Quality Authority (2013b) *Report on the Unannounced Monitoring Assessment of St Vincents University Hospital, Monitoring Programme for the National Standards for the Prevention and Control of Healthcare-Associated Infections*. Health Information and Quality Authority, Dublin.

Health Information and Quality Authority (2013c) *Report on the Unannounced Monitoring Assessment of Tallaght Hospital, Monitoring Programme for the National Standards for the Prevention and Control of Healthcare-Associated Infections*. Health Information and Quality Authority, Dublin.

Health Protection Surveillance Centre (2012a) *EARS-Net Report for Quarter 1 2012*. Health Protection Surveillance Centre, Retrieved from <http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/EuropeanAntimicrobialResistanceSurveillanceSystemEARSS/EARSSSurveillanceReports/2012Reports/> on 30th August 2012.

Health Protection Surveillance Centre (2012b) *Point Prevalence Survey of Hospital Acquired Infections and Antimicrobial Use in European Acute Care Hospitals: May 2012 - Republic of Ireland National Report: November 2012*.

Health Protection Surveillance Centre, Dublin.

Health Protection Surveillance Centre (2013) *Point Prevalence Survey of Hospital Acquired Infections and Antimicrobial Use in European Acute Care Hospitals: May 2012 - Republic of Ireland Critical Care Report: February 2013*.

Health Protection Surveillance Centre, Dublin.

Health Protection Surveillance Centre (2014) *Trends in Staphylococcus aureus/MRSA bacteraemia in Ireland 2004 to the end of Q4 2013 (data correct as of 26th March 2014)*. Health Protection Surveillance Centre, Retrieved from <http://www.hpsc.ie/AMicrobiologyAntimicrobialResistance/EuropeanAntimicrobialResistanceSurveillanceSystemEARSS/ReferenceandEducationalResourceMaterial/SaureusMRSA/LatestSaureusMRSAdata/File,3989,en.pdf012Reports/> on 20th June 2014.

Health Service Executive (2007) *Say No to Infection, Infection Control Action Plan, March Briefing*. Health Service Executive. Retrieved from [http://www.hse.ie/eng/services/Publications/HealthProtection/Health\\_Care\\_Associated\\_Infection/The\\_prevention\\_and\\_control\\_of\\_Health\\_Care\\_Associated\\_Infections\\_in\\_Ireland\\_Background\\_Briefing\\_March\\_2007.pdf](http://www.hse.ie/eng/services/Publications/HealthProtection/Health_Care_Associated_Infection/The_prevention_and_control_of_Health_Care_Associated_Infections_in_Ireland_Background_Briefing_March_2007.pdf) on October 2009.

Health Service Executive (2012) *The National Healthcare Charter, You and Your Health Service*. Health Service Executive, Dublin.

Health Service Executive (2013a) *HSE Safe Care and Support, Supporting Services To Deliver Quality Healthcare: Acute Hospital Services June 2013 Quality Assessment and Improvement Workbook 3*. Health Service Executive, Dublin.

Health Service Executive (2013b) *National Operational Plan 2013, Implementing the National Service Plan 2013*. Health Service Executive, Dublin.

Health Service Executive & State Claims Agency (2012) *Detailed Breakdown of Adverse Events Involving Service Users 2011*. Health Service Executive and the State Claims Agency, Dublin.

Herwaldt L. & Supp B. (1998) Reduction of staphylococcus aureus nasal carriage and infection in dialysis patients. *Journal of Hospital Infection* **40**(Suppl B), S13-S23.

- Higgins J. & Green S., eds. (2009) *Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]*. The Cochrane Collaboration. Retrieved from [www.cochrane-handbook.org](http://www.cochrane-handbook.org) 20th March 2013.
- Higgins J., Thompson S., Deeks J. & Altman D. (2003) Measuring inconsistency in meta-analyses. *British Medical Journal* **327**(7414), 557-560.
- Higgins M. & Evans D. (2008) Nurses' knowledge and practice of vascular access infection control in haemodialysis patients in the Republic of Ireland. *Journal of Renal Care* **34**(2), 48-53.
- Hoen B., Paul-Dauphin A., Hestin D. & Kessler M. (1998) EPIBACDIAL: a multicentre prospective study on risk factors for bacteraemia in chronic hemodialysis patients. *Journal of the American Society of Nephrology* **9**(5), 869-876.
- Hollis S. & Campbell F. (1999) What is meant by intention-to-treat analysis? Survey of published randomised controlled trials. *British Medical Journal* **319**(7211), 670-674.
- Hopewell S., Clarke M., Lefebvre C. & Scherer R. (2007) Handsearching versus electronic searching to identify reports of randomized trials. *The Cochrane Database of Systematic Reviews 2007 Issue 2* Art. No.: MR000001. DOI: 10.1002/14651858.MR000001.pub2..
- Hosking J., Newhouse M., Bagniewska A. & Hawkins B. (1995) Data collection and transcription. *Controlled Clinical Trials* **16**(2 supplement), 66S-103S.
- Houghton C., Hunter A. & Meskell P. (2012) Linking aims, paradigm and method in nursing research. *Nurse Researcher* **20**(2), 34-39.
- Hughes J. (1988) Study on the efficacy of nosocomial infection control (SENIC Project): results and implications for the future. *Chemotherapy* **34**(6), 553-561.
- Humar A., Ostromecki A., Direnfeld J., Marshall J., Lazar N., Houston P., Boiteau P. & Conly J. (2000) Prospective randomised trial of 10% povidone iodine versus 0.5% tincture of chlorhexidine as cutaneous antisepsis for prevention of central venous catheter infection. *Clinical Infectious Diseases* **31**(4), 1001-1007.
- Humphreys H., Newcombe R., Enstone J., Smyth E., McIlvenny G., Fitzpatrick F., Fry C. & Spencer R. (2008) Four country healthcare associated infection prevalence survey 2006: risk factor analysis. *Journal of Hospital Infection* **69**(3), 249-257.

Huraib S., Askar A., Abu-Aisha H. & al-Wakeel J. (1994) Prevalence of infection from subclavian dialysis catheters with two different postinsertion catheter cares: a randomized comparative study. *Angiology* **45**(12), 1047-1051.

ICH (1994) *ICH Harmonised Tripartite Guideline, Guideline for Clinical Safety Data Management: Definitions and Standard for Expedited Reporting E2A*, Retrieved from <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html> on 24th March 2013.

ICH (1996) *ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6(R1)*, Retrieved from [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6\\_R1/Step4/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf) on 30th January 2011.

Institute for Healthcare Improvement (2006) *What is a bundle?* Retrieved from <http://www.ihl.org/IHI/Topics/CriticalCare/IntensiveCare/ImprovementStories/WhatsaBundle.htm> on 24th August 2012.

International Council of Nurses (2012) *Position Statement on Patient Safety*. ICN, Geneva. Retrieved from [http://www.icn.ch/images/stories/documents/publications/position\\_statements/D05\\_Patient\\_Safety.pdf](http://www.icn.ch/images/stories/documents/publications/position_statements/D05_Patient_Safety.pdf) on 17th January 2014.

International Federation of Infection Control (2011) *Basic Concepts of Infection Control* International Federation of Infection Control. Retrieved from [http://www.theifc.org/basic\\_concepts/index.htm](http://www.theifc.org/basic_concepts/index.htm) on 24th August 2012.

Irish Medicines Board (2006) *Guide to the Investigational Medicinal Product Dossier*. Irish Medicines Board, Dublin.

Irish Medicines Board (2014) *Guide to Clinical Trial Applications*. Irish Medicines Board, Dublin.

Ishizuka M., Nagata H., Takagi K. & Kubota K. (2009) Comparison of 0.05% chlorhexidine and 10% povidone-iodine as cutaneous disinfectant for prevention of central venous catheter-related bloodstream infection: a comparative study. *European Surgical Research* **43**(3), 286-290.

Jaffer Y., Selby N., Taal M., Fluck R. & McIntyre C. (2008) A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter related infection. *American Journal of Kidney Diseases* **51**(2), 233-241.

James M., Conley J., Tonelli M., Manns B., MacRae J. & Hennelgarn B. (2008) Meta-analysis: Antibiotics for prophylaxis against hemodialysis catheter related infections. *Annals of Internal Medicine* **148**(8), 596-605.

- Jha V., Wang A. & Wang H. (2012) The impact of CKD identification in large countries: the burden of illness. *Nephrology Dialysis Transplantation* **27**(suppl 3), iii32-iii38.
- Jindal K., Chan C., Deziel C., Hirsch D., Soroka S. & Tonelli M. (2006) Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. *Journal of the American Society of Nephrology* **17**(3 Suppl 1), S1-27.
- Johnson D., MacGinley R., Kay T., Hawley C., Campbell S., Isbel N. & Hollett P. (2002) A randomised controlled trial of topical exit site mupirocin application in patients with tunnelled, cuffed haemodialysis catheters. *Nephrology Dialysis Transplant* **17**(10), 1802-1807.
- Johnson D., van Eps C., Mudge D., Wiggins K., Armstrong K., Hawley C., Campbell S., Isbel N., Nimmo G. & Gibbs H. (2005) Randomised controlled trial of topical exit-site application of honey (Medihoney) versus mupirocin for the prevention of catheter associated infections in hemodialysis patients. *Journal of the American Society of Nephrology* **16**(5), 1456-1462.
- Jull A., Rodgers A. & Walker N. (2008a) Honey as a topical treatment for wounds. *Cochrane Database of Systematic Reviews 2008, Issue 4*. Art No. : CD005083. DOI: 10.1002/14651858.CD005083.
- Jull A., Walker N., Parag V., Molan P., Rogers A. & Honey as Adjuvant Leg Ulcer Therapy Trial Collaborators (2008b) Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *British Journal of Surgery* **95**(2), 175-182.
- Kairaitis L. & Gottlieb T. (1999) Outcome and complications of temporary haemodialysis catheters. *Nephrology Dialysis Transplant* **14**(7), 1710-1714.
- Kallen A. (2013) Identifying and classifying bloodstream infections among hemodialysis patients. *Seminars in Dialysis* **26**(4), 407-415.
- Kamaliah M., Haris Y. & Zaki S. (2004) Role of topical mupirocin as a prophylaxis in catheter related infection in haemodialysis patients. *International Medical Journal* **11**(1), 41-46.
- KDIGO CKD Work Group (2013) KIDGO 2012 Clinical practice guideline for the evaluation and management of Chronic Kidney Disease. *Kidney International* **3**(Suppl 1), 1-150.
- Kelly J., Usry G., Blackhurst D., Bushey M. & Steed C. (2006) Prevention of infections related to central venous catheters and arterial catheters in intensive care patients: a prospective randomized trial of chlorhexidine gluconate (CHG) versus povidone iodine (PI) (abstract). 15th Annual Scientific

Meeting of the Society for Healthcare Epidemiology of America, 9-12 April 2005, Los Angeles, California

Kelly P., Webster A. & Craig J. (2010) How many patients do we need for a clinical trial? Demystifying sample size calculations. *Nephrology* **15**(8), 725-731.

Kerr M. (2012) *Chronic Kidney Disease in England: The Human and Financial Cost*. NHS Kidney Care, Newcastle on Tyne.

Klevens R., Edwards J., Andrus M., Peterson K., Dudeck M., Horan T. & NHSN Participants in Outpatients Dialysis Surveillance (2008) Dialysis surveillance report: National Healthcare Safety Network (NHSN) - data summary for 2006. *Seminar in Dialysis* **21**(1), 23-28.

Klevens R., Edwards J., Richards C., Horan T., Gaynes R., Pollock D. & Cardo D. (2007) Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Reports* **122**(2), 160-166.

Klevens R., Tokars J. & Andrus M. (2005) Electronic reporting of infections associated with hemodialysis. *Nephrology News and Issues* **June**, 37-43.

Knasinski V. & Maki D. (2000) A prospective, randomized, controlled trial of 1% chlorhexidine 75% alcohol vs. 10% povidone iodine for cutaneous disinfection and follow-up site care with central venous and arterial catheters (abstract). National Association of Vascular Access Network Conference, San Diego.

Knowles S., Rolls K., Elliott D., Hardy J. & Middleton S. (2010) Patient care guidelines: A telephone survey of intensive care practices in New South Wales. *Australian Critical Care* **23**(1), 21-29.

Kohn L., Corrigan J. & Donaldson M., eds. (1999) *To Err is Human: Building a Safer Health System*. National Academy Press, Institute of Medicine, Washington, DC.

Koll B., Straub T., Jalon H., Block R., Heller K. & Ruiz R. (2008) The CLABs collaborative: a regionwide effort to improve the quality of care in hospitals. *The Joint Commission Journal on Quality and Patient Safety* **34**(12), 713-723.

Konner K. (1999) A primer on the av fistula—Achilles' heel, but also Cinderella of haemodialysis. *Nephrology Dialysis Transplantation* **14**(9), 2094-2098.

Kovesdy C. & Kalantar-Zadeh K. (2012) Observational studies versus randomized controlled trials: Avenues to causal inference in nephrology. *Advances in Chronic Kidney Disease* **19**(1), 11-18.

Kumwenda M., Wright F. & Haybrittle D. (1996) Survey of permanent central venous catheters for haemodialysis in the UK. *Nephrology Dialysis Transplant* **11**(5), 830-832.



- Labriola L., Crott R. & Jadoul M. (2008) Preventing haemodialysis catheter-related bacteraemia with an antimicrobial lock solution: a meta-analysis of prospective randomized trials. *Nephrology Dialysis Transplantation* **23**(5), 1666-1672.
- Lacson E., Wang W., Lazarus J. & Hakim R. (2010) Change in vascular access and hospitalization risk in long-term hemodialysis patients. *Clinical Journal of the American Society of Nephrology* **5**(11), 1996-2003.
- Lambie M., Rayner H., Bragg-Gresham J., Pisoni R., Andreucci V., Canaud B., Port F. & Young E. (2006) Starting and withdrawing haemodialysis-associations between nephrologists' opinions, patient characteristics and practice patterns (data from the Dialysis Outcomes and Practice Patterns Study). *Nephrology Dialysis Transplant* **21**(19), 2814-2820.
- Langgartner J., Linde H., Lehn N., Reng M., Scholmerich J. & Gluck T. (2004) Combined skin disinfection with chlorhexidine/propanol and aqueous povidone-iodine reduces bacterial colonisation of central venous catheters. *Intensive Care Medicine* **30**(6), 1081-1088.
- Laupland K. & Conly J. (2003) Treatment of staphylococcus aureus colonization and prophylaxis for infection with topical intranasal mupirocin: An evidence based review. *Clinical Infectious Diseases* **37**(7), 933-938.
- Le Corre I., Delorme M. & Cournoyer S. (2003) A prospective, randomized trial comparing a transparent dressing and a dry gauze on the exit site of long term central venous catheters of hemodialysis patients. *The Journal of Vascular Access* **4**, 56-61.
- Leape L., Brennan T., Laird N., Lawthers A., Localio A., Barnes B., Hebert L., Newhouse J., Weiler P. & Hiatt H. (1991) The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *New England Journal of Medicine* **324**(6), 377-384.
- LeBlanc A. & Cobbett S. (2000) A 0.5% chlorhexidine gluconate in 70% isopropyl alcohol swab was more effective than 2 other methods for intravenous skin antisepsis. *Evidence Based Nursing* **3**(2), 119.
- Lee H., Manns B., Taub K., Ghali W., Dean S., Johnson D. & Donaldson C. (2002) Cost analysis of ongoing care of patients with End-Stage Renal Disease: the impact of dialysis modality and dialysis access. *American Journal of Kidney Diseases* **40**(3), 611-622.
- Lee I. & Umscheid C. (2010) *Key questions for prevention of intravascular catheter-related infections. A review.* UPHS Centre for Evidence-based Practice, University of Pennsylvania, Pennsylvania. Retrieved from

<http://www.cdc.gov/hicpac/pdf/PennReviewHICPACMayCAI1.pdf> on 31st January 2011.

Lefebvre C., Manheimer E. & Glanville J. (2008) Chapter 6 Searching for studies. In *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (updated February 2008)*, The Cochrane Collaboration.

Legras A., Cattier B., DeQuin t., Boulain T. & Perrotin D. (1997) Etude prospective randomisee pour la prevention des infections liees aux catheters: chlorhexidine alcoolique contre polyvidone iodee (Prospective randomised trial for prevention of vascular catheter infection alcohol chlorhexidine versus povidone-iodine). *Reanubnatuib et Urgences* **6**(1), 5-11.

Levin A., Mason A., Jindal K., Fong I. & Goldstein M. (1991) Prevention of hemodialysis subclavian vein catheter infections by topical povidone-iodine. *Kidney International* **40**(5), 934-938.

Lewis S., Cooper C., Karen Gale C., Bonner P., Parker K. & Frauman A. (1999) Research priorities for nephrology nursing: American Nephrology Nurses' Association's delphi study. *American Nephrology Nurses' Association's Journal* **26**(2), 215.

Liangos O., Gul N., Madias N. & Jaber B. (2006) Long term management of the tunnelled venous catheter. *Seminars in Dialysis* **19**(2), 158-164.

Lindberg M. & Lindberg M. (2012) Haemodialysis nurses knowledge about methicillin-resistant *staphylococcus aureus*. *Journal of Renal Care* **38**(2), 82-85.

Little M., O'Riordan A., Lucey B., Farrell M., Lee M., Conlon P. & Walshe J. (2001) A prospective study of complications associated with cuffed, tunnelled haemodialysis catheters. *Nephrology Dialysis Transplant* **16**(11), 2194-2200.

LoBiondo-Wood G. & Haber J., eds. (2006) *Nursing Research Methods and Critical Appraisal for Evidence-Based Practice*, 6 edn. Mosby Elsevier, Philadelphia.

Lok C. & Moist L. (2007) Challenges for randomized controlled trials in nephrology: illustrations in vascular access science and care. *Journal of Nephrology* **20**(6), 632-645.

Lok C., Stanley K., Hux J., Richardson R., Tobe S. & Conly J. (2003) Hemodialysis infection prevention with polysporin ointment. *Journal of the American Society of Nephrology* **14**(1), 169-179.

Lok C., Thumma J., McCullough K., Gillespie B., Fluck R., Marshall M., Kawanishi H., Robinson B. & Pisoni R. (2014) Catheter-related infection and septicemia: Impact of seasonality and modifiable practices from the DOPPS. *Seminars in Dialysis* **27**(1), 72-77.

- Lopez-Vargas P., Craig J., Gallagher M., Walker R., Snelling P., Pedagogos E., Gray N., Divi M., Gillies A., Suranyi M., Thein H., McDonald S., Russell C. & Polkinghorne K. (2011) Barriers to timely arteriovenous fistula creation: A study of providers and patients. *American Journal of Kidney Diseases* **57**(6), 873-882.
- Loveday H., Wilson J., Pratt R., Golsorkhi M., Tingle A., Bak A., Browne J., Prieto J. & Wilcox M. (2014) epic3: National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *Journal of Hospital Infection* **86 Suppl 1**(S1), S1-70.
- Maiwald M. & Chan E. (2012) The forgotten role of alcohol: a systematic review and meta-analysis of the clinical efficacy and perceived role of chlorhexidine in skin antisepsis. *PLoS One* **7**(9), e44277.
- Maki D., Knasinski V., Narans L. & Gordon B. (2001) A randomized trial of 1% chlorhexidine - 75% alcohol tincture versus 10% povidone iodine for cutaneous disinfection with vascular catheters (abstract). Abstract 142. 11th Annual Society for Healthcare Epidemiology of America Meeting, 1-3 April 2001. Toronto, On, Canada
- Maki D., Ringer M. & Alvarado C. (1991) Prospective randomised trial of povidone iodine, alcohol and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *The Lancet* **338**(8763), 339-343.
- Marr K.A., Kong L., Fowler V.G., Gopal A., Sexton D.J. & Conlon Pj et a.l. (1998) Incidence and outcome of Staphylococcus aureus bacteremia in hemodialysis patients. *Kidney International* **54**(5), 1684-1689.
- Martin-Pena A., Luque Marquez R., Guerrero M., Espinosa N., Blanco Y., Ibeas J., Rios-Villegas M. & Cisneros J. (2012) Tunneled hemodialysis catheter-related bloodstream infections: a prospective multicentre cohort study from Spain. *Journal of Vascular Access* **13**(2), 239-245.
- Master List (2009) *US Cochrane Center. Master list of journals being searched*. Retrieved from [http:// apps1.jhsph.edu/cochrane/masterlist.asp](http://apps1.jhsph.edu/cochrane/masterlist.asp) in February 2009.
- Mazonakis E., Stirling C., Booth K., McClenahan J., Heron N. & Geddes C. (2009) The influence of comorbidity on the risk of access-related bacteraemia in chronic hemodialysis patients. *Hemodialysis International* **13**(1), 6-10.

McCann M., Clarke M., Mellotte G., Plant L. & Fitzpatrick F. (2013) Vascular access and infection prevention and control: a national survey of routine practices in Irish haemodialysis units. *Clinical Kidney Journal* **6**(2), 176-182.

McCann M., Clarke M. & Fitzpatrick F. (2012) Recruitment in a randomised controlled trial: overcoming the challenges. TCD Doctoral Colloquium, 13th Annual Interdisciplinary Research Conference, 6th November 2012, School of Nursing and Midwifery, Trinity College Dublin, Ireland.

McCann M., Clarke M., Mellotte G., Plant W. & Fitzpatrick F. (2012) *National Survey of Routine Practices in Irish Haemodialysis Units*, Dublin

McCann M., Einarsdottir H., Van Waeleghem J., Murphy F. & Sedgewick J. (2008) Vascular access management: an overview. *Journal of Renal Care* **34**(2), 77-84.

McCann M., Einarsdottir H., Van Waeleghem J., Murphy F. & Sedgewick J. (2010) Vascular access management III: Central Venous Catheters. *Journal of Renal Care* **36**(1), 25-33.

McCann M. & Moore Z. (2010) Interventions for preventing infectious complications in haemodialysis patients with central venous catheters. *Cochrane Database of Systematic Reviews 2010 Issue 1*. Art. No.: CD006894. DOI: 10.1002/14651858.CD006894.

McCrohan C. (2014) Personal Communication.

McDonnell G. & Russell A. (1999) Antiseptics and disinfectants: Activity, action, and resistance. *Clinical Microbiology Reviews* **12**(1), 147-179.

McGrath D. & McCrory D. (2005) An audit of pre-operative skin preparative methods. *Annals of The Royal College of Surgeons of England* **87**(5), 366-368.

McIntyre C., Hulme L., Taal M. & Fluck R. (2004) Locking of tunneled hemodialysis catheters with gentamicin and heparin. *Kidney International* **66**(6), 801-805.

McKnight K., Farmer A., Zuberbuhler L. & Mager D. (2010) Identification and treatment of protein-energy malnutrition in renal disease. *Canadian Journal of Dietetic Practice and Research* **71**(1), 27-32.

McQuaid M. (2014) Personal Communication.

Meffre C., Girard R., Hajjar J. & Fabry J. (1996) Povidone-iodine vs alcoholic chlorhexidine for disinfection of the insertion site of peripheral venous catheters: results of a multicentre randomised trial. The Sixth Annual Meeting of SHEA, the Society for Hospital Epidemiology of America, Washington DC, April 21-23, 1996. *Infection Control & Hospital Epidemiology* **17**(Suppl Part 2), 26.

Mendelssohn D., Ethier J., Elder S., Saran R., Port F. & Pisoni R. (2006) Haemodialysis vascular access problems in Canada: results from the dialysis outcomes and practice patterns study (DOPPS II). *Nephrology Dialysis Transplant* **21**(3), 721-728.

Mercuri M. & Gafni A. (2011) Medical practice variations: what the literature tells us (or does not) about what are warranted and unwarranted variations. *Journal of Evaluation in Clinical Practice* **17**(4), 671-677.

Mermel L., Allon M., Bouza E., Craven D., Flynn P., O'Grady N., Raad I., Rijnders B., Sherertz R. & Warren D. (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* **49**(1), 1-45.

Michel P., Quenon J., Djihoud A., Tricaud-Vialle S. & de Sarasqueta A. (2007) French national survey of inpatient adverse events prospectively assessed with ward staff. *Quality and Safety in Health Care* **16**(5), 369-377.

Miller M., Griswold M., Harris J., Yenokyan G., Huskins W., Moss M., Rice T., Ridling D., Campbell D., Margolis P., Muething S. & Brill R. (2010) Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. *Pediatrics* **125**(2), 206-213.

Milstone A., Passaretti C. & Perl T. (2008) Chlorhexidine: Expanding the armamentarium for infection control and prevention. *Clinical Infectious Diseases* **46**, 274-281.

Mimoz O., Pieroni L., Lawrence C. & Edouard A. (1996) Prospective, randomised trial of two antiseptic solutions for prevention of central venous or arterial catheter colonisation and infection in intensive care unit patients. *Critical Care Medicine* **24**(11), 1818-1823.

Mimoz O., Villeminey S., Ragot S., Dahyot-Fizelier C., Laksiri L., Petitpas F. & Debaene B. (2007) Chlorhexidine-based antiseptic solution vs alcohol-based povidone-iodine for central venous catheter care. *Archives of Internal Medicine* **167**(19), 2066-2072.

Miola J. (2009) Negligence and the legal standard of care: what is 'reasonable' conduct? *British Journal of Nursing* **18**(12), 756-757.

Moher D., Hopewell S., Schulz K., Montori V., Gøtzsche P., Devereaux P., Elbourne D., Egger M. & Altman D. (2010) CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *Journal of Clinical Epidemiology* **63**(8), e1-e37.

Moist L., Trpeski L., Na Y. & Lok C. (2008) Increased hemodialysis catheter use in Canada and associated mortality risk: Data from the Canadian Organ

Replacement Registry 2001-2004. *Clinical Journal of the American Society of Nephrology* **3**(6), 1726-1732.

Mokrzycki M., Zhang M., Cohen H., Golestaneh L., Laut J. & Rosenberg S. (2006) Tunnelled haemodialysis catheter bacteraemia: risk factors for bacteraemia recurrence, infectious complications and mortality. *Nephrology Dialysis Transplant* **21**(4), 1024-1031.

Moncasi E., Arenas Jimenez M., Alonso M., Martinez M., Gamen Pardo A., Rebollo P., Ortega Montoliu T., Martinez Terrer T., Alvarez-Ude F. & Grupo de Gestion de la Calidad de la Sociedad Espanola de Nefrologia (2011) Multicentre study of haemodialysis costs. *Nefrologia* **31**(2), 299-307.

Mudiwa L. (2013) Research to pinpoint real rate of adverse events. *Irish Medical Journal* **April**.

Murphy F. (2011) The ongoing challenges with renal vascular access. *British Journal of Nursing* **20**(4 intravenous supplement), S6-S14.

National Audit Office (2005) *A Safer Place for Patients: Learning to improve patient safety*. Stationary Office, London.

National Cancer Institute (2012) *NCI Directory of Cancer Terms*. National Cancer Institute. Retrieved from <http://www.cancer.gov/dictionary?CdrID=44930> on 4th October 2012.

National Clinical Effectiveness Committee (2013) *Prevention and Control of Methicillin Resistant Staphylococcus Aureus, National Guideline No 2*. Department of Health, Dublin. Retrieved from [http://www.patientsafetyfirst.ie/images/stories/docs/mrsa\\_national\\_guideline\\_complete\\_version.pdf](http://www.patientsafetyfirst.ie/images/stories/docs/mrsa_national_guideline_complete_version.pdf) on 27th April 2014.

National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (1979) *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*. National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, Washington. Retrieved from <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html> on 20th February 2013.

National Renal Office (2009) *Epidemiology of ESKD in Adults in Ireland, National Renal Office Annual Census on 31st December 2009*. National Renal Office, Health Service Executive, available online from <http://www.hse.ie/eng/about/Who/NRO/>, accessed on 27th September 2010, Dublin.

National Renal Office (2012a) *Epidemiology of ESKD in Adults in Ireland, Data from 2011 Census*. National Renal Office, Health Service Executive, Dublin. Retrieved from <http://www.hse.ie/eng/about/Who/NRO/eskdinadults.pdf> on 2nd August 2012

National Renal Office (2012b) *National Renal Programme 2012*. National Renal Office, Health Service Executive, Dublin. Retrieved from <http://www.hse.ie/eng/about/Who/NRO/nro.pdf> on 2nd August 2012, Dublin.

National Renal Office (2014) *Epidemiology of ESKD in Adults in Ireland, Data from 2013 Census*. National Renal Office, Health Service Executive, Dublin. Retrieved from <http://www.hse.ie/eng/about/Who/NRO/epidemiology.pdf> on 15th April 2014

Navaneethan S., Palmer S., Smith A., Johnson D. & Strippoli G. (2010) How to design a randomized controlled trial. *Nephrology* **15**(8), 732-739.

Ng L., Chen F., Fisoni R., Krishnan M., Mapes D., Keem M. & Bradbury B. (2011) Hospitalisation risks related to vascular access type among incident US hemodialysis patients. *Nephrology Dialysis Transplant* **26**(11), 3659-3666.

Niedner M. (2010) The harder you look, the more you find: Catheter-associated bloodstream infection surveillance variability. *American Journal of Infection Control* **38**(8), 585-595.

Nielsen J., Kolmos H. & Espersen F. (1998) Staphylococcus aureus bacteraemia among patients undergoing dialysis - focus on dialysis catheter related cases. *Nephrology Dialysis Transplant* **13**(1), 139-145.

Nillson K. (2014) Personal Communication.

Nissenson A., Dylan M., Griffiths R., Yu H., Dean B., Danese M. & Dubois R. (2005) Clinical and economic outcomes of Staphylococcus aureus septicemia in ESRD patients receiving hemodialysis. *American Journal of Kidney Diseases* **46**(2), 301-308.

NKF K/DOQI (2006a) *Clinical Practice Guidelines and Clinical Practice Recommendations 2006 Updates: Vascular Access*. National Kidney Foundation, New York. Retrieved from [http://www.kidney.org/professionals/kdoqi/pdf/VA\\_guideline.pdf](http://www.kidney.org/professionals/kdoqi/pdf/VA_guideline.pdf) on 31st January 2011.

NKF K/DOQI (2006b) *Infection Prevention and Control, Best Practice For Hemodialysis Vascular Access*. National Kidney Foundation, New York.

Noordzij M., Kramer A., Abad Diez J., Alonso de la Torre R., Arcos Fuster E., Bikbov B., Bonthuis M., Bouzas Caamaño E., Čala S., Caskey F., Castro de la Nuez P., Cernevskis H., Collart F., Díaz Tejeiro R., Djukanovic L., Ferrer-Alamar M., Finne P., García Bazaga M., Garneata L., Golan E., Gonzalez

Fernández R., Heaf J., Hoitsma A., Ioannidis G., Kolesnyk M., Kramar R., Lasalle M., Leivestad T., Lopot F., van de Luitgaarden M., Macário F., Magaz Á., Martín Escobar E., de Meester J., Metcalfe W., Ots-Rosenberg M., Palsson R., Piñera C., Pippias M., Prütz K., Ratkovic M., Resić H., Rodríguez Hernández A., Rutkowski B., Spustová V., Stel V., Stojceva-Taneva O., Süleymanlar G., Wanner C. & Jager K. (2014) Renal replacement therapy in Europe: a summary of the 2011 ERA–EDTA Registry Annual Report. *Clinical Kidney Journal* **7**(2), 227-238.

Nuffield Council on Bioethics (2002) *The Ethics of Research Related to Healthcare in Developing Countries*. Nuffield Council of Bioethics, London

Nuffield Council on Bioethics (2005) *The Ethics of Research Related to Healthcare in Developing Countries: A Follow Up Discussion Paper*. Nuffield Council of Bioethics, London

Nursing and Midwifery Council UK (2008) *The Code, Standards of Conduct, Performance and Ethics for Nurses and Midwives*. Nursing and Midwifery Council UK, London.

O'Horo J., Germana L. & Nasia Safdar A. (2011) Anti-infective locks for treatment of central line-associated bloodstream infection: A systematic review and meta-analysis. *American Journal of Nephrology* **31**, 415-422.

Odgaard-Jensen J., Vist G., Timmer A., Kunz R., Akl E., Schünemann H., Briel M., Nordmann A., Pregno S. & Oxman A. (2011) Randomisation to protect against selection bias in healthcare trials. *Cochrane Database of Systematic Reviews* 2011, Issue 4. Art. No.: MR000012. DOI: 10.1002/14651858.MR000012.pub3.

Pallant J. (2005) *SPSS Survival Manual*. 2 edn. Open University Press, Maidenhead.

Palomar M., Alvarez-Lerma F., Riera A., Diaz M., Torres F., Agra Y., Larizgoitia I., Goeschel C. & Pronovost P. (2013) Impact of a national multimodal intervention to prevent catheter-related bloodstream infection in the ICU: the Spanish experience. *Critical Care Medicine* **41**(10), 2364-2372.

Parahoo K. (2006) *Nursing Research Principles, Process and Issues*. 2 edn. Palgrave Macmillan, Basingstoke.

Parienti J., du Cheyron D., Ramakers M., Malbruny B., Leclercq R., Le Coutour X. & Charbonneau P. (2004) Alcoholic povidone-iodine to prevent central venous catheter colonization: A randomized unit-crossover study. *Critical Care Medicine* **32**(3), 708-713.



- Parker K., Vincent M. & Mitra S. (2012) Warfarin management in haemodialysis - are we meeting the British Haematology Society standards. *Journal of Renal Care* **38**(4), 202-206.
- Pastan S., Soucie J. & McClellan W. (2002a) Vascular access and increased risk of death among hemodialysis patients. *Kidney International* **62**(2), 620-626.
- Pastan S., Soucie J.M. & McClellan W.M. (2002b) Vascular access and increased risk of death among hemodialysis patients. *Kidney International* **62**(2), 620-626.
- Patel P., Kallen A. & Arduino M. (2010) Epidemiology, surveillance, and prevention of bloodstream infections in hemodialysis patients. *American Journal of Kidney Diseases* **56**(3), 566-577.
- Patel P., Yi S., Booth S., Bren V., Downham G., Hess S., Kelley K., Lincoln M., Morrissette K., Lindberg C., Jernigan J. & Kallen A. (2013) Bloodstream infection rates in outpatient hemodialysis facilities participating in a collaborative prevention effort: a quality improvement report. *American Journal of Kidney Disease* **62**(2), 322-330.
- Pegorana M. (2014) Personal Communication.
- Percival S., Kite P., Eastwood K., Murga R., Carr J., Arduino M. & Donlon R. (2005) Tetrasodium EDTA as a novel central venous catheter lock solution against biofilm. *Infection Control and Hospital Epidemiology* **26**(6), 515-519.
- Perl J., Lok C. & Chan C. (2006) Central venous catheter outcomes in nocturnal hemodialysis. *Kidney International* **70**(7), 1348-1354.
- Peveler R. (2002) Guideline adherence rates and interprofessional variation. *Quality and Safety in Healthcare* **11**(3), 208.
- Pisoni R., Arrington C., Albert J., Ethier J., Kimata N., Krishnan M., Rayner H., Saito A., Sands J., Saran R., Gillespie B., Wolfe R. & Port F. (2009) Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: an instrumental variable analysis. *American Journal of Kidney Diseases* **53**(3), 475-491.
- Pisoni R., Young E., Dykstra D., Greenwood R., Hecking E., Gillespie B., Wolfe R., Goodkin D. & Held P. (2002) Vascular access use in Europe and the United States: Results from the DOPPS. *Kidney International* **61**(1), 305-316.
- Plowman R., Gravel N., Griffin M., Roberts J., Swan A., Cookson B. & Taylor L. (2000) The socioeconomic burden of hospital acquired infection. *Euro Surveillance* **5**(4), 49-50.
- Pocock S. (1983) *Clinical Trials, A Practical Approach*. John Wiley & Sons, Chichester.

Polit D. & Beck C. (2006) *Essentials of Nursing Research- Methods, Appraisal, and Utilisation*. 6 edn. Lippincott Williams & Wilkins, Philadelphia.

Polit D. & Beck C. (2008) *Nursing Research Generating and Assessing Evidence for Nursing Practice*. 8 edn. Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia.

Polkinghorne K., McDonald S., Atkins R. & Kerr P. (2004) Vascular access and all cause mortality: a propensity score analysis. *Journal of the American Society of Nephrology* **15**(2), 477-486.

Port F., Pisoni R., Bragg-Greshan J., Satayathum S., Young E., Wolfe R. & Held P. (2004) DOPPS estimates of patient life years attributable to modifiable hemodialysis practices in the United States. *Blood Purification* **22**(1), 175-180.

Powe N., Jarr B., Furth S., Hermann J. & Briggs W. (1999) Septicemia in dialysis patients: Incidence, risk factors and prognosis. *Kidney International* **55**(3), 1081-1090.

Pratt R., Pellowe C., Wilson J., Loveday H., Harper P., Jones S., McDougall C. & Wilcox M. (2007) epic2: National evidence based guidelines for preventing healthcare associated infections in NHS hospitals in England. *Journal of Hospital Infection* **65**(Suppl 1), S1-S64.

Prescott R., Counsell C., Gillespie W., Grant A., Russell I., Kiauka S., Colthart I., Ross S., Shepherd S. & Russell D. (1999) Factors that limit the quality, number and progress of randomised controlled trials. *Health Technology Assessment* **3**(20), 1-139.

Profetto-McGrath J., Negrin K., Hugo K. & Smith K. (2010) Clinical nurse specialists' approaches in selecting and using evidence to improve practice. *Worldviews on Evidence-Based Nursing* **7**(1), 36-50.

Pronovost P., Needham D., Berenholtz S., Sinopoli D., Chu H., Cosgrove S., Sexton B., Hyzy R., Welsh R., Roth G., Bander J., Kepros J. & Goeschel C. (2006) An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine* **355**(26), 2725-2732.

Quadri K. & Huraib S. (1999) Manuka honey for central venous catheter exit site care. *Seminars in Dialysis* **12**(5), 397-398.

Quori A., Baamonde-Laborda E., Garcia-Canton C., Lago-Alonso M., Toledo-Gonzalez A., Monzon-Jimenez E., Jimenez-Diaz D., Checa de Andres M. & Molina-Cabrillana J. (2011) Surveillance for infections and other adverse events in dialysis patients in southern Gran Canaria. *Nefrologia* **31**(4), 457-463.

- Raad I., Hanna H., Alakech B., Chatzinikolaou I., Johnson M. & Tarrand J. (2004) Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. *Annals of Internal Medicine* **140**(1), 18-26.
- Ramanathan V., Riosa S., Al-Sharif A., Mansouri M., Tranchina A., Kayyal T., Abreo A., Aslam S., Nassar G. & Darouiche R. (2012) Characteristics of biofilm on tunneled cuffed hemodialysis catheters in the presence and absence of clinical infection. *American Journal of Kidney Diseases* **60**(6), 976-982.
- Ravani P., Palmer S.C., Oliver M., Quinn R., MacRae J., Tai D., Pannu N., Thomas C., Hemmelgarn B., Craig J., Manns B., Tonelli M., Strippoli G. & James M. (2013) Associations between Hemodialysis Access Type and Clinical Outcomes: A Systematic Review. *Journal of the American Society of Nephrology* **24**(3), 465-473.
- Ravani P., Parfrey P., Dicks E. & Barrett B. (2007) Clinical research of kidney diseases II: problems of study design. *Nephrology Dialysis Transplantation* **22**(10), 2785-2794.
- Rawnsley M. (1998) Ontology, epistemology and methodology: A clarification. *Nursing Science Quarterly* **11**(1), 1-4.
- Rayner H. & Pisoni R. (2010) The increasing use of hemodialysis catheters: Evidence from DOPPS on its significance and ways to reverse it. *Seminar in Dialysis* **23**(1), 6-10.
- Rayner H., Pisoni R., Bommer J., Canaud B., Hecking E., Locatelli F., Piera L., Bragg-Gresham J., Feldman H., Goodkin D., Gillespie B., Wolfe R., Held P. & Port F. (2004) Mortality and hospitalisation in haemodialysis patients in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrology Dialysis Transplant* **19**(1), 108-120.
- Reddy B. (2014) Personal Communication.
- Reddy B., Fagan L., Fallon U., Evans L., Abdul L. & Bergin E. (2010) Nurses influence on the surveillance and incidence of catheter-related bacteraemia in a haemodialysis population (abstract). 39th EDTNA/ERCA Conference, 18-21 September, Dublin, Ireland.
- Reed S., Friedman J., Engemann J., Griffiths R., Anstrom K., Kaye K., Stryjewski M., Szczech L., Reller L., Corey G., Schulman K. & Fowler V. (2005) Costs and outcomes among hemodialysis dependent patients with Methicillin Resistant or Methicillin Susceptible *Staphylococcus aureus* bacteremia. *Infection Control and Hospital Epidemiology* **26**(2), 175-183.
- Reichardt M. (2014) Personal Communication.

Renal Group 2009, Willis N., Mitchell R., Higgins G., Webster A. & Craig J. (2009) *Cochrane Renal Group [About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2009, Issue 4. Art. No.: RENAL]*. Retrieved from <http://www.mrw.interscience.wiley.com/cochrane/about/articles/RENAL/frame.html> in November 2009.

Render M., Hasselbeck R., Freyberg R., Hofer T., Sales A. & Almenoff P. (2011) Reduction of central line infections in Veterans Administration intensive care units: an observational cohort using a central infrastructure to support learning and improvement. *British Medical Journal Quality and Safety* **20**(8), 725-732.

Resar R., Griffin F., Haraden C. & Nolan T. (2012) *Using Care Bundles to Improve Health Care Quality. IHI Innovation Series White Paper*. Institute for Healthcare Improvement, Cambridge.

Richet H., Hubert B., Nitemberg G., Andremont A., Buu-Hoi A., Ourbak P., Galicier C., Veron A., Boisivan A. & Bouvier A. (1990) Prospective multicenter study of vascular-catheter-related complications and risk factors for positive central-catheter cultures in intensive care unit patients. *Journal of Clinical Microbiology* **28**(11), 2520-2525.

Rickard C., Courtney M. & Webster J. (2004) Central venous catheters: a survey of ICU practices. *Journal of Advanced Nursing* **48**(3), 247-256.

Rickard C. & Ray-Barruel G. (2010) *Systematic Review of Infection Control Literature Relating to Intravascular Devices*. National Health and Medical Research Council, Canberra.

Riella M. & Roy-Chaudhury P. (2013) Vascular access in haemodialysis: strengthening the Achilles' heel. *Nature Reviews Nephrology* **9**(6), 348-357.

Robinson B. & Port F. (2009) International hemodialysis patient outcomes comparisons revisited: The role of practice patterns and other factors. *Clinical Journal of the American Society of Nephrology* **4**(Supplement 1), S12-S17.

Rodríguez-Aranda A., Alcazar J., Sanz F., García-Martín F., Otero J., Aguado J. & Chaves F. (2011) Endoluminal colonization as a risk factor for coagulase-negative staphylococcal catheter-related bloodstream infections in haemodialysis patients. *Nephrology Dialysis Transplantation* **26**(3), 948-955.

Royal College of Nursing (2012) *Essential Practice for Infection Prevention and Control, Guidance for Nursing Staff*. Royal College of Nursing, London.

- Runciman W., Webb R., Helps S., Thomas E., Sexton E., Studdert D. & Brennan T. (2000) A comparison of iatrogenic injury studies in Australia and the USA. II: Reviewer behaviour and quality of care. *Internal Journal for Quality in Health Care* **12**(5), 379-388.
- Sackett D. (2002) *Evidence-based Medicine: How to Practice and Teach EBM*. 2 edn. Churchill Livingstone, London.
- Saeed Abdulrahman I., Al-Mueilo S., Bokhary H., Ladipo G. & Al-Rubaish A. (2002) A prospective study of hemodialysis access related bacterial infections. *Journal of Infection Chemotherapy* **8**(3), 242-246.
- Safdar N., Fine J. & Maki D. (2005) Meta-analysis: Methods for diagnosing intravascular device-related bloodstream infection. *Annals of Internal Medicine* **142**(6), 451-466.
- Safdar N., Kluger D. & Maki D. (2002) A review of risk factors for catheter-related bloodstream infection caused by percutaneously inserted, noncuffed central venous catheters. *Medicine* **81**(1), 466-479.
- Safdar N. & Maki D. (2004) The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. *Intensive Care Medicine* **30**(1), 62-67.
- Saghaei M. (2004) *Random allocation software, Version 1.0*. Retrieved from <http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html> in November 2009.
- Sainani K. (2010) Making sense of intention-to-treat. *Physical Medicine and Rehabilitation* **2**(3), 2-9-213.
- Samuels J. & Molony D. (2012) Randomized controlled trials in nephrology: State of the evidence and critiquing the evidence. *Advances in Chronic Kidney Disease* **19**(1), 40-46.
- Saraiva M. (2014) Personal Communication.
- SARI (2001) *A Strategy for the Control of Antimicrobial Resistance in Ireland*. Health Protection Surveillance Centre, Dublin.
- SARI (2009) *Prevention of Intravascular Catheter-Related Infection in Ireland*. Health Protection Surveillance Centre, Dublin.
- Schatz S., Pagenkemper J. & Beto J. (2006) Body weight estimation in chronic kidney disease: Results of a practitioner survey. *Journal of Renal Nutrition* **16**(3), 283-286.
- Schena F. (2000) Epidemiology of end stage renal disease: International comparisons of renal replacement therapy. *Kidney International* **57**(Suppl. 74), S39-45.

Schioler T., Lipczak H., Pedersen B., Mogensen T., Bech K., Stockmarr A., Svenning A. & Frolich A. (2001) Incidence of adverse events in hospitals. A retrospective study of medical records. *Ugeskr Laeger* **163**(39), 5370-5378.

Schulz K., Altman D. & Moher D. (2010) CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomized trials. *Annals of Internal Medicine* **152**(11), 726-732.

Schulz K. & Grimes D. (2002a) Allocation concealment in randomised trials: defending against deciphering. *The Lancet* **359**(9306), 614-618.

Schulz K. & Grimes D. (2002b) Generation of allocation sequences in randomised trials: chance, not choice. *The Lancet* **359**(9305), 515-519.

Schwab S. (2007) Hemodialysis vascular access: the Achilles' heel remains. *Kidney International* **72**(6), 665-666.

Schwartz D. & Lellouch J. (1967) Explanatory and pragmatic attitudes in therapeutical trials. *Journal of Chronic Diseases* **20**(8), 637-648.

Scientific Advisory Committee of the National Disease Surveillance Centre (2001) *A Strategy for the Control of Antimicrobial Resistance in Ireland, SARI*. National Disease Surveillance Centre, Dublin.

Scott R. (2009) *The Direct Medical Cost of Healthcare Associated Infections in US Hospitals and the Benefits of Prevention*. Centres for Disease Control and Prevention, Atlanta. Retrieved from [http://www.cdc.gov/hai/pdfs/hai/scott\\_costpaper.pdf](http://www.cdc.gov/hai/pdfs/hai/scott_costpaper.pdf) on 8th January 2013.

Sedgwick P. (2013) What is per protocol analysis? *British Journal of Medicine* **346**, 1-2.

Sesso R., Barbosa D., Leme I., Sader H., Canziani M., Manfredi S., Draibe S. & Pignatari A. (1998) Staphylococcus aureus prophylaxis in hemodialysis patients using central venous catheter: effect of mupirocin ointment. *Journal of the American Society of Nephrology* **9**(6), 1085-1092.

Sheehan G., Leicht K., O'Brien M., Taylor G. & Rennie R. (1993) Chlorhexidine versus povidone iodine as cutaneous antisepsis for prevention of vascular catheter infection (abstract). In: Programme and abstracts - Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology 414 (a1616), Washington DC.

Sheil W. & Conrad S., eds. (2008) *Websters New World Medical Dictionary*, 3 edn. Wiley Publishing Hoboken.

Shivnan J., McGuire D., Freedman S., Sharkazy E., Bosserman G., Larson E. & Grouleff P. (1991) A comparison of transparent adherent and dry sterile gauze dressings for long term central catheters in patients undergoing bone marrow transplant. *Oncology Nursing Forum* **18**(8), 1349-1356.

Singh A., Szczech L., Tang K., Barnhart H., Sapp S., Wolfson M. & Reddan D. (2006) Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. *New England Journal of Medicine* **355**(20), 2085-2098.

Small H., Adams D., Casey A., Crosby S., Lambert P. & Elliott T. (2008) Efficacy of adding 2% (w/v) chlorhexidine gluconate to 70% isopropyl alcohol for skin disinfection prior to peripheral venous cannulation. *Infection Control & Hospital Epidemiology* **29**(10), 963-965.

Smyth A., Redahan L., Mellotte G. & Wall C. (2010) Audit of catheter related bloodstream infections in haemodialysis patients at AMNCH (abstract). Irish Nephrology Society Spring Meeting, Dublin, Ireland.

Smyth E., McIlvenny G., Enstone J., Emmerson A., Humphreys H., Fitzpatrick F., Davies E., Newcombe R. & Spencer R. (2008) Four country healthcare associated infection prevalence survey 2006: overview of the results. *Journal of Hospital Infection* **69**(3), 230-248.

Soop M., Fryksmark U., Köster M. & Haglund B. (2009) The incidence of adverse events in Swedish hospitals: a retrospective medical record review study. *International Journal for Quality in Health Care* **21**(4), 285-291.

Stack A. (2010) Patient preferences for type of vascular access in haemodialysis: Predictors and variation across countries in DOPPS (abstract). 39th EDTNA/ERCA Conference, 18th - 21st September 2010, Dublin, Ireland

State Claims Agency (2013a) *Clinical Indemnity Scheme*. State Claims Agency, Dublin. Retrieved from [http://www.stateclaims.ie/ClinicalIndemnityScheme/publications/QA\\_brochure.pdf](http://www.stateclaims.ie/ClinicalIndemnityScheme/publications/QA_brochure.pdf) on 14th February 2013.

State Claims Agency (2013b) *Clinical Indemnity Scheme - Your Questions Answered*. State Claims Agency, Dublin. Retrieved from [http://www.stateclaims.ie/ClinicalIndemnityScheme/publications/QA\\_brochure.pdf](http://www.stateclaims.ie/ClinicalIndemnityScheme/publications/QA_brochure.pdf) on 14th February 2013.

Stel V., Zoccali C., Dekker F. & Jager K. (2009) The randomized controlled trial. *Nephron Clinical Practice* **113**(4), 337-342.

Stevenson K., Adcox M., Mallea M., Narasimhan N. & Wagnild J. (2000) Standardized surveillance of hemodialysis vascular access infections: 18 month experience at an outpatient, multi-facility hemodialysis centre. *Infection Control and Hospital Epidemiology* **21**(3), 299-203.

Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) (2009) *Prevention of Intravascular Catheter-Related Infection in Ireland* Health protection Surveillance Centre, Dublin.

Strippoli G., Tong A., Johnson D., Schena F. & Craig J. (2004) Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients. *Cochrane Database of Systematic Reviews 2004 Issue 4*. (Art.No.: CD004679. DOI: 10.1002/14651858.CD004679).

Syndnor E. & Perl T. (2011) Hospital epidemiology and infection control in acute care settings. *Clinical Microbiology Reviews* **24**(1), 141-173.

Tabachnick B. & Fidell L. (2007) *Using Multivariate Statistics*. 5 edn. Pearson Education, Inc., Boston.

Tacconelli E., Carmeli Y., Aizer A., Ferreira G., Foreman M. & D'Agata E. (2003) Mupirocin prophylaxis to prevent staphylococcus aureus infection in patients undergoing dialysis: a meta-analysis. *Clinical Infectious Diseases* **37**(12), 1629-1638.

Taylor C., Cahill J., Gerrish M. & Little J. (2008) A new haemodialysis catheter-locking agent reduces infections in haemodialysis patients. *Journal of Renal Care* **34**(3), 116-120.

Taylor G., Gravel D., Johnston L., Embil J., Holton D., Paton S., the Canadian Nosocomial Infection Surveillance P. & the Canadian Hospital Epidemiology C. (2004) Incidence of bloodstream infection in multicenter inception cohorts of hemodialysis patients. *American Journal of Infection Control* **32**(3), 155-160.

Tentori F., Blayney M., Albert J., Gillespie B., Kerr P., Bommer J., Young E., Akizawa T., Akiba T., Pisoni R., Robinson B. & Port F. (2008) Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *American Journal of Kidney Diseases* **52**(3), 519-530.

Tentori F., Zhang J., Li Y., Karaboyas A., Kerr P., Saran R., Bommer J., Port F., Akiba T., Pisoni R. & Robinson B. (2012) Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrology Dialysis Transplant* **27**(11), 4180-4188.

Thabane L., Ma J., Chu R., Cheng J., Ismaila A., Rios L., Robson R., Thabane M., Giangregorio L. & Goldsmith C. (2010) A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology* **10**(1), 1.

The Commission on Patient Safety and Quality Assurance (2008) *Building a Culture of Patient Safety. The Report of the Commission on Patient Safety and Quality Assurance*. Stationery Office, Dublin.



The Joint Commission (2012) *Preventing Central Line-Associated Bloodstream Infections: A Global Challenge, a Global Perspective*. Oak Brook, IL: Joint Commission Resources. Retrieved from [http://www.jointcommission.org/topics/hai\\_clabsi.aspx](http://www.jointcommission.org/topics/hai_clabsi.aspx) on 19th August 2012.

The NHS Information Centre (2011a) *National Kidney Care Audit Vascular Access Report 2010*. The NHS Information Centre, Leeds. Retrieved from <http://www.hqip.org.uk/assets/NCAPOP-Library/National-Kidney-Care-Audit-Vascular-Access-Report-2010.pdf> on the 1st May 2013.

The NHS Information Centre (2011b) *National Kidney Care Audit Vascular Access Report 2011*. The NHS Information Centre, Leeds. Retrieved from <https://catalogue.ic.nhs.uk/publications/clinical/kidney/nati-kidn-care-2011-vasc-acce/nati-kidn-care-2011-vasc-acce-rep.pdf> on the 1st May 2013.

The Renal Association (2009) *Clinical Practice Guidelines for Haemodialysis, Final Draft*. The UK Renal Association, Petersfield. Retrieved from <http://www.renal.org/Clinical/GuidelinesSection/Haemodialysis.aspx> on 30th July 2012.

The UK Renal Association (2007) *Clinical Practice Guideline for Haemodialysis, 4edn, Final Version*. The UK Renal Association, Petersfield. Retrieved from [http://www.renal.org/pages/media/download\\_gallery/HDfinal050207.pdf](http://www.renal.org/pages/media/download_gallery/HDfinal050207.pdf) on 24nd November 2009.

The UK Renal Association (2011a) *Clinical Practice Guidelines Vascular Access for Haemodialysis, 5 edn, 2008-2011 Final Version*. The UK Renal Association, Petersfield. Retrieved from <http://www.renal.org/Clinical/GuidelinesSection/Guidelines.aspx> on 12th May 2014.

The UK Renal Association (2011b) *Clinical Practice Guidelines, Acute Kidney Injury, 5th Edition, Final Version*. The UK Renal Association, Petersfield. Retrieved from [http://www.renal.org/Libraries/Guidelines/Acute\\_Kidney\\_Injury\\_-\\_Final\\_Version\\_08\\_March\\_2011.sflb.ashx](http://www.renal.org/Libraries/Guidelines/Acute_Kidney_Injury_-_Final_Version_08_March_2011.sflb.ashx) on 14th October 2011.

The UK Renal Registry (2011) *UK Renal Registry, The Fourteenth Annual Report, December 2011*. The UK Renal Registry, Bristol. Retrieved from <http://www.renalreg.com/Reports/2011.html> on 1st May 2013.

The UK Renal Registry (2012) *UK Renal Registry, The Fifteenth Annual Report, December 2012*. The UK Renal Registry, Bristol. Retrieved from <http://www.renalreg.com/Reports/2012.html> on 10th July 2013.

The UK Renal Registry (2013) *UK Renal Registry, The Sixteenth Annual Report, December 2013*. The UK Renal Registry, Bristol. Retrieved from <http://www.renalreg.com/Reports/2013.html> on 14th April 2014.

Thomas E., Studdert D., Burstin H., Orav E., Zeena, Williams E., Howard K., Weiler P. & Brennan T. (2000a) Incidence and types of adverse events and negligent care in Utah and Colorado. *Medical Care* **38**(3), 261-271.

Thomas E., Studdert D., Runciman W., Webb R., Sexton E., Wilson R., Gibberd R., Harrison B. & Brennan T. (2000b) A comparison of iatrogenic injury studies in Australia and the USA. I: Context, methods, casemix, population, patient and hospital characteristics. *International Journal for Quality in Health Care* **12**(5), 371-378.

Thomas L., Cullum N., McColl E., Rousseau N., Soutter J. & Steen N. (1999) Guidelines in professions allied to medicine. *The Cochrane Database of Systematic Reviews* 1999, Issue 1. Art No.: CD00349. DOI 10.1002/14651858. CD000349..

Thorpe K., Zwarenstein M., Oxman A., Treweek S., Furberg C., Altman D., Tunin S., Bergel E., Harvey I., Magid D. & Chalkidou K. (2009) A pragmatic-explanatory continuum indicator summary (PRECIS). *Journal of Clinical Epidemiology* **62**(5), 464-475.

Tokars J. (2000) Description of a new surveillance system for blood stream and vascular access infections in outpatient haemodialysis centers. *Seminar in Dialysis* **13**(2), 97-100.

Tokars J., Miller E. & Stein G. (2002) New national surveillance system for hemodialysis associated infections: Initial results. *American Journal of Infection Control* **30**(5), 288-295.

Tordoir J., Canaud B., Haage P., Konner K., Basci A., Fouque D., Koonman J., Martin-Malo A., Pedrini L., Pizzarelli F., Tattersall J., Vennegoor M., Wanner C., Wee P. & Vanholder R. (2007) European best practice guidelines on vascular access. *Nephrology Dialysis Transplant* **22**(suppl1), ii88-ii117.

Torgerson D. & Torgerson C. (2008) *Designing Randomised Trials in Health, Education and the Social Science*. Palgrave Macmillian, Basingstoke.

Treston-Aurand J., Olmsten R., Allen-Bridson K. & Craig C. (1997) Impact of dressing materials on central venous catheter infection rates. *Journal of Intravenous Nursing* **20**(4), 201-206.

Trinity College Dublin (2004) *Data Protection Compliance*. Trinity College Dublin. Retrieved from [http://www.tcd.ie/info\\_compliance/pdfs/dpcomply\\_proced.pdf](http://www.tcd.ie/info_compliance/pdfs/dpcomply_proced.pdf) on 21st February 2013.

- Trudel T., McCune A., Donahue K., Zuberbuhler L., Farmer A. & Mager D. (2010) Variables influencing adoption of practice-based guidelines in Canadian renal dietetic practice. *Journal of Renal Nutrition* **20**(4), 235-242.
- Ulrick U., Quan X., Zimring C., Joseph A. & Choudhary R. (2004) *The Role of the Physical Environment in the Hospital of the 21st Century: A Once-in-a-Lifetime Opportunity*, Centre for Health Design. Retrieved from <http://www.healthdesign.org/chd/research/role-physical-environment-hospital-21st-century> on 28th August 2013.
- Umscheid C., Mitchell M., Doshi J., Agarwal R., Williams K. & Brennan P. (2011) Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. *Infection Control and Hospital Epidemiology* **32**(2), 101-114.
- US Renal Data System (2012) *USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States*. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda. Retrieved from <http://www.usrds.org/adr.htm> on 1st May 2013.
- US Renal Data System (2013) *USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States*. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda. Retrieved from <http://www.usrds.org/> on 17th April 2014.
- Valles J., Fernandez I., Alcaraz D., Chacon E., Cazorla A., Canals M., Mariscal D., Fontanals D. & Moran A. (2008) Prospective randomised trial of 3 antiseptic solutions for prevention of catheter colonisation in an intensive care unit for adult patients. *Infection Control and Hospital Epidemiology* **29**(9), 847-853.
- Van der Graaf R. & van Delden J. (2009) What is the best standard for the standard of care in clinical research? *The American Journal of Bioethics* **9**(3), 35-43.
- Van Rijen M., Bonten M., Wenzel R. & Kluytmans J. (2008) Mupirocin ointment for preventing staphylococcus aureus infections in nasal carriers. *Cochrane Database Systematic Reviews 2008, Issue 4*. Art. No.: CD006216. DOI: 10.1002/14651858.CD006216.pub.
- Vanholder R., Canaud B., Fluck R., Jadoul M., Labriola L., Marti-Monros A., Tordoir J. & Van Biesen W. (2010) Diagnosis, prevention and treatment of haemodialysis catheter-related blood stream infections (CRBSI), a position

statement of European Renal Best Practice (ERBP). *Nephrology Dialysis Transplantation Plus* **3**(3), 234-246.

Viera A. & Bangdiwala S. (2007) Eliminating bias in randomized controlled trials: Importance of allocation concealment and masking. *Family Medicine* **39**(2), 132-137.

Villa G., Rodríguez-Carmona A., Fernández-Ortiz L., Cuervo J., Rebollo P., Otero A. & Arrieta J. (2011) Cost analysis of the Spanish renal replacement therapy programme. *Nephrology Dialysis Transplantation* **26**(11), 3709-3714.

Vincent C. (2006) *Patient Safety*. Elsevier Churchill Livingstone, Edinburgh.

Vincent C., Neale G. & Woloshynowych M. (2001) Adverse events in British hospitals: Preliminary retrospective record review. *British Medical Journal* **322**(7285), 517-519.

Watson R., Atkinson I. & Rose K. (2007) Pilot studies: to publish or not? *Journal of Clinical Nursing* **16**(4), 619-620.

Webster J., Gillies D., O'Riordan E., Sherriff K. & Rickard C. (2011) Gauze and tape and transparent polyurethane dressings for central venous catheters. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD003827. DOI:10.1002/14651858.CD003827.pub2.

Weijmere M., Vervloet M. & ter Wee P. (2004) Compared to tunnelled cuffed haemodialysis catheters, temporary untunnelled catheters are associated with more complications already within 2 weeks of use. *Nephrology Dialysis Transplant* **19**(3), 670-677.

Weston D. (2013) *Fundamentals of Infection Prevention and Control Theory and Practice*. 2 edn. John Wiley & Sons Ltd, Oxford.

WHO (2004) *World Alliance for Patient Safety: Forward Programme 2005*. World Health Organisation, Geneva.

WHO (2005) *World Alliance for Patient Safety, Global Patient Safety Challenge 2005-2006, Clean Care is Safer Care*. World Health Organisation, Geneva.

WHO (2006) *The WHO Guidelines on Hand Hygiene in Healthcare (Advanced Draft)*. *The World Alliance for Patient Safety, Global Patient Safety Challenge 2005-2006 Clean Care is Safer Care*. World Health Organisation, Geneva.

WHO (2011) *Report on the Burden of Endemic Health Care-Associated Infection Worldwide*. *Clean Care is Safer Care*. World Health Organisation, Geneva

WHO (2014) *Health Topics Infection Control*. World Health Organisation, Geneva. Retrieved from [http://www.who.int/topics/infection\\_control/en/](http://www.who.int/topics/infection_control/en/) on 12th January 2014.

- Wikstrom B., Jacobson S., Bragg-Greshan J., Eichleay M., Pisoni R. & Pont F. (2010) Dialysis outcomes and practice patterns study estimate of patient life-years attributable to modifiable haemodialysis practices in Sweden. *Scandinavian Journal of Urology and Nephrology* **44**(2w), 113-120.
- Wille J., Blusse van Oud Alblas A. & Thewessen E. (1993) A comparison of two transparent film type dressings in central venous therapy. *Journal of Hospital Infection* **23**(2), 113-121.
- Wilson R., Runciman W., Gibberd R., Harrison B., Newby L. & Hamilton J. (1995) The quality in Australian health care study. *The Medical Journal of Australia* **163**(9), 458-471.
- World Health Assembly (2002) *Quality of Care: Patient Safety, Resolution WHA55.18, 55th World Health Assembly*. World Health Assembly, Geneva.
- World Health Organisation (2013) *About Trial Registration*, WHO, Geneva, Retrieved from [http://www.who.int/ictrp/trial\\_reg/en/index.html](http://www.who.int/ictrp/trial_reg/en/index.html) on 14th February 2013.
- World Medical Association (2008) *Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects*. World Medical Association, Ferney-Voltaire. Retrieved from <http://www.wma.net/en/30publications/10policies/b3/> on 15th October 2012.
- Xi W., Harwood L., Diamant M., Brown J., Gallo K., Sontrop J., MacNab J. & Moist L. (2011) Patient attitudes towards the arteriovenous fistula: a qualitative study on vascular access decision making. *Nephrology Dialysis Transplantation* **26**(10), 3302-3308.
- Yahav D., Rozen-Zvi B., Gafter-Gvili A., Leibovici L., Gafter U. & Paul M. (2008) Antimicrobial lock solutions for the prevention of infections associated with intravascular catheters in patients undergoing hemodialysis: systematic review and meta-analysis of randomised controlled trials. *Clinical Infectious Diseases* **47**(1), 83-93.
- Yokoe D., Mermel L., Anderson D., Arias K., Burstin H., Calfee D., Coffin S., Dubberke E., Fraser V., Gerding N., Griffin F., Gross P., Kaye K., Klompas M., Lo E., Marschall J., Nicolle L., Pegues D., Perl T., Podgorny K., Saint S., Salgado C., Weinstein R., Wise R. & Classen D. (2008) Executive summary: A compendium of strategies to prevent Healthcare-Associated Infections in acute care hospitals. *Infection Control and Hospital Epidemiology* **29**(S1), S12-S21.
- Young E., Dykstra D., Goodkin D., Mapes D., Wolfe R. & Held P. (2002) Hemodialysis vascular access preferences and outcomes in the Dialysis

Outcomes and Practice Patterns Study (DOPPS). *Kidney International* **61**(6), 2266-2271.

Young J., Contreras G., Robert N., Vogt N. & Courtney T. (2005) Incidence and influencing factors associated with exit site infections on temporary catheters for hemodialysis and apheresis. *Nephrology Nursing Journal* **32**(1), 41-50.

Zarb P., Coignard B., Griskeviciene J., Muller A., Vankerckhoven V., Weist K., Goossens M., Vaerenberg S., Hopkins S., Catry B., Monnet D., Goossens H., Suetens C., National Contact Points for the ECDC pilot point prevalence survey & Hospital Contact Points for the ECDC pilot point prevalence survey (2012) The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. *Euro Surveillance* **17**(46), pii-20316.

Zegers M., de Bruijne M., Wagner C., Hoonhout L., Waaijman R., Smits M., Hout F., Zwaan L., Christiaans-Dingelhoff I., Timmermans D., Groenewegen P. & van der Wal G. (2009) Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. *Quality and Safety in Health Care* **18**(4), 297-302.

Zwarenstein M. & Treweek S. (2009) What kind of randomized trials do we need? *Journal of Clinical Epidemiology* **62**(5), 461-463.

## APPENDICES

### Appendix 4.1 Chapter 4 Literature search strategy

Database	Search terms
<b>CENTRAL</b>	<ol style="list-style-type: none"><li>1. MeSH descriptor Renal Dialysis, this term only</li><li>2. MeSH descriptor Hemofiltration explode all trees</li><li>3. (hemodialysis or haemodialysis):ti,ab,kw</li><li>4. (hemofiltration or haemofiltration):ti,ab,kw</li><li>5. (hemodiafiltration or haemodiafiltration):ti,ab,kw</li><li>6. dialysis:ti,ab,kw</li><li>7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6)</li><li>8. catheter*:ti,ab,kw</li><li>9. (central next line*):ti,ab,kw</li><li>10. (#8 OR #9)</li><li>11. MeSH descriptor Infection, this term only</li><li>12. MeSH descriptor Sepsis explode all trees</li><li>13. (infect*):ti,ab,kw</li><li>14. (sepsis or septic*):ti,ab,kw</li><li>15. (bacteremi* or bacteraemi*):ti,ab,kw</li><li>16. (#11 OR #12 OR #13 OR #14 OR #15)#17 (#7 AND #10 AND #16)</li></ol>
<b>MEDLINE</b>	<ol style="list-style-type: none"><li>1. Renal Dialysis/</li><li>2. exp Hemofiltration/</li><li>3. (hemodialysis or haemodialysis).tw.</li><li>4. (hemofiltration or haemofiltration).tw.</li><li>5. (hemodiafiltration or haemodiafiltration).tw.</li><li>6. dialysis.tw.</li><li>7. or/1-6</li><li>8. Catheterization/</li><li>9. Catheterization, Central Venous/</li><li>10. Catheters, Indwelling/</li><li>11. catheter\$.tw.</li><li>12. central line\$.tw.</li><li>13. or/8-12</li><li>14. Bacterial Infections/</li><li>15. Infection/</li><li>16. exp Sepsis/</li><li>17. infect\$.tw.</li><li>18. (sepsis or septic\$).tw.</li><li>19. bacter?emi\$.tw.</li><li>20. or/14-19</li><li>21. and/7,13,20</li></ol>

**EMBASE**

1. Hemodialysis/
2. Hemodiafiltration/
3. Hemofiltration/
4. (hemodialysis or haemodialysis).tw.
5. (hemofiltration or haemofiltration).tw.
6. (hemodiafiltration or haemodiafiltration).tw.
7. dialysis.tw.
8. or/1-7
9. Catheter/
10. Dialysis Catheter/
11. Indwelling Catheter/
12. exp Central Venous Catheter/
13. Subclavian Vein Catheter/
14. Blood Vessel Catheterization/
15. Vein Catheterization/
16. Catheterization/
17. catheter\$.tw.
18. central line\$.tw.
19. or/9-18
20. Infection/
21. Bacterial Infection/
22. Bacteremia/
23. Sepsis/
24. Septicemia/
25. Septic Shock/
26. infect\$.tw.
27. (sepsis or septic\$.tw.
28. bacter?emi\$.tw.
29. or/20-28
30. and/8,19,29



## Appendix 5.1 Overview of CHG RCTs

RCTs comparing CHG and povidone iodine solutions in patients with CVCs and arterial catheters								
Study/Country	Patient population	Participants (treatment/control)	Intervention	Control	Outcomes	Adverse reaction to CHG	Risk of bias	
Maki <i>et al.</i> (1991) US	ICU  CVC & arterial catheters	668 catheters (214/227/227)  3 arm trial	2% aq <sup>1</sup> CHG (214)  10% PVI <sup>2</sup> (227)  70% al <sup>3</sup> (227)		<u>All catheters local CRI<sup>4</sup></u> 2% aq CHG vs. PVI & 70% al 5/214 (2%) vs. 21/227 (9%) & 11/227 (5%) ( $p=0.02$ )  2% aq CHG vs. PVI 5/214 (2%) vs. 21/227 (9%) $p=0.004$ <u>CVC Local CRI</u> 2% aq CHG vs. PVI & 70% al 4/67 (6%) vs. 15/77 (19%) & 5/32 (16%) ( $p=0.02$ )  2% aq CHG vs. PVI 4/67 (6%) vs. 15/77 (19%) $p=0.02$ <u>All catheters CR bacteraemia<sup>5</sup></u> 2% aq CHG vs. PVI & 70% al 1/214 (0.5%) vs. 6/227 (2.6%) & 3/227 (1%); $p=0.18$ <u>CVC CR bacteraemia</u> 2% aq CHG vs. PVI & 70% al 1/67 (1%) vs. 5/77 (6%) & 2/32 (6%)	Erythema in 48.3% of CHG group; not significant when compared to rate of erythema in other group other solution	Allocation sequence Allocation concealment Blinding of intervention	unclear risk unclear risk low risk

<sup>1</sup>aq, aqueous; <sup>2</sup>PVI, Povidone Iodine; <sup>3</sup>Al, Alcohol; <sup>4</sup>Local CRI, Local catheter-related infection (colonisation); <sup>5</sup>CR bacteraemia, catheter-related bacteraemia

RCTs comparing CHG and povidone iodine solutions in patients with CVCs and arterial catheters

Study/Country	Patient population	Participants (treatment/control)	Intervention	Control	Outcomes	Adverse reaction to CHG	Risk of bias	
Sheehan <i>et al.</i> (1993) Canada	ICU  CVC & arterial catheters	189 (94/95)	2% aq <sup>1</sup> CHG (94/169 catheters)	10% PVI <sup>2</sup> (95/177 catheters)	<u>Catheter Colonisation</u> 3/169 (2%) vs. 12/177 (7%); p<0.05  <u>CRBSI</u> <sup>3</sup> 1/169 (1%) vs. 1/177(1%)	Not stated	Allocation sequence Allocation concealment Blinding of intervention	unclear risk unclear risk unclear risk
Legras <i>et al.</i> (1997) abstract in English, article in French  France	ICU  CVCs & arterial catheters	190 (88/102)	0.5% CHG in alcohol (strength of alcohol not stated) (88)	10% PVI (102)	<u>CR bacteraemia</u> 0/88 vs. 4/102 (4%); p=0.13	Not stated	Allocation sequence Allocation concealment Blinding of intervention	unclear risk unclear risk unclear risk

<sup>1</sup>aq, aqueous; <sup>2</sup>PVI, Povidone iodine; <sup>3</sup>CRBSI, Catheter-related bloodstream infections

RCTs comparing CHG and povidone iodine solutions in patients with CVCs and arterial catheters

Study/Country	Patient population	Participants (treatment/control)	Intervention	Control	Outcomes	Adverse reaction to CHG	Risk of bias
Humar <i>et al.</i> (2000) Canada	ICU  CVCs & pulmonary catheters	374 (181/193)  242 had CVC>72hrs (117 vs.125)  74% (180) tips available for analysis	10% PVI <sup>1</sup> (117)	0.5% tincture CHG (125)	<u>CR bacteraemia</u> <sup>2</sup> 4/117 (3%) vs. 4/125 (3%); NS <sup>3</sup>  <u>Catheter colonisation (tips)</u> 24/88 (27%) vs. 31/92 (34%); NS  <u>Exit site infection</u> 4/117 (3%) vs. 0/125; <i>p</i> =0.05	Not stated	Allocation sequence low risk Allocation concealment unclear risk Blinding of intervention low risk
Maki <i>et al.</i> (2001) US	General patient population  CVC, arterial and PICC <sup>4</sup>	Catheters (422/617)	1% CHG (422)	10% PVI (617)	<u>Catheter colonisation</u> 43/422 (10%) vs. 192/617 (31%); <i>p</i> <0.05  <u>CRBSI</u> <sup>5</sup> 4/422 (1%) vs. 23/617 (4%); <i>p</i> <0.05	Not stated	Allocation sequence unclear risk Allocation concealment unclear risk Blinding of intervention unclear risk

<sup>1</sup>PVI, Povidone Iodine; <sup>2</sup>CR bacteraemia, catheter-related bacteraemia; <sup>3</sup>NS, not significant; <sup>4</sup>PICC, Peripheral inserted central catheter; <sup>5</sup>CRBSI, Catheter-related bloodstream infection.

RCTs comparing CHG and povidone iodine solutions in patients with CVCs and arterial catheters

Study/Country	Patient population	Participants (treatment/control)	Intervention	Control	Outcomes	Adverse reaction to CHG	Risk of bias
Langgartner <i>et al.</i> (2004) Germany	General patient population ICU CVC	119 patients 140 catheters (52/45/43) 3 arm trial	10% PVI <sup>1</sup> (52) 0.5% CHG in 70% propanol (45) 0.5% CHG in 70% propanol followed by 10% PVI (CHG/PVI; 43)		<u>Catheter colonisation</u> PVI 16/52 (31%) 0.5% CHG 11/45 (24%) 0.5% CHG/PVI 2/43 (5%) $p=0.006$  0.5% CHG vs. 10% PVI 11/45 (24%) vs. 16/52 (31%) $p=0.32$  PVI vs. 0.5% CHG/PVI 16/53 (31%) vs. 2/43 (5%) $p=0.001$  0.5% CHG vs. 0.5% CHG/PVI 11/45 (24%) vs. 2/43 (5%) $p=0.01$	None observed	Allocation sequence Allocation concealment Blinding of intervention low risk unclear risk unclear risk
Kelly <i>et al.</i> (2005) [abstract] Country not stated	ICU CVCs and arterial catheters	164 (82/82)	2% CHG in 70% isopropyl alcohol (Chloraprep®) (82)	10% PVI (82)	<u>CRI</u> <sup>2</sup> 4/82 (5%) vs. 15/82 (18%) $p=0.01$ 5.1 vs. 14.5 episodes per 1000 catheter days <u>PBSI</u> <sup>3</sup> 1/82 (1%) vs. 8/82 (10%) $p=0.05$ 1.3 vs. 7.7 episodes per 1000 catheter days	Not stated	Allocation sequence Allocation concealment Blinding of intervention unclear risk unclear risk unclear risk

<sup>1</sup>PVI, Povidone Iodine; <sup>2</sup>CRI, Catheter-related infection; <sup>3</sup>PBSI, Primary bloodstream infection

RCTs comparing CHG and povidone iodine solutions in patients with CVCs and arterial catheters

Study/Country	Patient population	Participants (treatment/control)	Intervention	Control	Outcomes	Adverse reaction to CHG	Risk of bias
Valles <i>et al.</i> (2008) Spain	ICU  CVC and arterial catheters	631 catheters (211/226/194)  3 arm trial	2% aq <sup>1</sup> CHG (211)  0.5% CHG AI ([226], no strength of alcohol given)	10% aq PVI <sup>2</sup> [194]	<u>Catheter colonisation</u> 2% aq CHG vs. 10% aq PVI 34/211 (16%) vs. 48/194 (25%) p= 0.03  0.5% CHG AI vs. aq PVI 32/226 (14%) vs. 48/194 25%) p=0.01  2% aq vs. 0.5% CHG AI 34/211 (16%) vs. 32/226 (14%) p=0.20 <u>Catheter-related bacteraemia</u> No difference between groups 2% aq CHG vs. 10% aq PVI 9/211 (4%) vs. 9/194 (5%)  0.5% CHG AI vs. aq PVI 9/226 (4%) vs. 9/194 (5%)  2% aq vs. 0.5% CHG AI 9/211 (4%) vs. 9/226 (4%)	None observed	Allocation sequence low risk Allocation concealment unclear risk Blinding of intervention unclear risk
Garland <i>et al.</i> (2009) US	ICU Neonates  PICC <sup>3</sup>	48 (24/24)	2% CHG AI (no strength given) (24)	10% PVI (24)	<u>Catheter colonisation</u> 3/24 (12%) vs. 1/24 (4%) p= 0.61 <u>Catheter-associated BSI</u> 1/24 (4%) vs. 1/24 (4%); p=0.99	None observed	Allocation sequence low risk Allocation concealment unclear risk Blinding of intervention unclear risk

<sup>1</sup>aq, aqueous; <sup>2</sup>PVI, povidone iodine, <sup>3</sup>PICC, peripheral inserted central catheters

RCTs comparing CHG and other antiseptic solutions in patients with CVCs and arterial catheters

Study/Country	Patient population	Participants (treatment/control)	Intervention	Control	Outcomes	Adverse reaction to CHG	Risk of bias
Astle (2005) Canada	Dialysis centre	121 (57/64)	ExSept® (57)	0.5% CHG in 70% isopropyl alcohol (64)	<u>Exit site infection</u> 5/57 (9%) vs. 5/64 (8%); $p=0.85$ <u>CR bacteraemia</u> <sup>1</sup> 1/57 (2%) vs. 1/64 (1%); $p=0.93$ <u>Skin colonisation</u> 55/57 (96%) vs. 56/67 (83%); $p=0.007$	None observed	Allocation sequence high risk Allocation concealment high risk Blinding of intervention unclear risk
Bilir <i>et al.</i> (2013) Turkey	ICU  CVC & arterial catheters	57 (19/19/19)  3 art trial  109 catheters group breakdown not given	4% CHG (19)  10% PVI <sup>2</sup> (19)  Octenidine hydrochlorodine (19)		<u>Catheter-related sepsis</u> 4% CHG (nil) 10% PVI (10.5%) Octenidine hydrochlorodine (10.5%) Significant difference between groups ( $p=0.001$ )  Unclear if data relates to catheter or patient numbers <u>Catheter colonisation</u> 4% CHG (nil) 10% PVI (26.3%) Octenidine hydrochlorodine (21.5%) Significant difference between groups ( $p=0.001$ ) Unclear if data relates to catheter or patient numbers	None observed	Allocation sequence low risk Allocation concealment unclear risk Blinding of intervention low risk

<sup>1</sup>CR bacteraemia, catheter-related bacteraemia; <sup>2</sup>PVI, Povidone Iodine

RCTs comparing CHG based solutions and povidone iodine solutions in patients with CVCs and arterial catheters

Study/Country	Patient population	Participants (treatment/control)	Intervention	Control	Outcomes	Adverse reaction to CHG	Adverse reaction to CHG	Adverse reaction to CHG
Mimoz <i>et al.</i> (1996) France	ICU  CVC & arterial catheters	162 patients  315 catheter tips -170/145  CVC 87/71	0.25% CHG plus 0.025% Benzalkonium chloride plus 4% benzyl alcohol (170)	10% PVI <sup>1</sup> (145)	<u>All catheter colonisation</u> 12/170 (7%) vs. 31/145 (21%) rate per 1000 catheter days; $p=0.01$ <u>CVC catheter colonisation</u> 8/87 (9%) vs. 31/71(44%) per 1000 catheter days; $p=0.03$ <u>All catheter-related sepsis</u> 6/170 (3%) vs. 16/145 (11%) rate per 1000 catheter days; $p=0.05$ <u>CVC catheter-related sepsis</u> 5/87 (6%) vs. 19/71 (27%) per 1000 catheter days; $p=0.02$ <u>All catheter-related bacteraemia</u> 3/170 (2%) vs. 4/145 (3%) rate per 1000 catheter days; $p=0.40$	None observed	Allocation sequence Allocation concealment Blinding of intervention	unclear risk high risk low risk
Mimoz <i>et al.</i> (2007) France	ICU  CVCs	481 catheter tips  (242/239)	0.25% CHG plus 0.025% Benzalkonium chloride plus 4% benzyl alcohol (242)	5% PVI in 70% alcohol (239)	<u>Catheter colonisation</u> 28/242 (12%) vs. 53/239 (22%) $p=0.002$ <u>CRBSI</u> <sup>2</sup> 4/242 (2%) vs. 10/239 (4%) $p= 0.09$	None observed	Allocation sequence Allocation concealment Blinding of intervention	low risk low risk low risk
Atahan <i>et al.</i> (2012) Turkey	General patient population  CVCs	50 (23/27)	15% cetrimide , 1.5% CHG, ethanol (no strength given) (23)	10% PVI (27)	<u>CRBSI</u> 0/23 vs. 4/27 (15%) $p=0.02$ <u>Catheter colonisation</u> 6/23 (26%) vs.9/27 (33%) $p= 0.05$	Not stated	Allocation sequence Allocation concealment Blinding of intervention	high risk high risk unclear risk

<sup>1</sup>PVI, Povidone Iodine <sup>2</sup>CRBSI, catheter-related bloodstream infection

**RCTs comparing CHG solutions and other antiseptic solutions in patients with peripheral vascular catheters (PVC)**

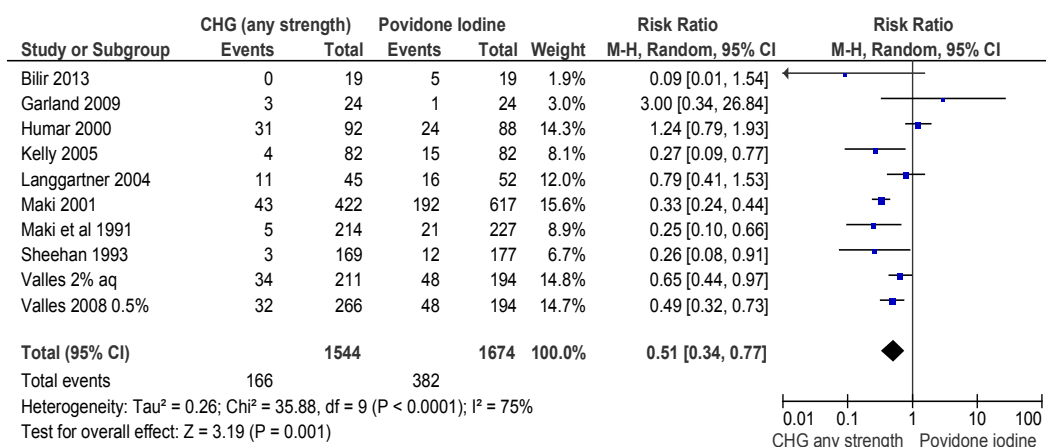
Study/Country	Patient population	Participants (treatment/control)	Intervention	Control	Outcomes	Adverse reaction to CHG	Adverse reaction to CHG	Adverse reaction to CHG
Meffre <i>et al.</i> (1996) abstract France	Surgical patients	1117 (568/549)	0.5% CHG in alcohol (568)	10% PVI <sup>1</sup> (549)	<u>PVC colonisation</u> 1.6% vs, 4% p=0.002  <u>Catheter-related infection</u> 0.5% vs. 0.5%	Not stated	Allocation sequence Allocation concealment Blinding of intervention	unclear risk unclear risk low risk
Corbbet & LeBlanc (2000) Canada	General patient population  PVC	244 (83/80/81)  3 arm trial	0.5% CHG in 70% alcohol (83)  70% alcohol followed by 10% PVI (80)	10% PVI <sup>1</sup> followed by 70% alcohol (81)	<u>LCI<sup>2</sup> (colonisation)</u> 5/83 (6%) vs. 2/80 (2.5%) vs. 3/81 (4%); p=0.62	Not stated	Allocation sequence Allocation concealment Blinding of intervention	unclear risk unclear risk low risk
Small <i>et al.</i> (2008) Canada	Elective cardiology patients admitted for ablation or insertion of pacemaker  PVC	170 (90/79)	2% CHG in 70% isopropyl alcohol (ChloraPrep®) (90)	70% isopropyl alcohol wipe (79)	<u>PVC colonisation</u> 18/91 (19.8%) vs. 39/79 (49%); p=0.001	None observed	Allocation sequence Allocation concealment Blinding of intervention	unclear risk unclear risk low risk

<sup>1</sup>PVI, Povidone Iodine; <sup>2</sup>LCI, local catheter infection

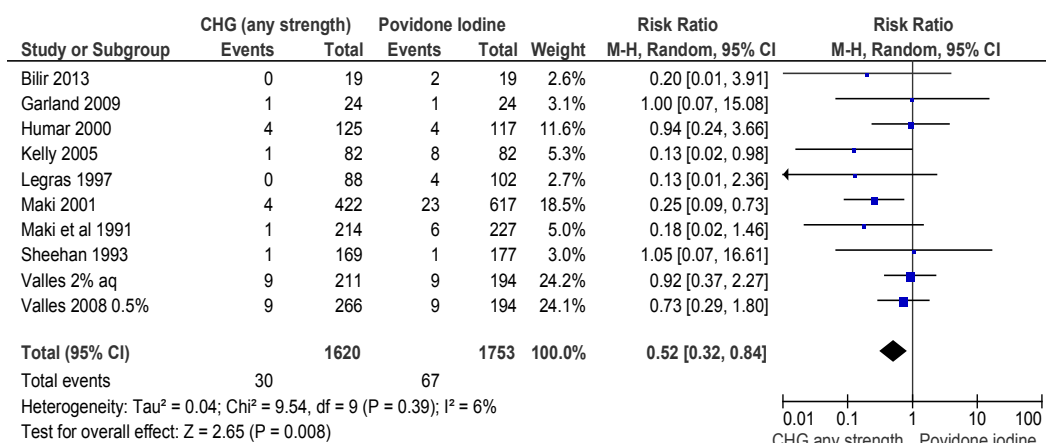


## Appendix 5.2 CHG meta-analysis forest plots

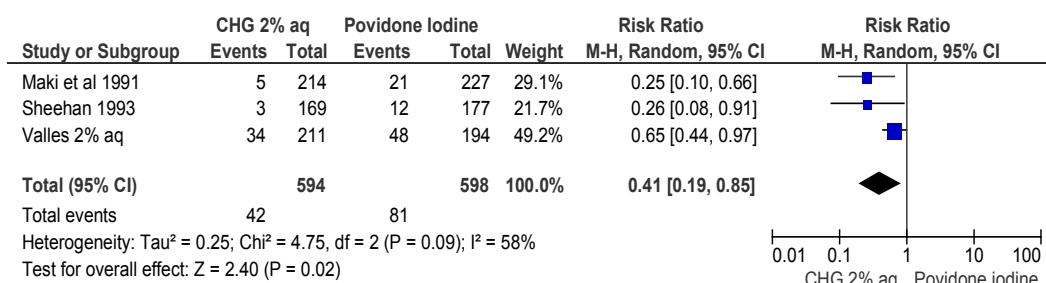
### CHG (any strength) versus povidone iodine: catheter colonisation



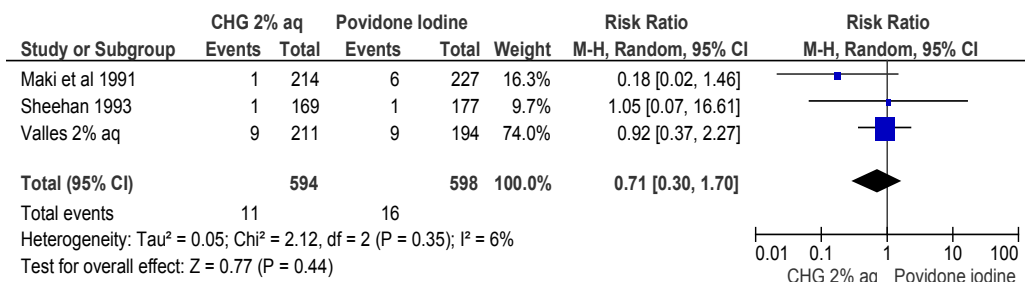
### CHG (any strength) versus povidone iodine: catheter-related bloodstream infection



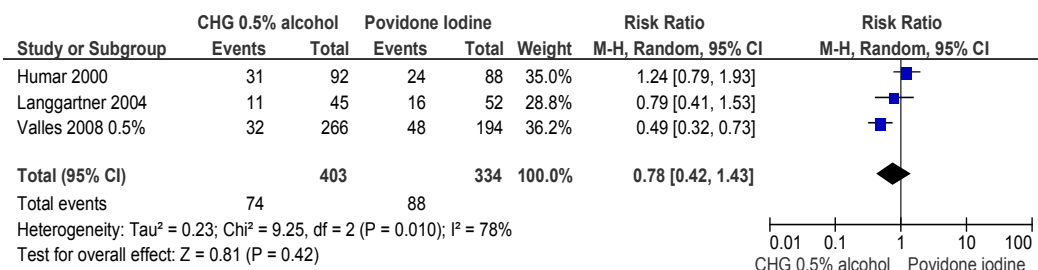
### CHG (2% aqueous) versus povidone iodine: catheter colonisation



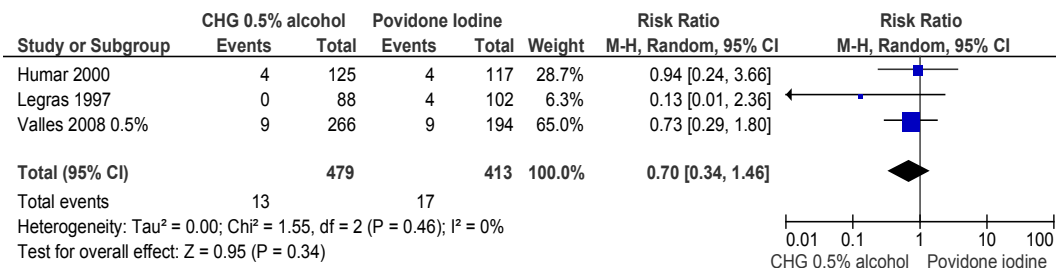
## CHG (2% aqueous) versus povidone iodine: catheter-related bloodstream infection



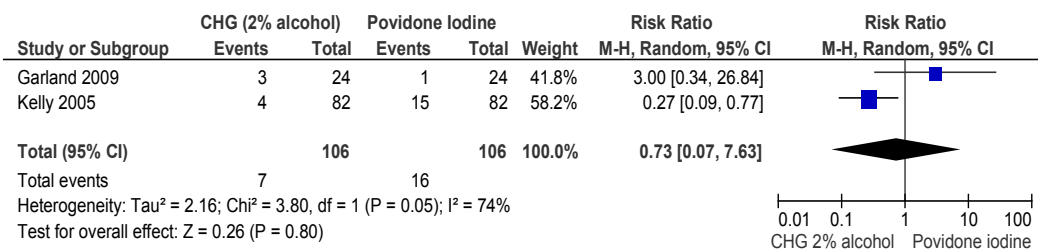
## CHG (0.5% alcohol) versus povidone iodine: catheter colonisation



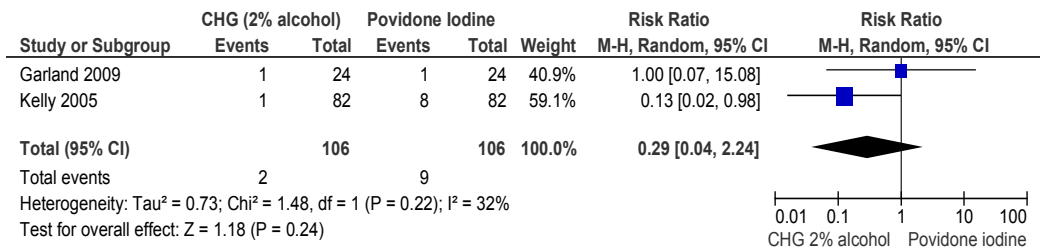
## CHG (0.5% alcohol) versus povidone iodine: catheter-related bloodstream infection



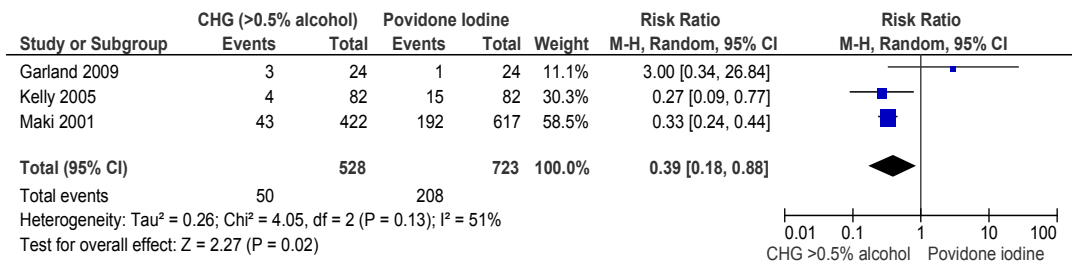
## CHG (2% alcohol) versus povidone iodine: catheter colonisation



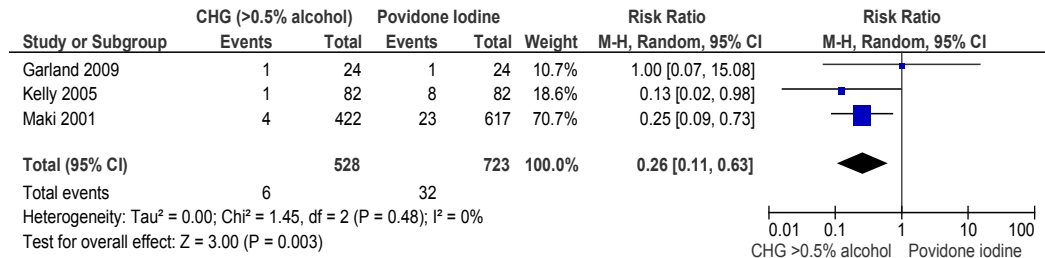
## CHG (2% alcohol) versus povidone iodine: catheter-related bloodstream infection



## CHG (>0.5% alcohol) versus povidone iodine: catheter colonisation



## CHG (>0.5% alcohol) versus povidone iodine: catheter-related bloodstream infection



## **Appendix 6.1      Routine practice survey**

### **Routine Practice in Irish Haemodialysis Units**

**The following survey should be completed by the Dialysis Unit's  
Clinical Nurse Manger**

Margaret McCann, Lecturer in the School of Nursing and Midwifery, Trinity College Dublin wishes to undertake a survey of routine practices in Irish Haemodialysis Units, as part of her PhD studies. We invite you to take part in this survey. If there is anything that you are not clear about, Margaret will be happy to explain it to you. Her contact details are provided below.

The majority of questions in the survey are tick boxes and we expect that it will take you no more than 10 minutes to complete. All the information collected in this survey will be treated in the strictest confidence and will be stored in a way that protects your dialysis unit's identity. Results from the study will be reported as group data and will not identify your dialysis unit in any way.

Completed surveys are to be returned to:

**Margaret McCann**  
**School of Nursing and Midwifery**  
**Trinity College Dublin**  
**24 D'Olier Street**  
**Dublin 2**  
**Mobile Number: 0872897809**  
**Email: [mmcann4@tcd.ie](mailto:mmcann4@tcd.ie)**

<b>Date (DD/MM/YYYY):</b> ____/____/____	<b>Dialysis Facility:</b> _____
<b>Q1 In relation to the creation of Arterio Venous Fistulas (AVF) in patients attending your dialysis unit, please indicate where the responsible vascular access surgeon is located (Tick one):</b> <input type="checkbox"/> [1] In this hospital only <input type="checkbox"/> [2] In other hospitals (please state the hospitals)  _____	<b>Q2 In order to ensure the timely creation of AVFs what type of access does your dialysis unit have to a vascular access surgeon (Tick one):</b> <input type="checkbox"/> [1] Dedicated theatre sessions <input type="checkbox"/> [2] No dedicated theatre sessions (If 'no dedicated theatre sessions' go to Q4) <input type="checkbox"/> [3] Unknown (If 'unknown' go to Q4)
<b>Q3 If you answered 'No dedicated theatre session or Unknown' in Q2 go directly to Q4</b>  <b>How many dedicated theatre sessions <u>per week</u> does the vascular surgeon have for the creation of AVFs/AVG:</b> _____	<b>Q4 In your dialysis unit, do patients with progressive renal failure routinely have a primary AVF created when the eGFR is between 17 and 12 ml/hr (Tick one):</b> <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No <input type="checkbox"/> [3] Other (specify) _____
<b>Q5 Does your dialysis unit routinely keep ongoing records (e.g., monthly/annually) of the following (Tick all that apply):</b> <input type="checkbox"/> [1] Percentage of patients with AVF <input type="checkbox"/> [2] Percentage of patients with Arterio Venous Grafts (AVG) <input type="checkbox"/> [3] Percentage of patients with Central Venous Catheters (CVC) <input type="checkbox"/> [4] No records of AVF, AVG or CVC rates are kept	<b>Q6 Does routine MRSA screening of patients attending the dialysis unit occur every three months (Tick one):</b> <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No <input type="checkbox"/> [3] Other (specify) _____
<b>Q7 How often are bacteraemia rates for dialysis patients with or without a CVC reviewed (Tick one):</b> <input type="checkbox"/> [1] Every month <input type="checkbox"/> [2] Every 3 months <input type="checkbox"/> [3] Other (specify) _____ <input type="checkbox"/> [4] Never reviewed (if 'Never reviewed' go to Q9)	<b>Q8 If you answered 'Never reviewed' in Q7 go directly to Q9</b>  <b>Are the following types of bacteraemias routinely reviewed (Tick one):</b> <input type="checkbox"/> [1] All bacteraemias <input type="checkbox"/> [2] Only bacteraemias caused by a specific organism (e.g. staph aureus)
<b>Q9 For each episode of bacteraemia, is a root cause analysis routinely undertaken (Tick one):</b> <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No <input type="checkbox"/> [3] Other (specify) _____	<b>Q10 Is a surveillance programme in place to monitor the incidence of infection associated with haemodialysis CVCs (e.g. the unit receives monthly/3 monthly reports on the number of bacteraemias, organism and source) (Tick one):</b> <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No
<b>Q11 Is a surveillance programme in place to monitor the incidence of infection associated with AVF/AVG (e.g. the unit receives monthly/3 monthly reports on the number of bacteraemias, organism and source) (Tick one)</b> <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No	<b>Q12 What surveillance programme is used to monitor the incidence of infection associated with AVF/AVG/CVC (Tick one or more):</b> <input type="checkbox"/> [1] CDC dialysis event protocol <input type="checkbox"/> [2] S. aureus bacteraemia <input type="checkbox"/> [3] Other (specify) _____

<p><b>Q13 Where are dialysis permanent cuffed CVCs routinely inserted (Tick one or more):</b></p> <p><input type="checkbox"/> [1] In interventional radiology</p> <p><input type="checkbox"/> [2] In theatre</p> <p><input type="checkbox"/> [3] Elsewhere (specify) _____</p> <p><input type="checkbox"/> [4] Unknown</p>	<p><b>Q14 Are dialysis permanent cuffed CVCs routinely inserted by (Tick one or more):</b></p> <p><input type="checkbox"/> [1] Consultant Nephrologist</p> <p><input type="checkbox"/> [2] Radiologist</p> <p><input type="checkbox"/> [3] Other (specify) _____</p> <p><input type="checkbox"/> [4] Unknown</p>
<p><b>Q15 Is a CVC checklist used routinely to ensure adherence to infection prevention and control practices at the time of insertion of dialysis permanent cuffed CVC (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No</p> <p><input type="checkbox"/> [3] Unknown</p>	<p><b>Q16 Is a prophylactic antimicrobial routinely administered prior to the insertion of a dialysis permanent cuffed CVC (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No (if 'No' go to Q18)</p> <p><input type="checkbox"/> [3] Unknown (if 'Unknown' go to Q18)</p>
<p><b>Q17 If you answered 'No' or 'Unknown' in Q16 go directly to Q18</b></p> <p><b>Which prophylactic antimicrobial is routinely administered prior to the insertion of a dialysis permanent cuffed CVC (Tick one or more):</b></p> <p><input type="checkbox"/> [1] Topical antimicrobial ointment</p> <p><input type="checkbox"/> [2] Intravenous antibiotic</p> <p><input type="checkbox"/> [3] Other (specify) _____</p>	<p><b>Q 18 Are antiseptic/Antimicrobial impregnated permanent cuffed CVCs used for some of your dialysis patients (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No</p>
<p><b>Q19 Are antimicrobial locks routinely used in dialysis patients' permanent cuffed CVCs (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No</p>	<p><b>Q20 Which solution is routinely used to lock a dialysis patient's permanent CVC (Tick one or more):</b></p> <p><input type="checkbox"/> [1] Heparin</p> <p><input type="checkbox"/> [2] Trisodium Citrate (e.g. 'Duralock')</p> <p><input type="checkbox"/> [3] Urokinase</p> <p><input type="checkbox"/> [4] Other (specify) _____</p>
<p><b>Q21 Are CVC care bundles routinely used in the dialysis unit (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No</p>	<p><b>Q22 Are written CVC care and maintenance guidelines available in the dialysis unit (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No</p>
<p><b>Q23 When a CVC infection is suspected in haemodialysis patients, is it routine practice to <u>always</u> take two sets of blood cultures (either through the CVC, dialysis circuit or peripherally) (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No</p> <p><input type="checkbox"/> [3] Sometimes</p>	<p><b>Q24 Are CVC sterile connect and disconnect packs routinely used in the dialysis unit (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No</p>
<p><b>Q25 Are dialysis patients with a CVC routinely connected to and from dialysis by (Tick one):</b></p> <p><input type="checkbox"/> [1] 1 RGN only</p> <p><input type="checkbox"/> [2] 2 RGN</p> <p><input type="checkbox"/> [3] 1 RGN and 1 Healthcare assistant</p> <p><input type="checkbox"/> [4] Other (specify) _____</p>	<p><b>Q26 Which routine antiseptic solution is routinely used for cleansing of AVF/AVG prior to needling (Tick one):</b></p> <p><input type="checkbox"/> [1] Povidone Iodine</p> <p><input type="checkbox"/> [2] 0.05% aqueous Chlorhexidine Gluconate (CHG)</p> <p><input type="checkbox"/> [3] 0.5% CHG in 70% alcohol</p> <p><input type="checkbox"/> [4] 2% CHG in 70% alcohol (Tick one):-</p> <p>[1] <input type="checkbox"/> ChlorPrep</p> <p>[2] <input type="checkbox"/> Sani Cloth CHG 2%</p> <p>[3] <input type="checkbox"/> Clinell Wipes</p> <p>[4] <input type="checkbox"/> Hydrex 2%</p> <p><input type="checkbox"/> [5] 2% aqueous chlorhexidine gluconate</p> <p><input type="checkbox"/> [6] Other (specify) _____</p>

<p><b>Q27 Which antiseptic solution is routinely used for CVC connection/disconnection (Tick one):</b></p> <p><input type="checkbox"/> [1] Povidone Iodine</p> <p><input type="checkbox"/> [2] 0.05% aqueous Chlorhexidine Gluconate (CHG)</p> <p><input type="checkbox"/> [3] 0.5% CHG in 70% alcohol</p> <p><input type="checkbox"/> [4] 2% CHG in 70% alcohol <b>(Tick one):-:</b></p> <p>[1] <input type="checkbox"/> Sani Cloth CHG 2%</p> <p>[2] <input type="checkbox"/> Clinell Wipes</p> <p>[3] <input type="checkbox"/> Hydrex 2%</p> <p><input type="checkbox"/> [5] 2% aqueous chlorhexidine gluconate</p> <p><input type="checkbox"/> [6] Other (specify) _____</p> <p><input type="checkbox"/> [7] Chlorhexidine gluconate trial</p>	<p><b>Q28 Which antiseptic solution is routinely used for CVC exit site care (Tick one):</b></p> <p><input type="checkbox"/> [1] Povidone Iodine</p> <p><input type="checkbox"/> [2] 0.05% aqueous Chlorhexidine Gluconate (CHG)</p> <p><input type="checkbox"/> [3] 0.5% CHG in 70% alcohol</p> <p><input type="checkbox"/> [4] 2% CHG in 70% alcohol <b>(Tick one):-</b></p> <p>[1] <input type="checkbox"/> ChloraPrep</p> <p>[2] <input type="checkbox"/> Sani Cloth CHG 2%</p> <p>[3] <input type="checkbox"/> Clinell Wipes</p> <p>[4] <input type="checkbox"/> Hydrex 2%</p> <p><input type="checkbox"/> [5] 2% aqueous chlorhexidine gluconate</p> <p><input type="checkbox"/> [6] Other (specify) _____</p> <p><input type="checkbox"/> [7] Chlorhexidine gluconate trial</p>
<p><b>Q 29 How often are CVC dressings routinely changed (Tick one):</b></p> <p><input type="checkbox"/> [1] Every dialysis session</p> <p><input type="checkbox"/> [2] Every 7 days</p> <p><input type="checkbox"/> [3] As determined by patient</p>	<p><b>Q 30 Is the dialysis patient's CVC routinely anchored between dialysis sessions (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No</p>
<p><b>Q31 What type of CVC dressing is used for the majority of dialysis patients (Tick one or more):</b></p> <p><input type="checkbox"/> [1] Transparent</p> <p><input type="checkbox"/> [2] Dry gauze</p> <p><input type="checkbox"/> [3] CHG dressing – biopatch with transparent dressing</p> <p><input type="checkbox"/> [4] Other (specify) _____</p>	<p><b>Q32 What is the trade name of the standard CVC dressing used (Tick one or more):</b></p> <p><input type="checkbox"/> [1] IV 3000</p> <p><input type="checkbox"/> [2] IV 3000 hand</p> <p><input type="checkbox"/> [3] Primapore</p> <p><input type="checkbox"/> [4] Mepore</p> <p><input type="checkbox"/> [5] Tegaderm transparent dressing</p> <p><input type="checkbox"/> [6] Biopatch with transparent dressing</p> <p><input type="checkbox"/> [7] Cosmopore</p> <p><input type="checkbox"/> [8] Other (specify) _____</p>
<p><b>Q33 Is a topical antimicrobial ointment routinely applied to the CVC exit site (Tick one):</b></p> <p><input type="checkbox"/> [1] Yes</p> <p><input type="checkbox"/> [2] No (if 'No' go to Q35)</p>	<p><b>Q34 If you answered 'No' in Q33 go directly to Q35</b></p> <p><b>What type of topical antimicrobial ointment is routinely applied to the CVC exit site (Tick one):</b></p> <p><input type="checkbox"/> [1] Mupirocin</p> <p><input type="checkbox"/> [2] Povidone Iodine ointment</p> <p><input type="checkbox"/> [3] Other (specify) _____</p>
<p><b>Q35 In the week that you completed this survey, what was the total number of ESRD haemodialysis patients in your unit (insert number):</b> _____</p>	<p><b>Q36 In the week that you completed this survey, what was the total number of ESRD haemodialysis patients in your unit with a CVC (insert number):</b> _____</p>
<p><b>Q37 In the week that you completed this survey, what is the total number of ESRD haemodialysis patients in your unit with a AVF (insert number):</b> _____</p>	<p><b>Q38 In the week that you completed this survey, what is the total number of ESRD haemodialysis patients in your unit with a AVG (insert number):</b> _____</p>

## Appendix 7.1 National Competent Authority algorithm to determine clinical trials

### IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				A NON-INTERVENTIONAL CLINICAL TRIAL?
Is it a medicinal product (MP)? <sup>1</sup>	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?
<p>If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP.</p> <p>If you answer yes to <u>any</u> of the questions below go to column B.</p>	<p>If you answer yes to the question below in column B the activity is not a clinical trial on a MP.</p> <p>If you answer no to this question below go to column C.</p>	<p>If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC.</p> <p>If you answer yes to <u>any</u> of the questions below go to column D.</p>	<p>If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC.</p> <p>If you answer yes to <u>any</u> of the questions below go to column E.</p>	<p>If you answer yes to <u>all</u> these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC. If your answers in columns A,B,C &amp; D brought you to column E and you answer no to <u>any</u> of these questions the activity is a clinical trial within the scope of the Directive.</p>
<p>A.1 Is it a substance<sup>2</sup> or combination of substances presented as having properties for treating or preventing disease in human beings?</p> <p>A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose?</p> <p>A.3 Is it an active substance in a pharmaceutical form?</p>	<p>B.1 Are you <u>only</u> administering any of the following substances?</p> <ul style="list-style-type: none"> <li>• Human whole blood<sup>3</sup>;</li> <li>• Human blood cells;</li> <li>• Human plasma;</li> <li>• Tissues except a somatic cell therapy medicinal product<sup>4</sup>;</li> <li>• A food product<sup>5</sup> (including dietary supplements) not presented as a medicine;</li> <li>• A cosmetic product<sup>6</sup></li> <li>• A medical device</li> </ul>	<p>C.1 To discover or verify/compare its clinical effects?</p> <p>C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics?</p> <p>C.3 To identify or verify/compare its adverse reactions?</p> <p>C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?</p>	<p>D.1 To ascertain or verify/compare the efficacy<sup>7</sup> of the medicine?</p> <p>D.2 To ascertain or verify/compare the safety of the medicine?</p>	<p>E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned?</p> <p>E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation?</p> <p>E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol<sup>8</sup>?</p> <p>E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study?</p> <p>E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice?</p> <p>E.6 Will epidemiological methods be used for the analysis of the data arising from the study?</p>



## Appendix 7.2 Confirmation of trial sponsor

THIS DOCUMENT IS NOT TO BE USED FOR  
PROMOTIONAL OR ENDORSING PURPOSES

Ms. Margaret Mc Cann  
Lecturer  
School of Nursing and Midwifery  
Trinity College Dublin  
24 D'Olier Street  
Dublin 2



**THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN**  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL

DUBLIN 2, DUBLIN 24, IRELAND  
TELEPHONE: +353 1 4542000

### Department of Nephrology

Medical Director: Dr. George Mellotte  
Dr. Mellotte's Sec: 01 414 2440  
g.mellotte@amh.ie  
Fax: 01 414 2384

Date: 25.11.09

Re: 'A randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% alcohol versus other forms of chlorhexidine gluconate, on central venous catheter related infections in haemodialysis patients'.

Dear Ms. Mc Cann,

As per EU clinical trials directive I wish to confirm my role as sponsor for the following clinical trial 'A randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% alcohol versus other forms of chlorhexidine gluconate, on central venous catheter related infections in haemodialysis patients'.

Yours sincerely,

Dr. George J. Mellotte, MB, FRCP, M. Sc.,  
Consultant Nephrologist & Senior Lecturer in Medicine

## Appendix 7.3 Delegation of tasks and duties related to trial

THIS DOCUMENT MUST NOT BE USED FOR  
PRESCRIPTIONS OR INVOICING PURPOSES



**THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN**  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND  
TELEPHONE +353 1 4142000

Clinical Trials Unit  
Irish Medicines Board  
Kevin O'Malley House  
Block A  
Earlsfort Centre  
Earlsfort Terrace  
Dublin 2

**Regarding:** EudraCT number 2010-019984-12; Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010 titled

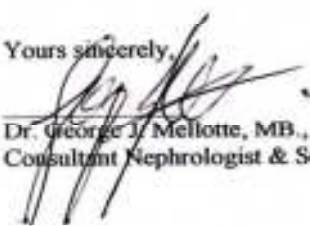
*'A multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent versus other forms of chlorhexidine gluconate which are in routine use, on central venous catheter-related infections in haemodialysis patients'*

12<sup>th</sup> April 2010

Dear Sir/Madam

As Clinical Sponsor and Chief Investigator I wish to confirm that I have delegated all tasks and duties related to the above clinical trial to Ms. Margaret McCann, PhD Student at the School of Nursing and Midwifery, Trinity College Dublin, 24 D'Olier Street, Dublin 2.

Yours sincerely,

  
Dr. George J. Mellotte, MB., FRCPL., M.Sc  
Consultant Nephrologist & Senior Lecturer in Medicine

## **Appendix 7.4      Education/Training for clinical trial design & conduct**

- October 2008, York University, 5 day workshop on 'Introduction to design and conduct of clinical trials and an introduction to statistics for clinical trials'.
- February 2010, Oxford University, 5 day 'Randomised Controlled Trials' module on the University of Oxford's Evidence-Based Health Care MSc.
- May 2010, study day on 'Epidemiology and Statistics for Healthcare Associated Infections Surveillance Course', provided by the Irish Society of Clinical Microbiologist, which was facilitated by Teresa Horan and Jonathan Edwards from the Centers for Disease Control and Prevention (CDC), with whom I discussed the trial protocol.
- November 2010, workshop on 'Good Clinical Practice', provided by the Irish Clinical Research Infrastructure Network, which was established by Molecular Medicine Ireland partners.
- June 2012, seminar on 'Clinical Trials' for Medical Practitioners, Sponsors and Investigators', which was facilitated by the IMB.

## Appendix 7.5 Confirmation of insurance cover, site OA & OV



Ms Joan McDonnell,  
Senior Administrator,  
Ethics and Medical and Research Department,  
Education & Research Centre,  
St Vincent's Healthcare Group Ltd  
Elm Park,  
Dublin 4.

Our Ref. CD/SON  
29 June 2011

Dear Joan,

**A Multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent versus other forms of chlorhexidine gluconate which are in routine use on central venous catheter-related infections in haemodialysis patients.**

Further to your email of 29 June 2011 we are pleased to confirm that cover under the Clinical Indemnity Scheme extends to St Vincent's University Hospital, the chief and principal investigators, for the trial in respect of the above.

Yours sincerely,

**Colum Diamond**  
Director  
Direct Line: 01 2666432  
Email: colum.diamond@aon.ie

Aon Risk Solutions | Risk Placement Speciality  
The Metropolitan Building | James Joyce Street | Dublin 1 | Ireland  
t+353 1 266 6000 | f+353 1 266 6623 | www.aon.ie  
MacDonagh Boland Crotty MacRedmond Limited t/a Aon is regulated by The Central Bank of Ireland.  
Registered in Ireland No. 5103 Registered Office: The Metropolitan Building, James Joyce Street, Dublin 1.  
Directors: P. Ahearne, P. Brady, G. Connolly, P. Connolly, G. Conway, B. Cox, B. Curtis, C. Diamond, G. Dixon, R. Endersen, B. Farrell,  
H. Foley, R. Fox, J. Grinbergs, R. McDunphy, K. McGoldrick, P. Moloney, J. Neary, O. Pepper, P. Purcell, D. Rutherford, D. Watkin.



Ms Carolyn Gallagher  
Pharmacy Administrator  
The Adelaide & Meath Hospital, Dublin  
Incorporating the National Children's Hospital  
Tallaght  
Dublin 24

Our Ref. CD/SON  
29 September 2010

Dear Carolyn

**AMNCH-TCD-CHG-1-2010 Multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent versus other forms of chlorhexidine gluconate which are in routine use, on centra venous catheter-related infections in haemodialysis patients.**

I refer to your email of 23 inst. and with to advise that we are pleased to confirm that cover under the Clinical Indemnity Scheme extends to AMNCH and appropriate investigators for the trial in respect of the above.

Yours sincerely

## Appendix 7.6 Confirmation of insurance cover site OB

Trinity College Dublin Mail - FW: dnhla3839994 RE: Insurance cover for Chlorhexid... Page 2 of 5

---

**From:** "Leonard, Cathal (Allianz Ireland)" <cathal.leonard@allianz.ie>  
**Date:** Fri, 18 Feb 2011 16:40:19 +0100  
**To:** 'Joe O'Rourke' <joeorourke@mmpi.ie>  
**Subject:** dnhla3839994 RE: Insurance cover for Chlorhexidine Gluconate Trial

Joe

Cover is in order as per policy Terms and conditions and only in respect of Beacon Dialysis, TCD, AMNCH and the P.I will have to have their own insurances in place.

regards

Cathal

---

**Cathal Leonard ACII**

Healthcare Team

Allianz / Allianz House | Elm Park | Merion Road | Dublin 4 | Ireland

Phone: + 353 1 613 3714 | Fax: + 353 1 613 3643

Email: Cathal.Leonard@allianz.ie

<http://www.allianz.ie>

*Please consider the environment before printing this e-mail and any att.*

---

Sender: Iva.VBroukova [mailto:iva.vbroukova@allianz.ie]

11 OCT 2010

Received



MacDonagh Boland Crotty MacRedmond Limited t/a Aon MacDonagh Boland  
is regulated by The Financial Regulator

Registered in Ireland, No. 51622, Directors and Offices: Malton Building, Leeson Upper Street, Dublin 1

## Appendix 7.7 Professional indemnity cover



Insurance Brokers  
Reinsurance Brokers  
Actuaries and Consultants  
Risk Management Consultants

WILLIS  
ONEWO WALK QUAY, SAMPSON IT  
DUBLIN 4

T: +353 1 661 8211  
F: +353 1 661 4389  
E: info@willis.ie  
W: www.willis.com/ireland

Our Ref: ABB/EXT/6603

Your Ref:

Date: 04 November 2010

### TO WHOM IT MAY CONCERN

Dear Sirs,

### Re: Professional Indemnity Insurance – Trinity College Dublin

We act as Insurance Brokers to Trinity College and confirm details of their Professional Indemnity insurance cover as follows:-

- **Insured Title** The University of Dublin Trinity College and Ghala Ltd. and TCD Ethics Committee and Trinity FM
- **Business Description** University
- **Renewal Date** 1<sup>st</sup> October 2011
- **Insurer** RSA Insurance Ireland Ltd.
- **Limit of Indemnity** €12,000,000 in the aggregate
- **Territorial Limits** Worldwide
- **Jurisdiction** Worldwide (subject to special conditions for North American claims)
- **Excess** €25,000 each and every claim
- **Principal Exclusions** Cover for Clinical Trials  
Medical Malpractice

The policy provides an indemnity against legal liability for claims arising from all of the Insured's activities as a University. This includes but is not limited to research activities.

Cover is subject to the terms, conditions and exceptions of the policy.

Yours sincerely

### ANN MARIE MURPHY

Client Service Executive, Corporate Finance  
DD: +353 (0) 1 639 6403  
F: +353 (0) 1 669 4475  
E: annmarie.murphy@willis.ie

### CHIEF EXECUTIVE

Director: John Dwyer, Vincent Sheil, Alan Byrne, Jim Lyons, David Callaghan, Martin Conroy, Martin Cooney, Brian Corbett, Mary Deane, Mark Doyle, Kevin Fitzmaurice, Bob Fitzgerald, Colin Greene, Gavin Healy, Lindsay Jamieson, John Leonard, Eoin Mahony, Roddy Mahon, Brian Murray, Declan O'Brien, Kevin O'Brien, Edward O'Donoghue, David O'Mahony, Joe O'Mahony, Aid O'Neil, Andrew Petherbridge, Peter Stanton, Shane Wall, Stephen Walsh

Registered in Ireland number 3812  
Registered office: OneWO Walk Quay, SAMPSON IT, Dublin 4  
Willis Risk Services (Ireland) Limited (trading as Willis) is

## Appendix 7.8 Public liability cover



Insurance Brokers  
Reinsurance Brokers  
Actuaries and Consultants  
Risk Management Consultants

WILLIS  
GRAND MELLOUAF, BARRON ST  
DUBLIN 4

T: +353 1 661 6211  
F: +353 1 661 4369  
E: info@willis.ie  
W: www.willis.com/ireland

TO WHOM IT MAY CONCERN

Our Ref: [AMMEXT 6403]

Your Ref: |

Date: [07 October 2010]

Dear Sirs,

**Re: Our Client - Trinity College Dublin**

We act as Insurance Brokers to the above named Client, and confirm details of their insurance cover as follows:-

- **Insured Title** Provost, Fellows & Scholars of the College of the Holy and Undivided Trinity of Queen Elizabeth near Dublin
- **Business Description** University
- **Renewal Date** 1<sup>st</sup> October 2011
- **Insurer(s)** RSA Insurance Ireland Ltd. (and Chartis Insurance Ireland Ltd. on excess loss layer)
- **Limits (of Indemnity)**
  - Public Liability: €30 million any one event.
  - Employers Liability: €32.5 million any one event (incl. of costs and expenses).

Subject otherwise to the terms, conditions and exceptions of the policies.

Should you have any queries please contact the undersigned.

Yours sincerely

**ANN MARIE MURPHY**  
Client Service Executive, Corporate Risks  
DD: +353 (0) 1 639 6403  
F: +353 (0) 1 669 4475  
E: annmarie.murphy@willis.ie

COMPANY  
Directors: John Barry, Richard Burt, Neil Byrne, Joe Byrne, David Cahill, Martin Casey, Mairéad Conroy, Brian Curran, Mary Conboy, Mark Doyle, John Fitzgerald, Bob Fitzpatrick, Colm Greene, Sarah Healy, Lenny Johnson, John Linnane, Kim Mahony, Frank McArdle, Brian Murphy, Declan O'Brien, Robert O'Brien, Eamon O'Connell, David O'Donnell, John O'Mahony, Neil O'Shea, Andrew Pennington, Peter Treweek, Shane Wall, Stephen Walsh.

Registered in Ireland number 15072  
Registered office: Grand Mill Quay, Dame St, Dublin 4  
Willis Risk Services Ireland Limited (trading as Willis) is  
a member of the Willis Group of Companies



## Appendix 7.9 Letter of invite

(on headed note paper)

Insert Name and Address of Patient

**Study Title:** A multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent and other forms of chlorhexidine gluconate which are in routine use, on central venous catheter-related infections in haemodialysis patients

Dear *(insert patient name)*

My name is Margaret McCann, I am a PhD student in the School of Nursing and Midwifery at Trinity College Dublin. I am conducting a research study as part of my doctoral studies and I would like to invite you to participate.

This trial is about the antiseptic agent that is used to clean your central venous catheter and the skin around your catheter exit site. This solution is called chlorhexidine gluconate. There are many different strengths of this solution available. Your dialysis unit currently uses 0.05% aqueous chlorhexidine gluconate solution/0.5% chlorhexidine gluconate in 70% alcohol solution *(delete as appropriate)*.

This trial will compare the solution currently used in your dialysis unit to a 2% chlorhexidine gluconate in 70% alcohol solution. The aim of the trial is to determine which strength of chlorhexidine gluconate is the most effective in preventing your catheter from becoming infected.

Before you decide to participate please read the enclosed information leaflet, which provides further detail on the trial. I have also enclosed three copies of the trial consent form. If you agree to participate you will need to sign these forms in my presence. I will also sign the three consent forms. I will keep one for my records, put the second copy into your medical notes and give you the third copy for your own records.

If you or members of your family require any further information on the study or need any issues clarified please do not hesitate to contact me. I will be visiting the dialysis unit during the days of your dialysis sessions and can also be contacted by mobile phone (0872897809).

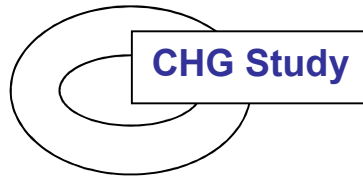
Thank you for giving this matter your consideration.

Yours sincerely,

---

Margaret McCann  
PhD Student  
School of Nursing and Midwifery, Trinity College Dublin  
Mobile: 0872897809 Email: mccannm1@tcd.ie  
EudraCT number 2010-019984-12 Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010/ISRCTN26577745 Clinical Sponsor/Chief Investigator:  
Dr. George Mellotte, Consultant Nephrologist, Adelaide & Meath Hospital,  
incorporating the National Children's Hospital, Tallaght, Dublin 12

## Appendix 7.10 Patient information leaflet



### Patient Information Leaflet

**Title of Study:** A multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent and other forms of chlorhexidine gluconate which are in routine use, on central venous catheter-related infections in haemodialysis patients

#### Information leaflet

You have been asked to participate because you receive haemodialysis using a central venous catheter. At each dialysis session your central venous catheter and skin around the catheter entry site are cleaned using an antiseptic agent called chlorhexidine gluconate.

The aim of this study is to find out which strength of chlorhexidine gluconate solution is the most effective in preventing central venous catheters from becoming infected. This study may not be of benefit to the individual patient. The study is being conducted in a number of dialysis centres in Ireland including your unit. I would like you to take part in the study.

This leaflet contains more information about the study. Please read it carefully and feel free to ask any questions before deciding whether to take part.

#### Why is the study being done?

Patients with central venous catheters are at a higher risk of developing infections, which can cause serious illness, increased length of hospitalization and even death. The use of such catheters is common in patients whose kidneys have failed.

Preventing catheter infections in dialysis patients will result in better patient outcomes and reduce healthcare costs. Chlorhexidine gluconate, an antiseptic skin cleanser is used to prevent catheter infection. Dialysis units in Ireland use different strengths of chlorhexidine gluconate such as:

- 0.05% aqueous chlorhexidine gluconate solution
- 2% aqueous chlorhexidine gluconate solution and
- 0.5% chlorhexidine gluconate in 70% alcohol solution.

However, international guidelines recommend the use of a 2% chlorhexidine gluconate in 70% alcohol solution. While there are various strengths of chlorhexidine gluconate in use there is no research evidence to show which strength is the most effective.

The study aims to resolve this uncertainty by determining which strength of chlorhexidine gluconate is the most effective in preventing central venous catheter-related infections in dialysis patients.

### **How will the study be carried out?**

Patients who are suitable for the study will receive an information pack during their visit to the dialysis centre. This information pack will include a letter inviting the patient to participate in the study, an information leaflet on the study and three copies of the study's consent form.

Now that you have received this information pack you should read it carefully and decide on whether to take part in the study. You can inform me of your decision when I next visit you in the dialysis unit. Once you agree to participate you will have to sign three copies of the consent form in my presence, give two copies to me and keep the third copy for yourself.

The study will use a research process called a randomised trial, in which patients are randomly allocated to different strengths of chlorhexidine gluconate solution in ways that reduce bias.

On the same day that you have signed the consent form you will be randomised to receive either 2% chlorhexidine gluconate in 70% alcohol or the chlorhexidine gluconate solution that is currently used in your dialysis centre. You and healthcare staff in your dialysis centre will not know which strength of chlorhexidine gluconate you are to receive, until after you have entered the study.

Following this, as per normal dialysis procedures when connecting to and disconnecting from the dialysis machine the hubs of your central venous catheter will be cleaned using the chlorhexidine gluconate solution that you have been assigned. When the dressing over your catheter has to be changed the skin around the catheter entry site will also be cleaned with this solution.

You will be monitored monthly for infection and information relating to these events will be collected from your medical records and analysed. You will be removed from the study if you develop an infection. Otherwise you will remain in the study for 12 months.

### **Why have I been offered entry to the study?**

You have been offered entry to the study because your Nephrology Consultant and Dialysis Clinical Nurse Manager after assessing your medical history believe that you meet the entry requirements for the study. The entry requirements for the study are as follows:

- You must be over 18 and require haemodialysis for chronic kidney disease
- You must use a permanent tunnelled central venous catheter
- You must have a catheter that was inserted at least four weeks prior to entry into the study

### **Could I be excluded from participating in the study?**

Yes you could. Your Nephrology Consultant and Dialysis Clinical Nurse Manager could decide that you cannot be in the study if any of the following are true:

- Your central venous catheter is used for purposes other than haemodialysis
- You have a known allergy to chlorhexidine gluconate solutions
- Your central venous catheter is made of material that can be damaged by solutions used in the study
- Your central venous catheter or central venous dressing are not standard practice for your unit
- If you are unable to give informed consent

### **What will happen to me if I agree to take part?**

The antiseptic solutions used in the study do not involve any invasive procedures and will simply be applied to the skin around your central venous catheter and onto the catheter itself. Data collected for the study will be obtained from your medical records.

When your catheter dressing is being changed by the dialysis nurse the skin around the catheter entry site will be cleaned using the chlorhexidine gluconate solution that has been assigned to you. The procedure for changing your catheter dressing remains as per normal dialysis care. If you have been assigned to the 2% chlorhexidine gluconate in 70% alcohol solution the skin around your catheter exit site will be cleaned using a product called ChlorPrep® with Tint.

During the process of connecting and disconnecting you to dialysis the dialysis nurse will clean the hubs of your catheter using the chlorhexidine gluconate solution that has been assigned to you. The actual procedure of connecting and disconnecting for dialysis is as per normal dialysis care. If you have been assigned to the 2% chlorhexidine gluconate in 70% alcohol solution your catheter will be cleaned using a product called Sani-Cloth CHG 2% medical device wipe.

Every month I will review your medical records for evidence of catheter-related infection. If you develop a catheter infection during the study your medical management will be as per the normal management of a catheter-related infection.

Information relating to the infection and its management will be collected from your medical records and analysed. Your participation in the study will be discontinued if you develop a catheter infection. If you do not develop an infection you will remain in the study for 12 months.

### **What do I have to do as part of the study?**

Dialysis nurses will be educated about the study and mechanisms will be put in place to ensure that they are aware of the solution to be used on your catheter.

One of these mechanisms will require some input from you. You can assist in maintaining dialysis nurses awareness of the study by reminding them of the type of cleaning solution to be used on your central venous catheter and the skin around your catheter exit site.

**What are the benefits of being in this study?**

There is no guarantee that the chlorhexidine gluconate solution used on your catheter will prevent it from getting infected. However, findings from the study will benefit others by determining which strength of chlorhexidine gluconate is the most effective in preventing catheter infection.

Findings from the study will also inform national and international practice guidelines on the most effective antiseptic agent for cleaning central venous catheters in patients on haemodialysis.

**Are there any risks in this study?**

The chlorhexidine gluconate antiseptic cleaning solutions used in the study are not new treatments but have been used in dialysis centres in Ireland and Europe for a number of years. Your dialysis centre already uses chlorhexidine gluconate to clean your central venous catheter. As your central venous catheter is already been cleaned by a chlorhexidine gluconate solution you are unlikely to react to the chlorhexidine gluconate agent during the course of the study. Allergic or irritation skin reactions have rarely been report with chlorhexidine gluconate.

Chlorhexidine gluconate product Chloraprep® with Tint contains alcohol. If you have been assigned to receive this product there is a risk that you may develop an allergic or irritation skin reaction to the alcohol. The chances of this occurring are rare.

Every time your catheter dressing is changed the dialysis nurse will assess the skin around the catheter entry site for any signs of a reaction to the solution. If you should develop a hypersensitive reaction to chlorhexidine gluconate or alcohol you will be withdrawn from the study, your physician will be informed and an alternative antiseptic cleansing agent will be prescribed.

**Can I leave the study at any time?**

Yes you can. You do not have to give any reason for leaving and your withdrawal from the study will not impact on the treatment that you will receive in the dialysis centre.

**What are our responsibilities to you as investigators?**

On completion of the overall study you will be informed of its findings through a patient newsletter.

**What happens at the end of the study?**

If you are assigned to use 2% chlorhexidine gluconate in 70% alcohol (Chloraprep® with Tint and Sani-cloth CHG 2% medical device wipe) at the end of the study the dialysis nurse will discontinue using this solution. Your central venous catheter care plan will be changed to the chlorhexidine gluconate solution that is normally used in your dialysis unit.

If you are assigned to receive the chlorhexidine gluconate solution that is routinely used in your centre at the end of the study your central venous catheter will continue to be cleaned using this solution.

At the end of the study I will analysis the data to determine which strength of chlorhexidine gluconate is the most effective in preventing central venous catheter-related infections.

**Who will see my medical information and is it kept private?**

I will be the only person collecting information from people taking part in the study. I will store this information in a secure place. At the start of the study I will need to see your medical records and collect information about your condition, date of birth, and dialysis prescription. I will also review your medical records once a month for information relating to any episode of catheter infection you may develop during the course of the study.

I will code all this information so it will not be linked to your name. As a result no one will be able to identify you. This coded information will be sent to a statistician to analysis the data. The information will remain coded and the statistician will not be able to identify you.

All information relating to you that is collected during the course of the study will be kept in a locked cabinet for five years. After this period this information will be destroyed by shredding all relevant documentation. Information gained from the study will be used by me at a later date to expand it to a multinational study.

Findings from the study will be presented at national and international scientific conferences and will be published in scientific journals. You will not be named and no one will be able to identify you in these papers.

In order to ensure that the trial has been conducted carefully the Department of Health and the Irish Medicines Boards may require access to your records.

**Who is funding this study?**

A company named CareFusion will supply the 2% chlorhexidine gluconate in 70% alcohol solution which will be used to clean the skin around your catheter exit site. This product is called Chloraprep. In addition, a company called PDI will provide 2% chlorhexidine gluconate in 70% alcohol wipes which will be used to clean the central venous catheter. This product is called Sani-cloth CHG 2%. These companies will have no influence over the conduct, analysis or reporting of the study.

**Who is organising the study?**

Dr. George Mellotte, Consultant Nephrologist, The Adelaide & Meath Hospital, Incorporating the National Children's Hospital, Tallaght, Chief Investigator and Clinical Trial Sponsor

Margaret McCann, School of Nursing and Midwifery, Trinity College Dublin, PhD Student

Professor Mike Clarke, Adjunct Professor, Dr, Fidelma Fitzpatrick, Consultant Microbiologist and Professor Cecily Begley, Academic Supervisors

Professor Alan Watson, St. Vincent's University Hospital and Beacon Renal Clinic, Principal Investigator

**Who has given permission for this study to take place?**

Approval for this study has been given by the hospital Research Ethics Committee and the Irish Medicines Board.

**How do I join the study?**

You can join the study by completing and signing the three enclosed consent forms at your next dialysis session. I will sign all three copies, keep one copy for my records, one copy for your medical chart and give the third copy to you.

**Where can I get more information?**

Please contact me with any questions you or your family may have now or at any time in the future.

**Margaret McCann**

**PhD Student**

**School of Nursing and Midwifery, Trinity College Dublin**

**24 D'Olier Street, Dublin 2**

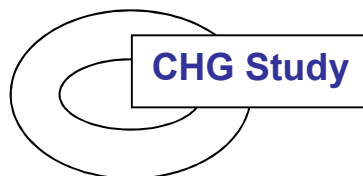
**Tel: 087 2897809**

**Email: [mccannm1@tcd.ie](mailto:mccannm1@tcd.ie)**

**Thanks you for your help**

EudraCT number 2010-019984-12 Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010/ISRCTN26577745 Clinical Sponsor/Chief Investigator: Dr. George Mellotte, Consultant Nephrologist, Adelaide & Meath Hospital, incorporating the National Children's Hospital, Tallaght, Dublin 12

## Appendix 7.11 Consent Form



**Project Title:** A multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent versus other forms of chlorhexidine gluconate which are in routine use, on central venous catheter-related infections in haemodialysis patients

Please tick the following:

This study has been explained to me. Yes No

I understand what will happen if I agree to be part of this study. Yes No

I confirm that I have read or had read to me the Patient Information Leaflet and I understand its contents. Yes No

I confirm that I have read or had read to me this consent form and I understand its contents. Yes No

I have had ample opportunity to ask questions, all of which have been satisfactorily answered. Yes No

I agree to join the chlorhexidine gluconate study. Yes No

I understand that my participation in this study is entirely **voluntary** and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care. Yes No

I understand that my records will be viewed by the researcher and I give my permission for this. Yes No

I understand that my identity will remain confidential at all times. Yes No

I am aware of the potential risks of this research study. Yes No

I have been given a copy of the Patient Information Leaflet and this Consent form for my records. Yes No



**FUTURE USE OF CODED DATA:**

I agree that I will not restrict the use to which the results of this study may be put. I give my approval that unidentifiable data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body, which safeguards the welfare and rights of people in biomedical research studies) Yes No

Patient \_\_\_\_\_  
Signature and dated Name in block capitals

To be completed by the Principal Investigator or his/her nominee.

I the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the procedures to be undertaken and any risks that may be involved as well as the possible benefits. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

\_\_\_\_\_  
**Signature**                      **Name in Block Capitals**                      **Qualification**  
**Date**

3 copies to be signed: 1 for patient, 1 for the Researcher and 1 for hospital records.

EudraCT number 2010-019984-12 Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010/ISRCTN26577745 Clinical Sponsor/Chief Investigator: Dr. George Mellotte, Consultant Nephrologist, Adelaide & Meath Hospital, incorporating the National Children's Hospital, Tallaght, Dublin 12

## Appendix 8.1 Research sites dialysis build environment

Descriptor	OA	OV	OB
Hospital beds (N)	629	479	Not applicable
Dialysis patients at start of trial (N)	89	77	146
Patients with CVC at start of trial (N)	61	46	89
Number of dialysis nurses at start of trial (N)	32	18	26
Routine CHG antiseptic solution	0.5% CHG in 70% isopropyl alcohol	0.05% aqueous CHG	0.5% CHG in 70% isopropyl alcohol
Year unit was built	1998	Ground floor unit 2006 4 <sup>th</sup> floor unit 1999	2004
Patient to nursing staff ratio	1:3	1:3	1:3
Dialysis stations plus isolation stations (N)	16	17	31
Isolation rooms (N)	4	4	1
Dialysis stations in isolation room (N)	1	2 stations in 3 rooms 1 station in 1 room	1
Type of station (chair or bed)	Predominately beds	Chair	Chair
Length of dialysis station Includes chair & dialysis machine <sup>1</sup>	1727-1955mm	1422-1168mm	1701mm
Space between dialysis stations <sup>1</sup>	302-812mm	406-660mm	914mm
Space for working at side of chair or bed <sup>1</sup>	787-812mm	482-711mm	1244mm
Distance between chair/bed centres <sup>1</sup>	2413-3048mm	1930-2184mm	2387mm
Mechanism used to separate dialysis stations	Curtains	Curtains	Glass barrier
Trolley used for aseptic technique	Bed table	Stainless steel trolley	Stainless steel trolley

<sup>1</sup>Lowest and highest measurement

The dialysis unit at research site OV consists of two centres, located on different floors of the hospital. The main dialysis centre (9 dialysis stations) is located on the ground floor and when compared to the other research sites is the most recently built unit. This unit is designated for outpatient dialysis only. The second centre (8 dialysis stations), located on the 4<sup>th</sup> floor, is the second oldest dialysis facility and caters for both outpatient and admitted dialysis patients. The largest unit can be found at research site OB. This unit has three floors, with two floors consisting of two wings. Each wing has six dialysis stations.

Research site OB, when compared to the other sites has the greatest dialysis space. Both OA and OV research sites had a similar distance between dialysis stations, with site OV having the smallest dialysis stations and the smallest bedside space.

Dialysis stations consist of the dialysis machine, dialysis chair or bed, bed side table and ancillary equipment or supplies needed for dialysis treatment. In relation to the build environment, haemodialysis guidelines recommend that dialysis stations should be in increments of three; only one of the research sites met this recommendation (OB).

Only one of the research sites (OA) provides a 7 day dialysis services, all operate from 7.30 to 20.30 and use each station for three patients per day, which is higher than that recommended by UK Renal Association haemodialysis guidelines (The Renal Association 2009).

## Appendix 8.2 Research site routine CVC care

Descriptor	OA	OV	OB
<b>Routine CHG antiseptic solution</b>	0.5% CHG in 70% isopropyl alcohol	0.05% aqueous CHG	0.5% CHG in 70% isopropyl alcohol
<b>One person/two person connect/disconnect</b>	1 RGN <sup>1</sup>	1 RGN	1 RGN
<b>Standard CVC dressing</b>	Dry gauze Mepore Transparent Tegaderm	Dry gauze Mepore Transparent IV 3000	Dry gauze Mepore Transparent IV 3000 Tegaderm
<b>Frequency of dressing change</b>	Weekly or patient dependent	Every dialysis session	Every dialysis session
<b>Use CVC dialysis packs</b>	Yes	Yes	Yes
<b>When is CVC dressing changed</b>	Before dialysis	Before dialysis	Before dialysis  Separate procedure
<b>Standard Catheter locking solution</b>	Duralock 46.7%	Duralock 30%	Duralock 30%
<b>CVC care maintenance guidelines</b>	Yes	Yes	Yes
<b>Protocol on obtaining blood cultures</b>	Yes	Yes	No
<b>Protocol on obtaining exit site swab</b>	Yes	Yes	Yes

<sup>1</sup>RGN, Registered General Nurse

Routine CVC care practices were standardised across all three units and underpinned by evidence-based practice guidelines. It was standard practice to use one RGN to connect and disconnect patients from dialysis. All three units used CVC on and off sterile dialysis packs, which contained all the relevant equipment necessary to connect and disconnect patients to and from dialysis. Standard CVC dressings consisted of a choice between dry gauze and transparent polyurethane semi-permeable dressing, the decision on which dressing to use was patient dependent. Changing of the CVC dressing was a separate procedure from connecting the patient to dialysis and occurred prior to the patient being connected to dialysis. The standard CVC locking solution was Duralock; one site (OA) used a different concentration of this solution. All three units used heparin for patients who could not tolerate Duralock or who

had difficulties with CVC blood flow. One of the units (OA) used urokinase for a small number of patients who experienced ongoing CVC flow problems. For patients who experienced a lack of blood flow from the CVC catheter it was standard practice to lock the CVC catheter for 30-45 minutes, using a tissue plasminogen activator. The aim of this medication was to remove any clots impeding blood flow from the CVC.

Due to lack of space within the dialysis unit, one unit (OA) used patients' bed tables as the aseptic technique trolley. This table was also used for meals and holding other materials during dialysis. Although this was not an ideal situation it reflects the reality of what occurs in clinical areas that are under increasing pressure for space. Bed tables were cleaned and disinfected between each patient and prior to connecting and disconnecting patients from dialysis. This type of issue reflects the messy world of clinical practice that pragmatic trials encounter and places the use of trial interventions within the context of what really takes place within clinical settings.

The types of CVC catheters used across the three units. All permanent cuffed CVCs were compatible with CHG and alcohol.

## Appendix 8.3 Permanent cuffed CVCs per research site

Descriptor	OA	OV	OB <sup>1</sup>
<b>Permanent cuffed CVC</b>	Palindrome catheter	ASH Split Permcath Catheter	Palindrome catheter
			Mahurkar
			Quinton
			Hemo-flow
			ASH Split Perm Catheter
			Jetflow
<b>Compatible with CHG</b>	Yes	Yes	Yes
<b>Compatible with alcohol</b>	Yes	Yes	Yes

<sup>1</sup> Patients at research site OB used various permanent cuffed CVC as they were referred to the unit from a variety of parent hospital dialysis units (n=6). All permanent cuffed CVCs were compatible with CHG and alcohol.

## Appendix 8.4 Research sites: letters of permission

Elm Park  
Dublin 4  
Tel: +353 1 221 4000  
Fax: +353 1 221 4001  
Web: www.st-vincent.ie

**St. Vincent's University Hospital**

DEPARTMENT OF NEPHROLOGY  
PH: 221 4493 FAX: 221 4136

Ms Margaret McCann  
Lecturer  
School of Nursing and Midwifery  
University of Dublin  
Trinity College  
2 D'Olier Street  
Dublin 2

Date: 22/10/09

RE: Randomised control trial on chlorhexidine gluconate

Dear Ms McCann

Thank you for your letter of the 12th October. As per discussion on September the 18<sup>th</sup> I am happy that you access patients at the Beacon Renal Clinic with a view to participating in this study. The one proviso is that there is a documented IRB approval for your parent institution and approved consent form. Pending a review of these, I would be happy for you to start.

Yours sincerely,

  
Prof. Alan Watson  
Consultant Renal Physician

  
**St Vincent's HealthCare**  
A HSE GROUP  
GROUP CHIEF EXECUTIVE: Mr. Nicholas C. Jensen  
BOARD OF DIRECTORS: Chairman Prof. Noel O'Brien, Mr. Edward J. Bergin, Dr. Eugene Butler, Mr. Gerard English, Prof. W. S. Eccles, Mr. Nicholas C. Jensen, Mr. Ian Lymbury, Dr. Anne MacDonagh, Ms. Eileen McCarroll, Mr. Patrick Minahan, Mr. Michael Naughton, Prof. Diarmuid O'Donoghue, Dr. Phaedra O'Leary, Mr. William R. Quinn, Mr. Eamon Scully, Dr. Michael Sweeney  
Registered in Dublin, Ireland. Company Registration No. 222865. Registered Office: Elm Park, Dublin 4.



Margaret McCann <mccannm4@tcd.ie>

---

## permission to access haemodialysis patients in SVUH

Watson, Alan (Dialysis) <A.Watson@st-vincent's.ie>  
To: Margaret McCann <mccannm4@tcd.ie>

10 June 2011 12:28

fine

---

**From:** Margaret McCann [mailto:mccannm4@tcd.ie]  
**Sent:** 09 June 2011 15:32  
**To:** Watson, Alan (Dialysis); Hollan John (OFFICE)  
**Cc:** Margaret McCann  
**Subject:** permission to access haemodialysis patients in SVUH

Dear Professor Watson and Dr Hollan

while I have received permission from you to access your patients in Beacon I have no record of such permission for patients attending the dialysis unit in SVUH. In order to complete my paper work for the trial master file I need permission from you both to access patients under your care who attend SVUH dialysis unit (email confirmation will be sufficient).

Kind regards  
Margaret

—  
Margaret McCann  
Lecturer  
School of Nursing and Midwifery  
Trinity College Dublin  
24 D'Olier Street  
Dublin 2  
Ireland  
Tel +35318968542  
Email Disclaimer located at following link:

[http://www.stvincents.ie/Departments/Information\\_and\\_Communication\\_Technology/ICT\\_Department/Email\\_Disclaimer.htm](http://www.stvincents.ie/Departments/Information_and_Communication_Technology/ICT_Department/Email_Disclaimer.htm)





Margaret McCann <mccannm4@tcd.ie>

---

## Chlorhexidine trial

---

Holan John [OFFICE] <J.Holan@svuh.ie>  
To: "mccannm4@tcd.ie" <mccannm4@tcd.ie>

15 April 2011 07:32

Dear Margaret,

Sincere apologies for the delay in getting back to you. Please feel free to access any of the patients in my care in the Beacon (I don't have too many - most of them are Alan's). Best of luck with your study.

Kind regards,  
John

John Holan MB, MRCP, PhD  
Consultant Nephrologist  
St. Vincent's University Hospital  
Elm Park  
Dublin 4  
IRELAND

Ph: +353 1 221 4488  
Fax: +353 1 221 4136  
E-mail: [jholan@svuh.ie](mailto:jholan@svuh.ie)

Email Disclaimer located at following link:

[http://www.stvincents.ie/Departments/Information\\_and\\_Communication\\_Technology ICT Department/Email\\_Disclaimer.htm](http://www.stvincents.ie/Departments/Information_and_Communication_Technology ICT Department/Email_Disclaimer.htm)

---



Margaret McCann <mccannm4@tcd.ie>

---

## permission to access haemodialysis patients in SVUH

---

Hollan John (OFFICE) <J.Hollan@svuh.ie>  
To: Margaret McCann <mccannm4@tcd.ie>

9 June 2011 16:47

Hi Margaret,

Please feel free to go ahead on my patients in SVUH.

Kind regards,

John Hollan

John Hollan MB, MRCP, PhD

Consultant Nephrologist

St. Vincent's University Hospital

Elm Park

Dublin 4

IRELAND

Ph: +353 1 221 4493

Fax: +353 1 221 4136

E-mail: [j.hollan@svuh.ie](mailto:j.hollan@svuh.ie)

---

**From:** Margaret McCann [mailto:mccannm4@tcd.ie]  
**Sent:** 09 June 2011 15:32  
**To:** Watson, Alan (Dialysis); Hollan John (OFFICE)  
**Cc:** Margaret McCann  
**Subject:** permission to access haemodialysis patients in SVUH

THIS INFORMATION MUST NOT BE USED FOR  
PRESS RELEASES OR INVITING PURPOSES



**THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN**  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT DUBLIN 24, IRELAND  
TELEPHONE: +353 1 4142000

Dr Margaret McCann,  
Lecturer,  
University of Dublin,  
Faculty of Health Science School of Nursing and Midwifery,  
Geo Building,  
24 D'Olier Street,  
Dublin 2.

**Department of Nephrology**

Medical Director / Consultant Nephrologist – Dr. George Mellito  
Consultant Nephrologist – Dr. Catharina Wall  
Dr. Mellito's Sec: 01 414 2445  
Dr. Wall's Sec: 01 414 2551  
george.mellito@amh.ie  
Unit Fax: 01 414 2564

Date: 20.10.09

Dear Margaret,

Thank you for your letter dated 12 October 2009. I would have no issues including any of my patients in AMNCH or Beacon Clinic for randomised controlled trial of Chlorhexidine gluconate.

If there are ethics requirements for this I would advise you to organise same. The decision regarding ethics and background for that I will leave to your expertise.

Yours sincerely,

  
Dr. George J. Mellito, MB, FRCPI, M. Sc., (09958)  
Consultant Nephrologist & Senior Lecturer in Medicine

Direct Dial Directory  
Haemodialysis Unit: 414258 Peritoneal Dialysis Unit: 414437 Renal Day Ward: 414404 Renal Ward: 414405  
Admin: 414253, 414440, 414298 Renal Reg. On-Call: 087-0175325

02/09/09

THIS INFORMATION MUST NOT BE USED FOR  
PROMOTIONS OR REVENUE PURPOSES



**Ms Margaret McCann,**  
Lecturer,  
School of Nursing and Midwifery,  
Department of Health Sciences,  
24 D'Olier Street,  
Dublin 2.

**THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN**  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL

TEL: 01 452 1411  
TELEPHONE +353 1 452 1411

**Department of Renal Medicine.**  
Medical Director: Dr. George Mellett  
Consultant Nephrologist: Dr. Catherine Wall  
Dr. Mellett's Sec: 414266  
Dr. Wall's Sec: 414273  
Unit Fax No: 414284

Date: 30<sup>th</sup> March 2010

Dear Margaret,

Thank you for your letter regarding a request to approach my patients for inclusion in a clinical trial. I am more than happy for you to proceed with this. You can take it from this letter that you have my written permission to access my patients regarding this study. I would of course appreciate a copy of the study protocol and the letter of support from the Ethics Committee.

Yours sincerely,

**Dr. Catherine Wall, M.B., M.Sc., F.R.C.P.I., (MCN 17411)**  
Consultant Nephrologist and General Physician.

Direct Dial Directory  
Haemodialysis Unit: 414235    Peritoneal Dialysis Unit: 414231    Renal Day Ward: 414264    Renal Ward: 414232  
Admin: 414233, 414245, 414230    Renal Reg. On-Call: 087-8170325



Margaret McCann <mccannm4@tcd.ie>

---

## Chlorhexidine Gluconate Trial

---

Leavey, Sean <Sean.Leavey@hse.ie>  
To: Margaret McCann <mccannm4@tcd.ie>  
Cc: "Walker, Dr Frank" <Dr.Frank@hse.ie>, "Abernethy, Elizabeth" <Elizabeth.Abernethy@hse.ie>

30 March 2011 15:28

Margaret please feel free to approach the Waterford patients in beacon renal who have CVCs...thanks

---

**From:** Margaret McCann [<mailto:mccannm4@tcd.ie>]  
**Sent:** 29 March 2011 15:36  
**To:** Leavey, Sean  
**Cc:** Margaret McCann  
**Subject:** Chlorhexidine Gluconate Trial

Dear Dr Leavey

As you know I am conducting a clinical trial comparing different strengths of chlorhexidine gluconate in the maintenance and care of haemodialysis patients CVCs.

As you are aware Waterford dialysis unit couldn't participate as they were already using the experimental intervention (2% chlorhexidine gluconate in 70% alcohol) and reported very positive results.

The research is currently taking place in AMNCH and Beacon Renal. There are patients in Beacon Renal who are from the Waterford dialysis units, I am therefore seeking your permission to access those patients who are eligible for the study.

If you require any further information please do not hesitate to contact me (my mobile is 0872897809)

I look forward to hearing from you



Margaret McCann <mccannm4@tcd.ie>

## Chlorhexidine gluconate trial in Beacon Renal

Yvonne O'Meara <yomeara@mater.ie>  
To: Margaret McCann <mccannm4@tcd.ie>

1 April 2011 13:46

Hi Margaret  
I am happy for my patients to participate.  
Yvonne

Dr Yvonne O'Meara, M.D., F.R.C.P.I.  
Consultant Nephrologist / Senior Lecturer in Medicine  
Mater Misericordiae University Hospital / UCD School of Medicine  
44 Eccles Street  
Dublin 7  
Ireland  
Tel. +353 1 716 4566  
Fax. +353 1 716 4535  
email [yomeara@mater.ie](mailto:yomeara@mater.ie)

---

**From:** Margaret McCann [<mailto:mccannm4@tcd.ie>]  
**Sent:** 30 March 2011 17:50  
**To:** Yvonne O'Meara  
**Cc:** Margaret McCann  
**Subject:** Chlorhexidine gluconate trial in Beacon Renal

Dear Yvonne

As you know I am conducting a clinical trial comparing different strengths of chlorhexidine gluconate in the maintenance and care of haemodialysis patients with CVCs.  
The research is currently taking place in AMNCH and Beacon Renal. Dr George Melotte is Clinical Sponsor.

Professor Watson, medical director of Beacon Renal has granted me access to the unit.  
Beacon Renal uses 0.5% chlorhexidine gluconate in 70% alcohol and this is being compared to 2% CHG in 70% alcohol. The trial has received REC and IMB approval.

I am in the process of recruiting patients and am seeking your permission to access patients under your care who may attend Beacon Renal and who are eligible for the trial.

If you require any further information please do not hesitate to contact me (my mobile is 0872897809)

I look forward to hearing from you

Kind regards  
Margaret McCann

—  
Margaret McCann  
Lecturer  
School of Nursing and Midwifery  
Trinity College Dublin  
24 D'Olier Street  
Dublin 2



Margaret McCann <mccannm4@tcd.ie>

## Irish medicine board approval for chlorhexidine gluconate trial

3 messages

Margaret McCann <mccannm4@tcd.ie>  
To: peterconlon@beaumont.ie

24 March 2010 16:11

Dear Peter

I will be submitting my application for Irish Medicine Board approval in early April. I am required as part of this application process to submit a short CV from each local site Principal investigator. I would be grateful if you could email me a short CV. I need this before Friday 2nd April.

By the way did you get a chance to discuss this trial at the renal executive or would I be better off sending individual letters to each consultant looking for formal written permission to access their patients?

Kind regards  
Margaret

Margaret McCann  
Lecturer  
School of Nursing and Midwifery  
Trinity College Dublin  
24 D'Olier Street  
Dublin 2  
Ireland  
Tel: +35318968542

peterconlon@beaumont.ie <peterconlon@beaumont.ie>  
To: Margaret McCann <mccannm4@tcd.ie>

24 March 2010 16:21

> Each consultant has agreed to allow patients participate

pc  
(Quoted text hidden)

\*\*\*\*\* DISCLAIMER \*\*\*\*\*

The opinions, conclusions and other information expressed in the above message, or contained within attachments to the above message, are not given or endorsed by Beaumont Hospital unless otherwise indicated by an authorised representative independent of this message.

This e-mail message and any files transmitted with it are confidential and intended solely for the use of the individual or entity to whom they are addressed. If you have received this e-mail in error please notify the system manager.

This e-mail has been scanned for viruses.

Margaret McCann <mccannm4@tcd.ie>  
To: peterconlon@beaumont.ie

24 March 2010 16:29

THIS DOCUMENT MUST NOT BE USED FOR  
PROMOTIONAL OR COMMERCIAL PURPOSES



**THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN**  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL

THE ADELAIDE & MEATH HOSPITAL  
TELEPHONE: +353 1 4142000

**Office of the Director of Nursing**  
**Phone: 4142154 Fax: 4142057**  
e-mail: [ann.donovan@amh.ie](mailto:ann.donovan@amh.ie)

3<sup>rd</sup> November 2009

Ms. Margaret McCann,  
Lecturer,  
Trinity College,  
School of Nursing & Midwifery,  
24 D'Olier Street,  
Dublin 2.

Dear Ms. McCann,

I refer to your letter dated the 12<sup>th</sup> October in relation to your studies as part of your PhD.

I can confirm that you have permission to undertake the randomised trial as detailed in that letter.

I wish you well with your studies.

Yours sincerely,

Ann Donovan  
Director of Nursing

c.c. Cesira McCrohan, CNM2, Haemodialysis Unit  
c.c. Charlotte McMenamin, ADON





Ms. Margaret McCann  
Lecturer and PhD Candidate  
School of Nursing and Midwifery  
Trinity College Dublin  
24 D'Olier Street  
Dublin 2

11<sup>th</sup> November 2010

**Re: Request for written permission to access nursing staff  
at Beacon Renal for Randomised Controlled Trial on  
Chlorhexidine Gluconate**

Dear Ms. McCann

I wish to confirm receipt of your letter I received on the 8<sup>th</sup> March 2010 and I have considered your request and I am willing to support your application to access nursing staff in Beacon Renal Clinic for your study regarding the above.

Yours sincerely,

Raj Ramkaun  
Clinical Nurse Manager 3

Elm Park  
Dublin 4  
Tel: +353 1 221 4000  
Fax: +353 1 221 4001  
Web: www.st-vincents.ie

# St. Vincent's University Hospital

Department of Nursing

Ms. Margaret McCann,  
Lecturer,  
School of Nursing & Midwifery,  
Trinity College,  
Dublin 2.

17<sup>th</sup> February 2010.

**Re: Request for written permission to access St. Vincent's Dialysis Unit for randomized Controlled Trial on Chlorhexidine Gluconate**

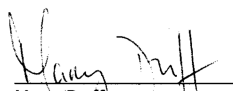
Dear Ms. McCann,

I wish to confirm receipt of your letter I received on the 16<sup>th</sup> October last and I have considered your request and I am willing to support your application to access nursing staff in Dialysis for your study regarding the above. Fortunately, there is no need to request Ethics approval to access nursing staff.

However, regarding the Renal Dialysis study itself and contacting patients in the Hospital, in order for this to be carried out at this institution you must now apply for ethical approval. Please contact the Ethics office, St. Vincent's University Hospital to obtain the forms needed to submit for approval.

I look forward to receiving further communication in the near future and should you require any further assistance please do not hesitate to contact me.

Yours sincerely,

  
Mary Duff  
Director of Nursing



**St. Vincent's Healthcare**

**GROUP CHIEF EXECUTIVE:** Mr. Nicholas C. Jermyn

**BOARD OF DIRECTORS: Chairman:** Prof. Noel Whelan, Mr. Edmond J. Bergin, Sr. Eugene Butler, Ms. Louise English, Prof. M. X. FitzGerald, Mr. Nicholas C. Jermyn, Mr. Joe Leyden, Sr. Anne MacEaney, Ms. Gemma McCrohan, Mr. Patrick Meade, Mr. Michael Meagher, Prof. Diarmuid O'Donoghue, Dr. Risteárd Ó Laoide, Mr. William R. Quinlan, Mr. Conor Sexton, Dr. Michael Somers.

Registered in Dublin, Ireland. Company Registration No: 338585 Registered Office: Elm Park, Dublin 4.

## Appendix 8.5 IMB approval



IRISH MEDICINES BOARD

2<sup>nd</sup> July 2010

Adelaide and Meath Hospital,  
Tallaght,  
Dublin 24.

### EUROPEAN COMMUNITIES (CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE) REGULATIONS, 2004

**RE: CT number: CT 900/493/1 - Chlorhexidine Gluconate/Isopropyl Alcohol**  
**Case number: 2082957**  
**EudraCT number: 2010-019984-12**  
**Protocol number: AMNCH-TCD-CHG-1-2010**  
**Title of trial: A multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent versus other forms of chlorhexidine gluconate which are in routine use, on central venous catheter-related infections in haemodialysis patients**

Dear Sirs,

The Irish Medicines Board has considered the application dated 12<sup>th</sup> April 2010 seeking authorisation to conduct the above clinical trial.

On the basis of the evidence available, the application is acceptable.

Please note that the date of this letter is the date of authorisation of the trial.

Yours sincerely,

Sinead Murphy  
A person authorised in that  
behalf by the said Board

Bord Leigheasra na hÉireann  
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2  
Tel: 353-1-676 4971 Fax: 353-1-676 7836  
Website: www.imb.ie

AUT-F0010-2

## Appendix 8.6 Research ethics committee approval

THIS NOTE/PAPER MUST NOT BE USED FOR PRESCRIPTIONS OR MEDICINE PURPOSES



**THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN**  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL

Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amhch.ie  
Secretariat Fax 4142371

TALLAGHT, DUBLIN 24, IRELAND  
TELEPHONE: +353 1 4142000

Ms. Margaret McCann  
Lecturer  
School of Nursing & Midwifery  
Trinity College Dublin  
24 D'Olier Street  
Dublin 2

July 21<sup>st</sup> 2010

**REC reference: 2010/27/03**

*(Please quote REC reference and EudraCT number on all correspondence)*

**Re: A Multicentre Randomised trial Comparing the Effects of 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol versus Other Forms of Chlorhexidine Gluconate which are in Routine Use on Central Venous Catheter Related Infections in Haemodialysis Patients.**

Dear Margaret,

Thank you for your letter dated June 14<sup>th</sup> 2010 which you sent in response to the Committee's letter of May 20<sup>th</sup> 2010.

The Chairman of the Committee has reviewed your response and has given ethical approval on behalf of the Committee. The following sites have been approved:

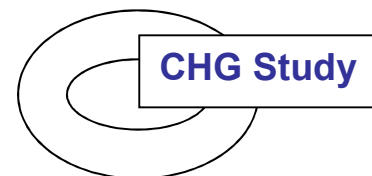
- Adelaide & Meath Hospital, Dublin, incorporating the National Children's Hospital.
- The Beacon Renal Medical Care,
- St. Vincent's University Hospital.

Full ethical approval is now in place for this study.

Yours sincerely,

Ms. Ursula Ryan  
Secretary  
SJH/AMNCH Research Ethics Committee

## Appendix 8.7 Randomisation instructions



### RANDOMISATION PROCESS

#### Protocol for Researcher's Phone Call to Randomisation Centre

1. The researcher (Margaret) will phone a designated research administrator (Annabel) at a pre-arranged time
2. Margaret will ask Annabel to take the envelope that contains the randomisation sequence list table to be used for this particular randomisation call from the locked drawer in the administrator's desk:
  - a. Envelope 1 (Randomisation Sequence for AMNCH/ Beacon Renal Medical Care)
  - b. Envelope 2 (Randomisation Sequence for SVUH)
3. Margaret will ask Annabel to tell her the next randomisation sequence list number in the table
4. Margaret will confirm that this number corresponds to the sequence list that should be used for that research site
5. Margaret will write this number into the master randomisation list (patient entry log book)
6. Margaret will give Annabel the unique patient identification number, which Annabel will write beside the randomisation sequence number
7. Annabel will then inform Margaret of the solution allocated to the participant
8. Margaret will enter this information into the appropriate section of the master randomisation list, opposite the participant's name
9. Annabel will faintly cross out this assignment from the randomisation sequence list to enable the identification of the next randomisation sequence list number for that research site
10. The above sequence of events will be used for the randomisation of each participant

EudraCT number 2010-019984-12; Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010, ISRCTN26577745/Protocol for Randomisation Process/V3/5<sup>th</sup> September 2010

**Appendix 8.8 Independent microbiologist review record sheet**

Name (Initial)	Date of Birth Trial Number	Problem	Investigations, results and documentation photocopied
<b>Chief Investigator/Principal Investigator (Insert name)</b>			<b>Decision</b>
<b>Independent Microbiologist (Insert name)</b>			<b>Decision</b>
<b>Agreed Primary Outcome</b>			<b>Decision</b>

## Appendix 8.9 Participants admitted to nephrology ward



### Chlorhexidine Gluconate Trial Dialysis Unit (Site OA)

#### Protocol for Trial Participants Admitted to Nephrology Ward

##### Title of trial

A multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleansing agent versus other forms of chlorhexidine gluconate which are in routine use, on central venous catheter-related infections in haemodialysis patients

##### Who is in the trial?

Haemodialysis patients with permanent cuffed central venous catheters who have meet the trial inclusion criteria and have consented to participate in the trial.

##### How do I know what patient is on the trial?

A clinical trial label will be attached to the front of patient's medical chart. Participation in the trial will also be documented in their medical chart and nursing notes.

##### What are the trial interventions?

Trial participants will be randomly allocated to either the experimental group or the control group.

The experimental group will receive 2% chlorhexidine gluconate in 70% isopropyl alcohol in the form of a ChlorPrep® 3ml applicator which will be used to cleanse the skin and exit site of the patients central venous catheter of trial participants.

The control group will receive 0.5% chlorhexidine gluconate in 70% isopropyl alcohol (the standard chlorhexidine gluconate solution that is used in their dialysis facility). This standard solution is hydrex pink solution which will be used to cleanse the skin and exit site of the patients central venous catheter.

##### When should the CVC dressing be changed?

The trial participants dressing should only be changed when the patients goes to the dialysis unit for his/her dialysis session.

##### What happens if a patient's CVC dressing needs to be changed on the ward?

For trial participants admitted to the nephrology ward:- if their CVC dressing becomes loose or damp after a shower the dressing can be replaced with a sterile dressing using an aseptic technique. However, the exit site should be left dry and not cleansed with any antiseptic solution, if at all possible. If a patient's exit site requires urgent cleansing then this procedure needs to be documented in the nursing notes indicating the solution that was used to cleanse the site.

# Appendix 8.10 Order declaration form for unlicensed IMP

Medisource Ltd.  
 Unit 11, Southern Cross Business Park, Bray, Co. Wicklow  
 email: orders@medisource.ie  
 www.medisource.ie  
 Phone: + 353 - 1 - 2866 356  
 Lo-Call: 1890 2866 356  
**Fax: +353-1-2866 288**



Form 4 05V 2 (revised 06/20)

Name of Doctor / Dentist: **Dr George Mellotte**  
 Business address: **The Dialysis Unit**  
**The Adelaide & Meath Hospital, Dublin 24**  
 Professional Registration Number: **009958**  
 Contact name and tel no: **Orders : Margaret McCann - 087 2897809**  
 Fax no: **01 - 8963000**  
 Purchase Order number / Reference: **FOC - Care Fusion**

Description of product	Quantity
1. _____	_____
2. _____	_____
3. _____	_____

Products not in stock are automatically placed on back order. Please place an 'X' in the box if you do not wish to accept the back order.

I accept the conditions of supply outlined on this form and I confirm that exempted unauthorised medicinal products sourced from Medisource will be handled and stored appropriately and will only be supplied by me to the order of a registered medical practitioner/dentist to fulfil special needs for a patient under his/her care.

Doctor/Dentist Signature \_\_\_\_\_  
 Date \_\_\_\_\_  
 Print name (use capital letters) \_\_\_\_\_

Note: Returns of unlicensed medicines are not accepted under any circumstances.

There will be a carriage charge of €8.95 on all orders below €50.

**This form must be completed in full, signed and faxed back to Medisource on +353-1-2866288**

Note: By ordering an exempt medicinal product from Medisource, you have confirmed that there is no licensed pharmaceutical equivalent suitable for the patient in Ireland.  
 Medisource Ltd. Registered in Ireland No. 28721



## Appendix 8.11 Ordering procedure for unlicensed IMP

THE ADLAIDE & MEATH HOSPITAL  
INCORPORATING THE NATIONAL CHILDREN'S HOSPITAL



**THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN**  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL

ADLAIDE, DUBLIN 8, IRELAND  
TEL: 01 414 4331

Department of Nephrology

Medical Director / Consultant Nephrologist - Dr George Mellite  
Consultant Nephrologist - Dr Catheter Wall  
Dr Mellite's Sec: 01 414 2840  
Dr Wall's Sec: 01 414 2353  
[george.mellite@adelaide.ie](mailto:george.mellite@adelaide.ie)  
This Fax: 01 414 2364

Date: 28/08/2010

REC 2010/2700  
EudraCT number 2010-019984-12  
Prot-AMNCH-ICD-CHG-1-0010  
ISRCTN26577745

**Title of Trial:** A multicentre randomised trial comparing the effects of 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin, exit site and catheter hub cleaning agent versus other forms of chlorhexidine gluconate which are in routine use, on central venous catheter-related infections in haemodialysis patients

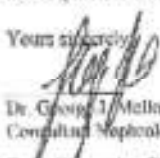
To Whom it May Concern

The above trial which has received joint St James/AMNCH research ethics and IMB approval will take place in the dialysis unit in AMNCH. The AMNCH aim of the trial is a comparison between 2% chlorhexidine gluconate in 70% isopropyl alcohol and 0.5% chlorhexidine gluconate in 70% isopropyl alcohol. These haemodialysis patients allocated to the 2% chlorhexidine gluconate in 70% isopropyl alcohol group will receive ChlorPrep® with Tix which will be used to cleanse the skin and exit site of their central venous catheter.

The ChlorPrep® with Tix 1ml applicator will be supplied free of charge by Carefusion and their Irish distributor Medicus who will supply one case (100 applicators) each week from September 2010 to July 2012. Dr Mellite will order this unlicensed product from Medicus, will submit a signed declaration form for each supply and request delivery of this product to the dialysis unit.

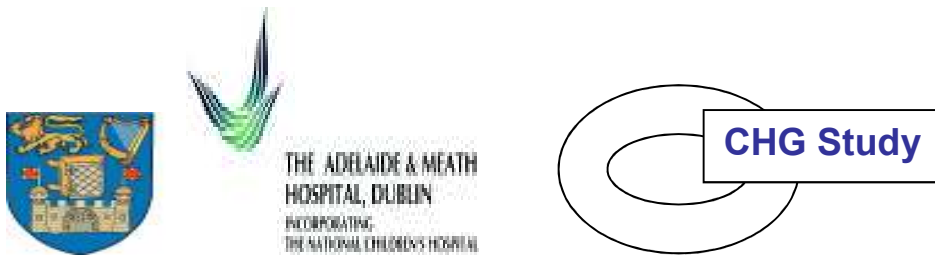
Pharmacy is aware that ChlorPrep is being ordered for use in an unlicensed clinical trial within the hospital but are not involved in the ordering process.

Yours sincerely

  
Dr. George J. Mellite, MB, FRCPL, MSc (09958)  
Consultant Nephrologist & Senior Lecturer in Medicine

EudraCT number 2010-019984-12  
Sponsor's Protocol Code Number Prot-AMNCH-ICD-CHG-1-0010  
ISRCTN26577745

**Appendix 8.12 Order form ChloroPrep® with Tint: Iskus Health Ltd**



**CHG CLINICAL TRIAL  
PRODUCT ORDER REQUEST**

**Date of Request:**

**Requestor:** Margaret McCann, Researcher  
**Email:** [mccannm4@tcd.ie](mailto:mccannm4@tcd.ie) **Mobile phone:**  
**Shipping Address:** C/O Margaret McCann, *Insert name of dialysis unit*

**Name of Supplier:** Iskus Health  
 Supply is FOC and CareFusion will be paying.

**Name of Contact Person:** Michael Dempsey, Iskus Health Ltd.  
**Email:** [mdempsey@iskushealth.com](mailto:mdempsey@iskushealth.com) **Phone:** 353 1 4048387  
**Mobile Phone** **Fax:** 353 1 4048381

**Order requests to be made via:** [info@iskushealth.com](mailto:info@iskushealth.com) or  
 Phone: 4048383 or 4048380

**Date Needed:**

Qty	Item Name and Description	Total Number
<b>For Trial Use Only</b> <b>On receipt of this delivery the following information is to be recorded by the researcher</b> <b>Vendor Invoice Number: Free of Charge, CareFusion to pay</b> <b>Batch Number:</b> <b>Expiry Date:</b>		

EudraCT number 2010-019984-12 Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010/ISRCTN26577745 Clinical Sponsor/Chief Investigator: Dr. George Mellotte, Consultant Nephrologist, Adelaide & Meath Hospital, incorporating the National Children's Hospital, Tallaght, Dublin 12

**Appendix 8.13 Order form for Sani-Cloth CHG: PDI**



**CHG CLINICAL TRIAL  
PRODUCT ORDER REQUEST and RECEIPT FORM**

**Date:**

**Requestor:** Margaret McCann, Researcher  
**Email:** [mccannm4@tcd.ie](mailto:mccannm4@tcd.ie) **Mobile phone:**

**Shipping Address:** Dialysis Unit, *insert name of dialysis unit*

**Name of Supplier:** PDI

**Name of Contact Person:** Mr Ron Tierney  
**Address:** Aber Park, Flint, CH6 5EX, UK  
**Email:** [ron.tierney@nice-pak.co.uk](mailto:ron.tierney@nice-pak.co.uk) **Phone:** 00441352736700  
**Mobile Phone** **Fax:** 00441352736823

**Date Needed:**

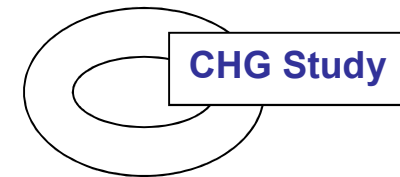
Qty	Unit of Issue	Item Name and Description	Total Number

**For Trial Use Only**  
**On receipt of this delivery the following information is to be recorded by the researcher**

**Vendor Invoice Number: Free of Charge no invoice given**  
**Batch Number (Lot Number):**  
**Expiry Date:**

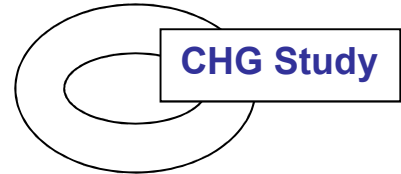
EudraCT number 2010-019984-12 Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010/ISRCTN26577745 Clinical Sponsor/Chief Investigator: Dr. George Mellotte, Consultant Nephrologist, Adelaide & Meath Hospital, incorporating the National Children's Hospital, Tallaght, Dublin 12

**Appendix 8.14 Record of medicinal product delivery**



Date Ordered (dd/mm/yyyy)	Date Received (DD/MM/YYYY)	Quantity	Batch Number	Expiry Date	Method of Shipment	Condition of Packaging	Date and Signature

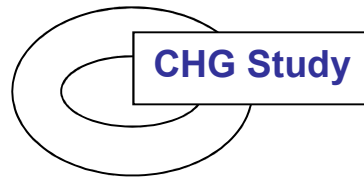
**Appendix 8.15 Record of control medicinal product supplies**



**Record Chart of  
Hydrex Pink Supplies from AMNCH Pharmacy**

Date DD/MM/YYYY	Number of Bottles Supplied to Clinical Trials Press	Batch Number	Expiry Date

## Appendix 8.16 Instructions on administration of trial IMPs



### **Trial Participants Allocated to Receive ChloraPrep® with Tint and Sani-Cloth CHG 2%**

The following applies to trial participants allocated to ChloraPrep® with Tint and Sani-Cloth CHG 2%.

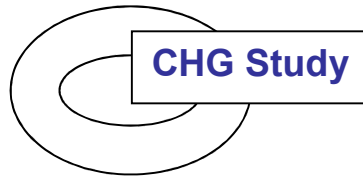
#### Role of Nurse connecting/disconnecting patients

Prior to commencing dialysis the nurse assigned to connect the patient to dialysis needs to:-

- Determine if a patient with a CVC is participating in the trial and what solution they have been assigned. The nurse can check with:-
  - the patient;
  - review the front of the patients dialysis folder for a clinical trial label, which will indicate the patients participation in the trial and the group that they have be allocated to;
  - review the log of patients participating in the trial located in the CNM II office.
- The nurse needs to assess if the patient's CVC dressing needs to be changed. Frequency of dressing change is as per local policy.
- If the CVC dressing needs to be changed the nurse will remove a ChloraPrep® with Tint 3ml applicator from the clinical trials press and use this to cleanse the CVC exit site.
  - This applicator consists of a plastic applicator with two small plastic wings on either side of the applicator and a sponge tip at one end. The applicator is held with the sponge facing downward and the wings are squeezed gently together to pop the enclosed ampoule, releasing the antiseptic solution onto the sponge. The sponge is gently pressed against participants' skin to apply the antiseptic solution.

- Using a back and forth motion as demonstrated in the training sessions apply the solution over 30 seconds. It is important to allow the solution to air dry, which can take approximately 30-60 seconds. If the solution is not allowed to air dry prior to applying the CVC dressing a skin rash may develop.
- The type of CVC dressing used will be as per local policy.
- When using ChloroPrep® with Tint it is important to protect the patients clothing as the solution can stain. The sterile drape can be used to protect the patient's clothes and needs to be tucked into the shirt or blouse of the patient. Once the dressing has been changed if there is any visible stain on the skin beyond the dressing this needs to be removed using normal saline. A sterile swab from the dressing pack can be used to protect the patient's cloth during dialysis.
- The nurse will use Sani-Cloth CHG 2% medical device wipes during the process of connecting/disconnect the patient.
  - Use an aseptic technique and CVC on/off sterile packs.
  - For each catheter hub, use one wipe to cleanse the outer aspect of the hub cap. This also includes cleaning the catheter material, working away from the cap.
  - After the cap is removed and prior to the removal of the CVC lock solution, a second wipe is used to cleanse the exposed catheter hub.
  - When disconnecting participants from dialysis, for each catheter hub, one wipe is used to cleanse the connection joint between the dialysis tube and catheter hub. Once the dialysis line is disconnected, a second wipe is used to cleanse the exposed catheter hub, prior to instilling the normal saline flush and the CVC locking agent.
  - A brisk rubbing action for at least 30 seconds is used when cleaning the catheter. The solution must be allowed to air dry.
- After connecting/disconnecting a patient the nurse assigned to that patient will document in the trial record documentation sheet:
  - If CVC dressing was changed, exit appearance, if CVC exit swab was taken;
  - Solution used to cleanse the exit site;
  - Solution used to connect/disconnect the patient

## Appendix 8.17 Protocol on use of control IMP



### Trial Participants Allocated to Receive Hydrex® Pink 200ml bottle

- Trial participants allocated to receive Hydrex® Pink (200ml) will each have their own labelled bottle for their individual use.
- The Researcher will apply the initial individualised label onto the Hydrex® Pink bottle when the patient commences the trial.
- A supply of individualised labels will be kept in each trial participant's dialysis folder.

**For Clinical Trial Use Only**

Chlorhexidine Gluconate Trial

**Patient Name: Joe Bloggs**

**DOB: 04/06/1954**

**Hospital Number:**

Sponsor/Principal Investigator: Prof. George Mellotte

Researcher: Margaret McCann

Trial Reference Code: EudraCT number 2010-019984-12;

Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010

- The trial participant's individualised labelled bottle will be kept in a clinical trials container, which is located on top of the clinical trials press.
- When a trial participant's bottle is opened a discard date should be entered into the expiry sticker by the dialysis nurse. This discard date is seven days after the bottle has been opened.
- If there is no individualised labelled bottle in the trials container a new bottle is to be removed from the clinical trials press, an individualised clinical trials label is to be removed from the patient's dialysis folder and applied to this new bottle.



### **Trial Participants Allocated to Receive Hydrex® Pink 600ml bottle**

- On each wing of the dialysis unit there will be one Bottle of Hydrex® Pink labelled for 'CVC Use Only' and will also have the following clinical trial label.

**For Clinical Trial Use Only**

Chlorhexidine Gluconate Trial

Sponsor: Dr. George Mellotte

Principal Investigator: Professor Alan Watson

Researcher: Margaret McCann

Trial Reference Code: EudraCT number 2010-019984-12;

Sponsor's Protocol Code Number Prot-AMNCH-TCD-CHG-1-2010

- Only one clinical trial bottle should be opened on each wing of the dialysis unit at any one time.
- A stock level of 4 bottles of Hydrex® Pink will be maintained in the clinical trials press.
- Each week the responsible staff nurse will check the stock level of Hydrex® Pink in the clinical trials press and from supplies sent by pharmacy replace stock that has been used (ensuring that stock level is at 4 bottles).
- On placement of stock into press the nurse will apply the 'CVC Use Only' label and the clinical trials label.
- The responsible nurse will document the number of Hydrex® Pink bottles supplied to the clinical trials press; their batch number and expiry date in the Hydrex® Pink Batch Numbers record sheet, which is located in the clinical trial press.
- The 'CVC Use Only' label will include a start date and discard date.
- A discard date should be entered when the bottle is opened. The discard date should be seven days after the bottle has been opened. The person opening the bottle is responsible for entering this date onto the sticker.
- It is the responsibility of the nursing staff to check the discard date on all opened bottles of Hydrex® Pink, each morning prior to the first dialysis session

## Appendix 8.18 Instructions on administration of control IMPs



### Trial Participants Allocated to Receive Hydrex® Pink/ Unisept solution

The following applies to trial participants allocated to Hydrex® Pink/ Unisept solution

#### Role of Nurse connecting/disconnecting patients

Prior to commencing dialysis the nurse assigned to connect the patient to dialysis needs to:-

- Determine if a patient with a CVC is participating in the trial and what solution they have been assigned. The nurse can check with:-
  - the patient;
  - review the front of the patients dialysis folder for a clinical trial label, which will indicate the patients participation in the trial and the group that they have be allocated to;
  - review the log of patients participating in the trial located in the CNM II office.
- The nurse needs to assess if the patient's CVC dressing needs to be changed. Frequency of dressing change is as per local policy.
- If the CVC dressing needs to be changed the nurse will use Hydrex® Pink/ Unisept solution that was removed from the clinical trials press and use this to cleanse the CVC exit site.
  - Unisept solution:
    - One sachet is used for skin and exit site catheter care. Using a circular motion the solution is applied to the skin using a sterile swab soaked in the solution.
    - The solution is applied for approximately 30 seconds and allowed to air dry, this may take longer than 60 seconds as it is an aqueous solution.
    - Frequency of cleansing the CVC exit site and type of CVC dressing used is a per unit policy.

- Hydrex® Pink:
  - Approximately 25mls of the solution is decanted from a clinical trial labelled bottle into a sterile galipot.
  - The solution is applied for approximately 30 seconds and allowed to air dry, this takes approximately 30-60 seconds.
  - Frequency of cleansing the CVC exit site and type of CVC dressing used is a per unit policy.
- For connecting/disconnect the patient, the nurse will use Hydrex® Pink/ Unisept solution that was removed from the clinical trials press.
  - Unisept solution:
    - One sachet of Unisept is used to connect and disconnect patients from dialysis.
    - For each catheter hub, one sterile swab soaked in 0.05% aqueous CHG is used to cleanse the outer aspect of the hub cap including cleaning the catheter material, working away from the cap.
    - On removal of the hub cap, each exposed hub is cleansed with a sterile swab soaked in Unisept. A brisk action is used to remove any debris on the catheter hub.
    - Similar procedures are to be used when disconnection participants from dialysis.
    - In total four sterile swabs soaked in Unisept were used when connecting participants to dialysis and four used when disconnecting.
  - Hydrex® Pink:
    - Decant approximately 25ml of Hydrex® Pink into a sterile galipot.
    - For each catheter hub, one sterile swab, soaked in the solution, is used to cleanse the outer aspect of the hub cap including cleaning the catheter material, working away from the cap.
    - On removal of the hub cap, each exposed hub is cleansed with a soaked sterile swab. A brisk action is used to remove any debris on the catheter hub.
    - Similar procedures took place when disconnection from dialysis.

- In total four sterile swabs soaked in Hydrex Pink are used when connecting participants to dialysis and four used when disconnecting.
- After connecting/disconnecting a patient the nurse assigned to that patient will document in the trial record documentation sheet:
  - If CVC dressing was changed, exit appearance, if CVC exit swab was taken;
  - Solution used to cleanse the exit site ;
  - Solution used to connect/disconnect the patient

## Appendix 8.19 Trial solutions record Sheet (Example)

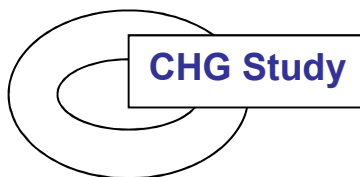
### CHLORHEXIDINE GLUCONATE TRIAL *(Insert Research Site)*

The following information must be documented at each dialysis session

The patient is to receive the following solutions: **(insert solution)**

Patient Initial Study ID No	Date of dialysis Session	Solution used for dialysis connect Tick one	Solution used for dialysis disconnect Tick one	Solution used for CVC exit site care Tick one	Adverse Reaction to Solution Tick One	Exit Site Appearance Tick One	Tick if any of the following were done	Tick if any of the following were given to the patient	CVC lock Post HD Tick one	Signature of Dialysis Nurse
□□□ □□□□□	___/___/___ DD/MM/YYYY	Sani-Cloth <input type="checkbox"/> Hydrex <input type="checkbox"/>	Sani-Cloth <input type="checkbox"/> Hydrex <input type="checkbox"/>	ChloraPrep® <input type="checkbox"/> Hydrex Pink <input type="checkbox"/> Not dressed <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Normal <input type="checkbox"/> Abnormal <input type="checkbox"/>  Doc type of abnormality	Exit Swab <input type="checkbox"/>  <b>Blood culture</b> Peripheral <input type="checkbox"/> CVC <input type="checkbox"/>	<b>Antibiotics</b> IV antibiotics <input type="checkbox"/> Prescription <input type="checkbox"/>  Doc type of antibiotics prescribed	Duralock <input type="checkbox"/>  Other <input type="checkbox"/>	
□□□ □□□□□	___/___/___ DD/MM/YYYY	Sani-Cloth <input type="checkbox"/> Hydrex <input type="checkbox"/>	Sani-Cloth <input type="checkbox"/> Hydrex <input type="checkbox"/>	ChloraPrep® <input type="checkbox"/> Hydrex Pink <input type="checkbox"/> Not dressed <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Normal <input type="checkbox"/> Abnormal <input type="checkbox"/>  Doc type of abnormality	Exit Swab <input type="checkbox"/>  <b>Blood culture</b> Peripheral <input type="checkbox"/> CVC <input type="checkbox"/>	<b>Antibiotics</b> IV antibiotics <input type="checkbox"/> Prescription <input type="checkbox"/>  Doc type of antibiotics prescribed	Duralock <input type="checkbox"/>  Other <input type="checkbox"/>	

**Appendix 8.20 Denominator data collection form**



**Denominators for Outpatient Dialysis  
Census Form – completed once per month**

\* required for saving

Record the number of chronic hemodialysis patients who received hemodialysis at your center on the first two working days of the month. Count each patient only once. If a patient has both an implanted access (graft or fistula) and a catheter, count this patient as having the catheter.	
<b>Facility Study ID number:</b> OA	
<b>Study Comparison</b> 2% CHG in 70% alcohol <b>V's</b> 0.5% CHG in 70% alcohol/0.05% aqueous CHG (delete as appropriate)	
<b>*Month:</b>	<b>*Year:</b>
<b>*Vascular Access Type</b>	<b>*Number of Chronic Haemodialysis Patients</b>
Graft	
Fistula	
Temporary central line	
Permanent central line	
Port access device (e.g., Lifesite)	
<b>*Total patients</b> (sum of all patients listed above)	
<b>Data Collector Signature</b> _____	
<b>Date</b>	

(Modified Version of CDC/NHSN Outpatient Dialysis Census Form)

## Appendix 8.21 Dialysis event form

Dialysis Event Form		1/2
Facility Study ID number: <input type="checkbox"/> [1] OA <input type="checkbox"/> [2] OB <input type="checkbox"/> [3] OV	Patient Study ID number:	Date of Birth: ___/___/___
Allocated Intervention (Tick one): <input type="checkbox"/> [1] 2% CHG in 70% alcohol <input type="checkbox"/> [2] 0.5%CHG in 70% alcohol <input type="checkbox"/> [3] 0.05% aqueous CHG		
<b>Vascular Access: (Tick all that apply) Date of Insertion Date Unknown Site of CVC</b>		
<input type="checkbox"/> [1] Fistula	___/___/___	<input type="checkbox"/> [1]
<input type="checkbox"/> [2] Graft	___/___/___	<input type="checkbox"/> [1]
<input type="checkbox"/> [3] Permanent CVC (Tunnelled)	___/___/___	<input type="checkbox"/> [1] <input type="checkbox"/> [1] Jug <input type="checkbox"/> [2] Sub <input type="checkbox"/> [3] Fem
<input type="checkbox"/> [4] Temporary CVC (Non-tunnelled)	___/___/___	<input type="checkbox"/> [1] <input type="checkbox"/> [1] Jug <input type="checkbox"/> [2] Sub <input type="checkbox"/> [3] Fem
<b>Event Details *Specify Event: (Tick one or more)</b>		
<input type="checkbox"/> [1] Local access infection (as per case definition) Date first recorded: ___/___/___ Was an exit site swab taken <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No		
<input type="checkbox"/> [1] Problem(s): (Tick one or more) Date first recorded: ___/___/___ <input type="checkbox"/> [1] Pus, redness, or increased swelling at vascular access site If applicable, tick the access site(s) with pus, redness, or increased swelling: <input type="checkbox"/> [1] Graft <input type="checkbox"/> [2] Fistula <input type="checkbox"/> [3] Permanent central line <input type="checkbox"/> [4] Port access device <input type="checkbox"/> Vascular access problem <u>without</u> infection (Tick all that apply): <input type="checkbox"/> [1] Clotting <input type="checkbox"/> [2] Bleeding <input type="checkbox"/> [3] Other <input type="checkbox"/> [1] Fever $\geq 37.8^{\circ}\text{C}$ ( $100^{\circ}\text{F}$ ) oral or $\geq 38^{\circ}\text{C}$ ( $101^{\circ}\text{F}$ ) rectal <input type="checkbox"/> [1] Wound (NOT related to vascular access) with pus or increased redness <input type="checkbox"/> [1] Cellulitis (skin redness, heat, or pain without open wound) <input type="checkbox"/> [1] Other infection e.g. respiratory or urinary tract infection requiring oral antibiotic <input type="checkbox"/> [1] Other (specify) _____		
<input type="checkbox"/> [1] Blood Culture (Tick one) Date blood culture taken: ___/___/___ Site of blood culture: <input type="checkbox"/> [1] Peripheral <input type="checkbox"/> [2] Catheter Device <input type="checkbox"/> [3] Dialysis Circuit Lines <input type="checkbox"/> [4] Unknown Blood culture result: <input type="checkbox"/> [1] Positive <input type="checkbox"/> [2] Negative <input type="checkbox"/> [3] Unknown Patient with a positive blood culture: <b>*suspected source of positive blood culture (Tick one):</b> <input type="checkbox"/> [1] Vascular access <input type="checkbox"/> [2] A source other than the vascular access <input type="checkbox"/> [3] Contamination <input type="checkbox"/> [4] Uncertain If source of positive blood culture was vascular access was it diagnosed as: <input type="checkbox"/> Catheter-associated bloodstream infection (as per case definitions) <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No <input type="checkbox"/> [3] Unknown <input type="checkbox"/> Catheter-related bloodstream infection (as per case definitions) <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No <input type="checkbox"/> [3] Unknown		
<input type="checkbox"/> [1] In-Unit IV antimicrobial Start Date: ___/___/___ Stop Date: ___/___/___ IV antibiotic started in cases of confirmed or suspected access infection (Tick one): <input type="checkbox"/> [1] Vancomycin <input type="checkbox"/> [2] Daptomycin <input type="checkbox"/> [3] Linezolid <input type="checkbox"/> [4] Other (specify): _____ IV antibiotic started in cases of confirmed or suspected infection other than access (specify): _____		
<input type="checkbox"/> [1] Hospitalization Date of admission: ___/___/___ Date of discharge: ___/___/___ Reason for hospitalization: <input type="checkbox"/> [1] Infection <input type="checkbox"/> [2] Catheter-related Infection <input type="checkbox"/> [3] Vascular access problems <input type="checkbox"/> [4] Other (specify): _____		
<b>[1] Catheter Removal</b>		
Date of removal: ___/___/___ Reason for removal: <input type="checkbox"/> [1] Catheter-related infection <input type="checkbox"/> [2] Catheter dysfunction <input type="checkbox"/> [3] Other (specify): _____		
<b>[1] Death</b>		
Date of Death: ___/___/___ Cause of Death: <input type="checkbox"/> [1] catheter-related Infection <input type="checkbox"/> [2] unknown <input type="checkbox"/> [3] other (specify): _____		
<b>[1] Adverse Reactions to Study Intervention:</b>		
Date of Adverse Reaction: ___/___/___ Type of adverse reaction: <input type="checkbox"/> [1] Skin sensitivity [2] Contact dermatitis [3] Hypersensitivity reaction		
Data Collector Signature _____		Date: ___/___/___

## Appendix 8.22 Trial register form



### Trial Register Form

#### **Part 1 Assessment of eligibility**

Date: \_\_\_\_\_

Name:

Date of Birth:

Address:

Hospital Medical Chart Number:

Dialysis Facility Code:

#### **Eligible for Chlorhexidine Gluconate Study**

- Patients over the age of 18 who require haemodialysis for end stage renal disease
- Patients on long term haemodialysis using permanent tunnelled cuffed CVC
- Patients whose permanent tunnelled cuffed CVC has been inserted at least four weeks prior to entry into the study

#### **Exclusion Criteria for Chlorhexidine Gluconate Study**

- Patients whose CVC is used for purposes other than access for haemodialysis
- Patients with a known allergy to any component of the interventions
- Patients whose CVC material is not compatible with interventions
- Patients who are using central venous catheters or dressings which are not standard practice for the unit
- Patients who are unable to give informed consent



**Part 2 Is the patient eligible for the study**

Yes

No

- If the patient is not eligible to participate in the study please give reasons using the inclusion and exclusion criteria listed in Part 1

**Part 3 Patient Information Pack**

Date and time information pack was given to the eligible patient:

\_\_\_\_\_

**Part 4 Consent**

Date and time: \_\_\_\_\_

Consent form signed Yes

No

- ***If no, do not proceed to randomisation***, and give reason why consent form was not signed:

**Part 5 Randomisation and allocation of participant study ID number**

Date and time of randomisation: \_\_\_\_\_

Randomisation sequence number:

**Randomisation**

Allocated to 2% Chlorhexidine Gluconate in 70% isopropyl alcohol

Chlorhexidine Gluconate routinely used in dialysis centre

(0.05% aqueous CHG/ 0.5% CHG in 70% alcohol; **delete as appropriate**)

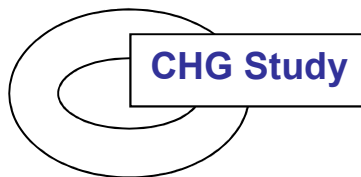
Participant's study ID number:

Data collector signature \_\_\_\_\_

**Appendix 8.23 Baseline collection form**



THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL



Patient Baseline Information Form	
<b>Facility Study ID Number:</b> <input type="checkbox"/> [1] OA <input type="checkbox"/> [2] OB <input type="checkbox"/> [3] OV	<b>Patient Study ID Number:</b>
<b>Allocated Intervention:</b> <input type="checkbox"/> [1] 2% CHG in 70% alcohol <input type="checkbox"/> [2] 0.5% CHG in 70% alcohol <input type="checkbox"/> [3] 0.05% aqueous CHG	
<b>Gender</b> <input type="checkbox"/> [1] Male <input type="checkbox"/> [2] Female	<b>Date of Birth:</b> ___ / ___ / ___
<b>Aetiology of ESRD</b> <input type="checkbox"/> [1] Diabetes <input type="checkbox"/> [2] Glomerulonephritis <input type="checkbox"/> [3] Hypertension <input type="checkbox"/> [4] Polycystic Kidney Disease <input type="checkbox"/> [5] Interstitial nephritis <input type="checkbox"/> [6] Unknown <input type="checkbox"/> Other (specify) _____	<b>Co-morbidities</b> <input type="checkbox"/> [1] Diabetes <input type="checkbox"/> [2] Immunosuppressive Therapy <input type="checkbox"/> [3] Malignancy
<b>Last Recorded Serum Albumin (g/l)</b> _____	<b>Previous Immunosuppression in the last 12 months</b> <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No <input type="checkbox"/> [3] Unknown
<b>Date started haemodialysis:</b> ___ / ___ / ___	
<b>Central Venous Catheter Access History</b> Previous Central Venous Catheter: <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No If yes, number of previous catheters: _____ <input type="checkbox"/> [6] Not applicable  Reason for catheter removal: <input type="checkbox"/> [1] infection <input type="checkbox"/> [2] problems with access <input type="checkbox"/> [3] Other (specify) _____ <input type="checkbox"/> [4] Unknown <input type="checkbox"/> [5] Not applicable  Previous Central Venous Catheter Infection: <input type="checkbox"/> [1] Yes <input type="checkbox"/> [2] No <input type="checkbox"/> [3] Unknown Type of CVC infection: <input type="checkbox"/> [1] Local access infection <input type="checkbox"/> [2] CVC-associated bloodstream infection <input type="checkbox"/> [3] Catheter-related bloodstream infection <input type="checkbox"/> [4] Unknown <input type="checkbox"/> [5] Not applicable  Date of last infection: ___ / ___ / ___  Date of current catheter insertion: ___ / ___ / ___ <input type="checkbox"/> unknown  Site of current catheter insertion: <input type="checkbox"/> [1] Jugular Rt <input type="checkbox"/> [2] Jugular Lf <input type="checkbox"/> [3] Subclavian R <input type="checkbox"/> [4] Subclavian Lf <input type="checkbox"/> [5] Other (specify) _____	
<b>Central Venous Catheter Dressing:</b> <input type="checkbox"/> [1] Dry Gauze <input type="checkbox"/> [2] Transparent <input type="checkbox"/> [3] Dry gauze and transparent Frequency of Dressing Change: <input type="checkbox"/> [1] Day of Dialysis <input type="checkbox"/> [2] Every 7 days <input type="checkbox"/> [3] Other (specify) _____	
<b>Central Venous Catheter Locking Solution</b> <input type="checkbox"/> [1] Heparin <input type="checkbox"/> [2] Duralock (specify strength ___ ) <input type="checkbox"/> [3] Other (specify) _____	
<b>Date Form completed:</b> ___ / ___ / ___	<b>Data Collector Signature:</b> _____

**Appendix 8.24 Adverse event form**

<b>Chlorhexidine Gluconate Trial</b>	
<b>Facility Study ID Number:</b>	<b>Participant Study ID Number:</b>

Has the participant had any Adverse Events during this study?     Yes     No (If yes, please list all Adverse Events below)

AE No	Adverse Event (diagnosis (if known) or signs/symptoms)	Start Date dd/mm/yyyy	Stop Date dd/mm/yyyy	Severity 1 = Mild 2 = Moderate 3 = Severe	Relationship to Study Treatment	Action Taken 1 = None 2 = Discontinued permanently 3 = Discontinued temporarily	Withdrawn due to AE?	Expected?	Serious Adverse Event?	If SAE does it require reporting (See SOP)	Initial
1.					<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	
2.					<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	

**Appendix 8.25 Adverse reaction**



THE ADELAIDE & MEATH  
HOSPITAL, DUBLIN  
INCORPORATING  
THE NATIONAL CHILDREN'S HOSPITAL



**CHG Trial  
Adverse Reaction Form**

**Name of hospital (Tick one only):** AMNCH  Beacon  SVUH

**Name of person completing this form:** Margaret McCann  
(use BLOCK CAPITALS please)

**Signature of person completing this form:** \_\_\_\_\_

**Date form completed (DD/MM/YYYY):**

**Date Adverse Reaction occurred (DD/MM/YYYY):**

**Patient's details (or affix addressograph):**

**Name:**

**Address:**

**DOB (DD/MM/YYYY):**

**Medical record number:**

**Patient's study ID number:**

Description of Adverse Reaction (Skin sensitivity; contact dermatitis; hypersensitive reaction)	Action Taken	Outcome of Adverse Reaction	Expected?	Serious Adverse Reaction

## Appendix 8.26 Safety monitoring

The following action plan was put in place for any participants complaining of itch or discomfort around CVC exit site:

- Dialysis staff contacted the researcher outlining the participant's complaint (participants complaints related mainly to an itchy sensation under dressing and around CVC exit site). In a majority of cases no visible redness was noted;
- I visited the participant, reviewed the CVC exit site and documented my observations in the dialysis event form. Dialysis staff were instructed to clean the CVC exit site with normal saline, this action would rule out heat as the cause of itchiness;
- I revisited the participant at their next dialysis session and if the participant had no further complaints, the assigned solution was recommenced;
- If the participant continued to complain of an itchy sensation post recommencement of the assigned solution, dialysis staff were instructed to use an alternative type of CVC exit site dressing (in most cases participants used a dry gauze dressing and were changed to a transparent dressing) and use normal saline to clean the exit site;
- I revisited the participant at their next dialysis session and if the participant had no further complaints dialysis staff were instructed to recommence the assigned solution, ensure that skin was dry prior to applying the alternative dressing. If participants continued to complain of an itchy sensation, the assigned solution was discontinued and an adverse reaction form completed. The participant, dialysis staff and principal investigator/sponsor were informed.
- Participants allocated to receive Chloraprep® with Tint were returned to the routine solution used in the dialysis centre.
- If participants were allocated to the control solution, which was the routine antiseptic solution used by the dialysis centre, dialysis staff would make the decision on what alternative antiseptic agent could be used.

## **Appendix 8.27 Trial Monitoring Committee**

### **CHG Trial Monitoring Committee**

Interim Data

Meeting held by phone 5<sup>th</sup> July 2012.

Present: Declan Devane (Chair), Catherine Comiskey, Jerome Fennell

---

#### ***Purpose***

Review and advise on unblinded interim analysis of outcome data and adverse event reports

#### ***Discussion***

Arguments for and against stopping the trial were considered. In particular, the higher incidence of infection rates in the control arm in Tallaght although not statistically significant was considered clinically important. The committee was conscious that the trial had finished in Tallaght and that the other two sites did not show significant clinical differences.

After discussion, it was agreed that there was no particular ethical or scientific reason to stop the trial now and that the trial should continue to completion.

We would be happy to review the data at trial end.

## Appendix 9.1 Eligibility assessment and recruitment

	OA N (%)	OB N (%)	OV N (%)	Total N (%)
Number of patients with a CVC <sup>1</sup>	65 (32)	92 (46)	44 (22)	201
Number of patients not eligible for trial <sup>2</sup>	15 (23)	20 (22)	17 (39)	52 (26)
Number of patients eligible for trial	50 (77)	72 (78)	27 (61)	149 (74)
Number of eligible patients who refused to participate <sup>3</sup>	21 (42)	17 (27)	6 (22)	44 (30)
Number of patients randomised per site	29 (28)	55 (52)	21 (20)	105 (100)

<sup>1</sup>CVC, Central Venous Catheter; <sup>2</sup>reasons for not being eligible include: unable to give informed consent ( $n=17$ ), allergic to routine CHG solution ( $n=10$ ), did not use standard CVC ( $n=3$ ), under the age of 18 ( $n=1$ ), critically ill at the time of assessment ( $n=5$ ), used an arterio-venous fistula (AVF) ( $n=8$ ), were scheduled to transfer to another haemodialysis unit or transfer to peritoneal dialysis ( $n=3$ ), were unable to adhere to the trial protocol ( $n=4$ ) or required strict isolation ( $n=1$ ); <sup>3</sup>Reasons for refusing to participate: stay on current treatment ( $n=30$ ), gave no reason ( $n=5$ ), unwell post first recruitment meeting and subsequently died ( $n=5$ ), could not adhere to the trial protocol ( $n=4$ ).

## Appendix 9.2 Lost to follow-up

Research Site	Main Comparison		Sub comparison 1	Sub comparison 2
	Intervention	Comparator	0.5% CHG in 70% isopropyl alcohol (n=42) N (%)	0.05% aqueous CHG (n=10) N (%)
(N)	(n=53) N (%)	(n=52) N (%)		
OA (2)	2	0	0	-
OB (12)	6	6	6	-
OV (2)	1	1	-	1
Total (16) <sup>1</sup>	9 (17)	7 (13)	6 (14)	1 (10)

<sup>1</sup>Reasons for lost to follow-up: transferred to another haemodialysis unit (n=4), changed to peritoneal dialysis (n=2), transplanted (n=5), renal function returned (n=4), unexpected extended holiday outside Ireland (n=1).

## Appendix 9.3 Discontinued assigned solution

Research Site	Main Comparison		Sub comparison 1	Sub comparison 2
	Intervention	Comparator	0.5% CHG in 70% isopropyl alcohol (n=42) N (%)	0.05% aqueous CHG (n=10) N (%)
(N)	(n=53) N (%)	(n=52) N (%)		
OA (6)	4	2	2	-
OB (10)	5	5	5	-
OV (1)	0	1	-	1
Total (17)	9 (17)	8 (15)	7 (17)	1 (10)



## Appendix 9.4 Primary outcomes per 100 patient-months main comparison

Main Comparison 2% CHG in 70% alcohol vs. Comparator								
	2% CHG in 70% alcohol (n=53)			Comparator (n=52)			Overall I rate	
	Dialysis Events	Patient- months	Rate (95% CI)	Dialysis Events	Patient- months	Rate (95% CI)	P <sup>3</sup>	
CRBSI <sup>1</sup>	1	3012	0.03 (0.03 to 0.04)	2	3012	0.07 (0.06 to 0.08)	0.62	0.1
CABSI <sup>2</sup>	1	3012	0.03 (0.03 to 0.04)	4	3012	0.13 (0.12 to 0.15)	0.22	0.17
Local access infection	3	3012	0.10 (0.09 to 0.11)	4	3012	0.13 (0.12 to 0.15)	0.70	0.23

<sup>1</sup>CRBSI, Catheter-Related Bloodstream Infection; <sup>2</sup>CABSI, Catheter-Associated Bloodstream Infection; <sup>3</sup>p, p-value mid-p exact test

**Appendix 9.5 Sensitivity analysis for primary outcomes**

Sensitivity analysis 2% CHG in 70% alcohol vs. Comparator									
	Most pessimistic			Intervention worst, comparator best			Intervention best, comparator worst		
	2% CHG	Comparator	<i>p</i>	2% CHG	Comparator	<i>p</i>	2% CHG	Comparator	<i>p</i>
CABSI <sup>1</sup>	10	11	0.77	10	4	0.092	1	11	0.002

<sup>1</sup>CABSI, Catheter-Associated Bloodstream Infection

**Appendix 9.6 Primary outcomes per 100 patient-months sub-comparison 1**

Sub Comparison 1 2% CHG in 70% alcohol vs. 0.5% CHG in 70% alcohol							
	2% CHG in 70% alcohol (n=42)			0.5% CHG in 70% alcohol (n=42)			P-Value
	Dialysis Events	Patient-months	Rate per 100 patient-months	Dialysis Events	Patient-months	Rate per 100 patient-months	<i>P</i> <sup>4</sup>
CRBSI <sup>1</sup>	0	2294	NA <sup>3</sup>	2	2294	0.09	0.25
CABSI <sup>2</sup>	1	2294	0.04	2	2294	0.09	0.62
Local access infection	3	2294	0.13	4	2294	0.17	0.73

<sup>1</sup>CRBSI, Catheter-Related Bloodstream Infection; <sup>2</sup>CABSI, Catheter-Associated Bloodstream Infection; <sup>3</sup>NA, Not Applicable;

<sup>4</sup>*p*, p-value mid-p exact test

**Appendix 9.7 Primary outcomes per 100 patient-months sub comparison 2**

Sub Comparison 2 2% CHG in 70% alcohol vs. 0.05% aqueous CHG							
	2% CHG in 70% alcohol (n=11)			0.05% aqueous CHG (n=10)			P- Value
	Dialysis Events	Patient- months	Rate per 100 patient-months	Dialysis Events	Patient- months	Rate per 100 patient-months	P <sup>4</sup>
CRBSI <sup>1</sup>	1	718	0.14	0	718	NA	0.50
CABSI <sup>2</sup>	0	718	NA <sup>3</sup>	2	718	0.28	0.25
Local access infection	0	718	NA	0	718	NA	NA

<sup>1</sup>CRBSI, Catheter-Related Bloodstream Infection; <sup>2</sup>CABSI, Catheter-Associated Bloodstream Infection; <sup>3</sup>NA, Not Applicable;

<sup>4</sup>p, p-value, mid-p exact test

**Appendix 9.8 Secondary categorical outcomes per 100 patient-months main comparison**

<b>Main Comparison</b>								
<b>2% CHG in 70% alcohol vs. Comparator</b>								
	<b>2% CHG in 70% alcohol (n=53)</b>			<b>Comparator (n=52)</b>			<b>P<sup>1</sup></b>	<b>Over all rate</b>
	<b>Dialysis Events</b>	<b>Patient- months</b>	<b>Rate (95% CI)</b>	<b>Dialysis Events</b>	<b>Patient- months</b>	<b>Rate (95% CI)</b>		
Access associated bacteraemia	2	3012	0.07 (0.06-0.08)	8	3012	0.27 (0.25-0.28)	0.06	0.33
Vascular access infection	5	3012	0.17 (0.15-0.18)	12	3012	0.40 (0.38-0.42)	0.10	0.56
Local access infection PO Antibiotics	1	3012	0.03 (0.03-0.04)	4	3012	0.13 (0.12-0.15)	0.22	0.17
Mortality at 12 months	5	3012	0.17 (0.15-0.18)	9	3012	0.30 (0.28-0.32)	0.30	0.46
Adverse reaction	4	3012	0.13 (0.12-0.15)	0	3012	0 (0-0.001)	0.06	0.13
Hospitalisation	37	3012	1.23 (1.19-1.27)	42	3012	1.39 (1.35-1.44)	0.58	2.62
Vascular access hospitalisation	4	3012	0.13 (0.12-0.15)	5	3012	0.17 (0.15-0.18)	0.75	0.30
Infection-related hospitalisation	12	3012	0.40 (0.38-0.42)	11	3012	0.36 (0.34-0.39)	0.83	0.76
Catheter infection-related hospitalisation	3	3012	0.1 (0.09-0.11)	6	3012	0.20 (0.18-0.22)	0.34	0.30
CVC removal	10	3012	0.33 (0.31-0.35)	15	3012	0.50 (0.47-0.52)	0.33	0.83
CVC removal dysfunction	6	3012	0.20 (0.18-0.22)	4	3012	0.13 (0.12-0.15)	0.55	0.33
CVC removal infection	3	3012	0.1 (0.09-0.11)	6	3012	0.20 (0.18-0.22)	0.34	0.30

<sup>1</sup>p-value, mid-p exact test

**Appendix 9.9 Secondary categorical outcomes<sup>1</sup>**  
**sub-comparison 1**

<b>Sub-comparison 1</b>						
<b>2% CHG in 70% alcohol vs. 0.5% CHG in 70% Alcohol</b>						
	<b>2% CHG (n=42)</b>	<b>0.5% CHG (n=42)</b>	<b>P<sup>2</sup></b>	<b>Relative Risk (95% CI)</b>	<b>Absolute Relative Risk (95% CI)</b>	<b>Total (n=84) N (%)</b>
	<b>N (%)</b>	<b>N (%)</b>				
Access associated bacteraemia	1 (2)	5 (12)	0.09 (0.20)	0.20 (0.02 to 1.64)	0.09 (-0.02 to 0.23)	6 (7)
Vascular access infection	4 (9)	9 (21)	0.13 (0.23)	0.44 (0.15 to 1.33)	0.12 (-0.04 to 0.27)	13 (15)
Local access infection PO Antibiotics	1 (2)	3 (7)	0.31 (0.62)	0.33 (0.04 to 3.08)	0.05 (-0.06 to 0.17)	4 (5)
Mortality at 12 months	4 (9)	5 (12)	0.72 (1.0)	0.80 (0.23 to 2.77)	0.02 (-0.12 to 0.17)	9 (11)
Adverse reaction	4 (9)	0	0.04 (0.12)	NA <sup>3</sup>	-0.10 (-0.22 to 0.01)	4 (5)
Hospitalisation	30 (71)	35 (83)	0.20 (.30)	0.86 (0.68 to 1.08)	0.12 (-0.06 to 0.30)	65 (76)
Vascular access hospitalisation	4 (9)	5 (12)	0.72 (1.0)	0.80 (0.23 to 2.77)	0.02 (-0.12 to 0.17)	9 (11)
Infection-related hospitalisation	11 (26)	11 (26)	1.0 (1.0)	1.0 (0.49 to 2.05)	0 (-0.18 to 0.18)	22 (26)
Catheter infection-related hospitalisation	2 (5)	6 (14)	0.14 (0.26)	0.33 (0.07 to 1.56)	0.09 (-0.04 to 0.23)	8 (9)
CVC removal	8 (19)	14 (33)	0.14 (0.21)	0.57 (0.27 to 1.22)	0.14 (-0.04 to 0.32)	22 (26)
CVC removal dysfunction	5 (12)	4 (9)	0.72 (1)	1.25 (0.36 to 4.33)	-0.02 (-0.17 to 0.17)	9 (11)
CVC removal infection	2 (5)	6 (14)	0.14 (0.26)	0.33 (0.07 to 1.56)	0.10 (-0.04 to 0.23)	8 (9)

<sup>1</sup>at least one episode; <sup>2</sup>p-value chi square (Fisher's Exact test); <sup>3</sup>NA, Not Applicable.

**Appendix 9.10 Secondary categorical outcomes per 100 patient-months sub-comparison 1**

<b>Sub Comparison 1 2% CHG in 70% alcohol vs. 0.5% CHG in 70% alcohol</b>							
	<b>2% CHG in 70% alcohol (n=42)</b>			<b>0.5% CHG in 70% alcohol (n=42)</b>			<b>P-Value</b>
	<b>Dialysis Events</b>	<b>Patient- months</b>	<b>Rate per 100 patient- months</b>	<b>Dialysis Events</b>	<b>Patient- months</b>	<b>Rate per 100 patient- months</b>	<b>P<sup>1</sup></b>
Access associated bacteraemia	1	2294	0.04	5	2294	0.22	0.12
Vascular access infection	4	2294	0.17	9	2294	0.40	0.18
Local access infection PO Antibiotics	1	2294	0.04	3	2294	0.13	0.37
Mortality at 12 months	4	2294	0.17	5	2294	0.22	0.75
Adverse reaction	4	2294	0.15	0	2294	NA <sup>2</sup>	0.06
Hospitalisation	30	2294	1.31	35	2294	1.52	0.54
Vascular access hospitalisation	4	2294	0.17	5	2294	0.22	0.75
Infection-related hospitalisation	11	2294	0.50	11	2294	0.50	1.00
Catheter infection-related hospitalisation	2	2294	0.09	6	2294	0.26	0.18
CVC removal	8	2294	0.35	14	2294	0.61	0.21
CVC removal dysfunction	5	2294	0.22	4	2294	0.17	0.75
CVC removal infection	2	2294	0.09	6	2294	0.26	0.18

<sup>1</sup>p-value, mid-p exact test; <sup>2</sup>NA, not applicable

## Appendix 9.11 Secondary categorical outcomes

### sub-comparison 2

Sub Comparison 2					
2% CHG in 70% alcohol vs. 0.05% aqueous CHG					
	2% CHG (n=11) N (%)	0.05%aq CHG (n=10) N (%)	P <sup>2</sup>	Relative Risk (95% CI)	Absolute Risk Reduction (95% CI)
Access associated bacteraemia	1 (9)	3 (30)	0.22 (0.31)	0.30 (0.04 to 2.46)	0.21 (-0.13 to 0.52)
Vascular access infection	1 (9)	3 (30)	0.22 (0.31)	0.30 (0.04 to 2.46)	0.21 (-0.13 to 0.52)
Local access infection PO Antibiotics	0	1 (10)	0.28 (0.48)	0.18 (0.01 to 3.41)	0.10 (-0.17 to 0.40)
Mortality at 12 months	1 (9)	4 (40)	0.10 (0.15)	0.10 ( 0.01 to 1.68)	0.31 (-0.06 to 0.61)
Adverse reaction	0	0	NA <sup>3</sup>	NA	NA
Hospitalisation	7 (64)	7 (70)	0.76 (1.0)	1 (0.50 to 1.66)	0.06 (-0.31 to 0.40)
Vascular access hospitalisation	0	0	NA	NA	NA
Infection-related hospitalisation	1 (9)	0	0.33 (1.0)	2.75 (0.12 to 60.70)	-0.1(-0.38 to 0.20)
Catheter infection-related hospitalisation	1 (9)	0	0.33 (1.0)	2.75 (0.12 to 60.70)	-0.1(-0.38 to 0.20)
CVC removal	2 (18)	1 (10)	0.60 (1.0)	1.82 (0.19 to 17.12)	-0.08 (-0.39 to 0.25)
CVC removal dysfunction	1 (9)	0	0.33 (1.0)	2.75 (0.12 to 60.70)	-0.1 (-0.38 to 0.20)
CVC removal infection	1 (9)	0	0.33 (1.0)	2.75 (0.12 to 60.70)	-0.1 (-0.38 to 0.20)

<sup>1</sup>at least one episode; <sup>2</sup>p-value chi square (Fisher's Exact test); <sup>3</sup>NA, Not Applicable.



**Appendix 9.12 Secondary categorical outcomes per 100 patient-months sub-comparison 2**

	Sub Comparison 2 2% CHG in 70% alcohol vs. 0.5% CHG in 70% alcohol						P- Value <i>P</i> <sup>1</sup>
	2% CHG in 70% alcohol ( <i>n</i> =11)			0.05% aqueous CHG ( <i>n</i> =10)			
	Dialysis Events	Patient- months	Rate per 100 patient- months	Dialysis Events	Patient- months	Rate per 100 patient- months	
Access associated bacteraemia	1	718	0.14	3	718	0.42	0.37
Vascular access infection	1	718	0.14	3	718	0.42	0.37
Local access infection PO Antibiotics	0	718	NA <sup>2</sup>	1	718	0.14	0.50
Mortality at 12 months	1	718	0.14	4	718	0.56	0.22
Adverse reaction	0	718	NA	0	718	NA	NA
Hospitalisation	7	718	0.97	7	718	0.97	1.0
Vascular access hospitalisation	0	718	NA	0	718	NA	NA
Infection-related hospitalisation	1	718	0.14	0	718	NA	0.50
Catheter infection-related hospitalisation	1	718	0.14	0	718	NA	0.50
CVC removal	2	718	0.28	1	718	0.14	0.62
CVC removal dysfunction	1	718	0.14	0	718	NA	0.50
CVC removal infection	1	718	0.14	0	718	NA	0.50

<sup>1</sup>p-value, mid-p exact test; <sup>2</sup>NA; not applicable

**Appendix 9.13 Continuous secondary outcomes per 100 patient-months main comparison**

<b>Main Comparison</b>								
<b>2% CHG in 70% alcohol vs. Comparator</b>								
	<b>2% CHG in 70% alcohol (n=53)</b>			<b>Comparator (n=52)</b>			<b>P<sup>1</sup></b>	<b>Total Rate</b>
	<b>Dialysis Events</b>	<b>Patient-months</b>	<b>Rate (95% CI)</b>	<b>Dialysis Events</b>	<b>Patient-months</b>	<b>Rate (95% CI)</b>		
IV antimicrobial starts	58	3012	1.93 (1.88-1.98)	75	3012	2.50 (2.43-2.55)	0.14	4.42
Positive blood cultures	8	3012	0.27 (0.25-0.28)	18	3012	0.60 (0.57-0.63)	0.05	0.86
Hospitalisation	90	3012	2.99 (2.93-3.05)	110	3012	3.65 (3.58-3.72)	0.16	6.64
Infection-related hospitalisation	16	3012	0.53 (0.50-0.56)	23	3012	0.76 (0.73-0.79)	0.27	1.29
Vascular access hospitalisation	5	3012	0.17 (0.15-0.18)	6	3012	0.20 (0.18-0.22)	0.77	0.37
Catheter infection-related hospitalisation	3	3012	0.1 (0.09-0.11)	7	3012	0.23 (0.22-0.25)	0.23	0.33

<sup>1</sup>p-value, mid-p exact test

## Appendix 9.14 Continuous secondary outcomes sub-comparison 1 & 2

	Sub comparison 1 0.5% CHG in 70% Alcohol			Sub comparison 2 0.05% aqueous CHG		
	Mean (SD)		<i>p</i> <sup>1</sup>	Mean (SD)		<i>p</i>
	2% CHG ( <i>n</i> =42)	0.5% CHG ( <i>n</i> =42)		0.2% CHG ( <i>n</i> =11)	0.05% aq CHG ( <i>n</i> =10)	
IV antimicrobial starts	1.12 (1.45)	1.43 (1.56)	0.35 (0.35)	1.0 (1.20)	1.50 (1.72)	0.44 (0.63)
Positive blood cultures	0.07 (0.34)	0.30 (0.71)	0.10 (0.10)	0.45 (0.7)	0.60 (1.08)	0.71 (1.0)
Hospitalisation	1.8 (1.65)	2.31 (2.21)	0.20 (0.30)	1.45 (1.51)	1.30 (1.34)	1.0 (1.0)
Vascular access hospitalisation	0.12 (0.40)	0.14 (0.42)	0.80 (0.73)	0.00 (0.000)	0.00 (0.000)	NA <sup>2</sup>
Infection related hospitalisation	0.36 (0.70)	0.55 (1.15)	0.36 (0.80)	0.1 (0.30)	0.00 (0.000)	0.34 (0.34)
Catheter infection-related hospitalisation	0.05 (0.22)	0.17 (0.44)	0.12 (0.13)	0.1 (0.30)	0.00 (0.000)	0.34 (0.34)

<sup>1</sup>*p*-value independent two sample *t*-test (Mann-Whitney); <sup>2</sup>NA, not applicable

**Appendix 9.15      Continuous secondary outcomes per 100 patient-months sub-comparison 1**

<b>Sub Comparison 1</b>							
<b>2% CHG in 70% alcohol vs. 0.5% CHG in 70% alcohol</b>							
	<b>2% CHG in 70% alcohol (n=42)</b>			<b>0.5% CHG in 70% alcohol (n=42)</b>			<b>P<sup>†</sup></b>
	<b>Dialysis Events</b>	<b>Patient- months</b>	<b>Rate per 100 patient- months</b>	<b>Dialysis Events</b>	<b>Patient- months</b>	<b>Rate per 100 patient- months</b>	
IV antimicrobial starts	47	2294	2.05	60	2294	2.62	0.21
Positive blood cultures	3	2294	0.13	12	2294	0.52	0.02
Hospitalisation	74	2294	3.22	97	2294	4.23	0.08
Infection-related hospitalisation	15	2294	0.65	23	2294	1.0	0.20
Vascular access hospitalisation	5	2294	0.22	6	2294	0.26	0.77
Catheter infection-related hospitalisation	2	2294	0.09	7	2294	0.30	0.11

<sup>†</sup>p-value, mid-p exact test

**Appendix 9.16 Continuous secondary outcomes per 100 patient-months Sub-comparison 2**

<b>Sub Comparison 2</b>							
<b>2% CHG in 70% alcohol vs. 0.05% aqueous CHG</b>							
	<b>2% CHG in 70% alcohol (n=113)</b>			<b>0.05% aqueous CHG (n=10)</b>			
	<b>Dialysis Events</b>	<b>Patient- months</b>	<b>Rate per 100 patient- months</b>	<b>Dialysis Events</b>	<b>Patient- months</b>	<b>Rate per 100 patient- months</b>	<b>P<sup>1</sup></b>
IV antimicrobial starts	11	718	1.53	15	718	2.09	0.44
Positive blood cultures	5	718	0.70	6	718	0.83	0.77
Hospitalisation	16	718	2.23	13	718	1.81	0.58
Infection-related hospitalisation	1	718	0.14	0	718	NA	0.50
Vascular access hospitalisation	0	718	NA <sup>2</sup>	0	718	NA	NA
Catheter infection-related hospitalisation	1	718	0.14	0	718	NA	0.50

<sup>1</sup>p-value, mid-p exact test; <sup>2</sup>NA, not applicable

**Appendix 9.17 Proportion surviving CVC-related events including survival curves sub-comparison 1**

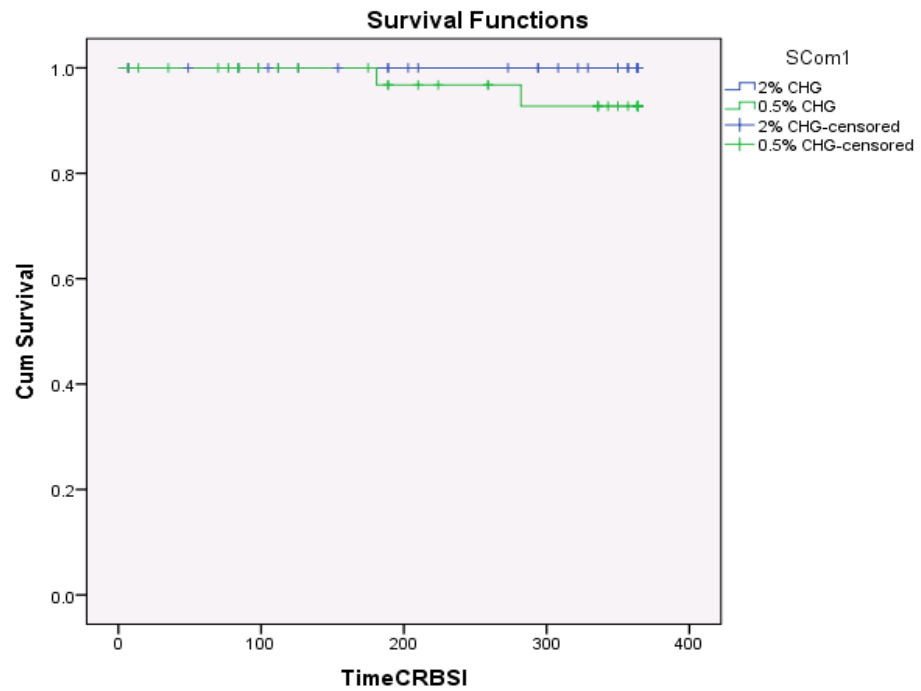
		Sub-Comparison1								
		2% CHG in 70% alcohol vs. 0.5% CHG in 70% alcohol								
		2% CHG in 70% alcohol N=42		Cumulative Events N		Remaining Cases N (%)		0.5% CHG in 70% alcohol N=42		
Time Interval		Cumulative Proportion Surviving at the Time		Cumulative Events N	Remaining Cases N (%)	Cumulative Proportion Surviving at the Time		Cumulative Events N	Remaining Cases N (%)	Log Rank Test
		Estimate	Std. Error			Estimate	Std. Error			
CRBSI <sup>1</sup>	6 months	0	0	0	29 (69)	0.97	0.03	1	28 (67)	$X^2=2.08$ , $df^3=1$ , $p=0.15$
	12 months	0	0	0		0.93	0.05	2		
CABSI <sup>2</sup>	6 months	0.97	0.03	1	28 (67)	0.94	0.04	2	27 (64)	$X^2=0.34$ , $df=1$ , $p=0.55$
	12 months	0.97	0.03	1		0.94	0.04	2		
Local access infection	6 months	0.93	0.04	2	28 (67)	0.95	0.03	2	29 (69)	$X^2=0.11$ , $df=1$ , $p=0.73$
	12 months	0.90	0.05	3		0.88	0.06	4		
CVC removal	6 months	0.92	0.05	3	29 (69)	0.86 <sup>4</sup>	0.06	5	28 (70)	$X^2=0.99$ , $df=1$ , $p=0.32$
	12 months	0.74	0.08	8		0.63 <sup>4</sup>	0.09	12		
CVC removal infection	6 months	0.97	0.03	1	30 (71)	0.91 <sup>5</sup>	0.05	3	27 (66)	$X^2=1.46$ , $df=1$ , $p=0.23$
	12 months	0.94	0.04	2		0.83	0.07	5		

<sup>1</sup>CRBSI, Catheter-related bloodstream infection; <sup>2</sup>CABSI, Catheter-associated bloodstream infection; <sup>3</sup>df, Degrees of freedom;

<sup>4</sup>data is estimated on 40 participants; <sup>5</sup>data is estimated on 41 participants

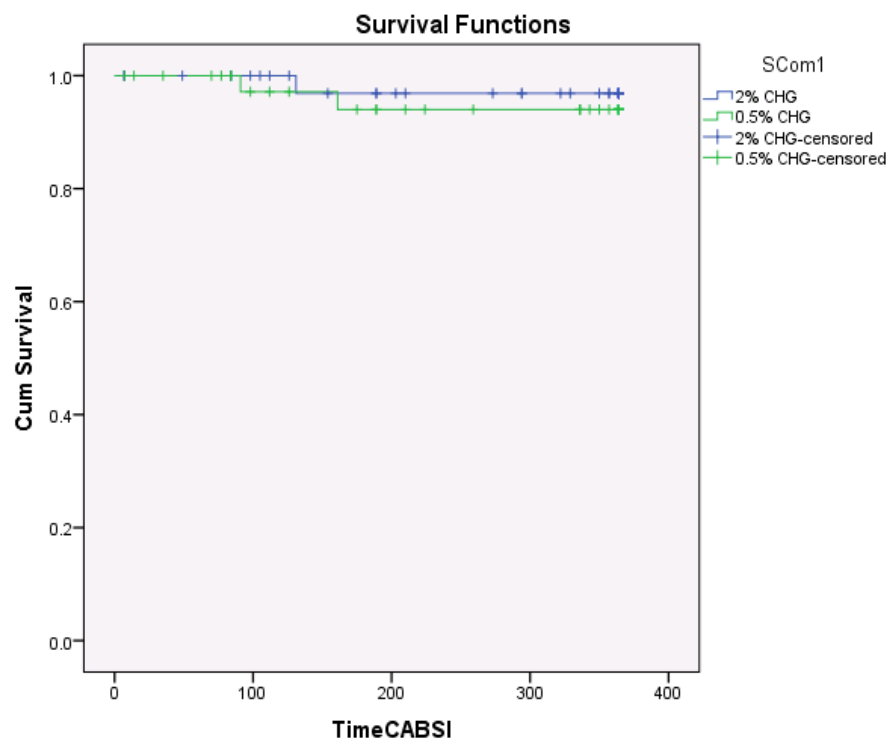
### Kaplan-Meier curve for time to CRBSI (sub-comparison 1)

2% CHG in 70% isopropyl alcohol (blue) v. 0.5% CHG in 70% alcohol (green)



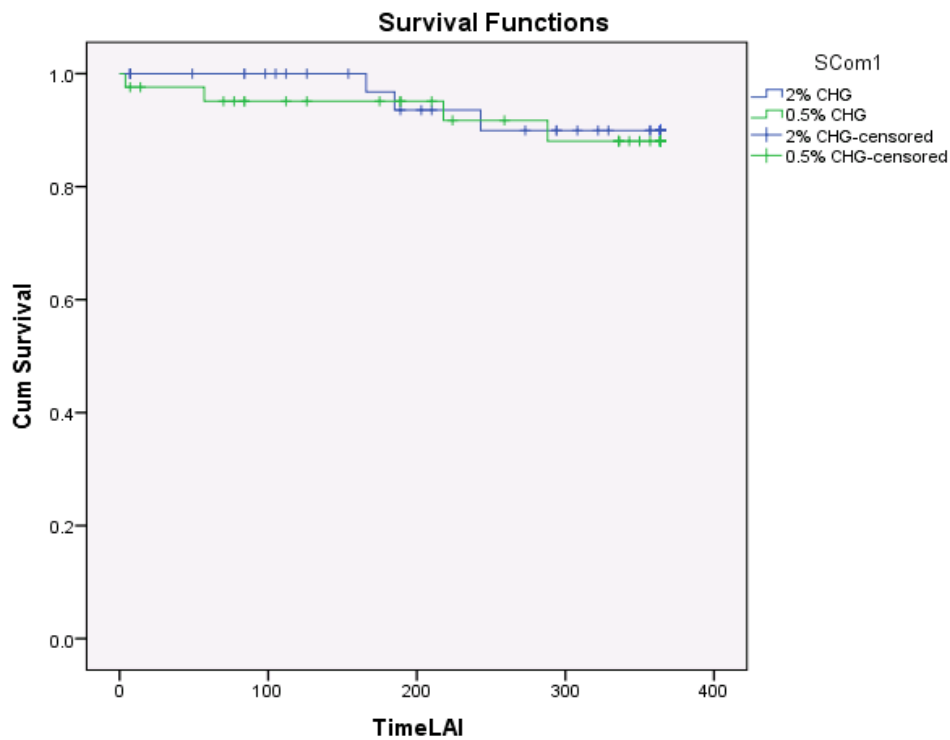
### Kaplan-Meier curve for time to CABSIS (sub-comparison 1)

2% CHG in 70% isopropyl alcohol (blue) v. 0.5% CHG in 70% alcohol (green)



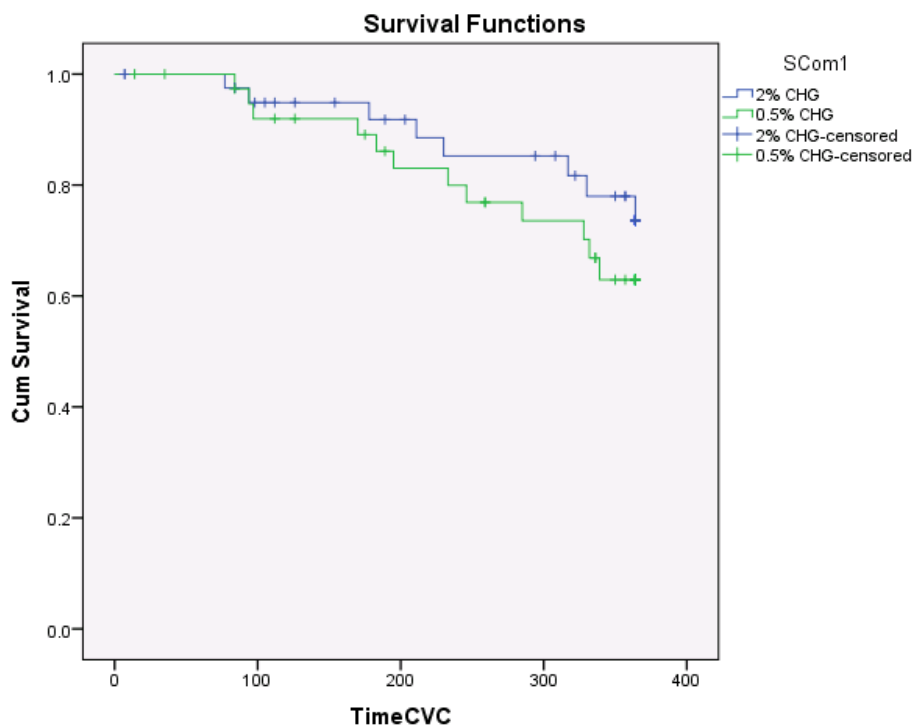
### Kaplan-Meier curve for time to LAI (sub-comparison 1)

2% CHG in 70% isopropyl alcohol (blue) v. 0.5% CHG in 70% alcohol (green)



### Kaplan-Meier curve for time to CVC removal (sub-comparison 1)

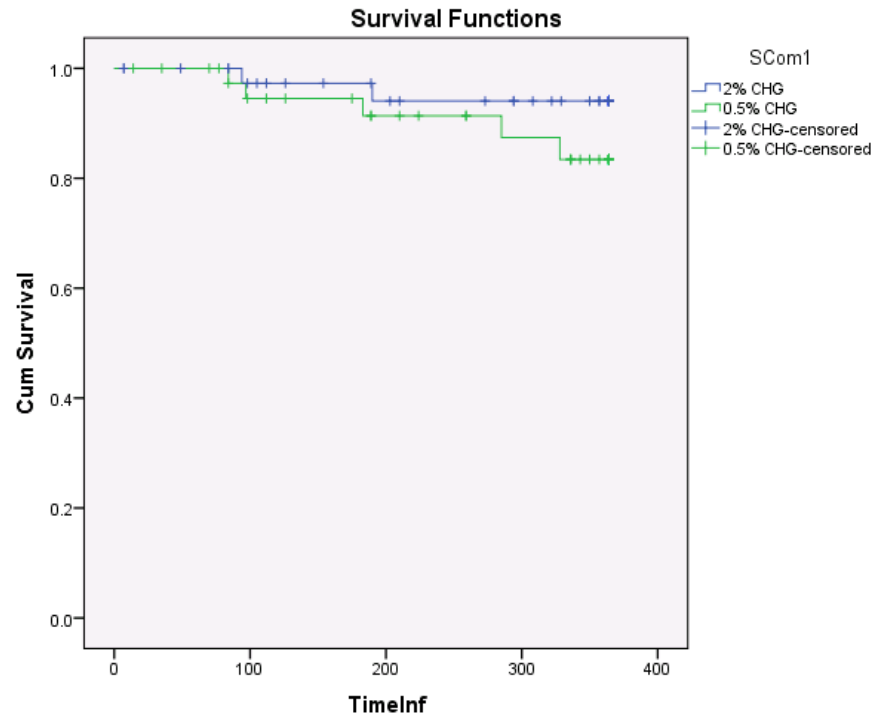
2% CHG in 70% isopropyl alcohol (blue) v. 0.5% CHG in 70% alcohol (green)





**Kaplan-Meier curve for time to CVC removal for infection (sub-comparison 1)**

2% CHG in 70% isopropyl alcohol (blue) v. 0.5% CHG in 70% alcohol (green)



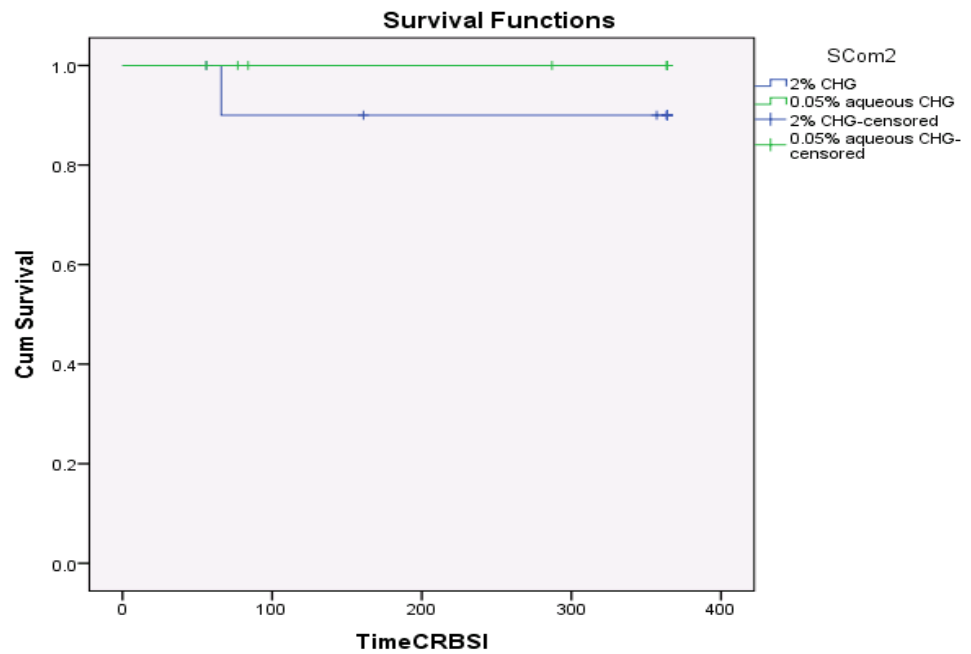
**Appendix 9.18 Proportion surviving CVC-related events including survival curves sub-comparison 2**

		Sub-Comparison 2 2% CHG in 70% alcohol vs. 0.05% aqueous CHG								
		2% CHG in 70% alcohol N=11		2% CHG in 70% alcohol vs. 0.05% aqueous CHG		0.05% aqueous CHG N=10				
Time Interval		Cumulative Proportion Surviving at the Time		Cumulative Events N	Remaining Cases N (%)	Cumulative Proportion Surviving at the Time		Cumulative Events N	Remaining Cases N (%)	Log Rank Test
		Estimate	Std. Error			Estimate	Std. Error			
CRBSI <sup>1</sup>	6 months	0.90	0.09	1	8 (73)	0	0	0	8(80)	$X^2=0.90$ , $df^3=1$ , $p=0.34$
	12 months	0.90	0.09	1		0	0	0		
CABSI <sup>2</sup>	6 months	0	0	0	8 (73)	0.89	0.10	1	6 (60)	$X^2=2.68$ , $df=1$ , $p=0.10$
	12 months	0	0	0		0.71	0.18	2		
Local access infection	6 months	0	0	0	8 (73)	0	0	0	7 (70)	NA <sup>4</sup>
	12 months	0	0	0		0	0	0		
CVC removal	6 months	0.81	0.12	2	7 (64)	0.87	0.12	1	7 (70)	$X^2=0.30$ , $df=1$ , $p=0.58$
	12 months	0.81	0.12	2		0.87	0.12	1		
CVC removal infection	6 months	0.90	0.09	1	8 (73)	0	0	0	8(80)	$X^2=0.90$ , $df=1$ , $p=0.34$
	12 months	0.90	0.09	1		0	0	0		

<sup>1</sup>CRBSI, Catheter-related bloodstream infection; <sup>2</sup>CABSI, Catheter-associated bloodstream infection; <sup>3</sup>df, Degrees of freedom; <sup>4</sup>NA, not applicable

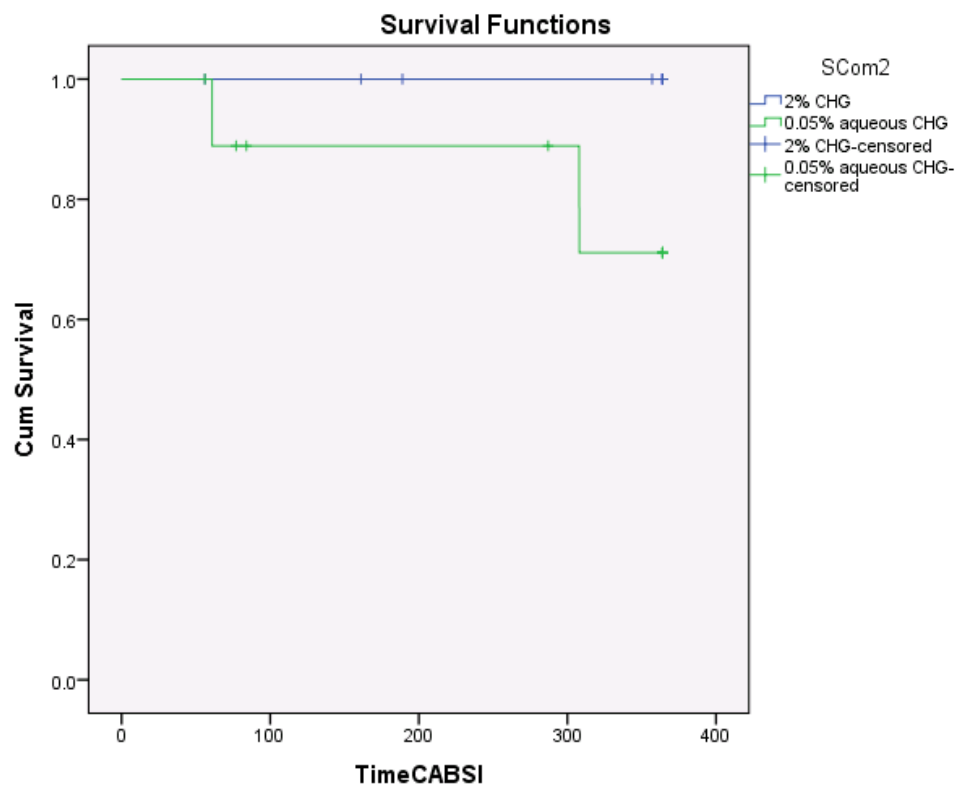
### Kaplan-Meier curve for time to CRBSI (sub-comparison 2)

2% CHG in 70% isopropyl alcohol (blue) v. 0.05% aqueous CHG (green)



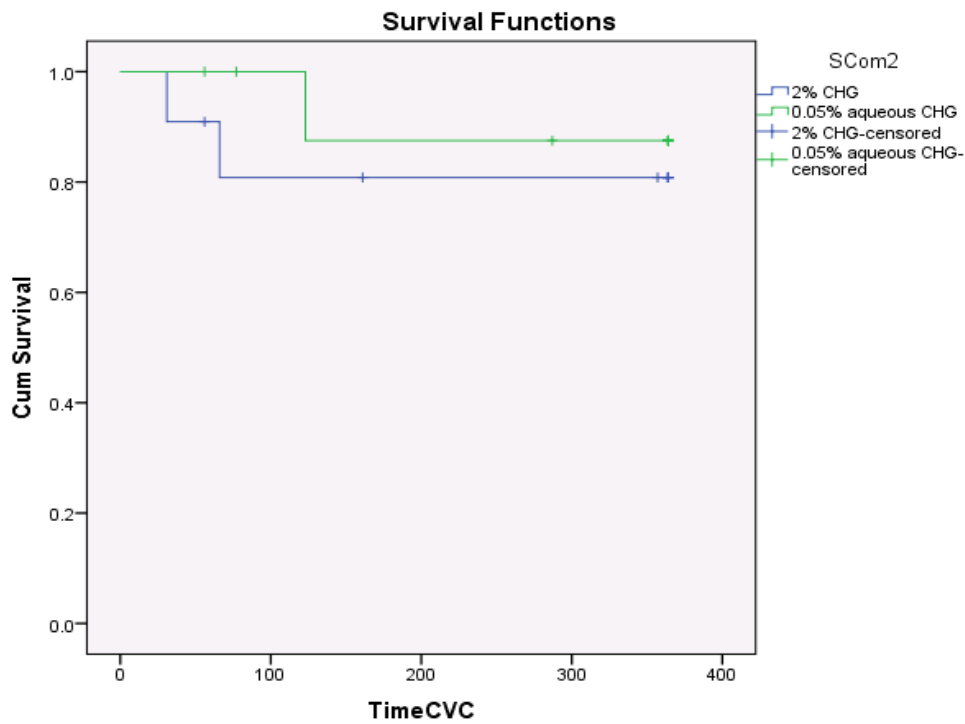
### Kaplan-Meier curve for time to CABSIS (sub-comparison 2)

2% CHG in 70% isopropyl alcohol (blue) v. 0.05% aqueous CHG (green)



### Kaplan-Meier curve for time to CVC removal (sub-comparison 2)

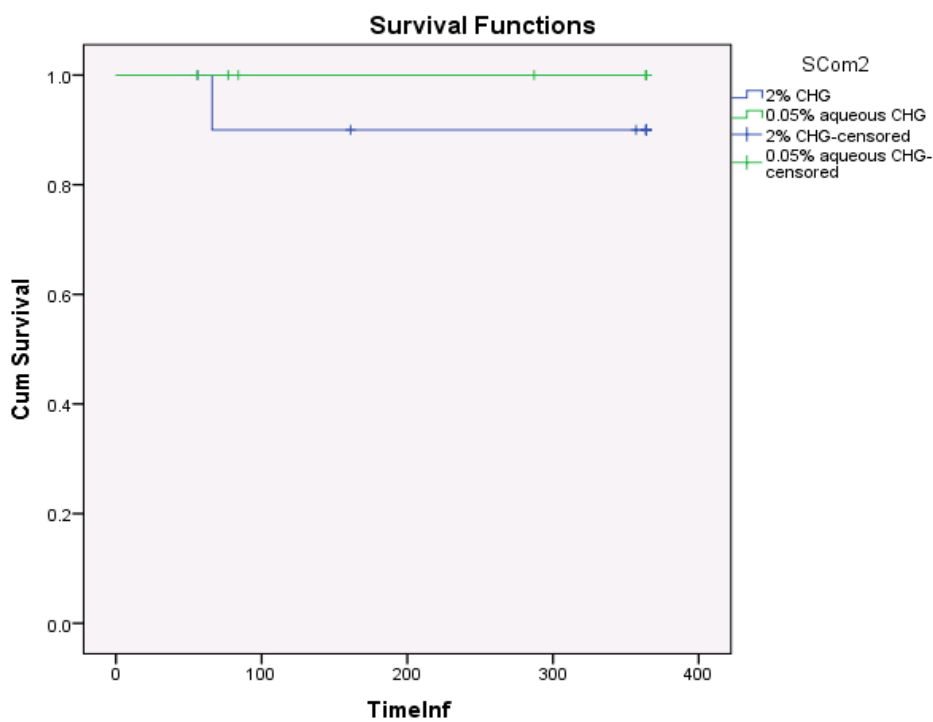
2% CHG in 70% isopropyl alcohol (blue) v. 0.05% aqueous CHG (green)



### Kaplan-Meier curve for time to CVC removal due to infection (sub-comparison 2)

(sub-comparison 2)

2% CHG in 70% isopropyl alcohol (blue) v. 0.05% aqueous CHG (green)



## Appendix 9.19 Forced entry logistic regression model

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	21.696	15	.116
	Block	21.696	15	.116
	Model	21.696	15	.116

Classification Table<sup>a</sup>

Observed		Predicted			Percentage Correct
		CABSI <sup>1</sup>			
		0	1		
Step 1	CABSI	0	100	0	100.0
		1	3	2	40.0
Overall Percentage					97.1

<sup>1</sup>CABSI, Catheter-associated bloodstream infection

a. The cut value is .500

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	18.507 <sup>a</sup>	.187	.587

a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

Variable(s) entered step 1: FacilityCode, Sex, Age, ComoDiabet, Comolmmuno, PreviousCVC, CVCinfection, DurationCVC, AntibioticsAny, Locksolution, SrAlbumin

	B	S.E	Wald	df	Sig,	Exp (B)	95% C.I. for Exp (B)	
							Lower	Upper
FacilityCode			.970	2	.616			
FacilityCode(1)	-1.828	2.404	.578	1	.447	.161	.001	17.900
FacilityCode(2)	.385	2.297	.028	1	.867	1.469	.016	132.414
Sex(1)	-20.420	4410.747	.000	1	.996	.000	.000	.
Age	-.013	.052	.060	1	.806	.987	.892	1.093
ComoDiabet(1)	-1.069	2.072	.266	1	.606	.343	.006	19.903
Comolmmuno(1)	1.319	1.793	.541	1	.462	3.739	.111	125.496
PreviousCVC(1)	3.135	2.327	1.816	1	.178	22.988	.241	2197.154
CVCinfection			1.973	2	.373			
CVCinfection(1)	-25.456	40693.306	.000	1	1.000	.000	.000	.
CVCinfection(2)	-21.731	40693.306	.000	1	1.000	.000	.000	.
DurationCVC	.057	.071	.662	1	.416	1.059	.922	1.216
AntibioticsAny(1)	-21.642	4584.319	.000	1	.996	.000	.000	.
Locksolution			.000	3	1.000			
Locksolution(1)	-22.680	41202.820	.000	1	1.000	.000	.000	.
Locksolution(2)	-3.860	40453.543	.000	1	1.000	.021	.000	.
Locksolution(3)	-18.747	44802.577	.000	1	1.000	.000	.000	.
SrAlbumin	.300	.285	1.108	1	.293	1.349	.772	2.357
Constant	14.091	57744.828	.000	1	1.000	1316728.690		

**Correlation matrix**

	Constant	Facility Code (1)	Facility Code (2)	Sex (1)	Age	Como Diabet (1)	Como Immun (1)	Pre CVC (1)	CVC Infect (1)	CVC Infect (2)	Dur CVC	Antib (1)	Lock (1)	Lock (2)	Lock (3)	SrAl
Constant	1.000	.000	.000	-.076	.000	.000	.000	.000	-.714	-.714	.000	-.159	-.697	-.710	-.641	.000
FacilityCode(1)	.000	1.000	.496	.000	.122	.499	-.081	-.390	.000	.000	-.292	.000	.000	.000	.000	-
FacilityCode(2)	.000	.496	1.000	.000	.012	-.151	.020	.079	.000	.000	.196	.000	.000	.000	.000	-
Sex(1)	-.076	.000	.000	1.000	.000	.000	.000	.000	.108	.108	.000	.000	.000	.000	.000	.000
Age	.000	.122	.012	.000	1.000	-.120	-.071	.013	.000	.000	.010	.000	.000	.000	.000	.434
Como Diabet(1)	.000	.499	-.151	.000	-.120	1.000	-.152	-.562	.000	.000	-.506	.000	.000	.000	.000	-
Como Immun(1)	.000	-.081	.020	.000	-.071	-.152	1.000	.547	.000	.000	.471	.000	.000	.000	.000	.091
Previous CVC(1)	.000	-.390	.079	.000	.013	-.562	.547	1.000	.000	.000	.633	-.001	.000	.000	.000	.529
CVC infection(1)	-.714	.000	.000	.108	.000	.000	.000	.000	1.000	1.000	.000	.113	.013	.013	.012	.000
CVC infection(2)	-.714	.000	.000	.108	.000	.000	.000	.000	1.000	1.000	.000	.113	.013	.013	.012	.000
DurationCVC	.000	-.292	.196	.000	.010	-.506	.471	.633	.000	.000	1.000	-.001	.000	.000	.000	.460
AntibioticsAny (1)	-.159	.000	.000	.000	.000	.000	.000	-.001	.113	.113	-.001	1.000	.111	.113	.102	-
Locksolution(1)	-.697	.000	.000	.000	.000	.000	.000	.000	.013	.013	.000	.111	1.000	.982	.887	.000
Locksolution(2)	-.710	.000	.000	.000	.000	.000	.000	.000	.013	.013	.000	.113	.982	1.000	.903	.000
Locksolution(3)	-.641	.000	.000	.000	.000	.000	.000	.000	.012	.012	.000	.102	.887	.903	1.000	.000
SrAlbumin	.000	-.536	-.004	.000	.434	-.661	.091	.529	.000	.000	.460	-.001	.000	.000	.000	1.00

## Appendix 9.20 Stepwise entry logistic regression model

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	7.282	1	.007
	Block	7.282	1	.007
	Model	7.282	1	.007
Step 2	Step	5.887	1	.015
	Block	13.170	2	.001
	Model	13.170	2	.001

Classification Table<sup>a</sup>

		Observed		Predicted		Percentage Correct
		CABSI <sup>1</sup>		0	1	
Step 1	CABSI	0	100	0	100.0	
		1	5	0	.0	
	Overall Percentage					95.2
Step 2	CABSI	0	100	0	100.0	
		1	5	0	.0	
	Overall Percentage					95.2

<sup>1</sup>CABSI, Catheter-associated bloodstream infection

a. The cut value is .500

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	32.921 <sup>a</sup>	.067	.211
2	27.034 <sup>a</sup>	.118	.371

a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.



**Variables in the equation**

		B	S.E	Wald	df	Sig,	Exp (B)	95% C.I. for Exp (B)	
								Lower	Upper
Step 1 <sup>a</sup>	Sex(1)	-18.962	5520.929	.000	1	.997	.000	.000	
	Constant	-2.241	.470	22.690	1	.000	.106		
	Sex(1)	-19.012	5153.388	.000	1	.997	.000	.000	
	AntibioticsAny(1)	-18.783	5715.280	.000	1	.997	.000	.000	
Step 2 <sup>b</sup>	Constant	-1.609	.490	10.793	1	.001	.200		

a. Variable(s) entered on step 1: Sex.

b. Variable(s) entered on step 2: AntibioticsAny.

## Appendix 9.21 Forced entry and stepwise logistic regression model with subset of predictor variables

### Forced entry

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	19.540	11	.052
	Block	19.540	11	.052
	Model	19.540	11	.052

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	20.663 <sup>a</sup>	.170	.534

a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

**Forced entry: variables in the equation**

	B	S.E	Wald	df	Sig,	Exp (B)	95% C.I. for Exp (B)		
							Lower	Upper	
Step 1 <sup>a</sup>	Sex(1)	-19.397	4787.190	.000	1	.997	.000	.	
	ComoDiabet(1)	.170	1.393	.015	1	.903	1.185	18.190	
	PreviousCVC(1)	1.548	1.509	1.051	1	.305	4.701	90.568	
	CVCinfection			2.511	2	.285			
	CVCinfection(1)	-19.877	40814.756	.000	1	1.000	.000	.	
	CVCinfection(2)	-17.293	40814.756	.000	1	1.000	.000	.	
	DurationCVC	.016	.052	.102	1	.749	1.017	1.125	
	AntibioticsAny(1)	-19.041	5239.345	.000	1	.997	.000	.	
	Locksolution			.000	3	1.000			
	Locksolution(1)	-19.187	41382.826	.000	1	1.000	.000	.	
	Locksolution(2)	-1.435	40533.023	.000	1	1.000	.238	.	
	Locksolution(3)	-18.338	45131.470	.000	1	1.000	.000	.	
	SrAlbumin	.145	.153	.903	1	.342	1.156	.857	1.559
	Constant	12.285	57997.150	.000	1	1.000	216494.327		

a. Variable(s) entered on step 1: Sex, ComoDiabet, PreviousCVC, CVCinfection, DurationCVC, AntibioticsAny, Locksolution, SrAlbumin.

**Stepwise entry**

Omnibus Tests of Model Coefficients				
		Chi-square	df	Sig.
Step 1	Step	7.282	1	.007
	Block	7.282	1	.007
	Model	7.282	1	.007
Step 2	Step	5.887	1	.015
	Block	13.170	2	.001
	Model	13.170	2	.001

Model Summary			
Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	32.921 <sup>a</sup>	.067	.211
2	27.034 <sup>a</sup>	.118	.371

a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

**Stepwise entry: variables in the equation**

		B	S.E	Wald	df	Sig,	Exp (B)	95% C.I. for Exp (B)	
								Lower	Upper
Step 1 <sup>a</sup>	Sex(1)	-18.962	5520.929	.000	1	.997	.000	.000	
	Constant	-2.241	.470	22.690	1	.000	.106		
	Sex(1)	-19.012	5153.388	.000	1	.997	.000	.000	
Step 2 <sup>b</sup>	AntibioticsAny(1)	-18.783	5715.280	.000	1	.997	.000	.000	
	Constant	-1.609	.490	10.793	1	.001	.200		

a. Variable(s) entered on step 1: Sex

b. Variable(s) entered on step 2: AntibioticsAny.

## Appendix 9.22 Multicollinearity tests

### Coefficients<sup>a</sup>

	Unstandardized Coefficients		Standardized Coefficients	<i>t</i>	Sig.	Collinearity Statistics		
	B	Std. Error	Beta			Tolerance	VIF	
Step 1 <sup>a</sup>	(Constant)	-.407	.367		-1.109	.270		
	FacilityCode	.026	.038	.083	.674	.502	.609	1.643
	Sex	.111	.042	.262	2.637	.010	.928	1.078
	Age	-.001	.001	-.097	-.938	.350	.859	1.164
	ComoDiabet	-.009	.047	-.019	-.185	.854	.908	1.102
	SrAlbumin	.006	.007	.127	.961	.339	.525	1.906
	Immunosupp	-.043	.046	-.093	-.941	.349	.928	1.077
	PreviousCVC	-.054	.046	-.127	-1.179	.241	.792	1.263
	CVCinfection	.081	.047	.181	1.720	.089	.822	1.217
	Locksolution	.026	.050	.053	.511	.610	.860	1.163
	AntibioticsAny	.097	.044	.222	2.192	.031	.893	1.120
	Duration of CVC	6.836E-005	.002	.004	.044	.965	.909	1.100

a. Dependent Variable: CABS (Catheter-associated bloodstream infection)

### Collinearity diagnostic

	Dimension	Eigenvalue	Condition Index	Variance Proportions											
				Constant	Facility Code	Sex	Age	Como Diabe	Sr Albumin	Immun osupp	Previous CVC	CVC infec	Lock	Antibi	Dur CVC
<b>Model 1</b>	1	8.348	1.000	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
	2	.831	3.169	.00	.00	.00	.00	.24	.00	.00	.08	.30	.00	.01	.04
	3	.827	3.177	.00	.00	.00	.00	.13	.00	.40	.03	.09	.00	.01	.05
	4	.575	3.810	.00	.00	.01	.00	.39	.00	.37	.00	.19	.00	.00	.00
	5	.443	4.342	.00	.00	.00	.00	.15	.00	.04	.09	.05	.00	.00	.76
	6	.374	4.722	.00	.00	.00	.00	.00	.00	.13	.66	.23	.00	.07	.10
	7	.344	4.924	.00	.01	.01	.00	.04	.00	.02	.03	.07	.00	.77	.00
	8	.097	9.291	.00	.52	.01	.00	.00	.01	.00	.03	.02	.04	.06	.00
	9	.080	10.233	.00	.01	.89	.07	.00	.00	.00	.01	.01	.02	.02	.00
	10	.040	14.391	.00	.07	.06	.77	.00	.01	.02	.00	.03	.14	.02	.01
	11	.038	14.729	.01	.00	.00	.01	.01	.06	.01	.00	.00	.65	.00	.03
	12	.002	62.596	.99	.39	.02	.14	.03	.92	.01	.07	.01	.15	.03	.00

a. Dependent Variable: CABS (Catheter-associated bloodstream infection)