Electroconvulsive therapy for depression and ketamine for relapse prevention: factors affecting response, cognition and research participation

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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 my own work, with contributions from others outlined below.

Studies 1-4 were completed in conjunction with my colleague Toni Galligan. Randomised treatment in Study 1 was completed with the assistance of Dr Enda Shanahan, anaesthetist and Louise Donnelly, research nurse. Research assistants who assisted with data entry for studies 1-4 are Gabriele Guscuite, Niamh Campbell, Claire Slattery and Meabh Foley. Dr Erik Kolshus provided training in the use of the Hamilton Rating Scale for Depression, used in Studies 1-4. Study 5 was completed in conjunction with research assistants Stephanie O'Connor and Caroline McHugh. I consulted with Dr Olivia Mason at the statistical consultation service, University College Dublin Centre for Support and Training in Analysis and Research, to confirm my planned approach to non-parametric data and correction for multiple comparisons in Study 2. For Study 2, Dr Ana Jelovac provided training to myself and Toni Galligan in the use of the Kopelman Autobiographical Memory Interview. All studies were designed in collaboration with my supervisor, Declan McLoughlin.

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Summary

This thesis comprises five clinical research studies.

Study 1. Pilot randomised controlled trial: Ketamine vs midazolam for depression relapse prevention following successful electroconvulsive therapy (ECT), the KEEP-WELL Trial (NCT02414932)

The objective of this study was to conduct a randomised controlled pilot trial of a four-week course of once-weekly ketamine or midazolam infusions for relapse prevention following ECT for depression to assess trial procedures for feasibility for a future definitive trial. Forty-three participants were recruited to a monitoring phase but only six of these were eligible and agreeable to randomised treatment. No participant completed the treatment protocol. The study found that the trial protocol is not feasible and therefore not suitable for a definitive trial. Future studies could consider open-label treatment, recruitment of participants who live very nearby.

Study 2. Prospective cohort study: Effects of mood and time on autobiographical memory before and after electroconvulsive therapy for depression

This study aimed to examine performance on the full Kopelman Autobiographical Memory Interview in severely depressed patients (n=27) before and after a course of ECT and to compare this with the performance of healthy controls (n=72) before and after a 4-week interval. I found that autobiographical memory is profoundly impaired in depressed people and that the Kopelman Autobiographical Memory Interview is likely not adequately sensitive to change to identify any overall change in autobiographical memory performance after ECT.

Study 3. Prospective cohort study: Effect of personality disorder on response to ECT for depression: a prospective cohort study

The aim of this study was to assess for association between scores on the brief personality screening tool, the self-reported Standardised Assessment of Personality – Abbreviated Scale (SAPAS) and response to ECT among patients with unipolar major depressive disorder (n=49). I found that while the presence of likely personality disorder on the SAPAS was associated with lower ECT response rate, it is unlikely to contribute to cognitive impairment.

Study 4. Prospective cohort study: Childhood trauma and response to ECT for depression: a prospective cohort study

This study aimed to examine report of childhood trauma and recent trauma in a severely depressed population referred for ECT (n=44) and assess for association between presence of childhood or recent trauma and response to ECT. I found that both childhood and recent trauma were common in depressed people having ECT and that the presence of childhood trauma is associated with reduced response rate to ECT.

Study 5. Retrospective chart review: Involuntary and voluntary electroconvulsive therapy: a case-control study

In this study I compared courses of involuntary ECT (n=48) with matched voluntary ECT courses (n=96) in terms of clinical and demographic factors, treatment requirements, and outcomes. I found that the groups were similar in many respects and results of clinical ECT research can therefore be generalised to people having involuntary ECT.

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List of Abbreviations

ACE-III: Addenbrooke's Cognitive Examination-III

APA: American Psychiatric Association

BP: Brief Pulse

BPRS: Brief Psychiatric Rating Scale

BT: Bitemporal

CADSS: Clinician-Administered Dissociative States Scale

CANTAB®: Cognitive assessment software produced by Cambridge Cognition

CBT: Cognitive Behavioural Therapy

CGI-I: Clinical Global Impression - Improvement Score

CGI-S: Clinical Global Impression - Severity Score

CI: Confidence Interval

CORE: Consortium for Research in Electroconvulsive Therapy

CRF: Case Report Form

CRTEQ: Childhood and Recent Traumatic Events Questionnaire

CSTAR: University College Dublin's Centre for Support and Training in Analysis and Research

CUAMI: Columbia University Autobiographical Memory Interview

CUAMI-SF: Columbia University Autobiographical Memory Interview, short form

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition

ECT: electroconvulsive therapy

EEG: electroencephalogram

EHI: Edinburgh Handedness Inventory

EKG: electrocardiogram

HNK: hydroxynorketamine

HPRA: Health Products Regulatory Authority

HRSD-24: Hamilton Rating Scale for Depression, 24-item

ICD-10: International Classification of Diseases, tenth edition

K-AMI: Kopelman Autobiographical Memory Interview

kg: kilogram

mC: millicoulomb

mg: milligram

MHA: Mental Health Act, 2001

MHC: Mental Health Commission

MoCA: Montreal Cognitive Assessment

MSMTRD: Maudsley Staging Method for Treatment Resistance in Depression

mTOR: mammalian Target of Rapamycin

NART: National Adult Reading Test

NART: National Adult Reading Test

NICE: National Institute for Health and Care Excellence

NMDAR: N-methyl-D-aspartate receptor

PPI: Participant and Public Involvement

PRISE: Patient-Rated Inventory of Side Effects

REC: Research Ethics Committee

RUL: Right Unilateral

SAPAS: Standardised Assessment of Personality – Abbreviated Scale

SCID: Structured Clinical Interview for DSM IV Disorders

SCID-II: Structured Clinical Interview for DSM-IV Axis II Personality Disorders

sMMSE: standardised Mini Mental State Exam

SSRI: selective serotonin reuptake inhibitor

UBP: Ultra-brief Pulse

YMRS: Young Mania Rating Scale

Table of Contents

1. Background

1.1 Depression

1.1.1 Impact and aetiology

Depression is the single largest contributor to global disability (7.5% of all years lived with disability in 2015) (World Health Organisation, 2017). The total number of people with depression globally was estimated at over 300 million in 2015 (World Health Organisation, 2017). Lost productivity, lost educational attainment, and the cost of provision of care both in the community and in inpatient units combine to make depression the most costly European brain disorder, accounting for 1% of the total European economy (Wittchen et al., 2011). Local population-based surveys showed that 8% of people in Ireland reported experiencing symptoms of at least moderate depression within the previous two weeks (Central Statistics Office, 2015). Risk of depression is increased by poverty, unemployment, stressful life events such as bereavement, medical illness and substance use (World Health Organisation, 2017). Research suggesting that the natural history of depression is such that untreated episodes may resolve within two months to one year is outdated (Lehmann, 1983) as depression is now treated on identification and modern estimates of the duration of untreated episodes is unavailable. The consequences of untreated depression include not only familial and societal burden imposed by impairment in social, occupational and educational functioning, but also risks of self-neglect, poor nutrition, experience of violence, and self-harm or suicide. In Ireland, although recent provisional data suggest the suicide rate is decreasing, suicide remains a public health concern, with a rate of 8.2 deaths by suicide per 100,000 population in 2016 (Central Statistics Office, 2017).

Mortality in people with mental illness is unacceptably high. In high-income countries people with mental disorders including depression die 15-20 years earlier than those in the general population (Thornicroft 2011, Wahlbeck et al. 2011). Not only is mortality greater

among people with mental illness, but the presence of depression increases cardiac mortality in patients with coronary heart disease (Penninx et al. 2001). Both the presence and severity of depression predict higher mortality in people with cancer diagnoses (Pinquart and Duberstein 2010).

There are many theories about the aetiology of depression, which is not yet fully understood. It seems certain that multiple interacting genetic and environmental factors influence the onset of the illness (Goldberg, 2006). There is strong evidence for both the monoamine hypothesis (Krishnan and Nestler, 2008) the hypothalamic-pituitary-adrenal axis dysfunction hypothesis (Pariante and Lightman, 2008), and the neurotrophic hypothesis (Hayley et al., 2005). There is also growing evidence of the role of inflammation (Kiecolt-Glaser et al., 2015), the influence of gut microbiota (Dinan and Cryan, 2012) and, to a lesser extent, micro-RNAs (Kolshus et al., 2014). The discovery of ketamine as a rapid-acting antidepressant (Berman et al., 2000) partly drove the advent of the neurotrophic hypothesis of depression, discussed below.

1.1.2 Diagnosis of depression

Depression is clinically diagnosed based on report or observation of characteristic symptoms. Two diagnostic classification systems for psychiatric disorders are available and in use - the International Classification of Diseases (tenth version, ICD-10, World Health Organisation) and the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association). In practice, clinicians informally apply diagnostic criteria at interview for routine diagnosis of depression, but for research purposes, structured interviews for diagnosis are available, such as the Structured Clinical Interview for Diagnosis of DSM-IV Disorders (SCID). Both ICD-10 and DSM criteria emphasise the primacy of pervasive depressed mood but have various other criteria for diagnosis. DSM-IV criteria require a change in baseline mood or new anhedonia maintained over a period

of two weeks and associated with impaired function as well as at least five of nine possible emotional, cognitive and biological symptoms of depression. These include appetite and weight change, change in sleeping pattern, loss of energy, poor concentration, guilt, and thoughts of death or suicide. These symptoms must not be better accounted for by a substance or medical disorder. The fifth edition of the DSM was released in 2013.

1.1.3 Treatment of depression

Evidence-based treatment options for depression include pharmacological, psychological and physical treatments (such as ECT). For mild depressive symptoms, exercise and other lifestyle measures such as stress reduction may suffice (Krogh et al., 2011). For people with a chronic health problem, low-intensity psychosocial or psychotherapeutic interventions (in particular, cognitive behavioural therapy, CBT), are the first recommended intervention (National Institute for Health and Care Excellence, 2016).

For those with moderate depressive symptoms that do not respond to lifestyle or low-intensity interventions, general practitioners are advised to commence antidepressant treatment with an agent based on patient choice (National Institute for Health and Care Excellence, 2016). Ideally, a combination of psychological and pharmacological approaches could be offered. Tertiary care with psychiatry services is less frequently indicated, and admission to an inpatient unit even less so. There are currently 2791 adult psychiatry inpatient beds in Ireland to serve a population of 4,588,252 (Mental Health Commission, 2016). In 2015, depressive disorders accounted for 27% of all inpatient psychiatric admissions (Health Research Board, 2016). Those who do require inpatient admission are likely to present with severe depressive symptoms such as psychotic features, psychomotor retardation, suicidality or physical deterioration. Rarely, people with treatment-resistant depression who do not have severe symptoms but require multiple medication changes or ECT may be admitted to facilitate treatment.

Pharmacological options for treatment of depression are limited by latency of effect, side effects, and limited response rates (O'Leary et al., 2015). Unfortunately, up to 60% of people may have an inadequate response to the first pharmacological intervention for depression (Fava, 2003). Partial response is associated with poorer overall outcomes including higher risk of relapse (Judd et al., 1998). The likelihood of remission drops substantially with each failed treatment step. For those who fail to respond to two anti-depressants, the likelihood of response is only 13.7% (Rush et al., 2006). Therefore, there is a pressing need for antidepressant treatments with a higher likelihood of initial response (O'Leary et al., 2015).

1.1.4 Depression relapse prevention

Over 50% of those who experience one depressive episode will have further episodes, with an average of 5-9 episodes per lifetime (Kessler et al., 2003). The first six months after remission represent the highest-risk period, with average time to relapse of only 3.5 months (Rush et al., 2006). Meta-analysed data from 4410 trial participants showed that continuation pharmacotherapy following successful acute treatment for depression reduced the odds of relapse by 70% (95% CI 62–78) (Geddes et al., 2004). There are only limited data beyond 12 months and little evidence to guide treatment discontinuation. In addition, the treatment benefit for an individual is unclear as this will depend on their individual risk of relapse, and many participants discontinued antidepressant treatment during the meta-analysed trials (Geddes et al., 2004). Therefore, for clinicians and patients, the best choice and optimum duration of continuation therapy remain obscure. Even with treatment, relapse rates are still too high, making depression relapse prevention an urgent clinical research question.

1.2 Electroconvulsive therapy for depression

1.2.1 Evidence base for use of electroconvulsive therapy for depression

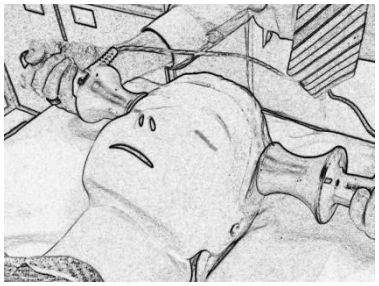
Electroconvulsive therapy (ECT) is the most acutely effective treatment for treatment-resistant depression and can be life-saving (UK ECT Review Group, 2003). Of those described above, who experience non-response or partial response after two antidepressants, 44-70% can achieve remission with ECT (UK ECT Review Group. 2003, Eranti et al., 2003, Prudic et al., 1996). The Consortium for Research in ECT (CORE) reported a 75% remission rate among depressed patients with thrice-weekly ECT, the vast majority of which occurred in the first four weeks of treatment (Husain et al., 2004). A landmark meta-analysis reported a standardised effect size of -0.91 (95% CI -1.27 to -0.54) for ECT compared to sham ECT (256 patients), and an effect size of -0.80 (95% CI -1.29 to -0.29) for ECT compared to antidepressant pharmacotherapy (1144 patients) (UK ECT Review Group, 2003).

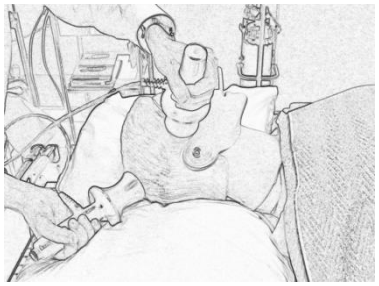
The National Institute for Health and Clinical Excellence (NICE) recommends the use of ECT for fast and short-term improvement of severe symptoms after all other treatment options have failed in severe depressive illness, a prolonged or severe episode of mania, or catatonia (NICE, 2009). However, early use of ECT is associated with shorter and less costly hospital stays (Markowitz et al., 1987). ECT has also been reported to enhance health-related quality of life in both the long- and short-term (McCall et al., 2006).

ECT involves administration of a short-acting anaesthetic and muscle relaxant. An electrical charge is then passed through the brain via electrodes placed on the head either bilaterally or unilaterally on the right side. Bifrontal ECT is administered in some centres but has no clear advantage (Dunne and McLoughlin, 2012), see Figure 1.1 for illustration of electrode placements. The electrical charge induces a modified generalized seizure, monitored by electroencephalogram (EEG). The minimal electrical dose necessary to elicit an adequate generalized seizure (e.g. >15 seconds of motor activity) is the threshold dose.

This is established at the first or second ECT session, and subsequent treatments are given at a multiple of times of the threshold or minimum dose. For bilateral ECT, treatment is generally administered at 1.5 times the threshold dose, and for right unilateral ECT this is usually four to six times the threshold dose (Kolshus et al., 2017).

Figure 1.1 Electrode placements in electroconvulsive therapy, adapted from Dunne and McLoughlin, 2013


Bilateral


Right unilateral


Bifrontal

In Ireland, ECT is administered twice weekly in a course of six to twelve treatments (Dunne and McLoughlin, 2013). Twice-weekly ECT is also standard in the UK and across Europe, but in the US and some Australian centres, thrice-weekly ECT is performed, with no clear advantage. Pulsewidth is also an important treatment parameter. The original sine-wave ECT has long been replaced by brief-pulse ECT (0.5-1.5 ms stimulus), which reduced cognitive adverse effects while maintaining antidepressant efficacy. In recent years, pulses of <0.5 ms (ultrabrief pulse ECT) have been utilised. Ultrabrief pulse ECT was found to further reduce cognitive adverse effects but antidepressant efficacy is not maintained at this pulse width, with a meta-analysis of brief pulse vs. ultrabrief pulse ECT showing a standardized mean difference of 0.25 (95% CI, 0.08–0.41; P = .004) in favour of brief pulse unilateral ECT (Tor et al,. 2015).

The exact mechanism of action of ECT remains unclear, though it appears to activate neuroplasticity pathways, and has been linked to neurophysiological, neurochemical and neuroplastic processes, including the inflammatory and the HPA-axis dysfunction hypotheses of depression (Ryan and McLoughlin, 2018). ECT may mediate its effects through upregulation of neurotrophic factors within the brain and increased neurogenesis

within the hippocampus (Merkl et al., 2009). It has been shown that although generalised seizures are necessary for the antidepressant response to ECT, the seizure alone is not sufficient for successful response, suggesting the dose of electrical stimulus may be more important than the time or manner in which it is administered. Studies showing normalisation of the brain structural changes seen in depression in patients successfully treated with ECT had historically been blighted by methodological problems. However, a rigorous 2016 neuroimaging study (Joshi et al, 2016) showed that depressed patients, who had smaller hippocampal and amygdalar volumes than healthy controls pre-ECT (a known finding), had a 10% volume increase in hippocampi and amygdala after a successful course of ECT. Volume changes correlated with clinical improvement in depression. The mechanism underlying volume change is unclear, though animal studies have shown that ECT induces neurogenesis.

Use of ECT is limited by concerns about cognitive side effects. The medical risks of ECT are related to the anaesthesia required for a modified seizure. The mortality associated with ECT is the same as that associated with minor procedures involving a general anaesthetic (1:80,000) (Munk-Olsen et al., 2007). Apart from raised intracranial pressure, there are few absolute contraindications but patients must be fit for general anaesthesia.

Another major concern is the risk of depressive relapse following successful ECT. In the first six months following successful ECT 34% of people relapse despite continuing antidepressant therapy, with the period of greatest risk being the first 3 months (Jelovac et al., 2013). Notably, these rates are similar to the relapse rates of patients who respond to pharmacological treatment only after ≥3 antidepressant steps and most likely reflect the recurrent nature of treatment-resistant depression (Rush et al., 2006). Taking antidepressants after ECT halved the risk (risk ratio=0.49, $p<0.0001$, NNT=3.3) for relapse at six months from nearly 80% (Jelovac et al., 2013). In one trial, 84% of those on placebo pharmacotherapy relapsed upon discontinuation of ECT (Sackeim et al., 2001). Some form

of continuation therapy is clearly essential. However, conducting clinical trials to assess for relapse after ECT is difficult. As the confidence interval for this 34% relapse rate (Jelovac et al, 2013) is 27.2- 41.5%, a SD of 7% is seen. A trial assessing for reduction in relapse rate should have 80% power to assess for a significant reduction in relapse rate beyond the standard deviation of 7%. However, dichotomous rating of relapse using standard criteria may be less clinically meaningful than reduction in depression severity scores among patients. In either instance, large samples of several hundred patients would be required for adequate power, likely requiring multisite trials. For example, in the Consortium for Research in Electroconvulsive Therapy (CORE) studies, 514 participants were assessed for relapse (Kellner et al, 2006).

Continuation ECT provides some protection against relapse to those who have responded to ECT for acute depression (Kellner et al., 2006). However, continuation ECT is not currently recommended in clinical guidelines, and further research is recommended by the National Institute for Health and Care Excellence (NICE, 2009).

1.2.2 Factors affecting response to electroconvulsive therapy for depression

Predicting response to ECT is a major concern for clinicians attempting to provide the best advice on treatment options to patients, and for patients and their families in deciding whether or not to pursue the treatment. Much research has focused on optimising ECT parameters including stimulus dose, laterality and pulsewidth (Kolshus et al., 2017, Tor et al., 2015). However, even with optimised treatment, identifying those most likely to respond to ECT for depression remains difficult (McCall and Fink, 2005). Although some predictors of response have been identified, contrasting evidence exists for almost all potential predictors (Pinna et al., 2016).

Meta-analysed data from 328 unipolar depressed patients found that only pharmacotherapy failure (OR = 1.67, 95% CI = 1.05 to 2.67) and chronicity of depression (OR = 1.84, 95% CI = 1.06 to 3.21) were significant predictors of remission (Dombrovski et al., 2005). Treatment resistance (failure of antidepressant pharmacotherapy) emerges as a predictor of lower odds of response to ECT in several studies. This was found to be a stable finding across diverse clinical settings and a range of pharmacotherapeutic agents (Prudic et al., 1996). A meta-analysis of data from 958 patients found that absence of treatment resistance was associated with a higher odds of remission following ECT for depression, with an odds ratio of 0.58 (95% CI 0.44 to 0.75) compared to those with previous pharmacotherapy failure (Heijnen et al, 2010). However, this is not always a consistent finding, and treatment resistance did not predict remission from depression following ECT in a long-running study of 345 depressed participants by the Consortium for Research in Electroconvulsive Therapy (Rasmussen et al., 2007). In the combined studies by this research group, factors which did emerge as predictors of greater likelihood of ECT treatment response were presence of psychosis, older age, and presence of features of atypical depression such as hypersomnia (Fink, 2014). Older age is relatively consistently associated with higher likelihood of response to ECT (O'Connor et al., 2001). Presence of psychotic symptoms among depressed people having ECT predicts both higher response rate and earlier response (Petrides et al, 2001). However, subtypes of depression such as melancholic or atypical depression are not consistently associated with response (Fink et al., 2007).

In clinical practice, some factors which may influence response to ECT are inpatient status, presence of psychotic symptoms, absence of schizoaffective disorder and older age (Nordenskjold et al, 2012, deVreede et al., 2005). Rapid response during the course of ECT may also be a predictor of ultimate remission following ECT (Kho et al., 2004).

Biomarkers have also been investigated for potential to predict ECT treatment response but, to date, none are sufficiently reliable for clinical use (Pinna et al., 2016).

Despite much research, clinicians and patients have little clear guidance on understanding an individual's likelihood of response to ECT for depression. Age, treatment resistance and presence of psychotic symptoms seem to be the most reliable potential predictors of response. Identification of new possible candidates for factors predicting response to ECT may provide more information for patients and clinicians to use in deciding whether to proceed with ECT.

1.2.3 Cognitive effects of electroconvulsive therapy

Cognitive side-effects of ECT are among the most important factors limiting prescription and uptake of ECT (Rose et al., 2003). Factors affecting cognitive side-effects of ECT are many, and include pre-existing cognitive impairment and treatment factors such as laterality and pulsewidth (McClintock et al., 2014). The effect of the combination of pre-existing depression, treatment with ECT, residual depressive symptoms, as well as individual patient factors, on cognitive performance during and after ECT has not been fully elucidated. There are few strong predictors of cognitive impairment during and after ECT and questions about the extent and persistence of some cognitive side-effects remain unanswered. There is an absence of standardised instruments designed specifically for cognitive assessment during ECT, while existing instruments may not detect subtle or patchy impairments that affect quality of life post-ECT.

Table 1.1 Cognitive side-effects of ECT

Side Effect	Description
Anterograde Amnesia	Impaired ability to remember new information from the time of commencing ECT onwards
Retrograde Amnesia	Impaired ability to remember information learned before commencing ECT
Autobiographical Amnesia	Impaired ability to remember events personally experienced at a particular time and place (episodic autobiographical memories e.g. something that happened at a wedding you attended) and pieces of general information (semantic autobiographical memories, e.g. year of graduation) from one's own life
Subjective Memory Difficulty	The experience of feeling as though one has a problem with one's memory, regardless of performance on objective memory testing
Impaired Executive Function	Impairment in higher brain functions such as judgement, planning and completing complex tasks

Definitions adapted from Lezak, 2012.

1.2.3.1 Acute and sub-acute cognitive effects

Acute cognitive side-effects include disorientation, impaired attention, and amnesia for the immediate time period of the ECT treatment and recovery. Disorientation is very common immediately following ECT and is transient, rarely persisting beyond 60 minutes (Sobin et al., 1995). Time to reorientation can be measured as the time at which correct responses to 4/5 questions about orientation to person (name, date of birth, current age), place (name of hospital) and time (day of the week) are given, with 0 minutes corresponding to when the patient resumes spontaneous breathing (Semkovska et al., 2016). In a trial of high-dose (6 times threshold) right unilateral ECT vs bitemporal ECT at 1.5 times threshold, median time to recovery of orientation with RUL ECT was 19 minutes vs 26 minutes with bitemporal ECT (Semkovska et al., 2016). Longer time to reorientation has been reported to be associated with more persistent retrograde memory impairment following a course of ECT (Martin et al., 2015, Sobin et al., 1995) and has also been associated with better mood

outcomes, though this requires further study (Bjølseth et al., 2016). Persistent disorientation, for example disorientation beyond 90 minutes, is difficult to accurately predict but has been associated with older age (Martin et al., 2015), poor cognitive function at baseline (Sobin et al., 1995) and presence of psychotic symptoms (Calev et al., 1991). Higher stimulus doses result in longer time to reorientation but may be necessary for treatment efficacy.

Cognitive side-effects occurring during the course of ECT and resolving soon after completion include anterograde amnesia and non-memory cognitive effects, such as impaired executive function. ECT does not cause impairment in the ability to learn new skills or movements (procedural memory), and other aspects of implicit memory such as perceptual priming (the ability to use cues and associations to remember multiple items) are seemingly unaffected, though not often studied (Squire et al., 1984, Vakil et al., 2000).

Anterograde amnesia during the course of ECT is common and is generally limited to a period of days to weeks after completion of the course, returning to pre-ECT baseline or improving beyond baseline two or more weeks after completion of a treatment course (Semkovska and McLoughlin, 2010). Verbal memory is more affected than visual memory, but impairment in either can result in practical difficulties for patients during the course of ECT, such as remembering medication dose changes, names of staff, and aspects of the ECT treatment itself.

There is no evidence of cumulative cognitive impairment with repeated applications of ECT, including maintenance ECT (Brus et al., 2017, Petrides et al., 2011, Russell et al., 2003, Smith et al., 2010). The CORE studies from the USA of continuation ECT vs. continuation pharmacotherapy after successful ECT for depression found no differences between the groups in cognitive outcomes at 24 weeks of treatment. Anterograde memory improved in both groups 12 weeks after completion of the acute ECT course, regardless of use of continuation ECT (Smith et al., 2010).

Meta-analysis showed small to medium impairments in visual episodic memory (worse for delayed visual recall than for immediate visual recall) during the course of ECT, with recovery or improvement beyond baseline by 15 days post-ECT (Semkovska and McLoughlin, 2010). In one study, deficits were identified in visual and visuospatial memory in people having ECT, with some of these deficits persisting after one month, (Falconer et al, 2010), however ECT was administered at twice the seizure threshold, likely to amplify cognitive problems. In another study, visual memory and learning improved during the course of ECT, a finding which correlated with improvement in depression (Maric et al, 2016), but in this study ECT was administered three times per week and the finding may thus not be generalizable to centres which administer twice-weekly ECT.

A meta-analysis concluded that deficits in executive functioning can be found soon after completing a course of ECT, suggesting these are also present during the treatment course (Semkovska and McLoughlin, 2010). However, all executive functioning measures included in the analysis showed improvement in performance at 4-15 days post ECT compared with pre-ECT baseline, and improvements continued beyond 15 days follow-up. Working memory, as measured by digit span backward, was not impaired at 0-3 days post-treatment and improved (compared to pre-ECT assessments) at follow-up more than 15 days post-treatment (Semkovska and McLoughlin, 2010).

Up to one-third of patients report persistent subjective memory difficulty post-ECT (Rose et al., 2003), with some reports of persistence for years. Qualitative evidence reviewed by NICE suggested that the experience of cognitive impairment was variable among those who had received ECT, but that it often outweighed the person's perception of any benefit from ECT (NICE, 2009).

Subjective memory difficulty does not correlate with objective performance on cognitive assessment or any subset of memory functions, but correlates somewhat with depression severity. Assessment tools such as the Squire Subjective Memory Assessment (Squire et

al., 1979) or the Subjective Assessment of Memory Impairment (Kumar et al., 2016) have been used in ECT research. Remission following ECT may be associated with lower risk of subjective memory difficulty, while younger, female patients may be more at risk (Brus et al., 2017). It has been alternatively hypothesised that persistent subjective memory difficulty after ECT represents misattribution of the effects of age, mood or somatic complaints on memory (Fink, 2007). In addition, patients may become anxious about memory after ECT and misperceive a problem where their memory function is within the normal experience (Andrade et al., 2016). Regardless of the aetiology of subjective memory difficulty, the perception of cognitive side-effects from ECT has a strong impact on patients' overall treatment experience (Knight et al., 2017).

1.2.4 Retrograde Amnesia

The ability to remember events from one's own life is strongly associated with identity. Thus autobiographical amnesia is distressing (Rose et al., 2003) and consequently is the focus of research on ECT-related retrograde amnesia. More recent memories may be more vulnerable to loss during ECT than distant memories (Lisanby et al., 2000).

Patient factors that confer increased risk of retrograde amnesia are estimated lower premorbid IQ, advancing age (Sackeim et al., 2007), impaired global cognition at baseline (Sobin et al., 1995), and longer time to reorientation (Martin et al., 2015, Sobin et al., 1995). As with anterograde amnesia, retrograde amnesia is more likely with more ECT treatments. High-dose right unilateral brief-pulse ECT is associated with higher percentage recall of autobiographical information than brief-pulse bitemporal ECT (Kolshus et al., 2017). In turn, ultrabrief-pulse right unilateral ECT is associated with less retrograde amnesia than brief pulse right unilateral ECT, but is significantly less efficacious in treatment of depression (Tor et al., 2015). Effect sizes for these predictors are moderate, for example, unilateral ECT showed an advantage in retrograde autobiographical memory

of -0.46 (Hedges' G), with a 95% confidence interval of -0.87 to -0.04 (Kolshus et al., 2017).

Though there is no high-level evidence of persisting retrograde amnesia after ECT, this does not preclude individuals having difficulty for a longer period than research findings suggest. Some individual studies have shown persistent impairment in autobiographical memory (up to three years) and there have been case reports of profound autobiographical memory loss after ECT (Fink, 2007). There is currently no standardised instrument for assessment of this major cognitive effect of ECT (Semkovska and McLoughlin, 2013). As a result, the precise nature and extent of autobiographical retrograde amnesia post-ECT is not clear, a major gap in our knowledge and the focus of much research.

1.2.5 Assessment of cognitive effects

Remarkably, there are no specifically designed recommended instruments for cognitive testing in ECT practice. Although NICE, along with the American Psychiatric Association (APA, 2010), recommends a documented baseline assessment of potential risks and benefits of ECT for each individual, including anticipated cognitive effects, the guidelines do not suggest instruments for testing (NICE, 2009). This absence of specific recommendations may reflect the lack of suitable instruments for assessment. Despite limitations in existing instruments, and in line with measurement-based care, there is enough evidence to recommend the practice of performing a global assessment of cognition at baseline, during the course of ECT (e.g. after six treatments), at a set time after ECT, e.g. within three days after the last ECT treatment, and after 1-2 months.

Ideally an assessment would include a measure of: immediate and delayed verbal recall, attention, working memory, autobiographical memory, and at least one aspect of executive function.

Though use of the Mini Mental State Exam (sMMSE) (Molloy et al., 1991) has become common, it is inadequate for monitoring adverse cognitive side-effects of ECT. The MMSE is a screening tool for dementia that is insensitive to change, does not assess executive function, and can only detect substantial impairment (Tombaugh and McIntyre, 1992).

Although no purposely designed instrument for assessment of cognition before and after ECT exists, global cognitive assessments that incorporate measures of executive function are available, and screening batteries have been suggested (Martin et al., 2013). The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and the Addenbrooke's Cognitive Assessment Version III (ACE-III) (Hodges and Larner, 2017, Hseih et al, 2013) have the advantages of being sensitive to minor impairment as well as change. The ACE-III takes longer than the MoCA to administer but has high sensitivity to cognitive deficits, is freely available and does not require specialised training. Parallel, validated versions of both the MoCA and ACE-III are available for retesting during and after ECT. For more detailed cognitive assessment, a battery of assessments such as the CANTAB® (Cognitive assessment software, Cambridge Cognition 2017) can identify more subtle or discrete impairments in specific cognitive functions (Falconer et al., 2010, J Fray et al., 1996, Tsaltas et al., 2011).

Detailed repeat cognitive assessment is burdensome for patients and may not be practical in routine practice and is thus usually only performed as part of a research study.

1.2.5.1 Retrograde amnesia assessment

The assessment of retrograde autobiographical amnesia is particularly difficult. Inability to retrieve information, whether on free or cued testing, indicates that memory decay has occurred over time (i.e. forgetting). Some memory decay is normal. It cannot be assumed that reduced consistency of recall is unique to depressed people treated with ECT, or to

depressed people. Recall of autobiographical information normally declines over time in non-depressed people and consistency of recall in healthy controls declines even after an interval of two months (Semkovska et al., 2012). Estimates of normal rate of loss of autobiographical memories range from 27% after 6 weeks (Talarico and Rubin, 2003) to 31–42% after 2 months (Anderson et al., 2000).

It is difficult to separate the effect of ECT from the effect of change in depression severity on the normal rate of loss of previously reported memories. To do so would require robust normative information on the performance of:

- non-depressed people,
- depressed persons not treated with ECT,

on the instruments used for retrograde memory assessment in ECT, before and after an interval of weeks. Unfortunately, this is not currently available.

Depression is associated with impaired ability to identify separate incidents from one's own life experience (reduced specificity of episodic autobiographical memory, or over-generalisation) and poor recollection of detail of the identified events (Jelovac et al., 2016). Reduced specificity in depressed patients prior to ECT (compared with non-depressed controls) was shown to persist at three months after ECT regardless of treatment response (Jelovac et al., 2016, Verwijk et al., 2015). Thus depressed patients may score poorly on episodic autobiographical memory assessment even when their semantic autobiographical memory may seem unimpaired (Verwijk et al., 2015). Testing retrograde memory is challenging for depressed patients experiencing reduced memory specificity and may result in patients providing information that is very limited or over-general.

The ideal instrument for assessment of retrograde autobiographical amnesia would be short and simple to administer and would provide scores for memory detail (semantic and episodic) as well as a consistency score on retesting after ECT. Results could be measured

against the general population (and also depressed persons not treated with ECT) at baseline and after several weeks of normal life. Unfortunately, currently used instruments for retrograde amnesia, e.g. the Columbia University Autobiographical Memory Interview (CUAMI, or the short form CUAMI-SF) (McElhiney et al., 2001, McElhiney et al., 1995) and the Kopelman Autobiographical Memory Interview (Kopelman et al., 1989), do not fulfil all these criteria (Sackeim, 2014, Semkovska and McLoughlin, 2013, 2014).

The Columbia University Autobiographical Memory Interview is the most widely used instrument for assessment of autobiographical amnesia in ECT research (Sackeim et al., 2000). However, normative data for comparison of both healthy controls and depressed people not having ECT have not been published (Semkovska and McLoughlin, 2013). Episodic recall is not measured separately to semantic recall, and the short form still takes 20-25 minutes to administer. Another disadvantage to the CUAMI-SF is that only information provided in the initial assessment is retested for consistency of recall. Therefore, scores cannot improve and the percentage recall score may be based on successful recall of very little information, i.e. a floor effect. Despite these drawbacks, the CUAMI has been useful in showing differences in retrograde amnesia associated with different ECT treatment modalities, such as laterality and pulse-width (Kolshus et al., 2017, Sackeim et al., 2000, Sackeim et al., 2008).

The Kopelman Autobiographical Memory Interview (Kopelman et al., 1989) was originally designed for assessment of amnestic patients but has also been used in ECT research (Sienaert et al., 2010). It assesses both semantic and episodic autobiographical memory separately, with items scored on specificity and detail. It does not provide a measure of recall consistency and caution is required due to suggestions of a lack of sensitivity of instrument to ECT-related retrograde amnesia (Jelovac et al., 2016). It is long (+25 minutes) and burdensome for depressed patients to complete. However, some normative data on the performance of healthy controls is available, and the instrument

allows for improvement of scores on retesting should memory improve during or after a course of ECT.

1.2.6 Prevention of cognitive effects

There is good evidence that modification of ECT treatment factors (laterality, pulsewidth, frequency) can help reduce the occurrence and severity of cognitive side-effects. Higher electrical stimulus (in relation to seizure threshold), though important for antidepressant effect, is associated with greater effect on cognition (Sackeim et al., 1993). More frequent ECT treatment (thrice-weekly vs twice-weekly) is associated with greater cognitive impairment (Lerer et al., 1995), and, though now unused, sine-wave stimulation resulted in more severe and persistent effects on cognition than contemporary brief-pulse stimuli (Sackeim et al., 2007). Right unilateral (RUL) ECT is consistently associated with less severe and persistent cognitive effects (Sackeim et al., 1993, Sackeim et al., 2007). Antidepressant efficacy equal to bitemporal ECT can be achieved by administering RUL ECT at six times threshold dose (Kolshus et al., 2017).

Trials of ultrabrief pulse (UBP) ECT have shown a cognitive advantage over brief pulse (BP) ECT (Tor et al., 2015, Verwijk et al., 2012). Global cognition, anterograde memory (learning and recall) and retrograde memory were less affected by high-dose RUL UBP than RUL BP ECT (Tor et al., 2015). Although the cognitive benefit of UBP over BP ECT is consistent, UBP ECT is significantly less efficacious in treating depression than BP ECT and requires more treatments to achieve remission (Tor et al., 2015).

Meta-analysis of bifrontal *vs.* bitemporal ECT suggested bifrontal ECT may have slightly less impact on global cognitive function (as represented by decline in MMSE score) than bitemporal ECT (Dunne and McLoughlin, 2012), but there is currently not enough

evidence to recommend routine use of bifrontal ECT with regards to its having substantial cognitive advantages over bitemporal or unilateral ECT.

Research focusing on reducing the frequency and severity of adverse cognitive effects of ECT has resulted in trials of ketamine anaesthesia for ECT (McGirr et al, 2017) and augmentation of ECT with cognitive training (Choi et al., 2017), although neither of these has led to clearly improved cognitive outcomes. Acetylcholinesterase inhibitors have been found to result in significantly better performance in cognitive testing after ECT although there is large heterogeneity between studies (Henstra et al., 2017) and their use remains experimental.

Most importantly, the cognitive effect of ECT of most concern to patients is that of retrograde autobiographical amnesia (Rose et al., 2003). Regardless of the progress made as above in understanding and preventing cognitive effects of ECT, as long as there is no accurate assessment of the impact of ECT on autobiographical memory performance, this side-effect cannot be understood or prevented. Understanding the uses and limitations of currently used instruments for assessing autobiographical memory in ECT would therefore be a major contribution to the ultimate goal of prevention of cognitive side effects.

1.3 Ketamine

1.3.1 Mechanism of action

Ketamine is a competitive glutamate N-methyl-D-aspartate receptor (NMDAR) antagonist with half-life of 2-3 hours (Kohrs and Durieux, 1998). It is a commonly used agent in paediatric medicine, veterinary medicine, and anaesthesia. It has a remarkably rapid antidepressant effect, targeting core symptoms, in treatment-resistant depression when given as single sub anaesthetic doses, usually a 40 minute 0.5 mg/kg intravenous infusion (McGirr et al., 2017). Thereafter robust antidepressant effects with responder rates of

approximately 70% occur within 2-4 hours and persist for a few days (McGirr et al., 2017). The antidepressant effect therefore persists beyond immediate NMDAR blockade. These findings have led to the most exciting development in treating and understanding depression in over 50 years and represent a paradigm shift away from conventional slow-acting monaminergic antidepressants (Sanacora et al., 2008). Neuroplasticity (neuronal adaptation) is a key pathogenic feature of depression (Hayley et al., 2005). Ketamine's antidepressant effects are associated with rapid reversal of the neuroplastic changes seen in an animal model of chronic stress (Li et al., 2011). Moreover, ketamine activates the mammalian target of rapamycin (mTOR) pathway in rats, leading not only to increased synaptic signalling but to an increased number of prefrontal cortical synapses. In a rat model of depression, when this key neuroplasticity pathway was blocked, ketamine's antidepressant effect was blocked (Li at al., 2010). It therefore seems as though ketamine has a powerful neuroplastic effect which is directly linked to its antidepressant effect.

The discovery of ketamine opened the door for a new glutamatergic hypothesis of the aetiology of depression (Autry et al., 2011). A summary of the body of evidence which accumulated following the initial report of ketamine's antidepressant activity concludes that "*it would be limiting to maintain that glutamate is in some way 'involved' in mood/anxiety disorders; rather it should be recognized that the glutamatergic system is a primary mediator of psychiatric pathology and, potentially, also a final common pathway for the therapeutic action of antidepressant agents*" (Sanacora et al., 2012). It has been shown that patients that do experience an antidepressant effect following ketamine administration exhibit increased cortical excitability during the timeframe of relief of depressive symptoms, suggesting that increased glutamate levels manifesting as ketamine-induced disinhibition may be key to the drug's antidepressant effect (Cornwell et al, 2012). However, other glutamatergic agents which have been studied have lately been found to lack antidepressant efficacy (Sanacora and Schatzberg, 2015). Further, a novel

antidepressant mechanism for ketamine which does not involve NMDAR antagonism was recently proposed. In an animal model, it was shown that metabolism of ketamine to the metabolite (2S,6S;2R,6R)-hydroxynorketamine (HNK) is essential for its antidepressant effect, mediated by activity independent of NMDAR blockade (Zanos et al., 2016).

It is clear that ketamine's effects are powerful, though as yet imprecisely understood.

1.3.2 Summary of ketamine trials in depression

1.3.2.1 Initial trials, 2000-2015

The first report of ketamine as an antidepressant was published almost 20 years ago, (Berman et al., 2000) and the field has produced wide excitement and a substantial number of reviews (for example: Machado-Vieira et al., 2009, aan het Rot et al., 2012, Krystal et al., 2013, Katalinic et al., 2013, Naughton et al., 2014, Newport et al., 2015,), and meta-analyses (Fond et al., 2014., Lee et al., 2015, McGirr et al., 2017, Caddy et al., 2014, Han et al., 2016, Li et al., 2017). Trials of ketamine from 2000 to 2014 primarily used the same dose and method of administration as that originally reported (Berman et al., 2000). Repeated doses were then investigated (aan het Rot et al., 2010, Murrough et al., 2013). While chronic, mostly recreational, high-dose ketamine use can cause uropathy and dependency (Forster et al., 2012), repeated (e.g. 2-3/week for two weeks) infusions of sub anaesthetic ketamine are safe with more sustained antidepressant effects (Murrough et al., 2013). However, patients and healthy controls can experience mild dissociative and psychotic symptoms with ketamine that resolve soon after finishing infusions, as well as moderate increases in blood pressure (Perry et al., 2007). To control for these effects of ketamine, and also avoid "carry-over" effects in crossover studies while improving blinding, researchers moved to use of the active comparator midazolam rather than inactive placebo saline (Murrough et al., 2013). A sub anaesthetic dose of 0.045mg/kg of midazolam was used as this dose mimics some of the effects of ketamine at 0.5mg/kg. To

date, few factors have been shown to affect antidepressant response to ketamine but positive family history of alcohol dependence may increase the likelihood of response (Nicui et al., 2014). Benzodiazepine use was also suggested to attenuate the antidepressant response to ketamine (Frye et al., 2015). Some years after the completion of the first series of trials of ketamine for depression, meta-analyses confirmed the relatively short-lasting antidepressant effect at 0.5mg/kg (Caddy et al., 2014, McGirr et al., 2015).

1.3.2.2 Ketamine trials since 2015

Although a definitive trial has yet to be reported, ketamine trials since 2015 have focused on extending the use of ketamine and examining different doses and methods or schedules of administration. While the half-life of ketamine is 3 hours, in initial studies using repeat infusions the antidepressant effect was maintained to up to seven days (aan het Rot et al., 2010). Though much effort has focused on extending the antidepressant effect of ketamine beyond seven days, this has not yet been successful (Romeo et al., 2015). Further work has used ketamine doses lower than the original 0.5 mg/kg, which appear to lack antidepressant efficacy (Xu et al., 2015, Su et al., 2017). Bipolar depression has been the focus of many trials (McCloud et al., 2016). Trials of ECT augmentation with ketamine have had mixed results and there appears to be no benefit in terms of depression treatment or cognition (McGirr et al., 2016). Larger studies which have taken place since the above-referenced meta-analysis have confirmed this (Anderson et al., 2017, Fernie et al., 2017) Esketamine has also been studied in a proof-of-concept trial (Singh et al., 2016b) and several trials are now registered (on www.clinicaltrials.gov) using esketamine. Esketamine has a three- to four-fold higher affinity for NMDA receptors than R-ketamine (Singh et al., 2016b) and theoretically may therefore have greater antidepressant efficacy than the racemic formulations that are currently cheaply available. It is also possible that esketamine is better-tolerated than racemic ketamine but further studies are awaited.

Focus has also shifted from not only treatment of depressive episodes, but specifically, relief of suicidal ideation among depressed people (Wilkinson et al., 2017). At the time of writing, there were 131 registered trials of ketamine for depression on the trial database www.clinicaltrials.gov.

1.3.2.3 Factors affecting completion of ketamine trials

Reported clinical trials of ketamine for depression remain modest-sized with many open-label studies and no definitive trial has yet been conducted. Ketamine's robust acute antidepressant effect results in large effect sizes which in turn indicates smaller trials are required to investigate antidepressant effect. It is unclear whether trials remain modest-sized as these are possibly not required to show efficacy, or due to participant concerns about adverse effects or indeed if there are other logistical factors at play. The potential for abuse is rarely highlighted by media coverage of the field of ketamine research in psychiatry, (Zhang et al. 2017) but may remain a concern for potential participants. Detailed data on the proportion of participants eligible for ketamine trials and, of those, the proportion consenting to participation, are not available. Even more importantly for researchers planning future studies, reports of the reasons why participants decline or drop out are not available.

Additionally, trials of ketamine for depression published to date generally do not report on success of blinding. Saline placebo is potentially inadequate for participant and rater blinding when juxtaposed with the known acute effects of low-dose ketamine, such as dissociation. However, trials using midazolam as an active comparator (Murrough et al., 2013) have also not reported on success of blinding. So it is unclear whether exposing participants to midazolam in place of saline is a justified (albeit minor) risk. A more recent trial reports use of 0.02 mg/kg midazolam where participants have not had medication

washout, to avoid sedation which could compromise blinding, as sub-anaesthetic dose ketamine does not cause overt sedation (Grunebaum et al., 2017b).

Generalisability of trial results is also a concern as it is unclear whether those who participate in ketamine research represent those who are likely to require the treatment in clinical populations, i.e. are ketamine trial populations representative of a broad community sample of people with treatment-resistant depression. It is known that the evidence base for other antidepressants is not representative of those who will require treatment with these agents (Zimmerman et al., 2002). Data showing the reasons for ineligibility among those screened for trial participation would be useful to illustrate whether those who are ultimately recruited reflect the general characteristics of the group. A summary of published trials to date indicating participant numbers, ketamine dose, use of placebo, and whether the trial report includes report of success of blinding, or detail on reasons for any of: ineligibility, non-recruitment, dropout or non-adherence, is provided below.

Table 1.2 Summary of ketamine trials in depression

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
Antidepressant effects of ketamine in depressed patients Berman et al., 2000	7	0.5mg/kg over 40 min	0.9% saline	Some	No
Small-dose ketamine improves the postoperative state of depressed patients. Kudoh et al., 2002	70 MDD 20 ctrl	1.0 mg/kg of ketamine, 1.5 mg/kg of propofol, and 2 μg/kg of fentanyl	1.5 mg/kg of propofol and 2 μg/kg of fentanyl	No	No
A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression Zarate et al., 2006	18	0.5mg/kg over 40 min	0.9% saline	No	Crossover
Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial Mathew et al., 2010	26	0.5mg/kg over 40 min	None Open Label	No	N/A, but Yes for Riluzole
A Randomized Add-on Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Bipolar Depression DiazGranados et al., 2010	18	0.5mg/kg over 40 min	0.9% saline	Some	No

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression Aan Het Rot et al., 2010	10	0.5mg/kg x 6 infusions	None Open label	Some	N/A
The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [1H]-MRS Valentine et al., 2011	10	Saline infusion then 1/52 later 0.5mg/kg	0.9% saline Single-blind, crossover	Some	Crossover
Course of Improvement in Depressive Symptoms to a Single Intravenous Infusion of Ketamine vs Add-on Riluzole: Results from a 4-Week, Double-Blind, Placebo-Controlled Study Ibrahim et al., 2012	42	0.5mg/kg over 40 min	None Open label	Some	N/A
Replication of Ketamine's Antidepressant Efficacy in Bipolar Depression: A Randomized Controlled Add-On Trial Zarate et al., 2012	15	0.5mg/kg over 40 min	0.9% saline Crossover	No	Crossover
Serial infusions of low-dose ketamine for major depression Rasmussen et al., 2013	10	0.5mg/kg over 100 min	None Open label	No	N/A
Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression Sos et al., 2013	27	0.54 mg/kg within 30 min	0.9% saline Crossover	Some	Crossover

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial Murrough et al., 2013a	73	0.5mg/kg over 40 min	Midazolam 0.045mg/ kg	No	No
Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression Murrough et al., 2013b	24	0.5mg/kg over 40 min	None Open label	No	N/A
A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder Lapidus et al., 2014	20	50mg Intranasal	Intranasal saline	No	No
Pilot dose–response trial of i.v. ketamine in treatment-resistant depression Lai et al., 2014	4	0.1, 0.2, 0.3, 0.4 mg/kg Boluses	0.9% saline placebo	No	No
Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder Ghasemi et al., 2014	18	0.5mg/kg over 45 min vs ECT	None Open label	No	N/A
Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial Murrough et al., 2015a	24, 54% of these MDD	0.5 mg/kg	0.045mg/ kg midazolam	No	No

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression Loo et al., 2016	15	IV/ IM/ SC 0.1 mg/kg up to 0.5 mg/kg	Variable dose ketamine Crossover	No	Crossover
A Double-Blind, Randomized, Placebo Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression Singh et al, 2016a	67	0.5mg/kg over 40 min	0.9% saline	No	No
Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study Singh et al., 2016b	29	Esketamine 0.2 mg/kg or 0.4 mg/kg IV	0.9% saline	No	No
A Double-Blinded, Randomized, Placebo-Controlled Sub-Dissociative Dose Ketamine Pilot Study in the Treatment of Acute Depression and Suicidality in a Military Emergency Department Setting Burger et al., 2016	10	0.2 mg/kg	0.9% saline	No	No
Continuation phase intravenous ketamine in adults with treatment-resistant depression Voort et al., 2016	12 acute,5 continuation	0.5 mg/kg over 100 mins	None Open-label	No	Open-label

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
Dose-Related Effects of Adjunctive Ketamine in Taiwanese Patients with Treatment-Resistant Depression Su et al., 2017	71	0.2 mg/kg, 0.5 mg/kg	0.9% saline	Yes	No
Ketamine versus midazolam in bipolar depression with suicidal thoughts: A pilot midazolam-controlled randomized clinical trial Grunebaum et al., 2017a	16	0.5mg/kg over 40 min	0.02mg/kg midazolam	Some	Yes[1]
Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial Grunebaum et al., 2017b	80	0.5 mg/kg	0.02mg/kg midazolam	Yes	Yes[2]
ECT Trials					
Neuropsychological and mood effects of ketamine in electroconvulsive therapy: A randomised controlled trial Loo et al., 2012	51	0.5mg/kg bolus ECT	0.9% Saline bolus	Some	No
Rapid antidepressant effect of ketamine in the electroconvulsive therapy setting Abdallah et al., 2012	16	0.5mg/kg bolus before ECT	Regular anaesthesia	No	No

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
Effects of propofol and ketamine as combined anesthesia for electroconvulsive therapy in patients with depressive disorder Wang et al., 2012	48	0.8mg/kg	Propofol (1.5mg/kg) OR Propofol + ketamine	No	No
Effects of S-ketamine as an anesthetic adjuvant to propofol on treatment response to electroconvulsive therapy in treatment-resistant depression: a randomized pilot study Jarventausta et al., 2013	32	S-ketamine (0.4mg/kg) bolus	0.9% saline and regular anaesthesia		
Comparing effects of ketamine and thiopental administration during electroconvulsive therapy in patients with major depressive disorder: a randomized, double-blind study. Yoosefi et al., 2014	29	1 to 2 mg/kg ketamine	Thiopental 2 to 3 mg/kg	No	No
Antidepressant Effect of Combined Ketamine and Electroconvulsive Therapy on Patients With Major Depressive Disorder: A Randomized Trial Alizadeh et al., 2015	22	0.3 mg/kg Plus 1 mg/kg Propofol	Propofol 1 mg/kg	No	No
Mood and neuropsychological effects of different doses of ketamine in electroconvulsive therapy for treatment-resistant depression Zhong et al., 2016	90	0.8 mg/kg vs 0.5 mg/kg plus propofol 0.5 mg/kg	Propofol 0.8 mg/kg	No	No

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
Ketamine as the anaesthetic for electroconvulsive therapy: the KANECT randomised controlled trial Fernie et al., 2017	40	Bolus up to 2 mg/kg	Propofol up to 2.5 mg/kg	Yes	No
Ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in depression (Ketamine-ECT): a multicentre, double-blind, randomised, parallel-group, superiority trial Anderson et al., 2017	79	0·5 mg/kg bolus	0.9% saline	Yes	Yes[3]
A randomized clinical trial of adjunctive ketamine anesthesia in electroconvulsive therapy for depression Zhang et al., 2017	77	0.5 mg/kg bolus plus Propofol 0.5mg/kg	Propofol 1 mg/kg	No	No
Adjunctive ketamine					
Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study Hu et al., 2015	30	1 x 0.5 mg/kg plus escitalopram 10 mg/day	1 x 0.9% saline plus escitalopram 10 mg/day	No	No

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
Ninety-six hour ketamine infusion with co-administered clonidine for treatment-resistant depression: a pilot randomized controlled trial Lenze et al., 2016	20	0.6mg/kg/hour for 96 hours plus clonidine to a maximum of 0.6mg/day	0.5mg/kg ketamine over 40 mins	No	No
Efficacy and safety of oral ketamine versus diclofenac to alleviate mild to moderate depression in chronic pain patients: A double-blind, randomized, controlled trial Jafarinia et al., 2016	40	PO 150 mg daily	Diclofenac 150 mg PO	No	No
Secondary analyses					
*same as Mathew et al., 2010 Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression Price et al., 2009	26	0.5mg/kg over 40 min	None Open Label	No	N/A
*same as Murrough et al., 2013 Effects of ketamine on explicit and implicit suicidal cognition: a randomised controlled trial and treatment-resistant depression Price et al., 2014	57	0.5mg/kg over 40 min	Midazolam 0.045mg/kg	No	No

Trial title	N	Dose	Placebo	Reporting	
				Reasons for ineligibility	Blinding
*same as DiazGranados et al., 2010 Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression Lally et al., 2014	36	0.5mg/kg over 40 min	0.9% saline	No	No
*same as Murrough et al., 2013 Neurocognitive Effects of Ketamine and Association with Antidepressant Response in Individuals with Treatment-Resistant Depression: A Randomized Controlled Trial Murrough et al., 2015b	73	0.5mg/kg over 40 min	Midazolam 0.045mg/kg	No	No

[1] Of participants randomized to ketamine, five of seven correctly guessed their infusion drug during day 1 ratings versus seven of nine randomized to midazolam. Clinical assessors guessed correctly after four of seven ketamine and five of nine midazolam infusions.

[2]Raters correctly guessed 42% of midazolam and 44% of ketamine allocations, patients correctly guessed 55% of both allocations

[3] 56% of 54 participant guesses and 51% of 55 assessor guesses were correct at the end of ECT treatment

1.3.2.4 Ketamine and depression relapse prevention

Based on the combined body of literature demonstrating ketamine's antidepressant and neurotrophic effects, and the pressing need for better relapse prevention strategies, it is possible that ketamine could have a role in depression relapse prevention. One study has been published which sought to investigate ketamine for preventative, rather than acute antidepressant action (Voort et al., 2016). This open-label study had five participants in the continuation phase. Participants who had remitted from depression with thrice-weekly ketamine infusions (up to six infusions, where remission criteria were a Montgomery and Åsberg Rating Scale for Depression score of ≤9, 24 h after any acute-phase infusion) were invited to have four once-weekly infusions of ketamine following the acute-phase treatment. Detail about eligibility and participant flow is not available. The five participants who had remitted and were treated with continuation-phase ketamine showed further (small) improvements in depressive symptoms during the continuation phase, though only one remained well during a four-week follow-up. A study which also aimed to harness the potential for ketamine's neurotrophic actions to prevent, rather than treat, depression, randomised 330 non-depressed parturient women to receive 0.25 mg/kg ketamine or saline placebo as an intravenous bolus within five minutes of delivery (Xu et al., 2017). No difference was found in depression symptoms between the groups at three days or six weeks.

1.3.3 Current state of the field

Researchers remain divided about whether and under what regulatory conditions ketamine should be considered for routine clinical practice. (Sanacora and Schatzberg 2015, Ryan and Loo 2017, Sanacora et al., 2017, Singh et al, 2017) Although trial design aims to eliminate confounding factors such as concomitant pharmacological therapy, it is unlikely that the conditions in which most published clinical trials of ketamine for depression were

undertaken, could be provided in clinical practice, i.e. elective admission for medication washout and ketamine infusions. A naturalistic study reported that up to six infusions of sub anaesthetic dose ketamine could be safely administered to depressed patients who continue usual care within an existing clinical setting (Diamond et al., 2014). Further pragmatic clinical trials which include participants who remain on pharmacological therapy and which do not require inpatient admission are now required to test the real-world clinical usefulness of the therapy. In addition, examination of factors such as reasons for ineligibility, non-recruitment, non-adherence, dropout and success of blinding is now important to identify potential barriers to definitive trials.

1.4 Personality disorder

1.4.1 Diagnosis and screening for personality disorders

Personality disorder is an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture (American Psychiatric Association, 2000). Diagnosis of personality disorder can be made using a diagnostic interview, for example the structured clinical interview for DSM-IV axis II personality disorders, SCID-II (First et al., 1997). There are many types and subtypes of personality disorder, which often co-occur. However there are important differences between the classification systems used to define personality disorder (Widiger, 2003), some of which are controversial (Shedler and Westen, 2004). Alternative diagnostic methods such as prototype matching have also been proposed (Westen et al., 2006), but structured interview remains the gold standard for diagnosis of personality disorders. The SCID-II has good test-retest reliability among psychiatric patients (overall weighted kappa of 0.53) but is less reliable in non-psychiatric populations (overall weighted kappa of 0.38) (First et al., 1995). The SCID-II takes 30-60 minutes to perform (First et al., 1997) and requires significant patient input and concentration. Therefore, many people who present with one psychiatric

disorder and may have an underlying comorbid personality disorder may be unable to complete the diagnostic process. Screening instruments have therefore been proposed, both for discrete personality disorders, such as borderline personality disorder (Zanarini et al., 2003) or schizotypal personality disorder (Raine and Benishay, 1995), as well as for personality disorders as a diagnostic group, such as the Iowa Personality Disorder Screen (Langbehn et al., 1999). The Standardised Assessment of Personality – Abbreviated Scale (SAPAS) is validated for identifying likely personality disorder among people attending psychiatry services (Moran et al., 2003).

High comorbidity exists between personality disorders and depression. Up to 50% of people with depression may also have a comorbid personality disorder (Sanderson et al., 1992). People with personality disorder are more likely to experience episodes of depression than those without the diagnosis (McGlashan at al., 2000, Lenzenwanger et al, 2007). Comorbid depression and personality disorder is associated with poorer depression outcomes, including lower remission rates (Collins et al., 1990) and higher relapse rates (Newton-Howes et al., 2014, Alnaes et al., 1997).

1.4.2 Personality disorder and electroconvulsive therapy

Though comorbid personality disorder has a clear negative impact on response to other treatments for depression, as above, it is unclear if comorbid personality disorder affects response rates to ECT for depression. Studies using diagnostic classification systems prior to DSM-IV found that presence of comorbid personality disorder did not affect response to ECT for depression (Pfohl et al., 1984, Zimmerman et al., 1986, Newton-Howes et al., 2014). More recent studies have reported inconsistent results. Retrospective (Sareen et al., 2000, Kaster et al., 2017) and population-based (Nordenskjöld et al., 2012) studies have reported lower ECT response rates and higher relapse rates following successful ECT among those with depression and personality disorder compared to those with depression

alone. However, a prospective study found that only borderline personality disorder was associated with poorer ECT response and those with other personality disorders responded equally well to ECT as those without (Feske et al., 2004). People with personality disorder and depression may suffer the consequences of pessimism regarding ECT response rates in both clinical and research settings. It has been suggested that clinicians under-prescribe ECT for depressed patients with a personality disorder (DeBattista and Mueller, 2001) and people with personality disorder are often excluded from clinical trials (Zimmerman at al., 2004). Some of the difficulty in ascertaining whether personality disorder has an effect on response rates to ECT for depression may lie in the onerous nature of diagnostic interviews for personality disorder, which may not be feasible for depressed patients. Identifying a useful screening instrument for personality disorders for depressed people having ECT would therefore be of value.

1.5 Depression and childhood trauma

There is a well-established link between adverse childhood experiences and later depression (Brown et al., 1987). Childhood trauma such as traumatic sexual events, emotional abuse or neglect, and bereavement, is associated with greater risk of depression (Green et al., 2010). In particular, childhood emotional abuse (Chapman et al., 2004) and childhood sexual abuse (Kendler et al., 2004) have been specifically linked to later development of depression. A dose-response relationship between childhood adverse experiences and probability of lifetime and recent depressive disorder has also been reported (Chapman et al., 2004).

Childhood trauma is also associated with poorer depression treatment outcomes. A meta-analysis of data from over 23,000 participants in epidemiological studies found that childhood maltreatment was associated with a higher risk of depression recurrence (odds ratio=2.27, 95% CI=1.80–2.87). Meta-analysed trial data from over 3,000 clinical trial

participants found that childhood maltreatment was associated with treatment resistance (odds ratio=1.43, 95% CI=1.11–1.83) (Nanni et al., 2012). People who have experienced childhood trauma have more recurrent depressive episodes (Wiersma et al., 2009), greater suicidality (Sarchiapone et al., 2007), and lower rates of response and remission with pharmacotherapy, psychotherapy or combination therapy for depression (Williams et al., 2016, Harkness et al., 2012). Greater trauma severity and younger age at experiencing childhood trauma further reduce the likelihood of responding to pharmacotherapy for depression (Williams et al., 2016). Childhood trauma also influences age at depression onset and comorbidity with other psychiatric disorders (Bernet and Stein, 1999) but the pathway between childhood events and later depressive disorder remains unclear (Tyrka et al., 2013).

It is unclear whether childhood trauma affects response to ECT for depression. Along with childhood trauma, recent stressful life events are also strongly predictive of the onset of depression (Kendler et al., 1999). Recent trauma and childhood trauma are both associated with depressive symptoms (Comijs et al., 2007), but have not been studied in an ECT population. Predicting response to ECT remains difficult (see section 1.2.2). As childhood trauma has a known impact on response to other treatments for depression, understanding the impact of childhood and recent trauma on the likelihood of response to ECT may help clinicians and patients to make well-informed decisions about treatment options.

1.6 Involuntary electroconvulsive therapy

1.6.1 Use of involuntary electroconvulsive therapy

People with serious mental illness around the world are administered ECT under involuntary conditions. Rates of use of involuntary ECT vary across Europe and the USA from 1-3% to 20-29% of all ECT (Leiknes et al., 2012). In Ireland, the proportion of ECT

that is involuntary varies annually from 7.5- 15.9% (Mental Health Commission, 2013, 2014, 2015, 2016).

As with many aspects of ECT practice (Finnegan et al., 2018), pathways to involuntary treatment differ between jurisdictions (Harris, 2006). In Ireland, involuntary ECT can be administered to a person detained in an approved centre (a designated psychiatric hospital or unit, approved by the Mental Health Commission, MHC) under the Mental Health Act, 2001 (MHA). Involuntary ECT cannot be administered to a voluntary inpatient. There are several potential pathways to involuntary ECT in Ireland (Dunne et al., 2009). In each case, two consultant psychiatrists must review the patient and agree that ECT is necessary and that capacity is impaired.

In 2015, the Mental Health Act was amended to remove the word "unwilling" from the section of the Act pertaining to involuntary ECT. This was preceded by much lobbying from mental health interest groups. The original provision stated that persons who were detained in an approved centre who were "unable or unwilling" to consent to ECT could be administered involuntary ECT.

1.6.2 Involuntary ECT populations

As people having involuntary ECT are excluded from prospective clinical research, knowledge of the needs of this group is based on retrospective studies, which have, to date, been limited in size, see Table 1.3. In addition, the possibility of publication bias has been raised with regard to the number of individual case reports and small case series of successful courses of involuntary ECT (Methfessel et al., 2017). Greater prevalence of non-depressive disorders has previously been reported among those having involuntary ECT (Martin et al., 1987). Other studies have shown that those having involuntary ECT may be older (Plakiotis et al., 2014) and have less knowledge about the treatment

(Malcolm, 1989). The one-year re-hospitalisation rate after involuntary ECT was 66% in one study (Chu et al., 2014), not dissimilar to a one-year post-ECT relapse rate of 51.1% based on meta-analysed data from eight prospective research studies of patients having voluntary ECT (Jelovac et al., 2016).

Table 1.3 Summary of studies describing involuntary ECT courses

Year	Author	Design	Location	N=invol	N=vol	Characteristics of the involuntary ECT group
1986	Mahler at al.	Retrospective casenote review with control group for comparison	Missouri	N=19	N=24	More likely to have future involuntary admissions No difference in age, gender, diagnosis, no of treatments
1989	Malcolm	Retrospective casenote review with patient interviews performed post-ECT	Sheffield	N=27	N=73	Poorer knowledge of ECT
1999	Wheeldon et al.	Retrospective casenote review with patient interviews performed post-ECT, control group for comparison	Aberdeen	N=11	N=139	Younger More likely to be female Higher depression severity at baseline Greater decrease in HRSD after course of ECT Less likely to opt for ECT in future illness episodes
2011	Lamont et al.	Retrospective casenote review with control group for comparison	Sydney	N=17	N=26	More likely to be diagnosed with a non-depressive disorder
2013	Andersen et al.	Observational study	Denmark	N=152	N/A	Any involuntary treatment incl ECT: Younger, earlier onset of psychiatric diagnosis, more prior psychiatric admissions
2013	Mosknes et al.	Observational study	Asker, Norway	N=7	N/A	Involuntary ECT administered only when likely to be life-saving (seven of 241 courses) Four of seven people had further ECT in their lifetime Early improvement documented (day after first treatment)
2014	Chu et al.	Observational study	Taiwan	N=29	N/A	Unable to consent group: longer hospital stays, higher one-year recurrence, more psychotic disorders, fewer affective disorders when compared to 'unwilling to consent' group

Year	Author	Design	Location	N=invol	N=vol	Characteristics of the involuntary ECT group
2014	Plakiotis et al.	Observational study of whole ECT service	Victoria State, Australia	N/A	N/A	Old-old adults more likely than young-old adults to have involuntary ECT
2015	Rasmussen et al.	Observational study	Minnesota	N=24	N/A	Common use of maintenance ECT Heterogeneity of diagnoses among those having involuntary ECT No outcome data
2017	Methfessel et al.	Observational study	Heidelberg and Gottingen, Germany	N=8	N/A	Seven of eight patients showed a marked clinical response

1.6.3 Involuntary ECT and clinical research

The importance of representativeness of clinical trial populations for guiding evidence-based practice is particularly acute in psychiatry research (Finnegan and O'Donoghue, 2017). Trial populations in many psychiatric disorders are not generalizable to clinical samples. For example, interventional studies in schizophrenia would exclude 80% of clinical schizophrenia patients, predominantly those with more severe illness (Humphreys, 2014, Humphreys and Weisner, 2000). Similarly, trials in dementia would exclude 94.8% of clinical Alzheimer-type dementia registry patients (Schneider et al., 1997). Antidepressant efficacy trials in particular have been shown to be poorly representative of community depression populations (Zimmerman et al., 2002). The exclusion of people having involuntary ECT from clinical research samples likewise leads to concerns about whether the results of clinical trials can be generalised to those having involuntary treatment. Clinical trials have allowed great progress to be made in optimising ECT treatment to improve response rates and reduce side effects. However, conclusions about, for example, laterality and pulse-width, are made based on trial populations of those having elective ECT who have capacity to consent to research participation. Little is known about people who have involuntary ECT. It is therefore unclear whether their needs differ in any substantial way from the needs of voluntary ECT patients who comprise the research populations on which best ECT practice is based.

1.7 Overall summary of background

Depression is a common serious mental health problem. Much of the burden of the disorder lies in its recurrent nature and current relapse prevention strategies offer only limited protection. Childhood trauma and the presence of personality dysfunction are associated with greater risk for depression and lower response rates to pharmacological treatment for depression.

One effective acute treatment for depression is ECT. Though cognitive side-effects, particularly retrograde autobiographical amnesia, limit its use, ECT practice has been greatly optimised over recent decades. However, as this evidence base is comprised of studies on people having only voluntary ECT, it is not known whether improvements in ECT practice can be applied to also improve outcomes for people having involuntary ECT. Other unknown factors in ECT practice are whether personality dysfunction or childhood trauma affect response rates to ECT, and what the precise nature of the effect of ECT on autobiographical memory is. Relapse rates are high after successful ECT for depression.

Ketamine is a glutamate receptor antagonist which has a robust acute antidepressant effect, possibly mediated by activation of neuroplasticity cascades. Clinical trials of ketamine have been modest-sized and reasons for non-recruitment, non-randomisation and non-adherence are not available. The potential for ketamine to be used in relapse prevention after successful ECT for depression has not yet been investigated.

1.8 Hypotheses and objectives

1.8.1 Study 1

1.8.1.1 Objective

To conduct a randomised, controlled, double-blind pilot trial of ketamine compared to midazolam for depression relapse prevention following successful ECT, to assess feasibility of the treatment protocol and gather information on reasons for non-recruitment, non-randomisation and drop-out to inform a future definitive trial.

1.8.1.2 Hypothesis

I hypothesized that the treatment protocol would be feasible and that participant adherence to four treatment infusions would be feasible.

1.8.2 Study 2

1.8.2.1 Objective

To examine performance on the full Kopelman Autobiographical Memory Interview (K-AMI) in severely depressed patients before and after a course of ECT and to compare this with the performance of age- and gender- matched healthy controls before and after a 4-week interval. I also aimed to assess for differences in K-AMI performance between ECT responders and non-responders, and association between change in performance on the K-AMI and depression severity, as measured by HRSD-24 scores. These measures aimed to control for both the passing of time and contemporaneous mood status when comparing autobiographical memory between ECT patients and controls.

1.8.2.2 Hypothesis

I hypothesised that patients would perform less well than controls on the K-AMI and that the K-AMI would detect deterioration in autobiographical memory performance in patients following ECT.

1.8.3 Study 3

1.8.3.1 Objective

To examine scores on the brief screening questionnaire for personality disorder, the SAPAS, in unipolar depressed patients referred for ECT and to determine whether a difference exists in response to ECT among patients with unipolar major depressive disorder who were identified on the SAPAS as likely or unlikely to have an underlying personality disorder. A secondary objective was to examine cognitive performance before and after ECT in a subgroup of depressed patients and compare those above and below the SAPAS threshold.

1.8.3.2 Hypothesis

I hypothesised that over 50% of depressed ECT patients would score above the cut off score of three on the SAPAS, and that ECT response rates would be lower among those above the SAPAS threshold score for personality disorder. I also hypothesised that cognitive performance would not differ between those above and below the threshold score.

1.8.4 Study 4

1.8.4.1 Objective

To examine the incidence of childhood (before the age of seventeen) and recent (within three years) trauma in a sample of unipolar depressed patients referred for electroconvulsive therapy (ECT) and to assess for association between response to ECT for depression and presence of childhood or recent trauma.

1.8.4.2 Hypothesis

I hypothesised that childhood or recent trauma would occur in over 50% of depressed ECT patients and that those who reported childhood trauma do less well with ECT than those without a history of childhood trauma.

1.8.5 Study 5

1.8.5.1 Objective

To compare a large sample of involuntary ECT courses to an age- and gender-matched control group of voluntary ECT courses in terms of baseline demographic and clinical features, ECT treatment parameters and ECT treatment, and outcome variables.

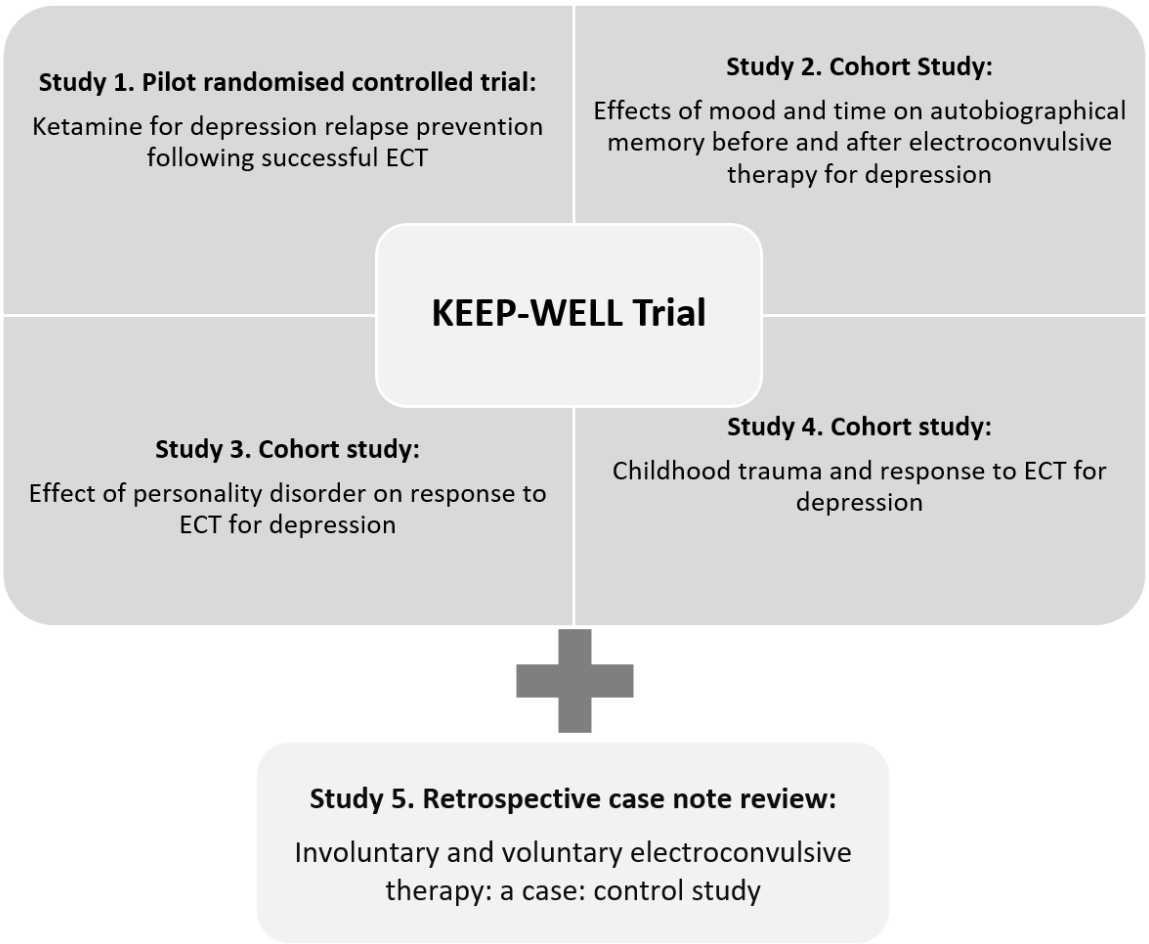
1.8.5.2 Hypothesis

I hypothesised that there would be no difference between involuntary and voluntary ECT courses in terms of treatment profiles and outcomes.

2. Materials and Methods

This work presented in this thesis is comprised of five studies. Four studies were conducted on the same population - participants in a randomised controlled pilot trial, the KEEP-WELL Trial, Study 1. Results of the trial itself are described in Chapter 3 (Study 1). Three other studies described here (Studies 2, 3, 4) are cohort studies involving the participants in the KEEP-WELL trial. For Study 2, a healthy control group was also recruited. Study 5 is a separate retrospective case note review. The backgrounds to the studies are summarised below.

Figure 2.1 Summary of Studies 1-5



2.1 Summary of Studies

2.1.1 Study 1. Ketamine for depression relapse prevention following successful ECT, the KEEP-WELL Trial

The KEEP-WELL trial, 'Ketamine for depression relapse prevention following electroconvulsive therapy: a randomised pilot trial' was funded by the Health Research Board, Ireland (HRA-POR-2014-604). The objective of the study was to conduct a randomised controlled pilot trial of a four-week course of once-weekly ketamine or midazolam infusions for depression relapse prevention following successful ECT to assess trial procedures for feasibility for a future definitive trial. Participants with unipolar depression referred for ECT were recruited (n=43) prior to commencing ECT and were assessed weekly during the ECT course using the primary clinical outcome, the 24-item Hamilton Rating Scale for Depression (HRSD-24). Those who met standard response criteria were invited, on completing ECT, to be randomised in a 1:1 ratio to a course of four once-weekly infusions of ketamine or the active comparator midazolam, and were assessed using a battery of instruments to monitor mood, physical health and psychotomimetic symptoms before, during and after the infusions. Participants were followed-up over six months using the HRSD-24 to assess for relapse. Information on recruitment, randomisation and follow-up rates and reasons for dropout was collected. Recruitment to the monitoring phase of the trial continued past the termination of the randomised treatment phase to allow ongoing recruitment to the cohort studies detailed below.

2.1.2 Study 2. Effects of mood and time on autobiographical memory before and after electroconvulsive therapy for depression

Autobiographical memory is known to be negatively affected by electroconvulsive therapy, but it is not clear how this effect differs from the effects of time and mood status

on recall of autobiographical memories and no ideal assessment for autobiographical memory currently exists. Previous ECT studies using the Kopelman Autobiographical Memory Interview (K-AMI) have been unable to account for these effects. This study aimed to examine performance on the full Kopelman Autobiographical Memory Interview in severely depressed patients (n=27) before and after a course of ECT and to compare this with the performance of healthy controls (n=72) before and after a 4-week interval. This takes into consideration both the passing of time and contemporaneous mood status when comparing performance. A secondary aim was to assess for association between change in performance on the K-AMI and mood status, as measured by scores on the 24-item Hamilton Rating Scale for Depression (HRSD-24), and association between performance in the K-AMI and response to ECT. In this prospective observational cohort study, depressed patients having ECT who were recruited to the monitoring phase of the KEEP-WELL Trial (Study 1) and a healthy control group were assessed at baseline and after an interval using the K-AMI. Depressed participants had assessments at baseline (pre-ECT) and at the end of the course of ECT. Healthy controls had assessments at baseline and at four weeks.

2.1.3 Study 3. Effect of personality disorder on response to ECT for depression

It is unclear whether personality disorder affects response to ECT and no study has reported on use of a brief personality screening questionnaire in an ECT population. The aim of this study was to assess for association between scores on the brief personality screening tool, the self-reported Standardised Assessment of Personality – Abbreviated Scale (SAPAS), and response to ECT among patients with unipolar major depressive disorder. In this prospective observational cohort study, depressed participants having ECT

(n=49) who were recruited to the monitoring phase of the KEEP-WELL Trial completed the SAPAS once at pre-ECT baseline and were monitored weekly for response to ECT.

2.1.4 Study 4. Childhood trauma and response to ECT for depression

Childhood trauma is a risk factor for later development of depression and is associated with lower response to pharmacotherapy for depression. It is not known whether the experience of childhood trauma affects response to ECT for depression. This study aimed to examine the incidence of childhood (before the age of seventeen) and recent (within three years) trauma in a sample of unipolar depressed patients referred for ECT (n=44), and to assess for association between response to ECT for depression and presence of childhood or recent trauma. In this prospective observational cohort study, depressed patients having ECT who were recruited to the monitoring phase of the KEEP-WELL Trial were assessed at pre-ECT baseline using the Childhood Traumatic Events Questionnaire and the Recent Traumatic Events Questionnaire and were assessed weekly for response to ECT using the HRSD-24.

2.1.5 Study 5. Involuntary and voluntary electroconvulsive therapy – a case-control study

It is not known whether results of clinical research in ECT (such as studies 1 through 4 above) can be used to guide treatment decisions for those having involuntary ECT, who are not represented in trial populations. This study aimed to compare courses of involuntary ECT with matched voluntary ECT courses in terms of clinical and demographic factors, treatment requirements, and outcomes. A retrospective case-control study was performed examining a five-year sample of involuntary ECT courses (n=48) and an age-, gender- and time-matched voluntary ECT control sample (n=98).

2.2 Materials

2.2.1 Demographic and baseline assessments

2.2.1.1 Participant background information

Demographic information (Appendix 1) was collected on all patients and controls and included age, self-identified gender, self-identified ethnicity, marital status, employment status, profession, years in education, height, weight, lifetime history of: smoking; alcohol abuse; or substance abuse, and family history of alcohol abuse, personal medical history and current medications. For depressed patient participants, additional information was collected on their course of depression, including age at onset, number of episodes of depression, duration of the current episode, current medications, as well as distance from home to the study centre.

2.2.1.2 Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)

The SCID (First et al., 1998) is a diagnostic interview which uses DSM-IV criteria to allocate psychiatric diagnoses (American Psychiatric Association, 2000). Although DSM-IV and ICD-10 criteria are comparable in some respects, the SCID is not designed to provide information on ICD-10 diagnoses (First and Westen, 2007). The research version of the SCID, as used here, is the gold standard for diagnosis of DSM-IV disorders. Among people with depression, when applying DSM-IV criteria, SCID has good inter-rater reliability (Kappa = 0.80) and fair test-retest reliability (Kappa =0.61) (Zanarini et al., 2000). SCID for depression was performed on all depressed participants at baseline. The full SCID involves nine sections. I performed the Current Major Depressive Episode subsection of the Mood Disorders section, Appendix 2. The extended mood disorders SCID was not performed as participants with bipolar illness were not eligible for recruitment to these studies and screening for bipolar disorder was conducted by treating teams as part of the admission assessment, prior to eligibility screening for research. The

SCID allows for information to be extracted from the respondent or other sources, e.g. clinical notes, collateral history, to allow application of timelines and severity scales to ascertain features of depression such as psychosis, chronicity and onset. There are therefore no limitations to completion of the assessment.

In these studies, the SCID for depression was performed at baseline with all depressed participants and additional information gathered from notes, nursing staff or family members where necessary for completion. DSM-IV allocates depression severity based on the number (the presence of five of nine listed symptoms indicated a depressive episode) and not severity of symptoms experienced, thus in this study, SCID was used to confirm diagnosis of major depressive episode and the prospective HRSD-24 scores repeated weekly, were used as a measure of depression severity. The SCID is conducted as a semi-structured interview with probe and follow-up questions to ascertain presence of symptoms of depression followed by depression subtype.

2.2.1.3 Maudsley Staging Method for Treatment Resistance in Depression (MSMTRD)

The MSMTRD (Fekadu et al., 2009) was designed to provide a measure of treatment resistance in depression. The method differs from other similar tools such as the Antidepressant History Treatment Form (Oquendo et al., 2003) as it uses a multi-dimensional method to consider treatment resistance including duration of depressive episode, severity of depressive episode, and treatment failures, Appendix 3. Treatment failures are rated categorically from 1-2 antidepressant failures (1 point) to >10 antidepressant failures (5 points). Failure of any pharmacological augmentation strategy and failure of electroconvulsive therapy are allocated one point each. The maximum total possible score is 15 and scores can be presented categorically with mild scores 3 – 6 indicating mild resistance, moderate scores 7 – 10 indicating moderate treatment resistance

and scores 11 – 15 indicating severe resistance. Psychotherapeutic treatment is not accounted for. Adequate treatment courses are not defined by the authors but were based on the Maudsley Prescribing Guidelines, British National Formulary and the Antidepressant History Treatment Form. For the purposes of this study, participant report of doses and durations of antidepressant and augmentation trials were confirmed where possible with clinical notes and drug prescription records and adequate doses were defined according to the Maudsley Prescribing Guidelines (Taylor et al., 2015). The MSMTRD has been assessed for validity in depressed inpatient populations and the total score as well as the dimensional scores (depression duration, severity and treatment failures) all predicted failure to remit with depression treatment among 88 patients (Fekadu et al., 2009). The MDMTRD also showed increased predictive power over other available similar instruments, e.g. the Antidepressant Treatment History Form, in a smaller follow-up study (Fekadu et al., 2009).

2.2.1.4 The National Adult Reading Test (NART)

The NART (Nelson and Willison, 1991), Appendix 4, is a test of premorbid reading ability which allows for estimation of a number of intelligence scale subscores, including estimated premorbid full-scale intelligence quotient (IQ), verbal IQ, and performance IQ. The test shows high correlation with the Wechsler IQ scales (Wechsler et al., 1997, Lezak, 2004), and both inter-rater and test-retest reliability are high at >0.90 (Nelson and Willison, 1991). The NART used here is an updated version of the 1982 original, and assesses reading ability based on pronunciation of fifty words which are spelled non-phonetically and thus cannot be correctly pronounced without familiarity, e.g. campanile, demesne, etc. The NART is thus a proxy measure of premorbid intelligence. Similar vocabulary and reading ability tests are commonly used as proxy measures of intelligence among adults. The NART is valid in depressed samples and across age ranges (Nelson and Willison,

1991) and is not affected by mood status (Crawford et al., 1987). To conduct the test, the interviewer provides direction to the respondent to attempt to pronounce aloud each word that they are shown, regardless of prior familiarity with the word. The interviewer shows 50 words, in a set order, one at a time, at a pace dictated by the respondent. The interviewer is permitted to provide neutral phrases of reassurance to reduce test anxiety throughout, regardless of the accuracy of responses. The words increase in difficulty (and likely unfamiliarity) as the test progresses and the interviewer records responses, using the number of errors to calculate scores. The test was adapted for these studies to promote inclusivity, with words printed in large font to allow for visual impairment, but ability to accurately see words in large font and fluent written and spoken English are required to properly complete the test. Scribing, mobility or hearing impairment do not limit completion of the test.

2.2.1.5 Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory (Oldfield, 1971), Appendix 5, provides a measure of handedness, an important potential confounder in neuropsychological testing. The seven-item inventory used here prompts respondents to choose a category which best describes their performance of a variety of tasks (e.g. striking a match, using a computer mouse), ranging from always left, usually left, left or right, usually right, to always right. Item responses are scored and the aggregated score provides a handedness quotient, ranging from -100 (complete left handedness) to +100 (complete right handedness).

2.2.1.6 Electroconvulsive therapy treatment information

Depressed participants having ECT consented to researchers accessing their clinical notes to gather information on the ECT course. Data were collected on: indication for ECT, number of ECT treatments administered, laterality of ECT, mean total charge in

millicoulombs, mean seizure duration (motor and EEG) in seconds, adverse events, changes in medication during the ECT course, and mean post-treatment time to reorientation in minutes.

2.2.2 Illness severity assessment

2.2.2.1 Hamilton Rating Scale for Depression, 24-item

The HRSD-24 (Hamilton, 1960, Beckham and Leber, 1985), Appendix 6, is the primary clinical outcome for all studies reported here and was used to assess mood at baseline and examine weekly depression severity to assess for response and remission following ECT. The 24-item Hamilton Rating Scale for Depression consists of a range of items scored from 0-2 or 0-4 which assess for presence and severity of biological, emotional and cognitive symptoms of depression, as well as psychotic and compulsive symptoms. Questions refer to the respondent's overall experience over the preceding seven days and contain both respondent-rated questions and observational items scored by raters, based on the appearance and presentation of the person being assessed.

The scale allows for collateral history from e.g. nursing staff to inform detail on items such as helplessness where patients may require assistance with basic activities. Symptoms of physical ill health, such as pain, poor sleep, poor appetite, etc., may result in inflated scores suggestive of depression, even where no affective, emotional or cognitive symptoms of depression are present. The original Hamilton Rating Scale (Hamilton, 1960) did not incorporate measures of psychosis or cognitive symptoms such as hopelessness, helplessness and worthlessness, and the 24-item version provides these additional measures. The maximum possible score is 77. The scale is reliant on respondent answers and sensitivity to presence and severity of depression may be limited where insight is poor, but does allow for some observational scoring e.g. where a person denies depressed mood but presents as depressed throughout the interview. The scale has been validated in

depressed groups but the limitations of the instrument including those highlighted above have been debated in recent years (Bagby, Ryder et al. 2004, Carroll 2005). Nonetheless, the Hamilton Rating Scale is one of the most commonly used clinician-administered depression severity rating scale in clinical trials (Williams, 2001), although the 24-item version is a newer adaptation of the original 21-item scale reported in many older trials. Despite its limitations, widespread use of the HRSD-24 in similar depression studies allows for comparison between groups and coincides with the move toward standardisation of clinical trial outcome measures. The scale has an accompanying Structured Interview Guide (Williams, 1988) used for training and rating as detailed in Data Quality Assurance, below. Respondent visual, hearing, scribing or mobility impairment do not affect ability to complete the assessment.

2.2.2.1.1 Response, remission and relapse

The primary clinical outcome measure for Studies 2-4 described here is response to ECT as measured using the HRSD-24. To be recruited to studies 1-4 patients must score ≥21 on the HRSD-24, indicating at least moderate depression severity. *Response* to ECT was defined as achieving ≥60% decrease from baseline HRSD-24 and a score ≤16 on two consecutive weekly ratings. *Remission* criteria were ≥60% decrease in HRSD from baseline and a score ≤10 on two consecutive weekly ratings. For Study 1, criteria for *relapse* were ≥10 point increase in HRSD-24 compared to post-ECT score plus HRSD-24 ≥16; in addition, increase in the HRSD-24 should be maintained one week later. Hospital admission, further ECT, and deliberate self-harm/suicide also constituted relapse. Timing of these events was recorded. Similar to all strict criteria applied to complex clinical scenarios, these cut-off scores for response, remission and relapse are somewhat arbitrary. The above were chosen to be comparable with previous ECT work at this study site

(Semkovska et al, 2016) and others (Sackeim, Dillingham et al. 2009, Kellner, Knapp et al. 2010).

2.2.2.1.2 HRSD-11

As described above, the 24-item HRSD refers to the respondent's overall experience over the previous week. For assessment of acute change in depression severity, e.g. over the course of an infusion clinic, as described here in Study 1, HRSD-24 questions were divided into dynamic (11) and non-dynamic (13) items. An 11-item modified HRSD consisting only of dynamic items susceptible to change in a matter of hours e.g. physical and emotional experience, was therefore performed for acute assessment of change in depression severity during infusion clinics. For non-dynamic items such as questions on sleep and appetite, which would not change acutely over the course of a few hours, scores were carried forward to result in a total score for a 24-item HRSD.

2.2.2.2 Clinical Global Impression Score

In Study 5, the Clinical Global Impression score (Guy, 1976) is reported as a measure of global baseline illness severity for psychiatric disorders (Clinical Global Impression: Severity Score, CGI-S) and global illness change (Clinical Global Impression: Improvement Score, CGI-I), Appendix 7. In the study site, local protocol requires that all patients having ECT must have a documented CGI-S score to indicate illness severity just before commencing ECT, and a documented CGI-I score prior to each twice-weekly ECT treatment. In Study 5, the CGI-I score for the final ECT treatment was recorded as the post-ECT CGI-I. The CGI is validated for use in depression (Guy, 1976) but has lower inter-rater reliability than the Hamilton Rating Scale for Depression (Cichetti and Prusoff, 1983) (the 24-item version of which is used in studies 1-4 here). Though the CGI scales have advantages for use in clinical practice – the scales are simple and convenient both to score and to communicate, and the instrument relies on clinical experience without

requiring training – the clinician-administered CGI scores for both severity and improvement do not correlate well with patients' view on the severity or course of their illness (Forkmann et al., 2011). However, the retrospective cohort study design of Study 5 required use of pre-existing clinical data. The research population included involuntarily admitted, severely unwell patients who did not have decision-making capacity to consent to participation in prospective studies, therefore reporting of documented CGI scores for both illness severity and improvement is used as an available outcome measure for illness course during ECT.

2.2.3 Cognitive assessments

2.2.3.1 Standardised Mini Mental State Examination (sMMSE)

The sMMSE is a standardised, freely available 12-item version of the Mini Mental State Examination (Cockrell and Folstein, 1988), a screening tool for dementia which is widely used and understood and requires little time for completion and no rater training (Molloy et al., 1991). Though use of the standardised Mini Mental State Exam (sMMSE, Appendix 8) has become common, it is inadequate for monitoring adverse cognitive side-effects of ECT (Semkovska and McLoughlin, 2010). The sMMSE is insensitive to change, does not assess executive function, and can only detect substantial impairment (Tombaugh and McIntyre, 1992). Here, the sMMSE was used as a screening measure for cognitive impairment at baseline for recruitment to studies. Participants must score >24 (of 30) in order to be eligible for recruitment. For assessment of cognition during the studies reported here, the sMMSE was used as part of a battery of tests including measures of frontal executive function. Parallel versions are not available and practice effect is possible among depressed participants as the sMMSE is standard practice in inpatient units and may have been performed on repeated occasions prior to research participation. However, the sMMSE has advantages of being widely used and reported in other depression and ECT research,

allowing for comparison between groups. In these studies, sMMSE scores are cautiously reported alongside supplementary assessments of broader cognitive function.

2.2.3.2 Digit span: forward and backward

The digit span subtest of the WAIS-R (Wechsler et al., 1997) assesses immediate short-term memory, attention and working memory, Appendix 9. The test is administered in a strict fashion with clear directions provided for raters and respondents to follow and parallel versions are used on repeat assessments to reduce practice effect. Respondents are informed that they will hear the rater read a series of numbers which must be repeated exactly in order to answer that item correctly. A trial question for both forward and backward spans is provided. Visual, scribing or mobility impairment will not affect the test but respondents must be able to hear the rater as digit series cannot be repeated. In the first part of the test (forward digit span), a series of numbers is read out by the rater at a rate of one per second using a consistent pitch. At the last digit of each series, the pitch of the rater voice should drop. The respondent then repeats the series of numbers. Each number level (e.g. four digits in a row) has two attempts (two separate series of four numbers are read aloud) and respondents can score 2 (both trials passed), 1 (one trial passed) or 0 (no trials passed). The test is discontinued after failure on both trials at one level. For forward digit spans, increasing series of numbers up to nine digits is tested and a total score (up to 16) and a maximum digit span (up to 9) is allocated. In the second part of the test (backward digit span), the series of numbers read by the rater must be correctly repeated by the respondent in backward order in order to answer correctly. Increasing series of up to eight digits are tested and respondents can score up to 14 in total for backward digit spans and can have a maximum backward digit span of up to eight.

2.2.3.3 Trail Making Test (A) and Trail Making Test (B)

Trail Making Test A (Part A Wechsler, 1989) tests motor and psychomotor speed. Trail Making Test B (Part B, Wechsler, 1989) tests set-shifting ability, a frontal executive function. Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper, Appendix 10. In Part A, the circles are numbered 1 to 25, and dispersed throughout the page, to be connected in ascending order. In Part B, the circles include both numbers (1 to 13) and letters (A to L). As in Part A, the respondent must connect the circles in ascending order but also must alternate between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The respondent is instructed that they will be timed and must connect the circles as quickly as possible, without lifting the pen from the paper. The rater brings any error to the immediate attention of the respondent and allows them to correct it. The test is discontinued if more than five minutes elapses without completion. The mean time for completion of Part A by healthy controls is 29 seconds, with more than >78 seconds indicating deficiency. For Part B the mean completion time is 75 seconds and >273 seconds is deficient. Parallel versions of the tests are available to reduce practice effects. Both tests require some visual acuity and scribing ability but are not affected by hearing or mobility impairment.

2.2.3.4 Addenbrooke's Cognitive Assessment-III (ACE-III)

The Addenbrooke's Cognitive Assessment is an assessment of global cognitive function which incorporates measures of frontal executive function (Hsieh et al., 2013, Noone, 2015). Although some rater training is required and the instrument takes longer to complete than the standardised Mini Mental State Exam, it has the advantage of being sensitive to change and providing subscales for a variety of cognitive functions (Mioshi et al., 2006). In these studies, the ACE-III was not required in full as a complete battery of cognitive testing was performed including Trail Making Tests A and B and digit spans.

Elements of the ACE-III were therefore selected to assess cognitive functions that were not assessed by other tests in the battery. These were: category and letter fluency, retrograde semantic memory (as not all participants could complete the full K-AMI), and verbal learning with immediate, delayed and cued recall items, Appendix 11.

Retrograde semantic memory in the ACE-III is measured on a four-item general knowledge scale. Verbal learning consists of three respondent repeats of a seven-item address read aloud by the rater. The ACE-III uses a British address, and for these studies, a fictitious but sensible Irish address was used instead. Immediate recall is tested on the third consecutive repeat. Following an interval of 20 minutes, delayed recall of the address is tested. Tests in the cognitive battery for these studies were therefore administered in a consistent order. If any of the seven address items are not recalled, cued options are given and a point for delayed recall can be obtained through cued recall. Parallel versions of the address were used to avoid practice effect on verbal learning. Delayed recall of three non-associated objects is also measured (immediate recall of these is not assessed). Visual, scribing and hearing impairment can all limit respondents' ability to complete the ACE-III.

2.2.3.5 Kopelman Autobiographical Memory Interview (K-AMI)

The Kopelman Autobiographical Memory Interview (K-AMI) (Kopelman et al. 1989) was originally designed for assessment of amnestic patients but has also been used in ECT research (Sienaert et al. 2010). It assesses both semantic and episodic autobiographical memory separately, with items scored on specificity and detail. A copy of the K-AMI is provided in Appendix 12. In the assessment, the participant is asked for a series of specific semantic memories, such as names and addresses, for Recent Life, Early Adult Life, and Childhood experiences. In addition, at each time point, the participant is asked to relate in as much detail as possible, a number of individual, discrete episodic memories based on prompts provided by the rater. The episodic memories are scored according to the richness

of detail provided. Scores are provided for subscales from recent life, early adult life, and childhood answers and can be aggregated into a total semantic score and total episodic score. The K-AMI does not provide a measure of recall consistency and caution is required due to suggestions of a lack of sensitivity of the instrument to ECT-related retrograde amnesia (Jelovac et al. 2016). It is long (+25 minutes) and can be burdensome for depressed patients to complete. It also requires significant rater training, detailed in Data Quality Assurance (section 2.3.8 below). As with all assessments of autobiographical memory it is impossible to verify the accuracy of the detail provided, but assessment of the K-AMI showed answers were accurate in 90% of the original sample, suggesting confabulation is not a major problem with this assessment (Kopelman et al. 1989).

The ideal instrument for assessment of retrograde autobiographical amnesia would be short and simple to administer and would provide scores for memory detail (semantic and episodic) as well as a consistency score on retesting after ECT. Results could be measured against the general population (and also depressed persons not treated with ECT) at baseline and after several weeks of normal life. Unfortunately, currently used instruments for retrograde amnesia, including the K-AMI and the Columbia University Autobiographical Memory Interview (CUAMI, or the short form CUAMI-SF), (McElhiney et al. 1995, 2001) arguably do not fulfil all these criteria, though this is the subject of debate (Semkovska and McLoughlin 2013, Sackeim 2014, Semkovska and McLoughlin 2014). Studies using the CUAMI and CUAMI-SF have substantially contributed to the understanding of autobiographical memory impairment in ECT, though caution is required in interpreting any studies of this cognitive function in ECT populations because of the absence of a ‘perfect’ instrument. The CUAMI has been shown to vary with patient subjective expressions of cognitive difficulties following ECT but there is debate about the public availability of normative data on performance of healthy controls on the CUAMI,

although the group performance of controls has been outlined by the developers of the instrument (Sackeim et al, 2014).

The K-AMI has the advantage of publicly available normative data on the performance of healthy controls (Kopelman et al, 1989) and the instrument allows for improvement of scores on re-testing should memory improve during or after a course of ECT. The K-AMI was chosen for investigation here due to the advantages described above and in order to investigate the outstanding research questions that limit the utility of this instrument, namely, the effect of mood status and the passage of time on performance on the K-AMI. The alternative instrument, the CUAMI, described in Section 4.1, does not allow for improvement of scores on retesting.

As with sensitive information provided in assessment of childhood trauma, respondents are informed prior to completing the K-AMI of the limits of confidentiality and the duty of mandatory reporting should they disclose abuse in childhood by an alleged perpetrator who is still alive (Children First Act, 2015). Fluent English and ability to hear the questions posed are required for completion but scribing, mobility or visual impairment do not affect completion.

2.2.4 Other assessments

2.2.4.1 Childhood and Recent Traumatic Events Questionnaire

The Childhood and Recent Trauma Events Questionnaire (Pennebaker and Susman, 1988) (CRTEQ) (Appendix 13) was designed for assessment of traumatic events and confiding in both childhood and recent life and was first described in 1988. The initial use of the CRTEQ was described in a sample of 200 Texan corporate employees (Pennebaker and Susman, 1988). It has since been used in studies of schizophrenia (Rajkumar et al., 2011),

social anxiety (Hoge et al., 2012), gene-environment interactions (Szentágotai-Tătar et al., 2015), and cognition (Entringer et al., 2009).

The CRTEQ requests "yes/no" answers to questions about the occurrence of specific types of trauma experienced in childhood (before the age of seventeen) and recently (within the past three years) and the age at which the trauma was experienced and optional detail. In the Childhood Traumatic Events Questionnaire, the categories of trauma assessed are bereavement, violence, traumatic sexual event, parental separation, serious illness or injury, and an 'other trauma' category. In the Recent Traumatic Events Questionnaire, categories of trauma assessed are bereavement, spousal separation, violence, traumatic sexual event, serious illness or injury, change in work role, and an 'other trauma' category. In both the childhood and recent trauma questionnaires, an open question allows documentation of any trauma experienced within the questionnaire timeframe not captured by previous questions ('other trauma'). Answers in this section were coded by raters into types of trauma, e.g. emotional trauma and neglect, financial stress. For each type of trauma in the CRTEQ, respondents provide a score (using a 7-point scale, where 1=not at all traumatic, 4=somewhat traumatic, 7=extremely traumatic) of their current perception of the severity of the trauma that they experienced in the past, and the level of confiding of the trauma, which can be aggregated into a total trauma score and total confiding score for childhood or recent trauma. The questionnaire is designed as a self-assessment. Participants were provided with instructions and left alone to complete the assessment privately and return it to the rater for later scoring. If significant visual impairment or literacy limited a participant's ability to complete the questionnaire, questions were read out by a trained interviewer. To maximise inclusivity and completion of the assessment, participants were encouraged to complete the questionnaire by self-assessment but if they were unable to do so independently due to depressive symptoms such as fatigue, amotivation or anxiety or if they requested support for completion, questions were read out

by a trained interviewer. A protocol for mandatory reporting of potential risks as well as provision of support for participants who reported childhood trauma for the first time was followed in accordance with national legislation (Children First Act, 2015).

Recall bias is a potential problem associated with all instruments which retrospectively assess for traumatic events (Paulhus, 1991). The effect of other types of potential responder bias, such as social desirability bias, is unclear. In the study reported here, responders were provided with clear instruction about the supports available to them and limits of confidentiality in the context of a first report of childhood abuse where the alleged abuser was alive. Although responders were afforded privacy for completion of the CRTEQ, it is possible that responders may have chosen not to disclose some traumatic events.

The instrument most commonly used for assessment of childhood trauma among depressed populations, the Childhood Trauma Questionnaire (Bernstein et al., 2003, Binder et al., 2008, Bradley et al., 2008), has no companion assessment for recent trauma. Recent trauma is also associated with onset of depression (Kendler at al., 1999) and therefore is important in understanding response to ECT and the CRTEQ was chosen on this basis. The CRTEQ as used here allows for some comparison with previous studies of depression which have used the Childhood Trauma Questionnaire as both divide traumatic events into categories of trauma.

2.2.4.2 Standardised Assessment of Personality – Abbreviated Scale (SAPAS)

The Standardised Assessment of Personality – Abbreviated Scale (SAPAS) is a self-report brief screening tool for identifying underlying personality disorder. It has been validated among people attending psychiatry services (Moran et al., 2003). The scale, Appendix 14, consists of eight questions which refer to longstanding and general traits, to which

participants provide “yes/no” responses. For example, one screening question is “in general, do you have difficulty making and keeping friends?” A cut-off score of 3 positive answers has a sensitivity of 0.94 and specificity of 0.85 in psychiatric populations for identifying the presence of any personality disorder (Moran et al., 2003). Among inpatients with depression, a cut-off score of three had a positive predictive value of 73.1% and was not associated with depression severity (Bukh et al,. 2010). The SAPAS has also been used to assess for outpatient response to pharmacological treatment (Gorwood et al., 2010). Negative cognitive bias (Paulhus, 1991) among depressed people may affect response to self-assessment screening tools such as the SAPAS. In Study 3, depressed patients referred for ECT completed the SAPAS at pre-ECT baseline. The questionnaire is designed as a self-assessment. To minimise social desirability response bias (Paulhus, 1991), participants were provided with instructions on how to complete the questionnaire and then left alone to complete the assessment and return it confidentially to the rater. As detailed for the CRTEQ above, to maximise completion and inclusivity, participants were encouraged to complete the questionnaire by self-assessment but if they were unable to do so or requested support for completion, questions were read out by a trained interviewer and responses recorded.

2.2.5 Assessment of potential side-effects

2.2.5.1 Young Mania Rating Scale (YMRS)

The YMRS (Young et al., 1978), Appendix 15, is a commonly used assessment tool for severity of mania and hypomania. The full scale assesses for emotional, biological and cognitive symptoms of mania and hypomania. In this study, the single mood item, rated 0-4, representing a range from normal mood to frank euphoria, is used to assess for possible mood elevation in infusion clinics. The item is observer-rated and the scale does not require training. Use of the YMRS mood item as part of a battery of instruments for

assessment of possible psychotomimetic effects of ketamine has been previously reported in ketamine clinical trials as part of safety and tolerability monitoring (Zarate et al., 2006).

2.2.5.2 Patient-rated Inventory of Side-effects (PRISE)

The PRISE (Wisniewski et al., 2006), Appendix 16, is a self-rated assessment of physical and cognitive symptoms for use in assessment of possible side effects of interventions. It prompts respondents to report presence or absence of a range of symptoms in nine symptom categories, including genitourinary function, cognitive function, sleep and sexual function. The questions relate to the preceding week but the timeframe can be amended to assess change over days or hours. Following identification of any symptom, a dichotomous rating for 'tolerable' or 'distressing' is provided for each symptom category. The PRISE was designed for use in assessment of side effects of pharmacological treatment of depression in the Sequenced treatment alternatives to relieve depression (STAR*D) trial (Rush et al., 2004, Rush et al., 2006) and is suited to assessment of acute change in symptoms. Its use has thus been reported in ketamine trials as part of a battery of tests to assess safety and tolerability (Murrough et al., 2013, Wan et al., 2015).

2.2.5.3 Clinician-administered Dissociative States Scale (CADSS)

The CADSS (Bremner et al., 1998) is a 23-item questionnaire for administration by raters for assessment of present-moment dissociative symptoms in respondents, Appendix 17. The scale assesses for dissociative symptoms in identity, proprioception, time perception, colour and depth perception, and other modalities. An open prompt question for each item is asked e.g. "do things seem to be moving in slow motion?" and if answered positively, is followed by a series of further questions to ascertain the severity of the symptom. Each item is scored 0-4 according to detailed instructions in the CADSS manual. It has

previously been used in ketamine trials as part of a battery of tests to assess for possible psychotomimetic side-effects of ketamine (aan het Rot et al., 2010, Wan et al., 2015).

2.2.5.4 Brief Psychiatric Rating Scale (BPRS)

The BPRS (Overall and Gorham, 1962) is an 18-item questionnaire assessing a wide variety of symptoms of psychotic disorders. It is a clinician-administered scale and incorporates patient self-report and clinician observation. Following the initial 16-item scale, two items were added and an interview guide developed (Rhoades and Overall, 1988). As reported by others, the four-item psychosis subscale was used in these studies as part of a battery of tests to assess for possible psychotomimetic effects of ketamine (aan het Rot et al., 2010, Wan et al., 2015). The subscale assesses domains of unusual thought content, suspiciousness, bizarre behaviour and hallucination, Appendix 18. Each item is scored from1-7 (very mild to extremely severe) thus in the four-item subscale, respondents can score a minimum of four. The manual provides prompt questions for each item and a detailed scoring system for various responses.

2.2.6 Case Report Form (CRF)

A CRF was compiled for all participants in the KEEP-WELL pilot trial, as required by the specifications of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. The contents of the CRF were reviewed and approved by the Research Ethics Committee of St James's and Tallaght Hospitals and the KEEP-WELL Trial Data Monitoring Committee. The contents and structure of the CRF are listed in Appendix 19. The CRF contains the materials described above as well as a number of trial-specific documents which relate to trial-specific operating procedures and protocols. For example, as detailed in the trial-specific protocol "Pharmacy Dispensing and Return Protocol:

Investigational Medicinal Products in the KEEP-WELL Trial" (Appendix 20), the anaesthetist who administers the trial infusion must complete both an Anaesthetist Blinded Information Checklist which is filed in the CRF, and an Anaesthetist Unblinded Information Checklist which is completed with a pharmacist on return of the remaining investigational medicinal products to the pharmacy following administration and is then stored securely with the randomisation list.

2.3 Method

2.3.1 Pilot trials

Randomised controlled trials continue to be seen as the gold standard of assessment of interventions (Oxford Levels of Evidence, 2009). However, underpowered and poorly representative trials may not be generalizable to clinical populations and are thus less clinically useful and economical. This is a problem for all medical disciplines, such that it has been identified in an European Union Regulation due for operation in 2018 (European Council, 2014), but has been repeatedly demonstrated to be problematic in psychiatry research, and samples in antidepressant trials are poorly representative of those who will require treatment with these agents (Zimmerman et al., 2002). Conduct of pilot and feasibility trials to identify whether trial protocols are suitable to progress to definitive trials can help to assess not only feasibility of trial protocols but also representativeness of trial populations. Ireland's Health Research Board places a high value on pilot trials as part of a strategy to improve the methodological quality of clinical trials in Ireland (Health Research Board, 2015).

A pilot trial is distinguished from pilot work - work completed to inform study design or logistics prior to completing a definitive study - in the use of randomisation and intervention. In addition, pilot trials are distinct from proof-of-concept trials, which are carried out to determine if an intervention is biologically active or inactive (Thabane et al.,

2010). Data collected as part of a pilot trial are sometimes combined with data from a subsequent definitive trial in order to increase statistical power (Wittes and Brittain, 1990), but this is not always appropriate, unless the definitive trial was *a priori* designed as an adaptive trial with an internal pilot trial component (Chow and Chang, 2008). Although structured guidelines exist to promote the quality of pilot trial reporting (Eldridge et al., 2016), many pilot trials are never published (Van Teijlingen and Hundley, 2001). However, publication of pilot trial data has been described as "*an ethical and scientific obligation*" to avoid duplication of research effort and unwarranted research spending (Thabane et al., 2010).

The traditional aim of pilot trials is to estimate a confidence interval for treatment effect to inform power calculations for a definitive trial (Craig et al., 2008) but caution is required when relying on pilot study data to inform power calculations as pilot trials may themselves be underpowered to assess scientific feasibility (Kraemer et al., 2006). There are other many reasons to conduct a pilot trial. Thabane *et al* summarise the reasons for performing a pilot study as comprising assessment of the feasibility of trial process, trial resources, trial management as well as trial scientific feasibility (Thabane et al., 2010). Variously, these aims could involve assessing rates of recruitment and retention, staffing requirements, time burden of assessments for participants and staff, capacity of the study staff and site, and data management.

As detailed in Chapter 1, the field of ketamine research in depression has been characterised by modest-sized trials, but the factors underlying this are unclear. Therefore, application of ketamine to a novel purpose (as in Study 1 here, depression relapse prevention) requires a pilot trial in order to assess feasibility of the trial protocol and gather information on reasons for non-recruitment, non-randomisation and dropout. Conduct of a pilot trial is necessary to prevent inappropriate use of research funding on a definitive trial which may fail to recruit sufficient numbers of participants to be adequately powered. In

addition, a pilot trial would help to assess whether a subsequent definitive trial would be able to recruit a trial population representative of the target population (here, people with depressive disorder). Logistical issues involving equipment, staffing and participant travel can be assessed in a pilot trial to improve and economise processes for a definitive trial.

2.3.2 Cohort studies

In Studies 2-4 described here, no intervention took place other than the passing of time (for controls and patients) and routine clinical care (for patients). Prospective cohort studies as reported in Studies 2-4 are observational studies, "*a family of studies in which investigators compare people who take an intervention with those who do not. The investigators neither allocate patients to receive the intervention not administer the intervention. Instead, they compare records of patients who had taken an intervention and been treated in routine practice with similar patients who had not taken the intervention* (Oxford Levels of Evidence, 2009)."

Such studies represent level II evidence as participants are not randomised and these studies are thus subject to potential confounding factors, known and unknown. In some circumstances the results of cohort studies may be aggregated and the aggregated results can represent level I evidence (Oxford Levels of Evidence, 2009). Although randomised controlled trials are viewed as the highest quality single study design, observational studies have a critical role in investigating many clinical research questions (Black 1996, Glasziou et al., 2004), including those in which randomised intervention would not be suitable or ethical. For example, as the evidence base for ECT for treating depression grew, it became clear that non-therapeutic or 'sham' ECT could no longer be used as a control treatment in randomised studies to investigate the effects of ECT in depression (Rasmussen, 2009). Therefore, for people who require ECT for treatment of depression, cohort studies such as those reported here can answer research questions such as the effects of ECT on

autobiographical memory, where a randomised controlled trial would not be ethical. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Von Elm et al., 2014) recognises the importance of observational studies and aims to improve the reporting of such studies, mirroring the available reporting guidelines for clinical trials (Schulz et al., 2010) and meta-analyses (Moher et al., 2009). STROBE Guidelines are followed in reporting Studies 2-4 described here.

2.3.3 Retrospective case note review studies

Studies which involve gathering and reporting previously recorded clinical information comprise a lower level of evidence than prospective studies (Oxford Levels of Evidence, 2009). Such studies are commonly used to answer research questions relating to situations where informed consent is not possible, such as in emergency medicine (Gilbert et al, 1996). Case-control studies are one type of retrospective cohort study, in which groups are selected for reporting based on matching of important clinical factors that could affect the outcome of interest (Matt and Mathew, 2013). Retrospective cohort studies generally suffer from poor methodology and reporting, such as poorly identified objectives (Worster and Haines, 2004). However, well-conducted retrospective studies have value in answering clinical research questions that are not suitable for prospective studies.

In Study 5, aggregated clinical data are reported which refer to people admitted involuntarily who receive involuntary ECT. Little is known about this group's needs and in what way they may differ from the needs of those who have elective voluntary ECT. Though there are possible methodological approaches to conducting ethical research in such situations (Finnegan and O'Donoghue, 2017), all prospective studies of people who have impaired capacity involve some risk to participants. Retrospective studies do not have participants and involve little risk to the individuals whose aggregated clinical data are reported. As no interventions or prospective assessments are involved, the risk to the

individuals whose aggregated data are reported consists primarily of data confidentiality and the potential for identification. In this respect, retrospective cohort studies (including case control studies) are similar to clinical audit, but without a gold standard for comparison of variables of interest. Ethical approval is required for use of aggregated clinical data for retrospective cohort studies. Specifically, ethical approval is required to publish such aggregated clinical data. However, where adequate measures are taken by researchers to ensure data confidentiality and to reduce the potential for identification, individual consent from persons to whom clinical data refers is not required for these studies. For example, separate researchers should collect and enter pseudonymised data from clinical notes for analysis and reporting by other researchers, who have not seen the data sources.

2.3.4 Study Location

St Patrick's Mental Health Services is Ireland's largest independent-sector mental health service provider and administers over one-third of all electroconvulsive therapy nationally (Mental Health Commission 2016). The two inpatient units combined (St Patrick's University Hospital and St Edmundsbury Hospital) comprise 300 inpatient beds. The hospital accepts referrals from the public health service for ECT but the vast majority of inpatients have private health insurance, along with over 50% of the Irish population (Landsdowne Millward-Brown, 2012).

2.3.5 Participants and consent

2.3.5.1 Depressed participants

People referred for ECT in St Patrick's Mental Health Services were screened and, if eligible, were recruited to the KEEP-WELL Trial before commencing ECT. These

participants are described in detail in Chapter 3 (results of Study 1). Prior to commencing recruitment, treating clinicians signed consent for inpatients under their care to be recruited to the trial if eligible. Once referred for ECT, patients' clinical notes were screened for exclusion criteria and then patients who did not have clear exclusion factors were approached by a researcher to request verbal consent for advanced screening such as a HRSD-24 or sMMSE assessment. Patients who met all eligibility criteria were then provided with verbal and written information (Patient Information Leaflet, Appendix 21) by a researcher and offered an opportunity to review and ask questions. Patients who were referred for ECT later than 6 pm on the evening before their first treatment were deemed to have too little time to adequately consider participant information to provide valid informed consent and were classed as ineligible due to late referral. Researchers returned to eligible potential participants to answer questions and meet with family members if requested, and if a participant expressed interest in participation, the Consent Form (Appendix 32) was completed with a clinician.

2.3.5.2 Healthy controls

Controls were recruited through advertising with volunteer agencies locally and nationally. People who had no lifetime history of mental illness and were physically well were invited to attend for two assessments, one month apart. No incentive was provided but travel expenses and parking costs were reimbursed. Participants initiated contact with the research team via email or phone and were initially screened for exclusion factors then sent a Control Participant Information Leaflet (Appendix 22) for review. After an interval, researchers followed up using the medium of the participant's choice to answer questions about the study. Participants who were eligible and interested were provided with a range of appointment times and, on attendance for their first appointment, were re-presented with the Participant Information Leaflet and given another opportunity to ask questions. The

Consent Form (Appendix 32) was then completed with a clinician. All control assessments took place in the study centre, St Patrick's University Hospital, lasting 70-90 minutes each, at the same time of day (07.00- 09.00).

2.3.6 Study procedures

Study procedures for Studies 1-4 are briefly summarised in Table 2.1. Study 5 is a retrospective case note review.

Table 2.1 Study procedures for Studies 1-4

Study		Baseline Interview	Interval	Post-ECT	Randomised Treatment	Follow-up
Study 1 Ketamine for depression relapse prevention following successful ECT	**Unipolar depressed patients**	*Baseline battery* **PLUS** SCID-IV MSMTRD	ECT treatment as usual Weekly HRSD-24 monitoring	*Follow-up battery* **PLUS** ECT treatment information	Four once-weekly infusions of ketamine or midazolam *Table Z*	Follow-up to week 26
Study 2 Effects of mood and time on autobiographical memory before and after electroconvulsive therapy for depression	**Unipolar depressed patients**	*Baseline battery* **PLUS** K-AMI	ECT treatment as usual	*Follow-up battery* **PLUS** K-AMI ECT treatment information	N/A	N/A
	Healthy controls	*Baseline battery* **PLUS** K-AMI	4- week interval	*Follow-up battery* **PLUS** K-AMI	N/A	N/A
Study 3 Effect of personality disorder on response to ECT for depression	**Unipolar depressed patients**	*Baseline battery* **PLUS** SAPAS	ECT treatment as usual	*Follow up battery* **PLUS** ECT treatment information	N/A	N/A
Study 4 Childhood trauma and response to ECT for depression	**Unipolar depressed patients**	*Baseline battery* **PLUS** CRTEQ	ECT treatment as usual	*Follow up battery* **PLUS** ECT treatment information	N/A	N/A

SCID-IV: Structured Clinical Interview for DSM-IV Axis I disorders, MSMTRD: Maudsley Staging Method for Treatment Resistant Depression, K-AMI: Kopelman Autobiographical Memory Interview, SAPAS: Standardised Assessment of Personality – Abbreviated Scale, CRTEQ: Childhood and Recent Traumatic Events Questionnaire.

In Table 2.1, the *baseline battery* consists of:

- 24-item Hamilton Rating Scale for Depression
- Demographic information, clinical information
- National Adult Reading Test
- Edinburgh Handedness Questionnaire
- Standardised Mini Mental State Exam (sMMSE)
- Verbal Fluency: Letter and category
- Verbal Learning (modified ACE III)
- Trail Making Tests A and B
- Digit Span: Forward and Backward

Accompanied by the following for depressed patient participants:

- Structured Interview for Diagnosis of DSM-IV disorders (SCID-IV)
- Maudsley Staging Method for Treatment Resistant Depression (MSMTRD)

The *follow-up battery* consists of:

- 24-item Hamilton Rating Scale for Depression
- Verbal Fluency: Letter and category
- Verbal Learning (modified ACE-III)
- Trail Making Tests A and B
- Digit Span: Forward and Backward
- Standardised Mini Mental State Exam (sMMSE)

Accompanied by ECT treatment information for depressed patient participants.

Study procedures for each infusion clinic for randomised participants in Study 1, the KEEP-WELL Trial, are summarised in Table 2.2.

Table 2.2 Study procedures at infusion clinics for randomised participants in Study 1, the KEEP-WELL Trial.

Timepoint	-60 minutes	0 minutes	+20 minutes	+40 minutes	+240 minutes
	Pre-infusion	*Start of infusion*	*Mid-infusion*	*End of infusion*	*Post-infusion*
Depression Severity	HRSD-24				HRSD-11
Physical Health	Pre-infusion vitals	Vitals monitored every ten minutes	Vitals monitored every ten minutes	Vitals monitored every twenty minutes	Post-infusion vitals
Psychotomimetic Effects	*Baseline* - CADSS - BPRS - YMRS		*Mid-infusion* - CADSS - BPRS - YMRS		*Post-infusion* - CADSS - BPRS - YMRS
Tolerability	*Baseline* - PRISE		*Mid-infusion* - PRISE		*Post-infusion* - PRISE
Participant Comfort	Arrival checklist				Departure checklist

HRSD-24: Hamilton Rating Scale for Depression, 24-item, CADSS: Clinician-Administered Dissociative States Scale, BPRS: Brief Psychiatric Rating Scale (Psychosis subscale); YMRS: Young Mania Rating Scale (mood item), PRISE: Patient-Rated Inventory of Side Effects.

2.3.7 Study approval and governance

2.3.7.1 Ethics and governance

Studies 1-4 were approved under one application to the Research Ethics Committee (REC) of St James's and Tallaght Hospitals (Appendix 23), which is authorised by the Department of Health and Children to review applications for ethical approval for clinical trials. Ethical approval for Studies 1-4 was also sought from the Research Ethics Committee of the study site, St Patrick's Mental Health Services (Appendix 24). Study 5 was approved by the Research Ethics Committee of St Patrick's Mental Health Services. In addition, the KEEP-WELL Trial (Study 1) was approved by the Health Products Regulatory Authority (HPRA, Appendix 25), which is the authorised body in Ireland for clinical trials approval under Directive 2001/20/EC of the European Parliament and of the Council of 4 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" (the "Clinical Trials Directive"), Appendix 27. All applications for clinical trial authorisation under the Directive are reviewed centrally under the EudraCT system (EudraCT Registry No.: 2014-004262-14). All requirements of the Clinical Trials Directive were met, including submission of an annual Development Safety Update Report to the HPRA for approval. The study was conducted in accordance with the principles that have their origin in the Declaration of Helsinki, in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC. A Trial Master File was compiled and managed by myself for the purposes of HPRA inspection. The Trial Master File contained the following documents written and maintained by the author:

- Clinical Trial Protocol (Appendix 26)

- Participant Information Leaflet: patients (Appendix 21)
- Participant Information Leaflet: controls (Appendix 22)
- Case Report Form (Appendix 19)
- Investigator's Brochure: ketamine
- Investigator's Brochure: midazolam
- Trial Specific Protocol: Emergency Unblinding of Trial Participants (Appendix 27)
- Trial Specific Protocol: Data Quality Assurance Protocol (Appendix 29)
- Trial Specific Protocol: Pharmacy Dispensing and Return Protocol for Investigational Medicinal Products (Appendix 20)
- Trial Specific Protocol: Charter for Trial Steering Committee (Appendix 28)
- Trial Specific Protocol: Charter for Data Monitoring Committee (Appendix 30)
- Certificate of Indemnity for clinical trial activity
- Funding documentation
- Confirmation of REC and HPRA approval
- Log of Delegated Responsibilities (Appendix 31)
- Trial equipment maintenance checklist
- Research staff file and Curriculum Vitae
- Training record for trial staff

The above documents were updated as required and reviewed on an annual basis. Each researcher working on the trial was required to read the updated documents annually and sign the Research Staff Signature Log, also in the Trial Master File. All researchers working on the trial completed mandatory certification on a two-yearly basis in Good Clinical Practice for Clinical Trials.

The KEEP-WELL Trial (Study 1) was publicly registered at www.clinicaltrials.gov and on the EudraCT database. Annual reports were submitted to the Health Research Board, the

REC of St James's and Tallaght Hospitals and the REC of St Patrick's Mental Health Services, in addition to the HPRA report.

Due to the sensitive nature of information collected during completion of the Childhood Traumatic Events Questionnaire (Study 4), the author acted as dedicated person for completion of mandatory reporting of potential abuse of a child or vulnerable adult in accordance with local policy.

An independent Data Monitoring Committee was formed which met on a six-monthly basis throughout the trial to review reports compiled by the author. A Trial Steering Committee was formed and met on a six-monthly basis throughout the trial to review the recommendations of the Data Monitoring Committee and a report compiled by the author, and to make a recommendation regarding continuation of recruitment and randomisation. A Trial Management Group consisting of the Principal Investigator, author and other researchers met weekly during the trial to discuss any protocol violations or recruitment difficulties.

Table 2.3 Meeting dates of Data Monitoring Committee and Trial Steering Committee

Trial Steering Committee	Data Monitoring Committee
04/03/15 - Organisational Meeting	20/05/15 - Organisational Meeting
16/12/15	25/11/15
08/06/16	25/05/16
11/01/17 - Final Meeting	23/11/16
	17/05/17 - Final Meeting

2.3.8 Data Quality Assurance

All raters underwent extensive training prior to commencing trial recruitment. Inter-rater reliability analysis for the primary clinical outcome, the HRSD-24, was performed at least six-monthly and results are presented in Table 2.4 below. Training on use of both the

HRSD-24 and the Kopelman Autobiographical Memory Interview consisted of the following steps:

1. Independent reading of assessment materials
2. Consensus meeting to agree detailed criteria for scoring according to manual
3. Observation of an experienced rater administering the assessment to depressed inpatients (with written informed consent) with a variety of clinical presentations
4. Conduct of five assessments supervised by an experienced rater and discussion
5. Video recording of five other assessments conducted independently for playback and discussion with experienced raters (with written informed consent)

Training on all other assessments consisted of independent reading of assessment materials, discussion with experienced raters, supervised conduct, discussion and then independent conduct of assessments.

Table 2.4 HRSD-24 Inter-Rater Reliability Assessment for KEEP-WELL Trial Raters

Date	No. of raters	Intraclass Correlation Coefficient
Mar 2015	2	0.96
Nov 2015	2	0.97
Mar 2016	3[a]	0.96
Jul 2016	5[a]	0.96
Nov 2016	3[a]	0.99
May 2017*	4[a]	0.95
Jul 2017*	5[a]	0.98

*: Randomisation to the KEEP-WELL Trial was concluded at this time point but raters continued to perform HRSD-24 assessments in the trial follow-up phase and were thus included in inter-rater reliability assessment, [a]Inter-rater reliability was assessed for researchers on multiple projects, two of whom were raters for the KEEP-WELL trial.

An eight-step Data Quality Assurance Protocol (Appendix 29) was compiled by the author for application by all researchers to any data collected during the conduct of these studies. As participant numbers were lower than expected, item 7 in the Protocol ("Every six months, statistical analyses will be carried out to uncover any remaining input errors") did

not take place as simple observation by two researchers was sufficient to uncover input errors. Similarly, due to the small numbers of participants, it was sufficient for data entry to be reviewed by the Trial Management Group on a weekly basis rather than by the Data Monitoring Committee on a six-monthly basis.

2.3.9 Participant and Public Involvement (PPI)

PPI has become a central component of clinical trial research and is particularly important where research is publicly funded. Two levels of PPI (provision of information, consultation) (Staniszewska et al., 2011) were incorporated into the completion of the studies described here.

2.3.9.1 Consultation

During the development of the pilot trial documents, input was sought from the Consumer Council of St Patrick's Mental Health Services. A Council member reviewed the Participant Information Leaflets in order to assess for use of plain language and completeness of information. In addition, the Council member consulted on trial procedures to improve participant comfort and reduce burden. A nominated member of the Consumer Council was a member of the Trial Steering Committee and was consulted on a six-monthly basis for suggested improvements in trial practice. Informal consultation took place with each trial participant (patients and controls) who were asked at final assessments and after each infusion (randomised patient participants only) if they could suggest improvements in trial procedures for participant convenience.

2.3.9.2 Information provision

A trial newsletter was posted to all stakeholders on a six-monthly basis, including participants (patients and controls) and volunteer organisations. The author presented trial

information to service users as part of a rota of clinicians who provide daily (weekday) lectures to hospital inpatients on a variety of topics. A programme of public communication was undertaken in 2015 in order to provide information to the public issues related to the trial, such as depression relapse prevention, ketamine in depression and trial recruitment, and included national radio interviews by the Principal Investigator and national newspaper articles. The trial was registered on the publicly available website, www.clinicaltrials.gov (updated on a six-monthly basis), and the EudraCT database (https://www.clinicaltrialsregister.eu/). Information regarding the trial was also publicly available through the research team's website (https://www.tcd.ie/medicine/psychiatry/research/projects/depression-neurobiology.php), updated on a six-monthly basis. Updates were also provided on the research site's intranet (quarterly), the newsletter of St Patrick's Mental Health Services (quarterly) and the twice-yearly hospital newsletter for general practitioners. In addition, a trial-specific email (thekeepwellstudy@gmail.com) was monitored daily by the author during the recruitment phase for expressions of interest from potential volunteer controls and all queries from the public (430 +) received a response. The author also presented to stakeholders in depression treatment as part of the public Aware lecture series (http://www.aware.ie/aware-monthly-lectures-2015/). Trial researchers attended public events such as volunteer fairs and public events on mental health, such as Wellbeing Fairs (https://www.stpatricks.ie/mental-health-takes-centre-stage-cork-fair-0).

2.3.10 Electroconvulsive Therapy

Healthy controls as described in Study 2 did not receive ECT. Depressed participants in Studies 1-4 were recruited following their referral for ECT for unipolar depressive disorder and prior to their first ECT treatment. Their research participation did not result in any change to their treatment and they received treatment as usual. They remained inpatients

for the duration of their ECT treatment and were managed by their treating team with recommendations from ECT clinicians regarding medications or laterality of ECT where clinically indicated. In Study 5, notes of patients who had previously been administered ECT were retrospectively reviewed.

Modified brief-pulse (1.0-msec pulse width; current amplitude 800 mA, Mecta 5000M device, Mecta Corp., Portland, Ore.; maximum 1200 mC) ECT was administered twice weekly according to the Royal College of Psychiatrists' guidelines (Dunne and McLoughlin, 2013), using methohexital (0.75 mg/kg–1.0 mg/kg) anaesthesia, and succinylcholine (0.5 mg/kg–1.0 mg/kg) for muscle relaxation (Dunne and McLoughlin, 2013). Seizure threshold was established by dose titration at the first session (Semkovska et al., 2016). Subsequent treatments were 1.5 x threshold for bitemporal and 6 x threshold for unilateral (d'Elia placement) ECT. Stimulus charge was titrated upward as required during the treatment course. Referring clinicians consulted with patients to determine the number of ECT sessions. Patients continued prescribed medications for the duration of the study. ECT treatment parameters were recorded, including seizure threshold (millicoulomb [mC]), mean stimulus charge (mC) for all sessions, motor and EEG seizure durations (seconds), and total number of sessions. The author administered 50% of all ECT treatments provided at the study site during the conduct of these studies.

2.3.11 Randomisation and Blinding

Depressed participants in the pilot KEEP-WELL Trial (Study 1) who met eligibility criteria for randomisation were allocated in a 1:1 ratio to a four-week course of either once-weekly ketamine or the active comparator midazolam. Randomisation by sealed-envelope system using a computerised random allocation was performed independently by statisticians at the Centre for Support and Training in Analysis and Research at University College Dublin (CTSAR). Raters and participants were blinded to allocation. Success of

blinding of participants and raters was assessed after the first infusion. Both groups continued usual care during the randomised treatment phase and thereafter. A trial-specific protocol for emergency unblinding (Appendix 27) was in place in order to provide for unblinding in the event of situations specified in the Trial Protocol. In order to allow for smooth use of the emergency unblinding protocol, the author met with Assistant Directors of Nursing in both inpatient units at the study centre and a drill emergency unblinding scenario was practiced twice during the recruitment phase with on-call nursing management staff.

2.3.12 Statistical analyses

All statistical analyses used a two-tailed $p<0.05$ level of significance unless otherwise specified and were performed using IBM SPSS Statistics, Version 22.0 (Armonk, NY: IBM Corp). Data are presented as mean (SD) unless otherwise specified. General principles are described here and detailed description of analyses performed in each study is provided in each chapter.

2.3.12.1 Study 1

Descriptive statistics were used throughout to examine baseline demographic and clinical features, ECT treatment parameters and assessments performed before, during and after randomised treatment infusions, as appropriate to the pilot trial design (Arain et al., 2010). Formal comparison of data between ketamine and midazolam treatment groups was not possible due to the small group size.

2.3.12.2 Studies 2-4

Variables were assessed for normality (Shapiro-Wilk test) and variance (Levene's test) and compared using t-test or Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables, when appropriate assumptions were met.

In Study 3, one-way ANCOVA was conducted for repeated measures.

Where correlations were examined, Spearman's rho was used for non-parametric data. . Bonferroni correction was used to control for multiple comparisons for all familywise comparisons and specified p values for statistical significance are provided.

Logistic regression was performed in Studies 3 and 4 and results of assumption testing and model fit are reported.

2.3.12.3 Study 5

Descriptive and simple comparative statistics were performed. After assessment for normality, means were compared using independent-samples t-tests. Categorical variables were compared using either χ^2 or Fisher's exact tests, as appropriate.

2.3.13 Contribution to these studies

I joined the research team when funding had been secured for Study 1, the KEEP-WELL pilot trial, and the design of the pilot trial was broadly complete. I collaborated with my supervisor to write the Trial Protocol and Trial-Specific Operating Protocols, Case Report Form and other trial documents. I liaised with pharmacy, nursing, and medical staff to write and implement these protocols and sources the necessary equipment, utilising grant administration staff support in Trinity College Dublin.

I wrote ethics committee applications and communicated with committees (Authorised Research Ethics Committee, Site Research Ethics Committee, and Health Products

Regulatory Authority) to obtain approval from the relevant authorities for the conduct of the trial. I established the logistical detail of the trial including all assessments and interventions and the design of the cohort studies. I completed the KEEP-WELL Trial and the cohort studies described here with one full-time research assistant (Ms Toni Galligan, MSc) and the assistance of a consultant anaesthetist (Dr Enda Shanahan, FCAI) and a research nurse (Ms Louise Donnelly) for seven infusion clinics. During clinics, I completed clinic set-up, logistical monitoring, and 50% of participant assessments. Following completion of the trial, three other research assistants assisted with remaining data entry arising from the cohort studies. I approached 50% of all referred patients for ECT and completed 100% of all consent processes for the trial and cohort studies. I completed 50% of all assessments at each time point among patients and controls. I was the Data Controller and Medical Monitor for the trial (responsible for data entry, confidentiality, and safety reporting) and was responsible for all other governance activities as outlined in the Log of Delegated Responsibilities (Appendix 31). I completed all data analysis independently for Studies 1, 3, 4 and 5. For Study 2, I consulted with a statistical consultation service (Centre for Support and Training in Analysis and Research, University College Dublin, http://www.cstar.ie) to confirm the appropriateness of planned analyses of non-parametric data, and for advice on controlling for multiple comparisons. I performed the analyses and completed interpretation of results for all studies. I wrote study reports for all studies detailed here and completed mandatory reporting to the relevant authorities.

3. Ketamine *vs* midazolam for depression relapse prevention following successful electroconvulsive therapy: a randomised controlled pilot trial:

3.1 Introduction

Electroconvulsive therapy (ECT) remains the most powerful treatment for acute depression (UK ECT Review Group, 2003). However, relapse rates are high, nearly 30% after three months and 40% after six months (Jelovac et al., 2013). Some protection from relapse is afforded by continuing antidepressant therapy (Geddes et al., 2003) and by continuation ECT (Kellner et al., 2016), but there is a need for new relapse prevention strategies following ECT. Ketamine, a competitive glutamate N-methyl-D-aspartate receptor antagonist, rapidly relieves core symptoms of acute depression in up to 70% of cases (Fond et al., 2014, McGirr et al., 2015, Caddy et al., 2014), though the effect wanes within days. It is given as a sub-anaesthetic dose (e.g. 0.5mg/kg) over 40 minutes and is safe in repeated doses, though increased blood pressure and dissociative symptoms are not uncommon during infusions (aan het Rot et al., 2010). Midazolam, a sedative and anxiolytic benzodiazepine, mimics some of the acute effects of ketamine at low doses and has been used as an active comparator to try improve blinding in clinical trials (Murrough et al., 2013). Ketamine activates neuroplasticity pathways, an action that may account for its antidepressant effect (Li et al., 2011, Duman et al., 2016). Harnessing this action to prevent depression relapse could be a major step in addressing the need for better relapse prevention strategies. No reported trials have explored the potential for ketamine to reduce depression relapse rates.

We conducted a randomised, controlled, double-blind pilot trial of ketamine compared to midazolam for depression relapse prevention following successful ECT. The goal was to assess feasibility of the treatment protocol and gather information on reasons for non-recruitment, non-randomisation and drop-out to inform a future definitive trial. We

hypothesized that the treatment protocol would be feasible and we aimed to randomize up to 40 participants.

3.2 Method

3.2.1 Trial Design

Trial procedures are as described in Chapter 2. The double-blind pilot trial design (Arain et al., 2010) focused on gathering information about feasibility of the trial protocol. Briefly, patients with major depressive disorder (DSM-IV criteria) (American Psychiatric Association, 2000) referred for ECT, who had no other Axis 1 disorders, no previous ECT or substance abuse within six months, and had a score ≥21 on the 24-item Hamilton Rating Scale for Depression (HRSD-24) (Beckham and Leber, 1985), were recruited to the Monitoring Phase and had weekly HRSD-24 assessments. ECT was administered as described in Chapter 2. Those who met response criteria following ECT (≥60% decrease from Baseline HRSD-24 score and score ≤16 on two consecutive weekly ratings) and who received at least five sessions of ECT and continued to meet other eligibility criteria were invited to participate in the Treatment Phase. Remission criteria were a ≥60% decrease in HRSD from baseline and score ≤10 on two consecutive weekly ratings. Randomisation by sealed-envelope system (not stratified) using a computerised random allocation was performed independently at the University College Dublin Centre for Support and Training in Analysis and Research, Participants were randomly allocated in a 1:1 ratio to a four-week course of either once-weekly ketamine at 0.5mg/kg or the active comparator midazolam at 0.045mg/ kg, in 50 ml of saline over 40 minutes, as per previous ketamine trials (Fond et al., 2014, McGirr et al., 2015, Caddy et al., 2014). Raters and participants were blinded to allocation. Both groups continued usual care during the randomised treatment phase and thereafter.

3.2.2 Randomised treatment

Ketamine/midazolam infusions were administered by a consultant anaesthetist and took place in the ECT clinic on a day when there were no other clinical activities. Ketamine psychotomimetic effects and adverse events were assessed before, during (+20 mins) and after (+240 mins) infusions of ketamine or midazolam using the Clinician-Administered Dissociative States Scale (CADSS) (Bremner et al., 1998), Brief Psychiatric Rating Scale (BPRS; four-item positive symptom subscale) (Overall and Gorham, 1962), Young Mania Rating Scale (YMRS; mood item) (Young et al., 1978) and Patient-Rated Inventory of Side Effects (PRISE) (Wisniewski et al., 2006). Participants were followed-up over six months following ECT to assess for relapse. Criteria for relapse were ≥10 point increase in HRSD-24 compared to post-ECT score plus HRSD score ≥16; or hospital admission, further ECT, or deliberate self-harm. No changes were made to the trial protocol following trial commencement.

Baseline assessments included the Maudsley Staging Method for Treatment Resistance in Depression (MSMTRD) (Fekadu et al., 2009), a multidimensional treatment resistance assessment in which scores 3-6 indicate mild resistance; 7-10: moderate resistance; 11-15: severe treatment resistance. Participants in this trial could score a maximum of 14 as one item relates to ECT treatment failure. The National Adult Reading Test (NART) (Nelson and Willison, 1991) was performed at baseline and estimated premorbid full-scale IQ was obtained.

3.2.3 Cognition

The standardised Mini Mental State Examination (sMMSE) (Molloy et al., 1991) was performed with all participants as a measure of global cognition at baseline and post-ECT follow-up. A battery of other cognitive assessments (non-prioritized secondary outcomes) was performed by a subset of depressed participants. Immediate short-term memory,

attention and working memory were measured using Forward and Backward Digit Spans (Wechsler et al., 1997). Motor and psychomotor speeds were assessed using the Trail Making Test (part A) (Wechsler et al., 1997). Frontal-executive function was rated by Trail Making Test (part B) (Wechsler et al., 1997) plus letter and category verbal fluencies performed as part of a modified Addenbrooke's Cognitive Examination III (ACE-III) (Hseih et al., 2013) which included a four-item scale for retrograde semantic memory. Anterograde verbal memory was tested using the verbal learning component of the ACE-III with immediate and delayed recall of a seven-item address and delayed recall of three non-associated objects (Hsieh et al., 2013). Parallel versions were used where available (ACE-III, digit spans) to reduce practice effects.

3.2.4 Statistical analysis

Baseline demographic and clinical features as well as ECT treatment parameters are presented using descriptive statistics. Data are presented as mean (SD) unless otherwise specified. Formal comparison of data between ketamine and midazolam treatment groups was not possible due to the small group size. For the subgroup analysis of those who completed cognitive assessments, scores were assessed for normality and due to skewedness, were compared using Mann-Whitney-U test. Data are presented as median (range). Bonferroni correction was applied to control for multiple comparisons and p was set at 0.005. Descriptive and comparative statistics were performed using IBM SPSS Statistics, Version 22.0 (Armonk, NY, USA: IBM Corp).

3.3 Results

3.3.1 Trial profile

Recruitment took place over an 18-month period from April 2015 to November 2016. The trial was then discontinued as the primary objective – to assess feasibility of the trial protocol – had been achieved. Figure 3.1 (CONSORT flow diagram) illustrates the trial profile and reasons for ineligibility, non-recruitment, non-randomisation and drop-out at each step. Additional detail on reasons for ineligibility is presented in Table 1.1. During the study period 175 persons were referred for ECT and screened for eligibility. Of these, 63 were eligible to take part in the Monitoring Phase, of whom 43 consented to be recruited and were assessed weekly. Consent for both the Monitoring Phase and Randomised Treatment phase took place at the start of the Monitoring Phase as required by the trial ethical approval. In the Monitoring Phase 26 of the participants (60.5%) met criteria for response to ECT and 23 of these met all eligibility criteria for the randomised Treatment Phase. Only six of the 23 eligible participants (26%) were willing to be randomised and received the allocated treatment. Participants received one (n=5) or two (n=1) infusions and no participant completed the full treatment protocol.

Figure 3.1 CONSORT Flow diagram for the KEEP-WELL Trial

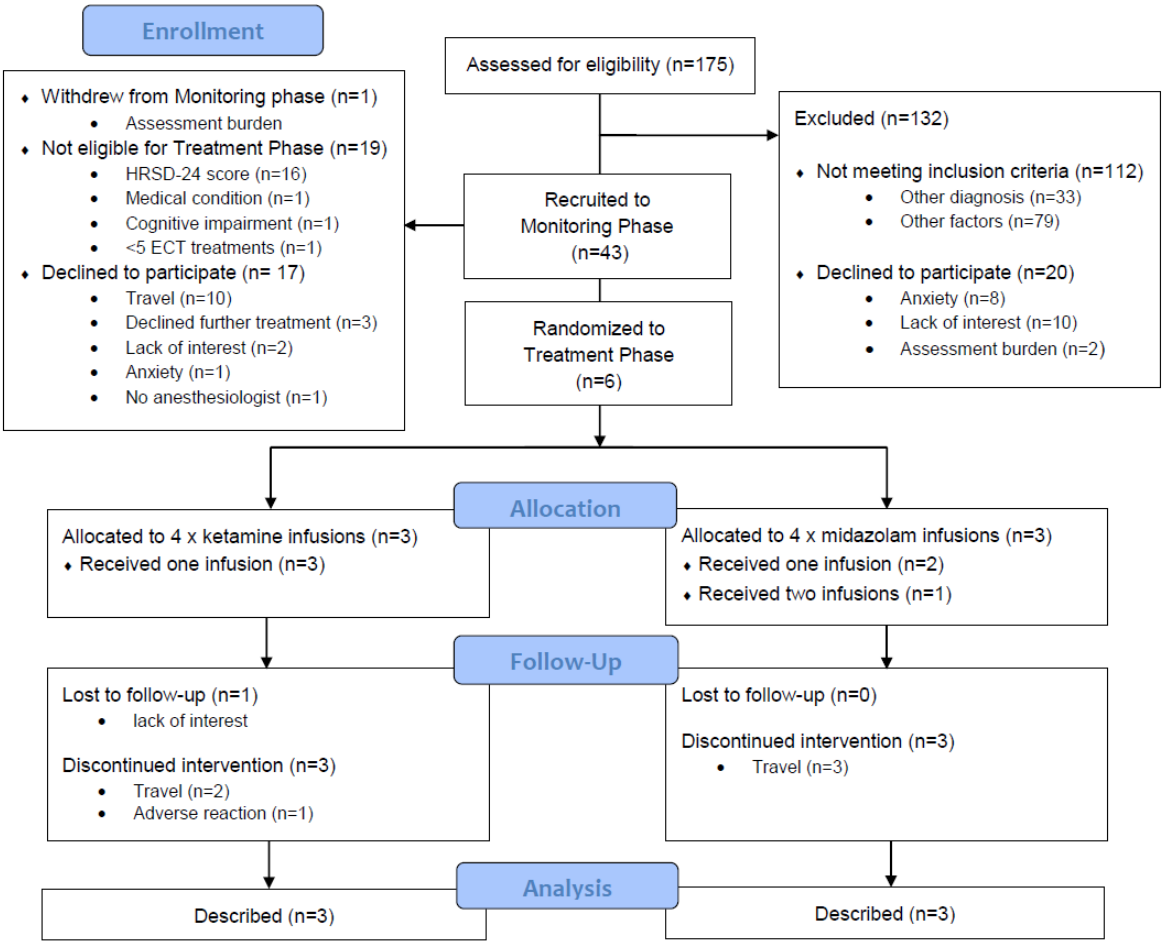


Table 3.1 Reasons for ineligibility to the KEEP-WELL trial

Factor	N
Total number of ECT referrals screened	**175**
Ineligible in total	112
Diagnosis other than unipolar MDE	***33***
Other active Axis I disorder	31
BPAD	*20*
Schizoaffective disorder	*4*
PTSD	*3*
Eating disorder	*2*
Schizophrenia	*1*
GAD	*1*
Did not meet SCID criteria	2
Factors other than diagnosis	***79***
Involuntary admission	22
Referral for maintenance ECT	13
HRSD-24 <21	11
ECT within 6 months	9
Subs abuse within 6 months	6
sMMSE <24	4
Unable to consent	6
Already in trial	3
No treating clinician consent	1
Late referral for ECT	4

MDE: Major Depressive Episode as per DSM IV diagnostic criteria; BPAD: Bipolar Affective Disorder as per DSM IV; PTSD: Post Traumatic Stress Disorder; GAD: Generalised Anxiety Disorder; SCID: Structured Clinical Interview for DSM disorders; ECT: electroconvulsive therapy; HRSD-24: Hamilton Rating Scale for Depression, 24-item; sMMSE: standardized Mini Mental State Exam.

3.3.2 Feasibility

This trial protocol was deemed not feasible as randomisation and adherence rates were inadequate, demonstrating that a definitive trial of ketamine for depression relapse prevention would not be possible using this trial protocol. Reasons for ineligibility, non-recruitment, non-randomization and non-adherence are detailed in Figure 2 and Table 1.1. Recruitment to the Monitoring Phase (43 people over 18 months, 68% of all those eligible for recruitment to this phase) was in line with expected figures from previous ECT studies at this site (Semkovska et al., 2016). Recruitment to the Treatment Phase was lower than expected, with six participants randomised in the Treatment Phase (26% of all those eligible for randomisation). Adherence was poor with participants having either one (five

participants) or two (one participant) infusions of the four infusions specified in the treatment protocol. Reasons cited for discontinuation were adverse reaction (one participant in the ketamine group, none in the midazolam group) and travel (two participants in the ketamine group, three in the midazolam group). Distance from the study centre to the participant's home differed between those who were eligible for randomisation and declined (mean of 97 (SD 91) km from home) and those who were eligible and consented to randomisation (mean of 37 (SD 62) km from home). On one occasion, a clinic was cancelled due to anaesthetist unavailability and one person was not randomised. In assessment of blinding, 66% of allocation guesses by participants were correct. Five of six participants guessed they received ketamine (three of whom were correct) and one correctly guessed their midazolam allocation. There were two blinded raters for each of six participants. Raters correctly guessed treatment allocation in nine of twelve guesses (75% of guesses correct).

Table 3.2 Baseline clinical and demographic factors of the unipolar depressed ECT patient group in the KEEP-WELL Trial Monitoring Phase

Variable	Mean (SD)
Age (years)	60.2 (15.8)
Gender n,% female	25 (58)
Pre-ECT HRSD-24	30.8 (7.3)
Age at onset of depression	41 (17.9)
Number of episodes of depression	4.1 (2.1)
Duration of this episode (days)	172.7 (151.1)
Years in education	13.5 (2.7)
Predicted full-scale IQ (NART)	110.1 (9.1)
Maudsley Staging Method for Treatment Resistance in Depression	7.5 (1.3)
Baseline sMMSE score	28.6 (1.3)
BMI	28.1 (5.4)
Indication for ECT (n, %)	
Rapid response required	2 (4.7)
Acute suicidality	1 (2.3)
Refractory to Medication	40 (93)
Marital status (n, % married)	25 (58)
Employment status (n, % employed)	14 (32)
Occupation (n, %)	
Professional	2 (4.65)
Managerial/Technical	7 (16.3)
Skilled Non-Manual	27 (62.8)
Partly Skilled	5 (11.6)
Unskilled Occupations	2 (4.65)
Psychotic symptoms (n, %)	1 (2.3)
Lifetime history of alcohol abuse (n, %)	4 (9.3)
Lifetime history of substance abuse (n, %)	1 (2.3)
Family history of alcohol abuse[a] (n, %)	7 (16.3)

Data are presented as mean and SD unless otherwise specified. [a]first and second degree relatives were accepted as family members. Abbreviations: BMI: body mass index; HRSD-24: Hamilton Rating Scale for Depression, 24-item; sMMSE: standardised Mini Mental State Exam.

3.3.3 Clinical and demographic parameters

Table 1.2 details the baseline clinical and demographic factors of the Monitoring Phase participants. All participants identified as White Irish ethnicity. Frequencies of medication use at baseline were: SSRI antidepressant (11 people, 26%); non SSRI antidepressant (30, 70%); mood stabiliser (22, 51%), antipsychotics (28, 65%); benzodiazepine (21, 49%). ECT treatment parameters and weekly HRSD-24 scores in the Monitoring Phase are presented in Table 1.3. Response criteria to ECT were met by 60.5% of Monitoring Phase

participants (n=26) and remission achieved by 51% (n=22). The majority of depressed participants (93%, 40) had been referred for ECT due to treatment resistance as assessed by their treating clinician. All participants had a pre-ECT HRSD-24 and 42 participants had a post-ECT HRSD-24 (one participant withdrew from the monitoring phase citing assessment burden). Weekly HRSD-24 scores on decreasing numbers of participants reflect the end of ECT courses due to response or other factors, such as medical illness. In order to progress to randomisation, participants had to display a ≥60% decrease from pre-ECT HRSD-24 score and score ≤16 on two consecutive weekly ratings.

Table 3.3 ECT treatment parameters and weekly HRSD-24 scores in the KEEP-WELL Trial Monitoring Phase

Variable	Mean (SD)	N
Laterality (n, %)		43
Right Unilateral	24 (56%)	
Bitemporal	19 (44%)	
Number of ECTs	8.5 (2.7)	43
Mean charge (mC)		43
Right Unilateral	595 (236)	24
Bitemporal	315 (166)	19
Mean motor seizure duration (s)	39.4 (14.3)	43
Mean EEG seizure duration (s)	49.6 (14.4)	43
Pre-ECT HRSD-24	30.8 (7.3)	43
Monitoring Phase Week 1 HRSD-24	19.7 (8.3)	41
Monitoring Phase Week 2 HRSD-24	15.5 (8.5)	40
Monitoring Phase Week 3 HRSD-24	12.9 (7.8)	34
Monitoring Phase Week 4 HRSD-24	17.1 (8.1)	24
Monitoring Phase Week 5 HRSD-24	10.8 (6.9)	14
Monitoring Phase Week 6 HRSD-24	14 (9.7)	4
Post-ECT HRSD-24*	11.8 (10.9)	42
Response criteria met (n, %)	26 (60.5%)	43
Remission criteria met (n, %)	22 (51%)	43

Data are presented as mean (SD) unless otherwise specified. Monitoring Phase participants were monitored weekly during ECT using the HRSD-24 and those who had a treatment course of less than five ECTs were ineligible for randomisation. *One participant withdrew after baseline assessments and did not have a post-ECT HRSD-24

3.3.4 Randomised Participants

Six participants were randomised, aged between 49 to 82 years, five females and one male (Table 1.4). The groups were too small for formal comparison of clinical outcomes or

baseline variables. Within the six-month follow up phase, one participant elected to discontinue follow-up after week 12, citing lack of interest in continuing assessments. Of the remaining five participants who completed full follow-up to relapse or to 26 weeks, two participants relapsed within the follow-up period (one in the ketamine group and one in the midazolam group), at weeks 20 and 26 respectively. Individual 26-week follow-up data are presented in Table 1.5.

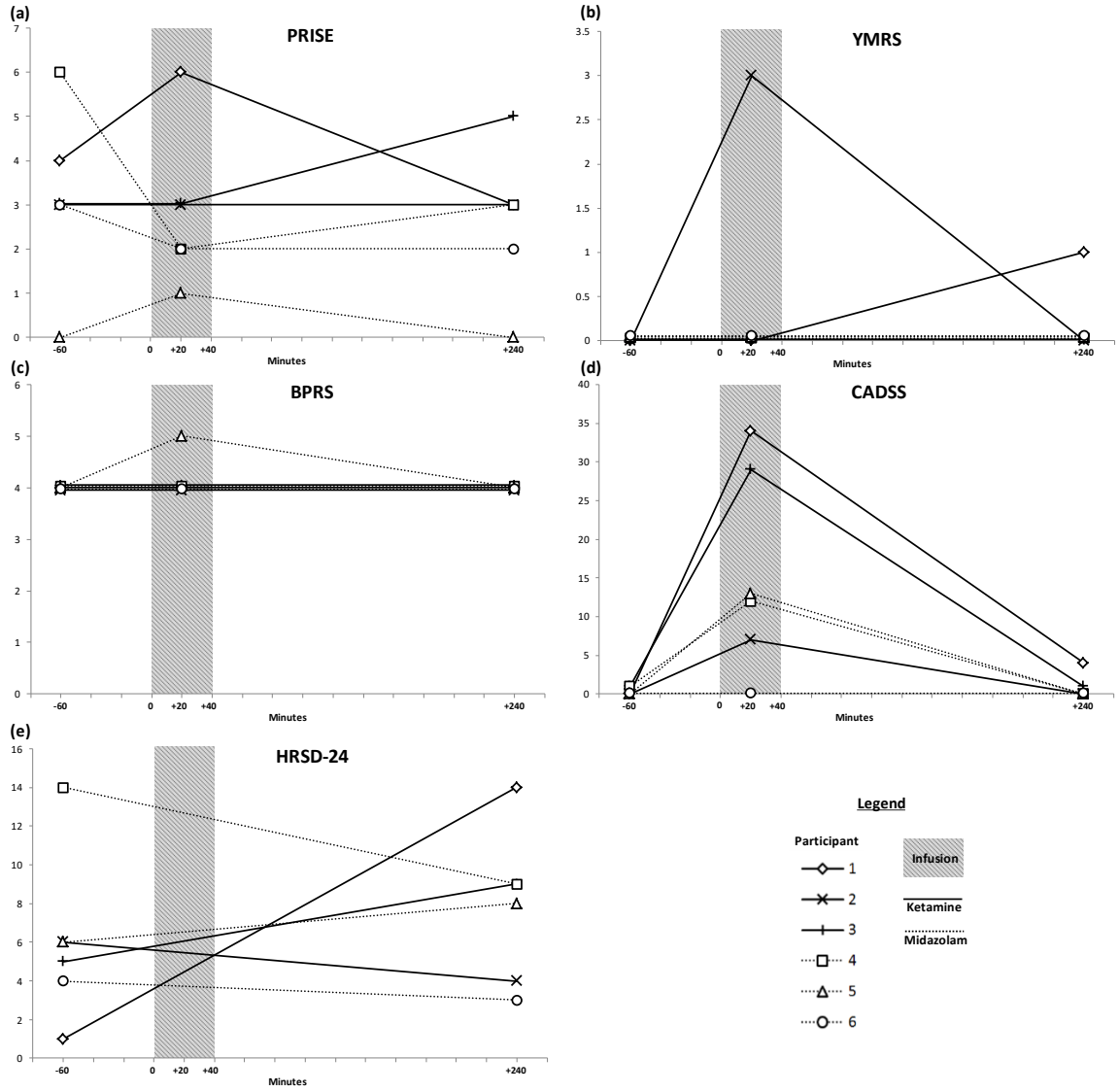
Table 3.4 Characteristics and pathway of randomised participants in the KEEP-WELL Trial

Participant	Age	Sex	Drug	Number of infusions	Pre-ECT HRSD-24	Adverse reaction	Reason	Relapse during 6-month follow-up	Time to relapse
1	80	F	Ketamine	1	29	Dissociation, nausea	Adverse reaction	Yes	Week 26
2	40	F	Ketamine	1	24	None	Travel	Drop out Week 12	
3	80	F	Ketamine	1	28	Mild dissociation	Travel	No	
4	82	M	Midazolam	1	23	None	Travel	Yes	Week 20
5	54	F	Midazolam	2	30	None	Travel	No	
6	49	F	Midazolam	1	32	None	Travel	No	

Table 3.5 HRSD-24 scores in follow-up phase for randomised participants in the KEEP-WELL Trial

Participant	Allocation	Week 6	Week 8	Week 12	Week 20	Week 26	Relapse/ readmission
1	Ketamine	1	3	2	2	21	Week 26
2	Ketamine	7	8	6	N/A	N/A	Dropout after week 12
3	Ketamine	1	1	3	2	2	
4	Midazolam	1	2	4	12	12	Week 20
5	Midazolam	6	10	3	4	2	
6	Midazolam	1	2	3	7	5	

Figure 3.2 Assessment results of randomised participants before, during and after the first infusion in the KEEP-WELL Trial



PRISE: Patient-Rated Inventory of Side Effects, YMRS: Young Mania Rating Scale, BPRS: Brief Psychiatric Rating Scale, CADSS: Clinician-Administered Dissociative States Scale, HRSD-24: Hamilton Rating Scale for Depression, 24-item.

3.3.5 Safety

Figure 3.2 illustrates pre-infusion, intra-infusion and post-infusion assessments for the first infusion for each randomised Treatment Phase participant. No serious adverse events or reactions occurred. One severe, non-serious, suspected adverse reaction occurred in a participant during a first ketamine infusion. This consisted of dissociative symptoms with disturbance in proprioception, and perception of space, colour, light, time and motion,

starting 25 minutes into the ketamine infusion and associated with distress and nausea. All symptoms resolved within five minutes after the end of the 40-minute infusion. The participant elected to discontinue randomised treatment. One other participant in the ketamine arm experienced mild dissociative symptoms not associated with distress or physical symptoms. Intra-infusion CADSS scores (at 20 minutes, half way through the infusion) for dissociation are higher in the ketamine group (mean 23.3 (4.3) compared to 6.2 (7.2) in midazolam group), accounted for by two of the three participants in the ketamine arm. As all participants were euthymic ECT responders, no change was expected in HRSD scores after infusions. Fluctuations in HRSD items were observed in both groups before, during and after infusions, primarily accounted for by changes in physical symptom scores. Those in the ketamine group demonstrated greater fluctuation in all assessments from pre- to post-infusion than the midazolam group. Vital signs were monitored as per the trial protocol. No persisting haemodynamic changes (defined as heart rate >110/minute or systolic/diastolic blood pressure >180/100 or >20% increase above pre-infusion BP for more than 15 minutes) were noted. Blood pressure increased during infusions in four of the six Treatment Phase participants (three of the ketamine group and one of the midazolam group) but did not require medical intervention on any occasion, with a mean diastolic elevation of 9.6 (SD 12.2) mmHg and a maximum diastolic elevation of 43 (SD 14) mmHg. Stable oxygen saturation, heart rate and electrocardiogram (ECG) rhythm were observed in all participants at fourteen timepoints over 300 minutes before, during and after infusions.

There were no striking differences between follow-up cognitive assessments compared with baseline results for the three participants who completed week 26 follow-up assessments (data not shown). Statistical analysis was not performed due to the small number of completed assessments.

Table 3.6 Cognitive performance pre- and post-ECT

Instrument	n	Pre-ECT	Post-ECT	Statistical analysis		
				U	Z	p
Letter fluency (of 7)	36	4.5 (0-7)	4.5 (0-7)	518	-0.3	0.8
Category fluency (of 7)	36	5 (0-7)	4.5 (0-7)	513	-0.3	0.7
Immediate recall (of 7)	36	7 (0-7)	7 (6-7)	450	-1.8	0.1
Delayed recall (of 10)	36	9 (0-10)	9 (0-10)	517	-0.1	0.9
Retrograde semantic memory (of 4)	36	4 (0-4)	4 (0-4)	394	-1.7	0.1
Forward digit span (of 14)	31	9 (3-14)	9 (5-14)	415	-0.3	0.8
Backward digit span (of 14)	31	7 (2-11)	6 (3-14)	336	-1.5	0.1
Trail-making test A (seconds)	29	36 (12-82)	33 (15-155)	367	-0.4	0.7
Trail-making test B (seconds)	29	75 (28-240)	76.5 (38-360)	328	-0.1	0.9
sMMSE (of 30)	43	29 (26-30)	28 (22-30)	454	-1.7	0.1

Data are presented as median (range). Mann-Whitney-U test was performed for all variables as the assumptions of the t-test were not met.

3.3.6 Cognition

Non-completers were older than the participants who completed cognitive assessments. There was no significant change between pre-ECT and post-ECT performance on any of the cognitive assessments examined in this subset of depressed Monitoring Phase participants. Caution is advised in interpretation of this finding as those with baseline cognitive impairment were excluded from participation and non-completers were older than those who completed cognitive assessments and are reported here.

3.4 Discussion

3.4.1 Summary of findings

This is the first report of the novel use of ketamine for depression relapse prevention following successful ECT. I found that while depressed ECT patients were eligible and willing to be recruited to a Monitoring Phase, recruitment and adherence rates in the Treatment Phase were low. Reasons for non-recruitment and non-adherence were primarily logistical, related to the need to travel for infusions. With no participants completing the treatment protocol, I conclude from this pilot trial that this trial protocol for the novel use

of ketamine in relapse prevention is not feasible and therefore not suitable for a definitive trial. However, data reported here on the reasons for ineligibility, non-recruitment and non-adherence identifies ways to improve trial design and recruitment for a future potential successful trial of ketamine for depression relapse prevention.

3.4.2 Context

In nearly twenty years since the first description of ketamine's antidepressant effect (Berman et al., 2000) no definitive trial has yet been reported. Meta-analytic data confirms ketamine's antidepressant effect (Fond et al., 2014, McGirr et al., 2015, Caddy et al., 2014) but trial samples remain modest (20-30 participants) with the largest reported trial to date consisting of 80 depressed participants (Grunebaum et al., 2017b). Researchers in the field remain divided about whether and under what regulatory conditions ketamine could and should be considered for routine clinical practice (Sanacora and Schatzberg, 2015, Singh et al., 2017, Ryan and Loo, 2017). This may be due not only to the absence of a definitive trial to date, but also to uncertainties about the generalisability of ketamine trial results. Figures on non-eligibility and non-recruitment, although recommended in reporting guidelines (Schultz et al, 2010), are not regularly available for ketamine trials. The underlying reasons for ineligibility and non-recruitment, as well as success of blinding, are not routinely reported. It is known that samples in antidepressant trials are poorly representative of those who will require treatment with these agents (Zimmerman et al., 2002), and it is unclear whether ketamine trial populations are representative of the broad population of people with depression who might benefit from the treatment. Data showing reasons for ineligibility among those screened for trial participation, such as presented here, are useful to illustrate whether those who are ultimately recruited reflect the characteristics of the target population.

Studies of ketamine for depression over the last fifteen years have focused on acute treatment with largely positive results (McGirr, 2015, Caddy et al., 2014), and also augmentation of ECT with adjunctive ketamine with mixed outcomes (Fond et al., 2014). The modest size of trials to date suggests the possibility of unidentified obstacles to recruitment of depressed participants to trials of ketamine for depression. Numbers of potential participants who declined are available for six trials. For example, in Loo et al (2012) 46% of those eligible for recruitment refused to participate. Ibrahim et al (2012) reported 30% of those eligible refused recruitment, and in Diazgranados et al (2010) 27% of eligible participants declined. For other studies, these proportions are unknown. Most importantly for researchers planning future studies, reports of the reasons why participants decline or drop out are not available. This pilot trial aimed to investigate the potential for use of ketamine in the novel application of depression relapse prevention. The trial methodology therefore differed from trials of ketamine for treatment of acute depression and cannot be directly compared with previous trials. However, this is the first trial report to provide detailed reasons for non-recruitment, non-randomisation and dropout, in the area of ketamine and depression, which may help guide future trial design in the field.

3.4.3 Strengths and limitations

In this study, although recruitment to the Treatment Phase was lower than anticipated, recruitment to the initial Monitoring Phase and response rate to ECT were similar to previously reported figures (Semkovska et al., 2016, Kolshus et al., 2017), with the difficulty lying primarily in recruiting and retaining participants in the Treatment Phase. In addition, the sample recruited to the Monitoring Phase is similar in age, gender and depression severity to other ECT cohorts (Semkovska et al., 2016). 68% of eligible potential participants agreed to recruitment to the initial Monitoring Phase, in line with recruitment in previous trials including depressed patients referred for ECT.

Anxiety and lack of interest were the most common reasons for non-recruitment of eligible participants to the Monitoring Phase. Lack of interest was also cited by five potential participants as a reason for declining randomised treatment. This may reflect the long treatment course of this group as indicated by their long episode duration (mean 25 (SD 21) weeks) and moderate treatment-resistance. It may also reflect a general difficulty in motivating participants to engage in relapse prevention research. However, trials of more established relapse prevention strategies in depression, such as continuation ECT (which may also require travel) have successfully recruited adequate trial populations (Kellner et al., 2006). It is possible that continuation therapies such as pharmacotherapy or ECT, which have resulted in successful response when used for acute treatment in the same individual, may be more attractive for relapse prevention trials.

Assessment burden also contributed to non-recruitment and led to withdrawal of one participant from the monitoring phase. Though anxiety was cited as a reason for non-recruitment, participants did not cite specific concern about the trial agents. The potential for abuse is rarely highlighted by media coverage of the field of ketamine research in psychiatry (Zhang et al., 2017) but may remain a concern for potential participants. In this study, infusions were generally well-tolerated, in line with previous studies, but one participant withdrew due to adverse effect.

Among those recruited to the Monitoring Phase, the 60.5% response rate to brief-pulse ECT for depression is in line with previous reports (Semkovska et al., 2016, Kolshus et al., 2017). The primary difficulty in achieving adequate recruitment to this trial was therefore in recruiting euthymic ECT responders to the Treatment Phase, with only 26% of those eligible agreeing to proceed to randomisation. The most common reason for not proceeding to randomisation was travel. Distance from home was greater for those who declined randomization. Although there have been successful trials which have included follow-up infusions on an outpatient basis (aan het Rot et al., 2010) (at a participant

number of ten), this study suggests that a well-powered ketamine trial is most likely to be successful in centres where a dedicated inpatient stay is available for research purposes, negating the need for travel. As it may not be possible in many centres to provide admission for research purposes, future studies may therefore consider recruiting only participants who live very nearby.

Most trials of ketamine in depression have used a subanaesthetic dose of 0.5mg/kg as originally reported (Berman et al., 2000) and report anaesthetist administration of the infusion. A recent trial reported anaesthetist supervision by telephone (Grunebaum et al., 2017), and as meta-analytical evidence concludes ketamine is safe in repeated administration, clinical psychiatry centres wishing to conduct ketamine trials could in future consider telephone supervision. Intranasal and other forms of ketamine administration may also overcome this difficulty and result in better powered studies.

Blinding is not regularly reported in ketamine trials. Saline placebo is potentially inadequate for participant and rater blinding when juxtaposed with the known acute effects of low-dose ketamine, such as dissociative symptoms. It is not yet clear what the value of midazolam is as an active comparator to ketamine. Here, despite use of midazolam, blinding of both participants and raters was not wholly successful, though numbers are too small to interpret. However, as almost all participants guessed that they were randomised to ketamine the limited experience in this trial suggests that midazolam has some useful role as a mimic of ketamine's psychoactive effects for blinding. The proportions of correct guesses by both participants and raters is similar to previously reported figures in which proportions of correct guesses were also above 50% or chance likelihood (Grunebaum et al., 2017).

Although trial design aims to eliminate confounding factors such as concomitant pharmacological therapy, it is unlikely that the conditions under which most published clinical trials of ketamine for depression were undertaken, could or would be replicated in

clinical practice, i.e. elective admission for medication washout and ketamine infusions. Pragmatic clinical trials that include participants who remain on pharmacotherapy and do not require specific inpatient admission are now required to test the real-world clinical usefulness of the therapy. Yet the trial protocol reported here did not have sufficient attraction for participants to overcome the disadvantages they identified, such as travel. While this study does not provide useful outcome data on ketamine as a potential depression relapse prevention method, the failure of the pilot trial may indicate that depressed persons, once well, are not sufficiently motivated by relapse prevention to overcome the other barriers to ketamine research identified here such as travel, intravenous administration, and anxiety. Therefore, proposed methods to overcome these barriers should be given due consideration by researchers planning similar trials. To investigate the potential for use of ketamine for depression relapse prevention, an open-label trial may be the most prudent next step.

3.5 Conclusion

This pilot trial protocol was not feasible but identified some of the barriers to successful conduct of clinical trials of ketamine for depression. Intranasal, oral or intramuscular formulations of ketamine in an open-label trial design may provide better opportunities to complete a pragmatic trial of ketamine in the novel application of depression relapse prevention.

4. Effects of mood and time on autobiographical memory before and after electroconvulsive therapy for depression

4.1 Introduction

Depression is a common serious mental health problem (World Health Organisation, 2017) and is associated with memory deficits (McDermott and Ebmeier, 2009). ECT is an effective acute treatment for depression (The UK ECT Review Group, 2003) but is associated with adverse cognitive effects (Semkovska and McLoughlin, 2010), some of which can be minimised by optimising treatment parameters (Kolshus et al., 2017; Tor et al., 2015). One recognised adverse cognitive effect of ECT is retrograde amnesia, particularly affecting autobiographical memory (Sackeim et al., 2007). This refers to the ability to remember events personally experienced at a particular time and place (episodic autobiographical memories, e.g. something that happened at a wedding you attended) and pieces of general information (semantic autobiographical memories, e.g. year of graduation) from one's own life. Retrograde amnesia for autobiographical memory is the side-effect of ECT of most concern to patients (Rose et al., 2003). It can be impaired by ECT but because of the difficulties in assessing autobiographical memory and the limitations of currently used assessments it is not clear to what extent or for how long (Semkovska et al., 2012). Nevertheless, individual studies have reported persistent impairment in autobiographical memory (up to three years) and there have been case reports of profound autobiographical memory loss after ECT (Fink, 2007). Consequently, elucidating the precise effect of ECT on autobiographical memory remains an important issue for clinicians and patients alike.

There is currently no standardised instrument for assessment of this major cognitive effect of ECT (Semkovska and McLoughlin, 2013). The Kopelman Autobiographical Memory Interview (K-AMI) (Kopelman et al., 1989) was originally designed for assessment of

amnestic patients but has also been used in ECT research (Jelovac et al., 2016; Mayur et al., 2013; O'Connor et al., 2010; Sienaert et al., 2010; Spaans et al., 2013; Verwijk et al., 2015). It assesses both semantic and episodic autobiographical memory separately, with items scored on specificity and detail. The K-AMI requests specific items of semantic information and episodic memories from Recent Life (in the last five years), Early Adult Life (college or first job, marriage, and children) and Childhood (before first school, first school, and secondary school). A new score is created each time the instrument is used, with subscores for semantic and episodic memory for each schedule, providing a cross-sectional score for autobiographical memory performance at that time. However, as the K-AMI does not require the same details to be provided at each assessment, it does not provide a measure of recall consistency (i.e. retrieval of the same autobiographical memory details provided at first assessment). One report of use of an adapted K-AMI showed loss of consistency of recall of between 11-15% in depressed patients after ECT (Spaans et al., 2013), but the K-AMI not designed for this purpose. Retrograde amnesia is defined as the loss of previously retrievable memories. Therefore, although the K-AMI can be used to provide a measure of autobiographical memory performance at pre-ECT and post-ECT assessments, it cannot assess for loss of previously retrievable memories as it does not assess consistency of recall.

The most commonly used instrument to date in the ECT literature, the Columbia University Autobiographical Memory Interview (CUAMI, or the short form CUAMI-SF) requests the same information to be repeated at reasssessment and scores the consistency of recall of previously provided answers (McElhiney et al., 1995; McElhiney et al., 2001). However, as depressed people have poor autobiographical memory at baseline, they may provide few memories at initial assessment and score poorly. Measuring consistency of recall of this small number of memories at post-ECT reassessment may not be a precise measure of autobiographical memory function. Though the CUAMI does measure

consistency of recall, it does not allow for improvement in score on reassessment. There are limited normative data for both healthy controls as well as depressed persons not being treated with ECT. Nonetheless, the CUAMI has been useful in showing differences in recall consistency of autobiographical memory associated with different ECT treatment modalities, such as laterality and pulse-width (Kolshus et al., 2017; Sackeim et al., 2000; 2008).

It has been suggested that the Recent Life memory section of the K-AMI lacks sensitivity to ECT-related autobiographical amnesia (Jelovac et al., 2016). The full K-AMI is long (+25 minutes) and burdensome for depressed patients to complete. However, some normative data on the performance of healthy controls is available (n=34 controls ranging in age from 20 to 78, Kopelman et al., 1989) and, unlike the CUAMI, the K-AMI allows for improvement of scores on re-testing should memory performance improve following a course of ECT. Additionally, the K-AMI tests three time points of autobiographical memories (Recent life, Early Adult life, and Childhood), allowing for examination of any temporal gradient to amnesia.

Accurate assessment of autobiographical memory in depressed people having ECT is obscured by the effect of mood disorder on memory as well as the normal effect of time on consistency of recall of autobiographical memories (Semkovska and McLoughlin, 2013). Performance on autobiographical memory testing is impaired in depressed people, a well-established finding that persists beyond recovery from depression (Bergouignan et al., 2008). Depressed people not having ECT exhibit impaired ability to recall episodic autobiographical memories and tend to recall events in general terms (van Vreeswijk and de Wilde, 2004). Reduced specificity of autobiographical memories in depressed patients prior to ECT (compared with non-depressed controls) was shown to persist at three months after ECT regardless of treatment response (Jelovac et al., 2016). Thus depressed patients may score poorly on episodic autobiographical memory assessment even when their

semantic autobiographical memory may seem unimpaired (Verwijk et al., 2015) and regardless of mood status.

In healthy controls, consistency of recall of autobiographical memories declines over time, with consistency of recall in healthy controls dropping within an assessment interval of two months (Semkovska et al., 2012; Urbanowitsch et al., 2013). Estimates of normal rate of loss of autobiographical memories range from 27% after six weeks (Talarico and Rubin, 2003) to 31–42% after two months (Anderson et al., 2000). Without robust information on the performance of non-depressed people on the instruments used for retrograde memory assessment in ECT, before and after an interval of weeks, it is difficult to separate the effect of ECT from the effect of change in depression severity on the normal rate of loss of previously reported memories.

I aimed to assess the utility of the K-AMI for measuring autobiographical memory in people having ECT. I performed the complete Kopelman Autobiographical Memory Interview (K-AMI) in severely depressed patients before and after a course of ECT and compared this with the performance of age- and gender-matched healthy controls before and after a 4-week interval. I also aimed to assess for differences in K-AMI performance between ECT responders and non-responders, and association between change in performance on the K-AMI and depression severity. These measures aimed to control for both the passing of time and contemporaneous mood status when comparing autobiographical memory between ECT patients and controls.

4.2 Method

4.2.1 Participants

I performed a prospective observational cohort study with two groups: depressed patients referred for ECT and a healthy control group. The study was approved by the Research

Ethics Committees of St James's and Tallaght Hospitals, Dublin, and the study site, St Patrick's Mental Health Services, Dublin. Depressed patients referred for ECT were recruited from St Patrick's Mental Health Services, a 300-bed independent-sector inpatient psychiatry unit which performs over 35% of all ECT in Ireland (Mental Health Commission, 2016). Patients were recruited to the monitoring phase of the KEEP-WELL pilot trial (NCT02414932), the protocol for which has been previously described (Finnegan et al., 2016). Recruitment to the monitoring phase of the trial concluded at 43 participants and recruitment to this and other cohort studies continued for a further six months to 50 participants. Patients were assessed weekly for response to ECT using the 24-item Hamilton Rating Scale for Depression (HRSD-24) (Beckham and Leber, 1985). Those who responded were invited to take part in a randomised controlled pilot trial of four, weekly infusions of ketamine *vs*. midazolam for depression relapse prevention and were followed-up over six months. In the present cohort study, patients recruited to the monitoring phase of the trial were compared to a healthy control group which was recruited to the cohort study only. Written informed consent was obtained after procedures were fully explained.

Depressed patients met eligibility criteria of being aged 18 years or older, diagnosed with unipolar major depressive disorder (DSM-IV), and had a HRSD-24 score ≥21 and a standardised Mini Mental State Examination (sMMSE) (Molloy et al., 1991) score of ≥24. Exclusion criteria included substance dependence within the previous three months, ECT in the previous six months, active suicidal ideation, and any other active Axis I diagnosis. Response was defined as ≥60 % decrease from baseline HRSD-24 score and score of ≤16 on two consecutive weekly ratings. Remission criteria were a ≥60% decrease in HRSD from baseline and score ≤10 on two consecutive weekly ratings. Healthy controls were recruited through advertisement in volunteer organisations, had no lifetime history of mental illness or substance dependence and spoke fluent English. All participants undertook two assessment sessions. Depressed patients referred for ECT had baseline

assessments one-two days before the first ECT session and a follow-up assessment three-four days after the last ECT treatment. Electroconvulsive therapy was administered as outlined in Chapter 2. Controls had a baseline assessment and a follow-up assessment four weeks later.

4.2.2 Instruments

For all participants, each assessment included a mood rating using the HRSD-24. Inter-rater reliability for the HRSD-24 was assessed using intra-class correlation on a six-monthly basis and was >0.95 on each occasion. Global cognitive function was assessed using the standardised Mini Mental State Exam (Molloy et al., 1991). Immediate short-term memory, attention and working memory were measured using Forward and Backward Digit Spans (Wechsler et al., 1997). Motor and psychomotor speeds were assessed using the Trail Making Test (part A) (Wechsler et al., 1997). Frontal-executive function was rated by Trail Making Test (part B) (Wechsler et al., 1997) plus letter and category verbal fluencies performed as part of a modified Addenbrooke's Cognitive Examination-III (ACE-III) (Hsieh et al., 2013). Anterograde verbal memory was tested using the verbal learning component of the ACE-III (delayed and immediate recall of a seven-item address and delayed recall only of three non-associated objects) (Hsieh et al., 2013). Parallel versions were used where available (ACE-III, digit spans). In addition, the National Adult Reading Test (Nelson and Willison, 1991) was used to assess premorbid intelligence, and the Edinburgh Handedness Inventory (Oldfield, 1971) was used to provide a measure of handedness. For the depressed patient group only, ECT treatment information was collected, and the Structured Clinical Interview for Diagnosis (SCID, DSM IV) (First et al., 1998) was used to confirm diagnosis. A multidimensional treatment resistance assessment, the Maudsley Treatment Resistance Scale for Treatment Resistant Depression (MSMTRD) (Fekadu et al., 2009), was also performed. MSMTRD scores of 3-6 indicate

mild resistance; 7-10, moderate; 11-15, severe treatment resistance. Participants in this study could score a maximum of 14 as one item relates to ECT treatment failure.

4.2.3 Kopelman Autobiographical Memory Interview

Two raters undertook training in administration and scoring of the K-AMI with an experienced rater and according to the manual (Kopelman et al., 1989). Assessments were performed by a single rater and responses were written verbatim for a second rater to score independently. Where a participant had not experienced the life event in question or a comparable alternative (e.g. attended a wedding or other social gathering), questions that had not been answered were marked on a pro-rata basis based on the participant's performance in other questions in the same schedule during that assessment. Raters distinguished such cases, where information had never been learned, from other situations, in which participants declined to answer as they could not recall the information. In cases of no answer due to impaired recall, these questions were allocated a score of zero. As previously noted, the K-AMI requests both semantic and episodic memories for Recent Life, Early Adult Life, and Childhood, and provides a new score at each assessment.

4.3 Statistical analysis

Data are presented as mean (SD) unless otherwise specified. Variables were assessed for normality and variance and compared using t-test or Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables. Scores on cognitive measures were compared for patients and controls at two timepoints using Mann-Whitney U tests. Change scores between timepoints for both the K-AMI subscales and other cognitive measures were calculated for patients and controls and compared using Mann-Whitney U tests. K-AMI performance was similarly compared between those who had

right unilateral and bitemporal ECT, and between ECT responders and non-responders. Spearman's rho for non-parametric data was used to assess for correlation between change scores for K-AMI from pre-to post-ECT assessments and change scores for HRSD-24, baseline sMMSE, and age. All tests were two-tailed and p was set at 0.05 unless otherwise specified. Bonferroni correction was used to control for multiple comparisons where indicated and specified p values for each family of comparisons are outlined below in the individual results sections.

Table 4.1 Baseline features of the depressed ECT patient group and the healthy control group

Variable	Depressed Patient Group N =27	Healthy Control Group N =72	Statistical Analysis (p)
Age in years	54.8 (14.0)	49.3 (15.0)	0.071
Number of medical conditions	1.7 (1.7)	0.34 (0.34)	<0.001
Baseline HRSD-24	30.4 (7.3)	3.6 (3.0)	<0.001
Handedness Quotient[a]	81.7 (16.3)	70.7 (35.6)	0.136
Predicted full-scale IQ, median (range)[b]	111.0 (106.8, 118.0)	118.0 (110.0, 122.0)	0.012
Gender, n (%) female	14 (51.9%)	45 (62.5%)	0.365
Employment, n (%) working	11 (42.3%)	49 (68.1%)	0.064
Marital status, n (%) married	17 (63.0%)	39 (54.2%)	0.905
Level of education[c]			
Primary	1 (3.7%)	0 (0)	
Secondary	11 (40.7%)	11 (15.3%)	<0.001
Tertiary	13 (48.1%)	35 (48.6%)	
Quaternary	2 (7.4%)	26 (36.1%)	
Socioeconomic status, n (%)[d]			
Professional	2 (7.4%)	19 (26.4%)	0.096
Managerial/Technical	6 (22.2%)	21 (29.2%)	
Skilled Occupations	17 (63.0%)	29 (40.3%)	
Partly Skilled	2 (7.4%)	3 (4.2%)	

Data are presented as mean (SD) unless otherwise stated. [a]derived from the Edinburgh Handedness Inventory, [b]derived from the National Adult Reading Test, Mann-Whitney U test was performed, [c]Kendall's Tau was performed as the assumptions of the χ^2 and Fisher's exact tests were not met, [d]Fisher exact test was used as the assumptions of the χ^2 test were not met.

4.4 Results

4.4.1 Participants

Of 50 depressed participants recruited to the whole ECT cohort, 27 completed all cognitive assessments at both timepoints. Compared to non-completers, completers reported here were younger (54.8 (SD 14.0) vs. 69.9 (SD 14.1) years, p=0.001) and ECT response rate was lower (48.1% here and 65% among non-completers) but did not differ in baseline HRSD-24, sMMSE, or gender. Of 80 healthy controls recruited to the total cohort, 72 completed cognitive assessments at both timepoints. Completer and non-completer controls did not differ with regards to age and gender (data not shown). Baseline demographic features of patients and controls are compared in Table 4.1. The groups are

matched for age, gender and handedness, and as expected, baseline HRSD-24 scores are higher among patients. Estimated premorbid intelligence, as well as educational attainment, was higher in controls.

Table 4.2 Clinical and ECT parameters of the depressed patient group

Variable	
Age at onset of depression	38.22 (16.15)
Number of previous episodes	4.18 (2.27)
Treatment resistance score[a]	7.65 (1.13)
Duration of current episode, median (range), weeks[b]	28.6 (3-104)
Psychotic features, n (%)	1 (3.7%)
Medication use, n (%)	
SSRI	7 (29.5%)
Non-SSRI antidepressant	18 (66.7%)
Antipsychotic	17 (63.0%)
Mood stabiliser	14 (51.9%)
Benzodiazepine	13 (48.1%)
Indications for ECT, n (%)	
Rapid response required	2 (7.4%)
Acute suicidality	1 (3.7%)
Refractory to medication	24 (88.9%)
Bitemporal ECT, n (%)	12 (44.4)
Number of ECT treatments	8.81 (3.33)
Mean motor seizure duration (seconds)	36.82 (13.29)
Mean EEG seizure duration (seconds)	46.92 (16.03)
Mean charge (mC)	
Bitemporal *n=12*	328.3 (200.2)
Unilateral *n=15*	617.2 (297.1)
Mean time to reorientation (minutes)	30.33 (7.85)
Pre-ECT HRSD-24	30.44 (7.28)
Post-ECT HRSD-24	14.18 (9.46)
ECT Response rate, n (%) responder	13 (48.1%)
ECT Remission rate, n (%) remitter	10 (37.0%)

Data are presented as mean (SD) unless otherwise stated. [a]Derived from the Maudsley Staging Method for Treatment Resistance in Depression. [b]Data are presented as median (range) due to non-parametric distribution.

4.4.2 Non-K-AMI cognitive performance

ECT and clinical treatment parameters of the patient group are displayed in Table 4.2. Twelve patients (45%) received bitemporal (BL) and 15 (55%) right unilateral (RUL)

ECT. Three patients switched laterality after five treatments (two from BL to RUL, one from RUL to BL) and were recorded as having the ECT type that was initially prescribed.

Table 4.3 Cognitive performance of depressed patients and controls at two timepoints

	Pre-ECT/Baseline			Post-ECT/After 4 Weeks			Statistical analysis: change between assessments (p)		Statistical analysis: change scores compared between groups (p)
	Depressed Patients (N=27)	Healthy Controls (N=72)	Statistical analysis (p)	Depressed patients (N=27)	Healthy Controls (N=72)	Statistical analysis (p)	Depressed patients (N=27)	Healthy Controls (N=72)	
sMMSE	29 (26, 30)	30 (24, 30)	0.009	27 (19, 30)	29 (25, 30)	<0.001	0.003	0.863	<0.001
Verbal fluency: category	5 (0, 7)	7 (2, 7)	0.001	4 (0, 7)	7 (4, 7)	<0.001	0.111	0.805	<0.001
Verbal fluency: letter	5 (1, 7)	6 (3, 7)	<0.001	5 (0, 7)	6 (1, 7)	<0.001	0.244	0.140	0.023
Digit span forward	9 (3, 14)	10 (3, 14)	0.003	9 (5, 14)	11 (5, 14)	0.004	0.523	0.539	0.486
Digit span backward	7 (3, 11)	7 (3, 14)	0.498	6 (3, 14)	8 (3, 13)	<0.001	0.038	0.212	0.005
Trail-making test A (seconds)	35 (12, 92)	23 (13, 48)	<0.001	31.5 (15, 155)	20 (12, 44)	<0.001	0.812	0.034	0.153
Trail-making test B (seconds)	81 (28, 240)	46 (23, 131)	<0.001	82 (38, 360)	42 (16, 100)	<0.001	0.634	0.434	0.050
Immediate recall	7 (6, 7)	7 (6, 7)	0.125	7 (6, 7)	7 (7)	0.102	0.556	0.314	0.602
Delayed recall	9 (2, 10)	10 (7, 10)	0.009	8 (2, 10)	10 (7, 10)	<0.001	0.472	0.657	0.062

Data are presented as median (range) for all assessments due to non-parametric distributions. For all comparisons, Mann-Whitney-U test was used. Bonferroni correction was applied to control for the number of cognitive assessments and p was set at 0.005.

Table 4.3 outlines scores on cognitive tests other than the K-AMI at baseline and reassessment in patients and controls. Bonferroni correction for multiple comparisons was applied and p was set at ≤0.005. At baseline, patients performed less well than controls. This pattern persisted after ECT. Among patients, there was little change following ECT except a small, but statistically significant, decline in the sMMSE (p=0.003), consistent with meta-analytic data (Semkovska and McLoughlin, 2010).

Table 4.4 Kopelman Autobiographical Memory Interview scores of depressed patients and healthy controls at two timepoints

	Pre-ECT/Baseline			Post-ECT/After 4 Weeks			Statistical analysis: change between assessments (p)	
	Depressed patients (N=27)	**Healthy controls (N=72)**	**Statistical analysis (p)**	**Depressed patients (N=27)**	**Healthy controls (N=72)**	**Statistical analysis (p)**	**Depressed patients (N=27)**	**Healthy controls (N=72)**
Semantic Memory								
Recent Life	19 (6.5, 21)	21 (16.5, 21)	<0.001	18 (10, 21)	21 (17.5, 21)	0.001	0.104	0.166
Early Adult Life	19.5 (6, 21)	21 (14.5 , 21)	0.014	20 (0, 21)	21 (17.5, 21)	<0.001	0.958	0.726
Childhood	18.5 (0, 21)	19.5 (12.5, 21)	0.094	18.5 (0, 21)	19.75 (14, 21)	0.006	0.614	0.380
Total	57 (12.5, 63)	60.25 (49.5, 63)	0.001*	55.5 (13, 62)	60.75 (52.5, 63)	<0.001*	0.467*	0.312*
Episodic Memory								
Recent Life	4 (0, 9)	8 (5, 9)	<0.001	3 (0, 8)	8 (5, 9)	<0.001	0.486	0.205
Early Adult Life	4 (0, 9)	8 (4, 9)	<0.001	4 (0, 9)	8 (4, 9)	<0.001	0.903	0.464
Childhood	5 (0, 9)	7 (3, 9)	<0.001	3 (0, 9)	8 (2, 9)	<0.001	0.131	0.164
Total	13 (0, 25)	22 (15, 27)	<0.001*	13 (0, 24)	23 (11, 27)	<0.001*	0.415*	0.128*

Data are presented as median (range) due to non-parametric distribution. Mann-Whitney U test was performed for all comparisons. *Bonferroni correction was applied to total scores to correct for multiple comparisons owing to the contribution of subscale scores, p was set at 0.01 for total scores.

4.4.3 K-AMI performance

Scores for performance on each subsection of the K-AMI at baseline and reassessment for the depressed patient and healthy control groups are shown in Table 4.4. Bonferroni correction was applied to total semantic and episodic scores to control for the aggregation of subscales and p was set at 0.01 for statistical significance for total scores. Correction was not applied to subscale comparisons as K-AMI scores are the primary study outcome. Controls performed better than depressed patients on every subscale and on total semantic and episodic scores at both timepoints. The differences were most pronounced in the episodic subscales. No significant change in performance from baseline to reassessment was identified on any subscale or total semantic or episodic score of the K-AMI either among patients or controls.

Table 4.5 Kopelman Autobiographical Memory Interview change scores in depressed patients and controls

	Depressed patients after ECT course (N=27)	**Healthy controls after 4 weeks (N=72)**	**Statistical analysis (p)**
Semantic Memory			
Recent Life	-0.5 (-10, 6.5)	+0.25 (-2, 4)	0.013
Early Adult Life	0 (-6, 4)	+0.05 (-3, 5)	0.535
Childhood	0 (-18.5, 6)	+0.27 (-4, 3.5)	0.303
Total	-1 (-32.5, 8.5)	+0.58 (-5, 5)	0.052*
Episodic Memory			
Recent Life	-1 (-5, 3)	+0.25 (-3, 4)	0.071
Early Adult Life	0 (-6, 5)	+0.12 (-3, 3)	0.617
Childhood	0 (-8, 2.5)	+0.37 (-3.5, 5)	0.011
Total	0 (-19, 7)	+0.74 (-8, 8)	0.038*

Data are presented as median (range) due to non-parametric distribution. Mann-Whitney U test was performed for all comparisons. *Bonferroni correction was applied to total scores to correct for multiple comparisons owing to the contribution of subscale scores, p was set at 0.01 for total scores.

4.4.4 K-AMI change over time

To further examine differences over time between patients and controls, change scores over time were calculated for all subscales for patients (Table 4.5). Depressed patients

showed large variability in change scores from pre-to post-ECT than controls after four weeks. Eleven patients (41%) showed improvement on total semantic memory, one (4%) had no change in score, and 15 (55%) patients showed disimprovement. In total episodic scores, 13 patients (48%) improved in score after ECT and six patients (22%) had no change, while eight (30%) showed disimprovement. Change scores for total semantic (p=0.052) and total episodic memory scores (p=0.038) did not differ between patients and controls after correction for multiple comparisons to control for the aggregation of subscale scores, with p set at 0.01 for total scores.

Table 4.6 Kopelman Autobiographical Memory Interview change scores and ECT response status plus correlation between K-AMI change scores and depression severity scores

Variable	ECT Responder (n=13)	ECT Non-responder (n=14)	p-value	Spearman's rho	
				rho	p
Semantic Memory					
Recent Life	0.0 (-10, 6.5)	-1.8 (-7.5, 2)	0.259[a]	-0.026	0.896
Early Adult Life	0.0 (-6, 4)	0.0 (-2.5, 4)	0.685[a]	0.138	0.491
Childhood	0.5 (-18.5 ,6)	-0.8 (-4, 3)	0.141[a]	-0.235	0.239
Total	1.0 (-32.5, 8)	-2.0 (-11.5, 7)	0.302[a]	0.062	0.759
Episodic Memory					
Recent Life	0.0 (-3, 1)	-1.0 (-5, 3)	0.685[a]	-0.125	0.534
Early Adult Life	0.0 (-5, 5)	-0.5 (-6, 4)	0.141[a]	-0.492	0.009
Childhood	0.0 (-3, 2)	-1.5 (-8, 2.5)	0.302[a]	-0.357	0.067
Total	0.0 (-7, 7)	-2.0 (-19, 7)	0.280[a]	-0.482	0.011

Change scores from pre- to post-ECT are compared between ECT responders and non-responders. In addition, Spearman's rho data are presented for assessing correlation between K-AMI change score and HRSD-24 change score for the whole depressed patient group. Data are presented as median (range) of change scores from pre-ECT to post-ECT K-AMI assessments. Bonferroni correction was applied to correct for multiple comparisons, p was set at 0.001 for statistical significance. [a]Mann-Whitney U test.

4.4.5 Autobiographical memory and mood status

Response criteria were met by 48.1% (13/27) of depressed participants. Remission was achieved by 37% (10/27). Responders were more likely to be prescribed a mood stabiliser (11/13) than non-responders (3/14, p=<0.001) but in all other demographic, clinical and ECT parameters, responders and non-responders did not differ (data not shown).

Differences from pre- to post-ECT were calculated for K-AMI scores for ECT responders and non-responders and assessed for normality, then compared using the Mann-Whitney U test (Table 4.6). Bonferroni correction was applied and p was set at 0.001. No significant differences in change in K-AMI on any subscale or total semantic or episodic scores were found between ECT responders and non-responders. In addition, as depression severity exists on a spectrum and dichotomised response status may not be an adequately sensitive indicator of mood status, the non-parametric Spearman's rho was used to assess for correlation between HRSD-24 change scores from pre-to post-ECT and K-AMI change scores (Table 4.6). No significant correlations were found between change in depression severity and change in score for any K-AMI subscale or the total semantic and episodic scores. Further, there was no difference between change scores of those who had right unilateral (n=16) and those who had bitemporal (n=11) ECT for total semantic (p=0.904) and total episodic scores (p=0.680). No correlation between mean time to reorientation was found for total semantic change score (Spearman's rho, 0.21, p=0.304) or total episodic change score (Spearman's rho, -0.13, p=0.525). Baseline sMMSE score also did not correlate with total semantic (Spearman's rho, 0.06, p=0.749) and total episodic (Spearman's rho, 0.034, p=0.868) change scores, nor did age, (Spearman's rho for semantic, -0.1, p=0.6, Spearman's rho for episodic, -0.08, p=0.672).

4.5 Discussion

4.5.1 Summary of findings

In this prospective cohort study, I aimed to assess the effect of ECT on autobiographical memory by comparing the performance of depressed patients with that of a large matched healthy control group, controlling for the effects of change over time and mood status. I found severely impaired autobiographical memory in depressed patients at baseline across

all three schedules of assessment (Recent life, Early Adult life, and Childhood) in the K-AMI. This finding was more pronounced for episodic memory, which was profoundly impaired. Despite statistically significant changes among patients in sMMSE, category fluency and backward digit span between assessments when compared with controls, the K-AMI did not identify any overall change in autobiographical memory in depressed people following ECT. However, there was wide variability in changes on the K-AMI among depressed people. In addition, I found that depressed persons' performance on the K-AMI was independent of ECT response status and change in depression severity. While scores on the K-AMI can be distinguished between groups of depressed people and healthy controls as previously shown (Kopelman et al., 1989), these findings are consistent with the previous suggestion that the measure is not adequately sensitive to detect change in autobiographical memory performance over time in depressed patients having ECT (Jelovac et al., 2016). Though the K-AMI detected individual-level change, it did not identify change between groups. Although the K-AMI has been modified for use to assess recall in one study (Spaans et al., 2013), it was not designed with a recall consistency component.

4.5.2 Context

As K-AMI data in this study were non-parametric, it is difficult to directly compare with other studies that reported report mean values. However, these results are broadly consistent with previous reports that identified profound episodic memory impairment in depressed people and no overall change on the K-AMI following ECT (Jelovac et al., 2016, Sienaert et al., 2010). Although this sample size is much larger, scores for healthy controls here are comparable to previous reports (Kopelman et al., 1989). Pre-ECT scores for depressed patients in this study are also comparable to K-AMI scores previously reported in depressed populations (Kho et al., 2006; Warren and Haslam, 2007), and

changes before and after ECT are similar to those in previous studies (Sienaert et al., 2010, Verwijk et al., 2015). One possibility to explain the finding of no overall change in K-AMI scores after ECT is that there is no effect of ECT on autobiographical memory performance. However, as autobiographical memory patterns differ between different forms of ECT (Kolshus et al., 2017; Sackeim et al., 2000; 2008), it is clear that ECT has some impact on this cognitive function and that with accurate assessment instruments there is a possibility of identifying and reducing this impact. The most likely explanation for my finding, therefore, is that the K-AMI probably lacks sufficient sensitivity to group-level change to identify the impact of ECT on autobiographical memory performance.

This cohort displayed large variability in change on the K-AMI following ECT, which was not explained by ECT laterality, age, baseline sMMSE, or time to reorientation. Other studies report similarly wide ranges of K-AMI change scores after ECT (Mayur et al., 2013, Spaans et al., 2013). This suggests that autobiographical memory performance in depressed people having ECT is characterised by wide variability. Further, as almost half of depressed patients showed improvement in total episodic memory from pre- to post-ECT, it is crucial that instruments to assess autobiographical memory in a depressed ECT population allow for improvement in scores. Poor baseline autobiographical memory in depressed people, as reported by us and others (Jelovac et al., 2016, Sienaert et al., 2010, Verwijk et al., 2015), may limit the ability of the CUAMI to detect the range of changes in autobiographical memory, both positive and negative, seen here.

4.5.3 Limitations

Limitations of the study include a relatively small patient group (n=27), which may limit the statistical power of the study. However, I applied stringent correction for multiple comparisons. It is important to note that without controlling for the aggregation of K-AMI

subscales to form total semantic and episodic scores (i.e. if p were set at 0.05) change over time in total scores would have been significantly different between patients and controls. However, the total scores are comprised of six subscale scores, only two of which showed any difference in change over time between patients and controls. This is a non-randomised study and, although I found no difference in K-AMI change following ECT between those who had RUL and BT ECT, the groups were not stratified and this must therefore be interpreted with caution. Three patients switched ECT laterality during the study and for all patients it is possible that the choice of laterality was related to previous cognitive adverse effects of ECT.

Premorbid IQ has been suggested as a possible confounding factor in assessment of autobiographical amnesia (Sackeim et al., 2007), and premorbid IQ differed between patients and controls in this study. However premorbid intelligence assessments (such as the NART, used here) are confounded by depression (Sackeim et al., 1992) and pre-treatment cognitive performance has been reported to be a stronger predictor of retrograde amnesia (Sobin et al., 1995). I compared change scores as well as raw scores in order to assess change over time independently of pre-treatment cognition

It is possible that assessing cognition immediately after the course of ECT is too early to detect any response-related improvement in cognition. A follow-up assessment of patients one month after ECT would therefore provide useful data about whether overall group cognitive performance improved to baseline or beyond, as meta-analytic data suggest it will (Semkovska and McLoughlin, 2010). As with all assessments of autobiographical memory it is impossible to verify the accuracy of the detail provided, but answers were accurate in 90% of the original K-AMI sample, suggesting confabulation is not uniquely problematic with this assessment (Kopelman et al., 1989).

As with many similar studies of cognition in ECT, completion rates of assessments (Eranti et al., 2007) and generalizability of research samples to a clinical ECT population (O'Connor et al., 2010) are problematic. In this study, ECT patients who had existing cognitive impairment (sMMSE ≤24) and those who were too unwell to consent were excluded. Excluded patients could not be assessed and may represent a subgroup of more severely unwell ECT patients who are more vulnerable to autobiographical amnesia. Even some healthy controls (n=8) elected not to complete all assessments, finding the AMI burdensome or intrusive, a limitation of both the instrument and the study. The ECT response rate in this study (13/27, 48.1%) is lower than that of those who did not complete cognitive assessments (15/23, 65%). This may be accounted for by the younger age of those described here, but also reflects the difficulty in achieving high completion rates of the K-AMI in depressed patients. Despite the lower response rate, the cohort described here is otherwise broadly similar to non-completers in the whole cohort, and to previously reported ECT cohorts in terms of demographic, clinical and ECT variables (Semkovska et al., 2016, Sineaert et al., 2010). Study strengths include a large age- and gender-matched control group, a broad cognitive battery which assessed multiple cognitive domains, and completion of the full K-AMI. Additionally, I reported high inter-rater reliability for the mood outcome (HRSD-24) and use of a considered, two-rater AMI scoring system. Time intervals between assessments for cases and controls were closely comparable.

4.6 Conclusion

Assessment of the precise effect of ECT on autobiographical memory remains difficult to achieve. In this study, although the K-AMI distinguished between scores of the depressed group and the healthy control group both at baseline and reassessment, the K-AMI was not sufficiently sensitive to identify any overall change in autobiographical memory in depressed patients following ECT. Therefore, larger future studies aiming to elucidate the

true effect of ECT on autobiographical memory, controlling for the effects of mood status and the passing of time, are unlikely to be successful using the K-AMI. Further, I found that autobiographical memory performance in depressed patients before and after ECT is characterised by wide variability. Thus, an ideal instrument for assessing autobiographical memory in ECT would need to allow for both positive and negative change in performance between pre- and post- ECT assessments.

5. Effect of personality disorder on response to ECT for depression

5.1 Introduction

Personality disorder is a recognised psychiatric diagnosis characterised by enduring maladaptive patterns of behaviour, cognition and inner experience (American Psychiatric Association, 2000). People with personality disorder are more likely to experience episodes of depression than those without the diagnosis (McGlashan at al., 2000, Lenzenwanger et al, 2007). Further, they are less likely to recover fully from episodes of depression (Collins et al., 1990) and experience poorer depression treatment outcomes overall (Newton-Howes et al., 2014, Alnaes et al., 1997). Among those with depression, 50% may have a comorbid diagnosis of personality disorder (Sanderson et al., 1992). Understanding the needs of this group is crucial for clinicians treating depression.

Electroconvulsive therapy (ECT) is a powerfully effective acute treatment for depression (UK ECT Review Group, 2003). It is unclear whether comorbid personality disorder affects response rates to ECT. Retrospective (Sareen et al., 2000, Kaster et al., 2017) and population-based (Nordenskjöld et al., 2012) studies have reported lower ECT response rates and higher relapse rates following successful ECT among those with depression and personality disorder compared to those with depression alone. However, a prospective study found that only borderline personality disorder was associated with poorer ECT response and those with other personality disorders responded equally well to ECT as those without (Feske et al., 2004).

Smaller studies using older diagnostic classification systems reported no difference in ECT response rates between those with personality disorder and depression and depression alone (Pfohl et al., 1984, Zimmerman et al., 1986, Newton-Howes et al., 2014). People with personality disorder and depression may suffer the consequences of pessimism regarding ECT response rates in both clinical and research settings. It has been suggested

that clinicians under-prescribe ECT for depressed patients with a personality disorder (DeBattista and Mueller, 2001) and people with personality disorder are often excluded from clinical trials (Zimmerman at al., 2004).

Personality disorder or traits can be diagnosed clinically following repeated assessments and collateral history, or using a structured diagnostic interview for personality disorder, e.g. Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (First et al., 1997). Patients referred for ECT are often severely depressed and the extensive patient input required to make a formal diagnosis of personality disorder may be impractical. The majority of self-report personality traits are stable pre- and post-ECT treatment (Blais et al., 1998). Therefore a self-report screening instrument to identify people who are likely to have comorbid personality disorder may be of value to ECT clinicians.

The Standardised Assessment of Personality – Abbreviated Scale (SAPAS) is validated for identifying likely personality disorder among people attending psychiatry services (Moran et al., 2003). The scale consists of eight yes/no questions that refer to longstanding and general traits. A cut-off score of 3 positive answers has a sensitivity of 0.94 and specificity of 0.85 for identifying the presence of any personality disorder (Moran et al., 2003). Those "above SAPAS threshold" are likely to have an underlying personality disorder and those "below SAPAS threshold" are not likely to have an underlying personality disorder. Among inpatients with depression, a cut-off score of 3 had a positive predictive value of 73.1% and was not associated with depression severity (Bukh et al., 2010). The SAPAS has been used to assess for outpatient response to pharmacological treatment (Gorwood et al., 2010), where personality dysfunction was associated with poor response to treatment, but has not been applied to examine response to ECT.

Depression is associated with multiple cognitive impairments (Fischer et al., 2008). People with personality disorders also display cognitive differences when compared to healthy

controls (Bazanis et al., 2002). In particular, schizotypal personality disorder is associated with impairment in working memory, episodic memory and delayed recall (Mitropolou et al, 2005). Borderline personality disorder is associated with frontal lobe dysfunction (Fisher et al., 2008, Dowson et al., 2004), though one study found that cognitive impairment in borderline personality disorder was only apparent when comorbid depression was present (Kremers et al., 2004). It has been suggested that people with personality disorders are less likely to be prescribed ECT for depression (DeBattista and Mueller, 2001) and cognitive side effects are the aspect of ECT that most limit its use (Rose et al., 2003). However, to date, only one study has reported on this issue using retrospective assessment of documented adverse effects among people with depression with or without borderline personality disorder, finding no difference between the groups (Kaster et al., 2017).

Though there is available literature on diagnosed personality disorder and ECT, no study has yet reported on the use of a brief personality screening tool in a depressed ECT population. I used the SAPAS to identify those likely to have an underlying personality disorder and hypothesised that those above the threshold would be less likely to respond to ECT but would be no more vulnerable to cognitive side-effects than those below the SAPAS threshold.

5.2 Method

5.2.1 Aim

I performed a prospective cohort study to determine whether a difference exists in response to ECT among patients with unipolar major depressive disorder who were identified on a screening instrument as likely or unlikely to have an underlying personality disorder. I also studied cognitive performance before and after ECT in a subgroup of depressed patients and compared those above and below the SAPAS threshold.

5.2.2 Participants

Participants were unipolar depressed patients referred for ECT recruited to the Monitoring Phase of KEEP-WELL pilot trial detailed in Chapter 3. Recruitment to the Monitoring Phase of the randomised pilot trial took place over eighteen months (n=43). Recruitment to this cohort study then continued for a further six months. Depressed inpatients recruited prior to commencing ECT and assessed using the SAPAS one to two days before commencing ECT, and were monitored on a weekly basis for response using the HRSD-24. ECT was administered as outlined in Chapter 2. Response was defined as ≥60% decrease from Baseline HRSD-24 score and score ≤16 on two consecutive weekly ratings and remission criteria were a ≥60% decrease in HRSD from baseline and score ≤10 on two consecutive weekly ratings.

5.2.3 Instruments

Each assessment included a mood rating using the HRSD-24 as outlined in Chapter 2. The Structured Clinical Interview for Diagnosis (SCID, DSM IV) (First et al., 1998) and the National Adult Reading Test (NART) (Nelson and Willison, 1991) were performed at baseline and predicted full-scale IQ was calculated based on the latter. The Maudsley Staging Method for Treatment Resistant Depression (MSMTRD) (Fekadu et al., 2009) was performed with scores of 3-6= mild resistance; 7-10= moderate and 11-15= severe treatment resistance.

5.2.3.1 Standardised Assessment of Personality – Abbreviated Scale

Participants completed the SAPAS once at baseline. The questionnaire is designed as a self-assessment. To minimise social desirability response bias (Paulhus, 1991), participants were provided with instructions on how to complete the questionnaire and then left alone

to complete it and return it confidentially to the rater. If significant visual impairment limited the participant's ability to complete the questionnaire, questions were read out to the participant by a trained interviewer. To maximise SAPAS completion, participants were encouraged to complete the questionnaire by self-assessment. However, if they were unable to do so, or requested support for completion, questions were read out by a trained interviewer and responses recorded.

5.2.3.2 Cognitive assessments

Cognitive performance was assessed before ECT and within 3 days after the final ECT treatment using a battery of cognitive assessments. As these were non-prioritised secondary assessments, these were performed only by a subset of patients. The assessment instruments are described in detail in Chapter 2. Briefly, global cognition was assessed using the standardised Mini Mental State Examination (sMMSE) (Molloy et al., 1991). Immediate short-term memory, attention and working memory were measured using Forward and Backward Digit Spans (Wechsler et al., 1997). Motor and psychomotor speeds were assessed using the Trail Making Test (part A, TMT-A) (Wechsler et al., 1997). Frontal-executive function was rated by Trail Making Test (part B, TMT-B) (Wechsler et al., 1997) plus letter and category verbal fluencies performed as part of a modified Addenbrooke's Cognitive Examination-III (ACE-III) (Hseih et al., 2013). Anterograde verbal memory was tested using the verbal learning component of the ACE-III (delayed and immediate recall of a seven-item address and three unlinked objects). Parallel versions were used where available (ACE-III, digit spans) to reduce practice effects.

5.2.4 Statistical analysis

Data are presented as mean (SD) unless otherwise specified. Although others have reported total SAPAS scores (Gorwood et al., 2010), it is unclear whether this can be considered a continuous variable as the impact of scores above and below the cut-off score on predictive value is unknown (Moran et al., 2003). As a cut-off score of 3 has a high predictive value for identifying underlying personality disorder, I relied on dichotomous measures ("above SAPAS threshold" and "below SAPAS threshold" groups) for the purposes of comparison with the primary outcome, ECT response. Baseline demographic features and SAPAS scores are presented using descriptive statistics. ECT, clinical, cognitive and response parameters were assessed for normality and variance and compared using t-test or Mann-Whitney-U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables, when appropriate assumptions were met. Spearman's Correlation Coefficient for non-parametric data was used to assess for association between total SAPAS score and HRSD-24 score at baseline. A one-way ANCOVA was conducted to determine the effect of being above SAPAS threshold (likely to have a personality disorder) on post-ECT HRSD-24 scores, controlling for pre-ECT HRSD-24 scores and number of ECTs. A binomial logistic regression was performed to ascertain the effect of being above SAPAS threshold and baseline HRSD-24 on the likelihood of response to ECT. A one-way ANCOVA was performed for each cognitive assessment to determine the effect of being either above or below the SAPAS threshold on post-ECT cognitive performance after controlling for pre-ECT cognitive performance. All tests were two-tailed and unless specified otherwise, p was set at 0.05 for statistical significance. Bonferroni correction was applied for all family-wise comparisons e.g. comparison of multiple cognitive assessments to control for multiple comparisons and where applied, p values are as outlined below. Correction was not applied for single comparisons such as correlation between SAPAS score and HRSD-24 score, or being above SAPAS threshold and HRSD-24 score.

5.3 Results

5.3.1 Population

Forty-nine depressed patients completed the SAPAS and other assessments. A cut-off score of 3 was used for the SAPAS to divide groups into “above threshold” (likely to have a personality disorder) and “below threshold (not likely to have a personality disorder) as this has good predictive value in this group (Moran et al., 2003, Bukh et al., 2010). A subgroup of 33 patients performed all cognitive assessments before and after ECT. Baseline features of the depressed patient group are presented in Table 5.1. The group is broadly similar to other depressed ECT cohorts (Semkovska et al., 2016) in age, gender and depression severity.

Table 5.1 Baseline features of the depressed ECT patient group in the SAPAS cohort study

Variable	Depressed patient group (n=49)
Age in years	60.51 (15.41)
Years in education	13.90 (3.06)
Number of medical conditions	1.96 (1.70)
Baseline HRSD-24	29.95 (7.25)
Predicted full-scale IQ[a]	110.52 (9.66)
Gender, n (%) female	28 (57.1%)
Lifetime history of substance abuse, n (%)	1 (2%)
Lifetime history of alcohol abuse, n (%)	4 (8.2%)
Family history of alcohol dependence, n (%)	7 (14.3%)
Employment, n (%) working	16 (33.3%)
Marital status, n (%) married	31 (63.3%)

Data are presented as mean (SD) unless otherwise stated. [a]derived from the National Adult Reading Test.

5.3.2 SAPAS scores

Table 5.2 outlines SAPAS scores among depressed patients. Over 60% of the group scored ≥ 3 on the SAPAS and were therefore identified as likely to have a personality disorder. The items that depressed patients most commonly scored positively on were perfectionism (40.8%) and dependence (38.8%) screening questions. To assess for possible impact of mood status on SAPAS score, I performed a correlation analysis of SAPAS score (performed at baseline) and baseline HRSD-24. Low, non-significant correlation was found (Spearman's rho= 0.14, p= 0.31), suggesting self-report SAPAS responses among depressed participants were not affected by their contemporaneous mood status.

Table 5.2 SAPAS scores of depressed ECT patients

Variable	Depressed ECT patients n=49	
	n	%
Difficulty making and keeping friends	11	22.4
Usually a loner	15	30.6
Difficulty trusting others	14	28.6
Normally loses temper easily	5	10.2
Normally impulsive	11	22.4
Normally a worrier	40	81.6
Depends on others a lot	19	38.8
Generally a perfectionist	20	40.8
Above threshold (score ≥3)	30	61.2
Total SAPAS score, mean (SD)	2.75 (1.55)	

5.3.3 Clinical and ECT parameters

Clinical and ECT parameters were compared between those who were above and below the SAPAS threshold (Table 5.3). Applying Bonferroni correction for multiple comparisons, p was set at ≤0.002 for statistical significance. The groups were similar at baseline in terms of illness severity, duration of episode, number of depressive episodes, and medication use. Those above the SAPAS threshold displayed more treatment resistance on the Maudsley Staging Method for Treatment Resistance in Depression (p=0.002). In addition, patients above the SAPAS threshold had more ECT treatments, a finding that was statistically significant before Bonferroni correction but not after (p=0.042). However, patients above SAPAS threshold did not differ from those below the threshold in terms of ECT laterality, mean total charge, or mean seizure duration.

Table 5.3 Clinical and treatment parameters of the above and below SAPAS threshold groups

Variable	Above SAPAS threshold (n=30)	Below SAPAS threshold (n=19)	Statistical analysis (p)
Age	59.23 (16.82)	62.53 (13.06)	0.472
Age at onset of depression	38.03 (16.41)	45.63 (17.40)	0.130
Pre-ECT HRSD-24	29.96 (6.73)	29.94 (8.20)	0.993
Post-ECT HRSD-24	15.83 (12.26)	7.89 (6.95)	0.014
Number of previous episodes	4.46 (1.88)	3.89 (2.51)	0.369
Treatment resistance score (of 15)[a]	8.10 (1.16)	7.00 (1.15)	0.002
Duration of current episode (weeks)	29.1 (34.10)	20.8 (16.50)	0.335
Gender, n (%) female	16 (53.3%)	12 (63.2%)	0.564
Presence of psychotic symptoms, n (%)	1 (3.3%)	0 (0%)	N/A
Medication use, n (%)			
SSRI	11 (36.7%)	3 (15.8%)	0.115
Non-SSRI antidepressant	23 (76.7%)	13 (68.4%)	0.524
Antipsychotic	22 (73.3%)	12 (63.2%)	0.451
Mood stabiliser	16 (53.3%)	11 (57.9%)	0.754
Benzodiazepine	15 (50.0%)	6 (31.6%)	0.524
Indications for ECT, n (%)			
Rapid response required	2 (6.7%)	0 (0%)	
Acute suicidality	1 (3.3%)	0 (0%)	0.521
Refractory to medication	27 (90%)	19 (100%)	
Bitemporal ECT, n (%)	12 (40.0%)	9 (47.4%)	0.768
Number of ECT treatments	9.70 (3.01)	7.82 (2.83)	0.042
Cumulative mean motor seizure duration (sec)	39.15 (17.42)	35.25 (8.79)	0.399
Cumulative mean EEG seizure duration (sec)	50.09 (16.19)	44.52 (10.49)	0.217
Cumulative mean charge (mC)[b]			
Bitemporal	*n=10* 298.30 (144.67)	*n=8* 333.00 (188.97)	0.664
Unilateral	*n=16* 636.12 (279.96)	*n=9* 677.88 (231.68)	0.708
ECT Response rate, n (%) responder	12 (40.0%)	15 (78.9%)	0.009
ECT Remission rate, n (%) remitter	10 (33.3%)	14 (73.7%)	0.009

5.3.4 ECT response rate

The overall ECT response rate among depressed patients was 55% (27/49). ECT remission criteria were met by 49% of depressed patients (24/49). The ECT response rate was 40% among those above the SAPAS threshold (12/30) (Table 5.3) and 79% (15/19), among those below the SAPAS threshold (Pearson's χ^2= 7.13, p=0.009). The relative risk of response in those above the SAPAS threshold was therefore 0.50, and presence of likely underlying personality disorder led to a relative risk reduction for response of 50%.

Total SAPAS scores differed significantly between ECT responders and non-responders (t= -2.862, df =47, p =<0.05). ECT response rates did not differ based on ECT laterality (χ^2= 0.11, df=1, p=0.74), nor did ECT remission rates (χ^2= 0.170, df =1, p=0.68). Treatment resistance score (t= -0.955, df= 45, p= 0.345) did not differ between ECT responders and non-responders. Number of ECT treatments was not significantly different between ECT responders and non-responders (t= -1.91, df=45, p=0.061).

Table 5.4 Logistic regression predicting likelihood of response to ECT for depression in the SAPAS cohort study

Covariate	B	SE	Wald	df	p	Odds ratio	95% CI for Odds ratio	
							Lower	Upper
Baseline HRSD-24	0.01	0.04	0.18	1	0.66	1.01	0.93	1.11
Above SAPAS threshold	-1.73	0.67	6.56	1	0.01	0.17	0.04	0.66

A significant main effect of being above SAPAS threshold on post-ECT depression severity scores was seen when controlling for pre-ECT HRSD-24 scores, F(1, 46) = 6.59, p=0.014. However, when also controlling for number of ECTs, this effect was no longer significant, F(1, 46)= 3.58, p=0.065. A binomial logistic regression was performed to ascertain the effect of being above SAPAS threshold on the likelihood of response to ECT, controlling for baseline HRSD-24 score (Table 5.4). Though treatment resistance and number of ECT treatments were different between those above and below the SAPAS

threshold, these were not significant predictors of ECT response (p=0.64 and p=0.13 respectively) and were not included in the final model. Baseline HRSD-24 score was found to be linearly related to the logit of the dependent variable when assessed via the Box-Tidwell procedure, after Bonferroni correction with significance accepted where $p \leq 0.016$. There were no studentized residuals with values greater than 2.5 standard deviations. The logistic regression model was statistically significant, $\chi^2(2)= 7.665$, p=0.002, and explained 19.4% (Nagelkerke R^2) of the variance in ECT response rate, correctly classifying 67.3% of ECT response/non-response cases. Sensitivity was 55.1%, specificity was 81.8%, positive predictive value was 78.9% and negative predictive value was 40%. Those who did not meet SAPAS threshold and were therefore not likely to have an underlying personality disorder had a 5.7 times higher odds of responding to ECT than those scored above the SAPAS cut off of 3 (95% CI 1.5-21.3). Baseline HRSD-24 score was not a significant predictor of ECT response in the model (p=0.66).

5.3.5 Cognitive performance before and after ECT

A battery of cognitive assessments was performed by a subset (n=33) of depressed ECT patients before and after ECT. Cognitive assessment non-completers were older and had shorter depressive episodes than those who completed both sets of cognitive assessments (data not shown). However, cognitive assessment non-completers did not differ from those described here in terms of baseline HRSD-24, number of ECTs or other ECT treatment parameters (data not shown). Applying Bonferroni correction for multiple comparisons (using ANCOVA), *p* was set at 0.005. There were no differences between those above and below the SAPAS threshold in post-ECT cognitive performance when controlling for pre-ECT performance, in any of ten cognitive assessments in the battery.

Table 5.5 Cognitive performance pre- and post-ECT in above SAPAS threshold and below SAPAS threshold groups of the subset of depressed ECT patients

	Pre-ECT		Post-ECT		Statistical analysis (p)*
	Above threshold n=20	Below threshold n=13	Above threshold n=20	Below threshold n=13	
sMMSE (of 30)	28.44 (1.41)	28.28 (1.38)	27.14 (2.61)	26.78 (2.42)	F(1,30)=0.006, p=0.93
Verbal fluency: category (of 7)	4.24 (2.06)	3.87 (2.27)	3.95 (1.98)	4.00 (2.19)	F(1.30)=0.717, p=0.40
Verbal fluency: letter (of 7)	4.52 (2.00)	3.75 (2.32)	4.50 (1.47)	4.07 (2.02)	F(1.30)=0.003, p=0.95
Digit span forward (of 14)	8.74 (2.66)	8.69 (2.84)	10.16 (4.83)	8.46 (2.10)	F(1,30)=3.230, p=0.08
Digit span backward (of 14)	6.74 (1.86)	6.00 (1.58)	7.00 (4.10)	5.38 (1.85)	F(1,30)=0.044, p=0.83
Trail-making test A (seconds)	43.66 (19.00)	43.00 (12.69)	46.42 (34.82)	49.81 (22.51)	F(1,30)=0.161, p=0.68
Trail-making test B (seconds)	88.70 (48.14)	103.00 (51.18)	89.16 (60.32)	144.11 (97.97)	F(1,30)=1.050, p=0.31
Retrograde semantic memory (of 4)	3.70 (0.91)	3.92 (0.27)	3.35 (1.18)	3.15 (1.34)	F(1,30)=0.173, p=0.68
Immediate recall (of 7)	6.60 (0.40)	5.50 (1.50)	6.90 (0.10)	7.00 (0.0)	F(1,30)=1.160, p=0.29
Delayed recall (of 10)	8.12 (1.93)	7.06 (3.00)	8.30 (1.72)	7.75 (2.25)	F(1,30)=0.043, p=0.84

Data are presented as mean (SD). *One-way ANCOVA performed for all comparisons

5.4 Discussion

5.4.1 Summary of findings

This is the first prospective study of a brief personality screening tool in a depressed ECT cohort. Those identified as likely to have an underlying personality disorder were strikingly less likely to respond to ECT than those with depression alone, similar to a previous study which relied on clinical personality disorder diagnosis (Sareen et al., 2000). Those who were below the SAPAS threshold had a 5.7 times higher odds of response to ECT than those identified on the SAPAS as having an underlying personality disorder, though the confidence interval for this estimate is wide (95% CI 1.5-21.3). Presence of underlying personality disorder led to a relative risk reduction for ECT response of 50%.

There is no clear explanation for this and interpretation should be cautious in view of the role of the SAPAS as purely a screening instrument. Despite the odds ratio for ECT response in favour of those below the SAPAS threshold, the group identified on the SAPAS as likely to have an underlying personality disorder nonetheless had a 40% response rate to ECT. The ECT rate for the whole group was similar to previous reports (Semkovska et al., 2016, Kolshus et al., 2017). While those above the SAPAS threshold had higher treatment resistance and more ECT treatments, these were not associated with ECT response. The higher number of ECTs likely reflects both higher treatment-resistance and poorer response to ECT, including use of additional treatments to try to achieve response. The groups did not differ in other important ECT treatment parameters (e.g. laterality, mean charge and seizure duration) or relevant clinical factors, such as length of episode, age at onset, number of episodes or baseline depression severity score. People having both right unilateral and bitemporal ECT were equally likely to respond. The above-SAPAS threshold group was no more likely to be prescribed benzodiazepines or mood stabilisers which could have affected seizure duration (Joo et al., 2017) and thus therapeutic response to ECT.

5.4.2 Context

One consistent predictor of response to ECT is absence of treatment resistance. This has an odds ratio of 1.9 for response to ECT (Heijnen et al., 2010). Odds ratios of 1.67 (for medication resistance) and 1.84 (for depression chronicity) were reported in a meta-analysis of predictors of remission after ECT for unipolar depression (Dombrovski et al., 2005). Assessment of the true effect of personality disorder on response to ECT requires larger sample sizes but the relatively large odds ratio in this study indicates this may have a substantial impact on response to ECT. In addition, these findings suggest that as personality disorder may be an important factor in stratifying patients for randomised ECT trials, the SAPAS may also be useful in clinical trials.

The proportion of depressed patients who had a SAPAS score above threshold is slightly higher here (61%) than in a previously reported sample of mixed inpatients and outpatients with first episode depression (47%) (Bukh et al., 2010). Another sample of depressed outpatients (half of which was first episode depression) had a higher overall SAPAS score (mean 3.89, SD 1.78) than this sample (mean 2.75, SD 1.55) but the proportion reaching SAPAS threshold was not reported (Gorwood et al., 2010). In that study, the number of previous episodes was associated with SAPAS score, whereas here the number of previous episodes did not differ between those above or below the SAPAS threshold. This sample consisted of patients with recurrent depression with an average history of four depressive episodes and it is possible that recurrent depression is associated with a higher incidence of personality disorder (Gorwood et al., 2010), which may partly explain the higher proportion of people above the SAPAS threshold in this study than the 47% reported in one previous study (Bukh et al., 2010). The SAPAS has good sensitivity and specificity for depressed inpatients (Moran et al., 2003, Bukh et al., 2010). It is possible that, rather than reporting lifetime tendency, depressed patients may have responded based on current traits related to inpatient care (e.g. depending a lot on others) or mood status. However, SAPAS

score was not associated with baseline HRSD-24 score here or elsewhere (Bukh et al., 2010) and self-report personality traits are stable pre- and post-ECT for depression (Blais et al., 1998).

Few studies have reported cognitive outcomes after ECT for people with and without comorbid personality disorder. A retrospective study suggested that people with personality disorder and depression are not different to those with depression alone in terms of cognitive impairment after ECT (Kaster et al., 2017). Here, prospective data in a subset of the depressed patient group showed that despite receiving a higher number of ECT treatments, those with likely underlying personality disorder displayed no difference in change in cognitive performance after ECT on the measures presented here than those with depression alone. These results indicate that people with depression and comorbid personality disorder are no more vulnerable to the cognitive side-effects of ECT than those with depression alone. I report on retrograde autobiographical memory in this group before and after ECT in Chapter 4.

5.4.3 Limitations

The numbers of those in the depressed group who were above the SAPAS threshold are small, limiting the analyses that can be performed to understand factors that may explain their poorer response to ECT. A matched, depressed, non-ECT control group would allow for clinically meaningful comparison. Although the study sample was similar to other depressed ECT cohorts in terms of age, gender and depression severity (Semkovska et al., 2016) the comparatively low incidence of psychotic features in the group may limit generalisability of these results to other ECT populations. I could not assess for comorbidities as people with an active Axis I diagnosis, such as PTSD, were excluded from the sample. Exclusion of potential participants with pre-ECT cognitive impairment, and missing data, may limit the possibility of detecting any cognitive impairment in the

whole group but would be unlikely to lead to bias between groups above or below the SAPAS threshold. However, this study has the advantages of prospective design, application of standardised diagnostic assessment of depression (SCID), and use of a mood rating scale (HRSD-24) by trained raters. ECT was administered according to guidelines (Dunne and McLoughlin, 2013, Mental Health Commission, 2016) and the overall ECT response rate was in line with previous reports (Kolshus et al., 2017). Further research using a diagnostic interview for personality disorder to validate use of the SAPAS in a depressed ECT population would provide more detail on possible underlying reasons for differences in response rates.

5.5 Conclusion

This study suggests that the SAPAS can be useful to help identify people who may have a less beneficial response to ECT due to likely underlying personality disorder. Response rates to ECT are lower in those identified as having a likely underlying personality disorder, a factor which may therefore be useful to consider when stratifying participants in randomised ECT trials. Nonetheless, those who were above the SAPAS threshold had a 40% chance of responding to ECT for depression, despite their higher treatment resistance. Cognitive performance before and after ECT did not differ between those above and below the SAPAS threshold. Personality disorder is therefore unlikely to be a contributing factor to cognitive impairment during ECT. People who are identified on a screening tool as likely to have an underlying personality disorder would benefit from further interview for diagnosis of personality disorder in order to tailor their follow-up treatment. Although they may do less well than people who do not have a personality disorder, those with personality disorder and depression should have the opportunity to avail of high-quality, adequately therapeutic, courses of ECT and can respond well despite severe treatment resistance.

6. Childhood trauma and response to ECT for depression

6.1 Introduction

Childhood trauma such as traumatic sexual events, emotional abuse or neglect, and bereavement, is associated with greater risk of depression (Chapman et al., 2004, Green et al., 2010) as well as poorer outcomes in depression treatment (Nanni et al., 2012) People who have experienced childhood trauma have more recurrent and persistent depressive episodes (Wiersma et al., 2009), greater suicidality (Sarchiapone et al., 2007), and lower rates of response and remission with pharmacotherapy, psychotherapy or combination therapy for depression (Harkness et al., 2012). Childhood trauma also influences age at depression onset and comorbidity with other psychiatric disorders (Bernet and Stein, 1999) but the pathway between childhood events and later depressive disorder remains unclear (Tyrka et al., 2013).

Electroconvulsive therapy is a powerfully effective acute treatment for depression (UK ECT Review Group, 2003). Much research has focused on optimising treatment parameters including stimulus dose, laterality and pulsewidth (Kolshus et al., 2017, Tor et al., 2015). Even with optimised treatment, identifying those most likely to respond to ECT for depression remains difficult (McCall and Fink, 2005, Nordenskjold et al, 2012), although some factors are consistent. Response to ECT is lower with greater treatment-resistance (Heijnen et al, 2010), but higher in the presence of psychotic symptoms (Petrides et al, 2001), as well as suicidality and older age (Fink, 2014). It is unclear whether childhood trauma also affects response to ECT for depression. Along with childhood trauma, recent stressful life events are also strongly predictive of the onset of depression (Kendler et al., 1999). As recent stressful life events are common among people with depression, many people being treated with ECT may have experienced recent trauma, with unknown possible impact on their likelihood of response.

I aimed to examine the incidence of childhood (before the age of seventeen) and recent (within three years) trauma in a sample of unipolar depressed patients referred for electroconvulsive therapy. I also aimed to assess for association between response to ECT for depression and presence of childhood or recent trauma. As detailed in Chapter 4, depressed ECT patients who score above the threshold for identification of a likely personality disorder on the brief screening instrument the Standardised Assessment of Personality - Abbreviated Scale (SAPAS) have lower odds of responding to ECT than those who score below the threshold. Here, I report on the incidence of childhood and recent trauma among depressed patients having ECT, the effect on response to ECT, and interaction between trauma and personality.

6.2 Method

6.2.1 Participants

In this prospective observational cohort study, participants were depressed people referred for ECT who were recruited to the monitoring stage of the KEEP-WELL pilot trial, described in Chapter 3. Recruitment to the monitoring phase of the trial concluded at n=43 and recruitment of depressed patients referred for ECT to this and other cohort studies continued to a total cohort of n=50. To assess for trauma, the Childhood and Recent Traumatic Events Questionnaire (CRTEQ) (Pennebaker and Susman, 1988) was assessed at pre-ECT baseline. ECT was administered as outlined in Chapter 2 and participants were monitored weekly for response to ECT using the HRSD-24. Response was defined as ≥60% decrease from Baseline HRSD-24 score and score ≤16 on two consecutive weekly ratings and remission criteria were a ≥60% decrease in HRSD from baseline and score ≤10 on two consecutive weekly ratings.

6.2.2 Instruments

Each assessment included a mood rating using the HRSD-24, as detailed in Chapter 2. The National Adult Reading Test (Nelson and Willison, 1991) was used to assess premorbid intelligence at baseline and the Standardised Assessment of Personality - Abbreviated Scale (SAPAS) (Moran et al., 2003) was performed with each participant. A SAPAS cut-off score of 3 has a sensitivity of 0.94 and specificity of 0.85 for identifying personality disorder in psychiatric populations. ECT treatment information was collected and the Structured Clinical Interview for Diagnosis (SCID, DSM IV) (First et al., 1997) and Maudsley Treatment Resistance Scale for Treatment Resistant Depression (MSMTRD) (Fekadu et al., 2009) were performed. In the latter, scores of 3-6= mild resistance, 7-10= moderate, and 11-15= severe treatment resistance. ECT was administered as outlined in Chapter 2.

6.2.3 Childhood and Recent Trauma Events Questionnaire (CRTEQ)

The CRTEQ was designed for assessment of traumatic events in both childhood and recent life. It has been used in studies of schizophrenia (Rajkumar et al., 2011), social anxiety (Hoge et al., 2012), gene-environment interactions (Szentágotai-Tătar et al, 2015) and cognition (Entringer et al., 2009). The CRTEQ requests “yes/no” answers to questions about specific types of trauma experienced in childhood (before the age of 17) and recently (within the past three years) and the age at which the trauma was experienced and optional detail. In the Childhood Traumatic Events Questionnaire, the categories of trauma assessed are bereavement, violence, traumatic sexual event, parental separation, and serious illness or injury. In the Recent Traumatic Events Questionnaire, categories of trauma assessed are bereavement, spousal separation, violence, traumatic sexual event, serious illness or injury, and change in work role. In both the Childhood and Recent traumatic events questionnaires, an open question allows documentation of any trauma experienced within

the questionnaire timeframe not captured by previous questions, i.e. “other trauma”. Answers in this section were coded by raters into types of trauma including emotional trauma and neglect. For each type of trauma in the CRTEQ, participants provide a score (using a 7-point scale, where 1=not at all traumatic, 4=somewhat traumatic, 7=extremely traumatic) of the perceived severity of the trauma which can be aggregated into a “total trauma score” for both childhood and recent trauma. The questionnaire is designed as a self-assessment. Participants were provided with instructions and left alone to complete the assessment privately and return it to the rater for later scoring. If significant visual impairment limited a participant’s ability to complete the questionnaire, questions were read out by a trained interviewer. To maximise completion of the assessment, participants were encouraged to complete the questionnaire by self-assessment but if they were unable to do so or requested support for completion questions were read out by a trained interviewer. A protocol for mandatory reporting of potential risks as well as provision of support for participants who reported childhood trauma for the first time was followed in accordance with national legislation (Children First Act, 2015).

6.2.4 Statistical analysis

All tests were two-tailed with α set at 0.05 unless otherwise specified. Variables were assessed for normality (Shapiro-Wilk test) and variance (Levene’s test) and compared using Mann-Whitney-U test for non-parametric continuous variables, and χ^2 test or Fisher’s exact test for categorical variables, when appropriate assumptions were met. Data are presented as median (range) unless otherwise specified. Bonferroni correction was applied for family-wise comparisons and where applied, p values are as outlined below. Correction was not applied for single comparisons such as correlations. Correlation between total trauma score and total change in HRSD-24 from pre-ECT baseline to post-ECT was assessed using Spearman’s rank-order correlation for non-parametric data. Logistic

regression was performed to assess for the effects of childhood trauma, likely presence of underlying personality disorder on the SAPAS screening instrument (as previously reported), and baseline HRSD-24 on the likelihood that depressed patients would respond to ECT.

6.3 Results

6.3.1 Participants

The CRTEQ was completed by 44 depressed patients of a total population of 50 patients recruited to the trial and other cohort studies. Those who chose not to complete the CRTEQ may have anticipated being distressed by the instrument or were too unwell to complete the questionnaire. Demographic features of the cohort are provided in Table 6.1. The group is similar in age, gender and depression severity to previously reported depressed ECT cohorts (Semkovska et al., 2016).

Table 6.1 Demographic and clinical features of the depressed patient group in the childhood trauma cohort study

Variable	n=44
Age in years	58 (25-82)
HRSD-24	
Pre-ECT	30 (21-47)
Post-ECT	9 (0-44)
Above SAPAS cut-off score (likely personality disorder), n (%)	26 (60.5%)
Predicted premorbid full-scale IQ	111 (89-126)
sMMSE score at baseline	29 (25-30)
Years in education	13 (8-19)
Gender, n (%) female	23 (52.3%)
Employment status, n (%) employed	15 (34.9%)
Socioeconomic status, n (%)	
Professional	3 (6.8%)
Managerial/Technical	7 (15.9%)
Skilled Occupations	29 (65.9%)
Partly Skilled	4 (9.1%)
Unskilled Occupations	1 (2.3%)
Marital status, n (%) married	27 (61.4%)
Lifetime smoker, n (%)	10 (22.7%)
Lifetime history of alcohol abuse, n (%)	5 (11.4%)
Lifetime history of substance abuse, n (%)	2 (4.5%)
Family history of alcohol dependence, n (%)	8 (18.2%)

Data are presented as median (range) unless otherwise specified

6.3.2 Childhood and Recent Traumatic Events Questionnaire

Results of the CRTEQ among depressed ECT patients are in Table 6.2. Twenty-six (59.1%) depressed patients reported some form of childhood trauma, and 37 (84.1%) reported some recent trauma. Sixteen (36.4%) patients experienced more than one type of childhood trauma. The most commonly reported types of childhood trauma were bereavement, a traumatic sexual event, and emotional abuse or neglect. The median score for reported severity of trauma was 5 (range 0-29), of a maximum possible score of 42. Of the 37 (84.1%) patients who reported at least one type of recent trauma, 18 (40.9%) had experienced more than one type of recent trauma. Bereavement, change in work role, and serious illness or injury were the most commonly reported types of recent trauma. The

median score for the reported severity of recent trauma was 6 (range 0-28), of a maximum possible score of 49.

Table 6.2 CRTEQ scores of depressed ECT patients in the childhood trauma cohort study

Childhood Traumatic Events Questionnaire		***Recent Traumatic Events Questionnaire***	
Variable	**n=44**	**Variable**	**n=44**
Presence of any childhood trauma (%)	26 (59.1%)	Presence of any recent trauma (%)	37 (84.1%)
Age at which trauma was experienced	6.5 (1-17)		
Number of types of childhood trauma		Number of types of recent trauma	
0	18 (40.9%)	0	7 (15.9%)
1	10 (22.7%)	1	19 (43.2%)
2	10 (22.7%)	2	11 (25.0%)
3	0 (0%)	3	5 (11.4%)
4	4 (9.1%)	4	2 (4.5%)
5	2 (4.6%)	5	0 (0%)
Types of childhood trauma (n, %)		Types of recent trauma (n, %)	
Bereavement	16 (37.2%)	Bereavement	22 (50%)
Parental separation	6 (13.6%)	Partner separation	2 (4.7%)
Traumatic sexual event	10 (22.7%)	Traumatic sexual event	0 (0%)
Violence	8 (18.2%)	Violence	0 (0%)
Serious illness or injury	7 (15.9%)	Serious illness or injury	13 (29.5%)
Other (emotional abuse or neglect)	10 (22.7%)	Major change in type of work	14 (31.8%)
		Other (financial, work or family stress)	13 (29.5%)
Total score: severity of childhood trauma	5 (0-29)	Total score: severity of recent trauma	6 (0-28)
Both childhood and recent trauma experienced (n, %)	24 (54.5%)		

Data are presented as median (range) unless otherwise specified.

6.3.3 Trauma and response to ECT

The ECT response rate was 56.8% (25/44) and remission rate was 47.7% (21/44). Depressed patients were compared based on presence (n=26) or absence (n=18) of childhood trauma (Table 6.3). Correction was not applied for the primary outcome of comparison of ECT response and remission rates. For all other comparisons, Bonferroni correction was applied to control for multiple comparisons and p was set at 0.0025. Those who had a history of childhood trauma had a significantly lower ECT response rate of 38.5% (10/26) compared with 83.3% (15/18) among those who had no history of childhood trauma, p=0.003. The relative risk of response in those who reported childhood trauma was therefore 0.45 relative to those with no childhood trauma, and childhood trauma led to a relative risk reduction for ECT response of 55%.

The childhood trauma group was also less likely to remit with ECT (26.9% (7/26) and 77.8% (14/18) with no childhood trauma remitted, p=0.001). Notably, ECT treatment parameters such as laterality, number of ECTs, mean charge and mean seizure durations did not differ between the groups. The groups also did not differ in terms of clinical characteristics such as baseline HRSD-24 score, treatment resistance score, duration of the current episode, medication use, age at onset of depression, number of depressive episodes, presence of recent trauma, or number of physical comorbidities.

The group that reported childhood trauma was somewhat more likely to be identified on the SAPAS screening questionnaire as having an underlying personality disorder although this was not significant after correction (73.1% in this group scored above the cut off score for identification of a likely underlying personality disorder and 41.2% in those with no childhood trauma, p=0.036). Total SAPAS score was correlated with total trauma score (Spearman's rank-order correlation coefficient rho=0.314, p=0.040). In addition, as previously explored in detail in this cohort, among those who scored above the cut-off

score for identification of a likely underlying personality disorder, ECT response rate was lower but this difference was not significant after correction (χ^2=8.029, p=0.005).

Age at onset did not differ between those who did and did not experience childhood trauma. In addition, total childhood trauma severity score did not show correlation with age at onset (Spearman's rank-order correlation coefficient rho=-0.274, p=0.72), nor did age at experiencing trauma (Spearman's rank-order correlation coefficient rho=-0.069, p=0.74). Total childhood trauma severity score was also not associated with total HRSD-24 change score from pre- to post-ECT (Spearman's rank-order correlation rho= -0.132, p=0.39).

Table 6.3 Clinical characteristics and ECT parameters of depressed patients in the childhood trauma cohort study

Variable	History of childhood trauma (n=26)	No history of childhood trauma (n=18)	Statistical analysis		
			U	Z	P
Age at onset of depression[a]	35.5 (14-76)	41.5 (16-75)	195	-0.93	0.35
Number of episodes[a]	4 (1-11)	4 (1-6)	165	-1.6	0.09
Treatment resistance score[a]	8 (6-10)	7 (5-10)	179	-0.98	0.38
Duration of episode in days[a]	97 (21-1095)	68.5 (21-390)	178	-1.32	0.18
Number of physical illnesses[a]	1 (0-5)	1 (0-6)	216	-0.43	0.66
Psychotic symptoms, n (%)	1 (4%)	0 (0%)			
Medication use, n (%)					
SSRI	8 (30.8%)	5 (27.8%)			0.83
Non-SSRI antidepressant	18 (69.2%)	13 (72.2%)			0.83
Antipsychotic	15 (57.7%)	14 (77.8%)			0.16
Mood stabiliser	14 (53.8%)	9 (50.0%)			0.80
Benzodiazepine	13 (50.0%)	6 (33.3%)			0.27
Number of ECTs[a]	9 (3-17)	8 (4-16)	216	-0.42	0.67
SAPAS-positive	19 (73.1%)	7 (41.2%)			0.03
Laterality, n (%)					0.88
Right Unilateral (RUL)	15 (57.7%)	10 (55.6%)			
Bitemporal (BL)	11 (42.3%)	8 (44.4%)			
Mean total charge (mC)[a]					
RUL (n=15, n=10)	538 (150-964)	649 (370-1019)	58	-0.94	0.34
BL (n=11, n=8)	342 (121-720)	286 (103-452)	31	-1.07	0.28
Mean seizure duration (s)[a]					
Motor	33.5 (23-76)	41 (18-98)	170	-1.5	0.12
EEG	45.5 (23-95)	47.5 (28-75)	221	-0.29	0.76
Recent trauma, n (%)[b]	24 (92.3%)	13 (72.2%)			0.10
Pre-ECT HRSD-24[a]	30 (21-46)	28 (21-47)	180	-1.28	0.20
Post-ECT HRSD-24[a]	14.5 (0-44)	6.5 (1-33)	141	-2.21	0.02
ECT response criteria met, n (%)	10 (38.5%)	15 (83.3%)			0.003
ECT remission criteria met, n (%)	7 (26.9%)	14 (77.8%)			0.001

Data are presented as median (range) unless otherwise specified. [a]Mann Whitney U test was used as the assumptions of the t-test were not met, [b]Fisher's exact test was performed as the assumptions of the chi-square test were not met.

In the subgroup of depressed patients who reported any childhood trauma (n=26), ECT responders (n=10, 38.5%) and non-responders (n=16, 61.5%) were compared. Although numbers are small, no significant differences were found between responders and non-responders among those who had experienced childhood trauma in terms of age at experiencing trauma, total childhood trauma severity score, and number of types of trauma experienced (data not shown).

Table 6.4 Logistic regression predicting likelihood of response to ECT for depression in the childhood trauma cohort study

Covariate	B	SE	Wald	df	p	Odds ratio	95% CI for Odds ratio	
							Lower	Upper
Baseline HRSD-24	1.894	2.13	0.791	1	0.37	6.64	0.10	432.10
Childhood trauma present	-1.678	0.818	4.208	1	0.04	0.18	0.03	0.92
Above SAPAS threshold	-1.609	0.812	3.93	1	0.04	0.20	0.04	0.98

As both childhood trauma and being above SAPAS threshold (likely to have a comorbid personality disorder) were associated with ECT response, a binomial logistic regression was performed to ascertain the effects of childhood trauma, likely personality disorder, and baseline HRSD-24 on the likelihood of response (Table 6.5). An interaction term for childhood trauma and being above SAPAS threshold was found not to be a significant predictor ($p=0.798$) and was not included in the final model. Baseline HRSD-24 score was found to be linearly related to the logit of the dependent variable when assessed via the Box-Tidwell procedure, after Bonferroni correction with significance accepted where $p\leq0.016$. There were no studentized residuals with values greater than 2.5 standard deviations. The logistic regression model was statistically significant, $\chi^2(4)=14.619$, $p=0.006$, and explained 38.6% (Nagelkerke R^2) of the variance in ECT response rate, correctly classifying 76.7% of ECT response/non-response cases. Sensitivity was 79.2%, specificity was 73.7%, positive predictive value was 79.1% and negative predictive value was 73.6%. Childhood trauma and presence of likely personality disorder were statistically significant predictor variables while baseline HRSD-24 was not. Those who had no history of childhood trauma had a 5.3 (95% CI 1.07-26.31), times higher odds of responding to ECT than those who reported any childhood trauma and those who did not have a likely underlying personality disorder on the SAPAS had a 5.0 (95% CI 1.01- 24.39) times higher odds of responding to ECT than those who did.

6.4 Discussion

6.4.1 Summary of findings

This is the first prospective study to examine report of childhood trauma and response to ECT. Childhood trauma in depressed patients was associated with significantly lower ECT response and remission rates and presence of childhood trauma was a significant predictor of poorer ECT response. People who were remarkably similar to those who reported childhood trauma in demographic, clinical and ECT treatment variables but who had not reported childhood trauma had a 5.3 times higher odds of responding to ECT. Childhood trauma led to a relative risk reduction of 55% for ECT response. Among those patients who reported childhood trauma, there were no differences between ECT responders and non-responders in characteristics of trauma, suggesting that the presence or absence of childhood trauma alone may be sufficient to impact on ECT response regardless of age, severity, or type of trauma. Clinical and ECT treatment parameters including pre-ECT depression severity and treatment resistance, were similar between groups and do not account for the difference in ECT response rates. However, underlying personality disorder was a predictor of poorer ECT response and may account for some of these differences.

6.4.2 Context

The odds ratio for response to ECT for an established predictor of response to ECT (absence of treatment resistance) is 1.9 (Heijnen et al., 2010). Previously, meta-analysed data from over three thousand trial participants led to an odds ratio of 1.43 for non-response to depression treatment among people with a history of childhood maltreatment (95% CI=1.11–1.83) (Nanni et al., 2012). Though numbers are small in this study, stringent correction was used for multiple comparisons, and even so, a large effect of childhood trauma on ECT response was found. However, a wide 95% confidence interval for this estimate was seen (1.01- 24.39). Assessment of the true effect of childhood trauma

on response to ECT is likely to require larger sample sizes but the odds ratio in this study indicates this is a potentially important factor in response to ECT and in stratification of randomised participants for ECT research.

Although some studies have reported higher incidence of childhood sexual abuse among people with personality disorder than those without (Ogata et al., 1990), a meta-analysis did not support this association in people with borderline personality disorder (Fossati et al., 1999). Here, depressed patients and particularly depressed non-responders to ECT were strikingly more likely than controls to be identified as having a likely underlying personality disorder on a screening instrument. As proposed by others (Okubo at al., 2017), these findings suggest the possibility of a pathway from childhood trauma to development of maladaptive personality traits and subsequent lower ECT response rate, although larger studies with diagnostic personality interviews are required to examine these relationships further.

A previous study found that depressed patients recalled significantly more severe emotional abuse, emotional neglect, and physical abuse than a healthy control group (Bernet and Stein, 1999). Here, emotional abuse or neglect was as commonly reported by depressed people as traumatic sexual events and less commonly than bereavement. Increasing number of types of childhood trauma has been shown to increase the risk of depression in later life (Felitti et al., 1998). In addition, childhood sexual abuse specifically increases risk of depression (Kendler et al., 2004). In this study, childhood trauma severity score was not associated with HRSD-24 change scores from pre- to post-ECT, but scores for reported severity of both recent and childhood trauma were low overall (median scores of 5 and 6 respectively out of maximum scores of 42 or 49), suggesting that this score may not be sensitive, or that the presence of trauma alone, regardless of the perceived severity of trauma, is associated with lower ECT response. The range of scores for severity of both childhood (0-29) and recent (0-28) trauma in this group is similar to the wide variation in

total severity of trauma on the CRTEQ reported in a healthy student group, where an aggregated mean score for severity of both childhood and recent trauma among those who experienced trauma was 11.1 with a standard deviation of 5.92 (Creech et al., 2011).

6.4.3 Limitations

Recall bias is a potential limitation of all studies employing retrospective assessments of trauma, such as the CRTEQ or Childhood Trauma Questionnaire (Bernstein et al., 2003) and retrospective application of a score of the perceived severity of trauma at the time it was experienced may not be a sensitive indicator of the burden of trauma. In this depressed sample negative cognitive bias could also have affected their recall at the time of pre-ECT assessment. Childhood trauma in depressed patients may be associated with earlier onset of depression and more lifetime depressive episodes (Bernet and Stein, 1999). Here, age at onset was somewhat younger in the group that reported childhood trauma but not significantly so. In addition, severity of trauma and age at experiencing trauma were not associated with age at depression onset, and a more detailed assessment of trauma in a larger group may be required for further evaluation of this area. Although incidence of comorbid disorders is known to be associated with childhood trauma (Bernet and Stein, 1999), those with comorbid Axis I disorders were ineligible for this study and comorbidity remains a potential confounding factor suitable for assessment in future studies. The low incidence of psychotic symptoms likely reflects the high level of decision-making capacity required for recruitment to clinical trials (Emanuel et al., 2000) but in other respects (age, gender, depression severity) the depressed group is similar to previously reported ECT cohorts (Semkovska et al., 2016).

6.5 Conclusion

Although lower than the overall ECT response rate, those who reported childhood trauma had an ECT response rate of 38.5%, despite high treatment resistance and high incidence of likely underlying personality disorder. People with a history of childhood trauma may be less likely to respond to ECT for depression than those without, but can become well with ECT. Further research to investigate the possible impact of childhood trauma and maladaptive personality traits on response to ECT for depression could help clinicians and patients better understand factors affecting their likelihood of response to ECT.

7. Involuntary and voluntary electroconvulsive therapy, a case-control study

7.1 Introduction

The importance of representativeness of clinical trial populations for guiding evidence-based practice is particularly acute in psychiatry research. The requirement for capacity to consent to research excludes a significant proportion of patients with severe mental illness, resulting in gaps in understanding the requirements of those treated involuntarily (Priebe et al., 2009). Antidepressant efficacy trials in particular have been shown to be poorly representative of community depression populations (Zimmerman et al., 2002). Electroconvulsive therapy (ECT) is an effective acute treatment for severe, often resistant, depression (UK ECT Review Group, 2003) and is sometimes administered in involuntary conditions around the world (Leiknes et al., 2012). Clinical research has led to developments in ECT treatment factors, e.g. laterality, dose and pulse-width, to optimise efficacy and reduce adverse effects (Kolshus et al., 2017, Tor et al., 2015). People having involuntary ECT are rarely recruited to clinical trials (Kellner et al., 2016). It is therefore not known whether such evidence can be generalized to those who involuntarily have ECT. Little is known about this clinical population (Chiu et al., 2014, Dare and Rasmussen, 2015, Methfessel et al., 2017) and how they may differ from those having voluntary ECT.

7.2 Method

I performed a retrospective casenote review to compare involuntary ECT courses to voluntary courses in terms of demographic, clinical, ECT treatment, and outcome variables. Ethical approval was obtained from the Research Ethics Committee of St Patrick's Mental Health Services (Protocol 01/13). Retrospective data were collected and pseudonymised prior to analysis; thus informed consent was not received. The study centre is a 300-bed independent-sector university psychiatry hospital, which has been accredited

by the Royal College of Psychiatrists' ECT Accreditation Service (ECTAS) annually since 2004 and administers approximately one-third of all ECT in Ireland each year (Mental Health Commission, 2016).

I included all involuntary courses of ECT in the five-year study period (May 2008 - April 2013), identified through the study centre ECT register, which is mandatorily completed at the first ECT treatment of every course. A control sample of time-, age- and gender-matched, acute voluntary ECT courses was selected by identifying two voluntary courses registered both immediately before and after the involuntary course in the ECT register and selecting for inclusion those of the same gender and similar age. Descriptive and simple comparative statistics were performed using IBM SPSS Statistics, Version 22.0 (Armonk, NY: IBM Corp). After assessment for normality, means were compared using independent-samples t-tests. Categorical variables were compared using either Chi-square or Fisher's exact tests, as appropriate.

7.3 Results

I identified 52 courses of involuntary ECT, accounting for 8.5% of all courses in the study center during this period, in line with national data for this time (Mental Health Commission, 2016). Data were gathered on 48 of the involuntary courses (92%) and 96 time-, age-, and gender-matched controls were selected.

Table 7.1 Involuntary and voluntary ECT courses

Variables	Involuntary (n=48)	Voluntary (n=96)	*t* or $\chi 2$	*P*
Clinical Variables				
Age in years	69.3 (12.8)	64.9 (14.8)	1.75	0.08
Years in education	12.7 (3.1)	13.1 (3.6)	0.61	0.54
Number of medical conditions	3.2 (1.7)	2.7 (2.0)	1.39	0.16
Gender (n, % female)	37 (77%)	71 (74%)	0.17	0.68
Employment[a] (n, % working)	5 (10%)	19 (20%)	Fisher's exact	0.36
Number of previous episodes	4.3 (3.5)	5.2 (5.0)	1.06	0.29
Number of failed medication trials	5.3 (3.7)	5.8 (3.6)	0.82	0.41
Duration of current episode (weeks)	13.8 (15.9)	17.9 (32.2)	0.82	0.41
Presence of psychotic symptoms (n, %)	34 (71%)	17 (18%)	39.48	<0.001
Diagnostic group[a] (n, %)				
Unipolar depression	31 (64.6%)	71 (74.0%)		
Bipolar depression	5 (10.4%)	17 (17.7%)		
Mania	3 (6.3%)	3 (3.1%)	Fisher's exact	0.04
Catatonia	2 (4.2%)	0 (0%)		
Schizoaffective disorder	7 (14.6%)	5 (5.2%)		
Indication for ECT (n, %)				
Rapid response required	13 (28.9%)	22 (22.9%)		
Acute suicidality	5 (11.1%)	4 (4.2%)	24.11	<0.001
Physical deterioration	14 (31.1%)	6 (6.3%)		
Refractory to medication	13 (28.9%)	64 (66.7%)		
CGI Severity score[b] (n, %)				
Normal	0 (0%)	0 (0%)		
Borderline ill	0 (0 %)	0 (0%)		
Mildly ill	0 (0%)	3 (3.2%)		
Moderately ill	2 (4.2%)	18 (18.8%)		<0.001
Markedly ill	6 (12.5%)	29 (30.2%)		
Severely ill	24 (50%)	41 (42.7%)		
Extremely ill	16 (33.3%)	5 (5.2%)		
ECT Treatment Parameters				
Number of ECT treatments	8.1 (2.9)	7.8 (2.6)	0.77	0.44
Mean EEG seizure duration (seconds)	47.3 (24.1)	43.4 (17.7)	1.08	0.28
Bitemporal ECT[a] (n, %)	46 (96%)	79 (83%)	Fisher's exact	0.03
Bitemporal ECT Mean charge (mC)[c]	348 (228)	339 (193)	0.24	0.81
Treatment outcomes				
CGI Improvement score[b] (n, %)[b]				
Very much improved	9 (18.8%)	22 (22.9%)		
Much improved	28 (58.3%)	42 (43.8%)		
Minimally improved	7 (14.6%)	29 (30.2%)	Fisher's exact	0.07
No change	3 (6.3%)	2 (2.1%)		
Minimally worse	0 (0%)	1 (1.0%)		
Much worse	1 (2.1%)	0 (0%)		
Readmitted within six months (n, %)	17 (35.4%)	43 (44.7%)	0.78	0.37

[a]Fisher's exact test was performed because the assumptions of the Chi-square test were not met; [b]Clinical Global Impression score; [c]Mean charge was compared for courses of bitemporal ECT only, ie n=46 in the involuntary group and n=79 in the voluntary group. Data are presented as mean (SD) unless otherwise specified.

In line with the sampling method, the groups were balanced for age and gender, and were also balanced in terms of educational attainment, employment status, and number of physical comorbidities (Table 7.1). Additionally, number of previous episodes, duration of episode and number of failed medication trials were similar between groups. Psychotic symptoms were strikingly more common in the involuntary ECT group, present in 71% of this group compared to 18% of the voluntary group ($p<0.001$). Baseline illness severity, determined by the Clinical Global Impression (CGI) severity score (Guy, 1976), differed significantly between groups ($p<0.001$), with a shift in distribution towards the more severely unwell end of the spectrum in the involuntary group. Additionally, the involuntary group was more commonly prescribed ECT for management of physical deterioration (31.1% *vs* 6.3%), whereas those in the voluntary group were more likely to receive ECT for medication-resistant illness (66.7% compared to 28.9% of the involuntary group).

Those in the involuntary group were slightly more likely to have been prescribed bitemporal ECT but other ECT parameters such as number of treatments, cumulative mean charge, and cumulative mean EEG seizure duration did not differ between groups. Outcomes on the Clinical Global Impression improvement score were similar with both groups most likely to be rated as "much improved" or "very much improved". The involuntary group had a lower readmission rate within six months (35.4%) but this was not significantly different to that in the voluntary group (44.7%).

7.4 Discussion

This is the largest ever reported cohort of people who received involuntary ECT, and the largest case-control study of involuntary *vs*. voluntary ECT. I found that patients who received involuntary ECT were remarkably similar to an age-, gender-, and time-matched control group in many respects, but differed strikingly in terms of high prevalence of psychotic symptoms, more severe baseline illness severity, and more need for management

of physical deterioration. This suggests that while both groups may be clinically alike, impairment in capacity to consent to ECT due to psychotic symptoms, coupled with physical deterioration, may be the characteristic which leads to the requirement for involuntary ECT.

Bitemporal ECT was slightly more commonly administered to those in the involuntary group but is equivalent to high-dose unilateral ECT (Kolshus et al., 2017). Otherwise, treatment parameters did not differ and those administered involuntary ECT required a similar number of ECT sessions, stimulus charge and seizure duration to achieve improvement. Despite differences in clinical presentation, with greater illness severity and more psychotic symptoms in the involuntary ECT group, both groups showed similar, largely positive, outcomes and had similar six-month readmission rates.

This study is limited by its retrospective observational design, a limitation of nearly all research on involuntary treatment. However, the groups were tightly matched as part of the case-control design. Although data were collected on 92% of the involuntary sample and the entire voluntary sample, missing data may lead to the possibility of bias.

Greater prevalence of non-depressive disorders has previously been reported among those having involuntary ECT (Lamont et al., 2011). Other studies have shown that those having involuntary ECT may be older (Plakoitis et al., 2014) and have less knowledge about the treatment (Malcolm, 1989) though these specific factors were not assessed in the present case-control study.

7.5 Conclusion

In this study, the voluntary and involuntary ECT groups were more similar than different. Although ideally trial reports should outline the reasons for exclusion, including

involuntary status, these data suggest that research findings on ECT practice for voluntary patients can be generalizable to those having involuntary ECT.

8. Conclusions and future directions

8.1 Conclusions

8.1.1 Study 1. The KEEP-WELL Trial

The results of this trial lead to the conclusion that this pilot trial protocol is not suitable for a definitive trial. Over an eighteen-month recruitment period, I found that, while recruitment to a monitoring phase of patients who had recovered from depression with ECT was in line with expected figures, randomisation rates and treatment protocol adherence were remarkably low. No conclusion about efficacy or tolerability can be drawn due to small participant numbers. Reasons given by participants for declining or discontinuing randomised treatment focused primarily on logistical difficulties such as travel. Examined in the context of other successful trials of ketamine for depression, I conclude that there is no reason why a trial of ketamine in the novel application of depression relapse prevention cannot be successful. However, future trials may wish to consider factors that were identified in this trial as problematic in order to increase the likelihood of successful randomisation figures.

8.1.2 Study 2. Effects of mood and time on autobiographical memory before and after electroconvulsive therapy for depression

The main conclusions of this study are:

1. Autobiographical memory is severely impaired in depression, particularly episodic memory, which is profoundly impaired.
2. This impairment does not change following ECT and both recovered and non-recovered ECT patients continue to have poor autobiographical memory after ECT.

3. Autobiographical memory in depressed people is characterised by wide variability. Therefore, an ideal assessment of autobiographical memory in depressed people having ECT needs to allow for both positive and negative change in score.
4. The K-AMI is likely not sufficiently sensitive to change in performance to be a useful assessment of autobiographical memory in people having ECT.
5. Performance of healthy controls on the K-AMI does not change before and after a one-month interval.

8.1.3 Study 3. Effect of personality disorder on response to ECT for depression

This study led to the following main conclusions:

1. The SAPAS screening instrument identifies a high proportion of depressed people having ECT as likely to have an underlying personality disorder.
2. People who are identified as having a likely personality disorder on the SAPAS are less likely to respond to ECT than those not identified as likely to have a personality disorder. Nonetheless they still display positive outcomes.
3. The SAPAS is a useful tool for clinicians to help identify people who may have a less beneficial response to ECT.
4. Personality disorder may be an important factor affecting response to ECT and could be considered as a stratification factor for clinical trials of ECT.
5. Personality disorder is unlikely to be a contributory factor to cognitive side-effects of ECT.

8.1.4 Study 4. Childhood trauma and response to ECT for depression

The conclusions of this study are:

1. Both childhood and recent trauma are commonly reported by depressed people having ECT.
2. Depressed people with childhood trauma are less likely to respond to ECT than those with no history of childhood trauma. However, they can still recover from depression with ECT.
3. Childhood trauma is a potentially important predictor of response to ECT and could be considered as a stratification factor for clinical trials in ECT.

8.1.5 Study 5. Involuntary and voluntary electroconvulsive therapy – a case-control study

In this study, the primary conclusions are:

1. People having voluntary and involuntary ECT are more similar than different.
2. Those who have involuntary ECT are more severely unwell than those who have voluntary ECT. In particular, they experience more psychotic symptoms and physical deterioration.
3. People having involuntary ECT do equally as well with the treatment as those who have elective ECT and require similar ECT treatment.
4. Research findings on ECT practice for voluntary patients can be generalizable to those having involuntary ECT. Because so little is known about the needs of this group, more detail could ideally be reported in clinical ECT research, such as the proportion of people ineligible for recruitment.

8.2 Summary of conclusions

Trials of ketamine for depression relapse prevention may be more successful if recruiting local populations, using intranasal ketamine or open-label design, or considering telephone

anaesthetist supervision. Depressed people experience profoundly impaired autobiographical memory, which does not change following ECT regardless of treatment response. The K-AMI is not an ideal instrument for assessing autobiographical memory in depressed groups during ECT. Among people who have ECT for depression, both childhood trauma and personality disorder may affect their likelihood of response to ECT. These findings can also be generalised to those who have involuntary ECT.

8.3 Future directions

The theoretical reasoning behind the KEEP-WELL Trial – that ketamine could have a beneficial effect on depression relapse prevention - remains sound. Although the trial protocol examined here is clearly not an effective framework to investigate this research question, there may still be merit to conducting further pilot trials of ketamine for relapse prevention which incorporate changes based on the results of this study. Future trials may wish to consider the logistical difficulties encountered, particularly in relation to travel. Measures which could increase the recruitment and randomisation rates include recruitment of participants who live very nearby, use of phone anaesthetist supervision, use of intranasal ketamine. Although intranasal ketamine is not yet licensed for use in Ireland (personal communication from the Health Products Regulatory Authority), there are several registered trials underway using this formulation, which may have more attraction for participants due to its less invasive method of administration. Though pragmatic trials are now required to assess the real-world usefulness of ketamine in depression, clinical centres may struggle to recruit adequate populations without considering the above factors.

Some of the data gathered during the KEEP-WELL Trial has already been applied to optimise design of follow-on studies. After examination of the information gathered in the KEEP-WELL Trial, I collaborated with my supervisor to design and complete a second pilot trial of ketamine for depression relapse prevention, the KINDRED Trial

(NCT02661061). In order to increase the pool of eligible participants for randomisation, this trial sought to recruit inpatients with a history of recurrent depression, currently receiving any inpatient treatment for acute depression. We received a two-year MRCG-HRB grant for completion of this study (MRCG-2016-23), which is still underway, with 28 participants with recurrent depression recruited to date, and nine people randomised. Further, as the infrastructure was in place for randomised treatment, our experience in these two trials was used to design and start a third pilot trial (Ketamine as an Adjunctive Therapy for Major Depression (KARMA-dep), NCT03256162), in which I have a limited role as an investigator. This is now underway and focuses on adjunctive treatment of acute depression with ketamine or midazolam.

Understanding factors which affect response rates to ECT is a major concern for clinicians and patients alike. The identification in these studies of two potentially important factors that may affect the likelihood of response to ECT – childhood trauma and underlying personality disorder – requires further investigation in larger samples. For both factors, large odds ratios in these studies suggest these could be useful stratification factors for randomising participants in ECT trials. Accurate communication of the finding that both likely underlying personality disorder and a history of childhood trauma are associated with lower response rates to ECT is important to avoid contributing to stigma or pessimism (among both patients and clinicians) about the potential for individual response to ECT. It is important to consider that people who have either of these risk factors, as well as long depressive episodes with relatively high treatment resistance, still had positive responses to ECT. Also, these studies have important limitations and therefore verification in larger samples will be useful.

Accurate assessment of autobiographical memory during ECT remains elusive. Future work could focus on identifying an ideal assessment instrument. Neither the K-AMI nor the CUAMI currently appear to fit the criteria for an ideal assessment. Though both of

these instruments could potentially be adapted to meet these criteria (however, the sensitivity to change of the K-AMI would remain a problem), a new instrument which assesses both positive and negative change plus a measure of recall consistency with sufficient sensitivity to change, would be of significant benefit to patients, clinicians and researchers. Normative data for healthy controls of a variety of ages, as well as a range of expected scores among depressed people not having ECT, would contribute to the usefulness of any such instrument. It is clear that depression itself has a profound impact on autobiographical memory, and research focusing on understanding autobiographical memory impairment in all depressed people, not just those having ECT, would be of great benefit to those interested in the impact of ECT on autobiographical memory.

People around the world require involuntary treatment in certain circumstances, including involuntary ECT. This is a consistent feature of mental health services. Therefore, as involuntary ECT is likely to be required by a small group of people each year, understanding their needs is important, although difficult to achieve. This study suggests that the findings of clinical trials and other prospective studies, which can only recruit capacious voluntary ECT patients, can be generalised to those having involuntary ECT. However, attempts to directly address the needs of this group through specific research, perhaps utilising non-traditional consent methods, should continue.

Overall, these studies add to a body of work which aims to gradually optimise ECT practice to increase response rates, reduce cognitive side-effects, and reduce relapse rates for both voluntary and involuntary patients. Future work will hopefully continue to improve ECT practice in these ways, perhaps by finding an ideal assessment instrument for autobiographical memory, a robust relapse prevention method, and identifying factors which could be used to help patients decide whether to proceed with ECT based on their potential for therapeutic response.

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Appendices

List of papers published during this work

Finnegan M, Ryan K, Shanahan E, Harkin A, Daly L, McLoughlin DM. (2016) Ketamine for depression relapse prevention following electroconvulsive therapy: protocol for a randomised pilot trial (The KEEP-WELL trial). Pilot and Feasibility Studies 2(38):1-11

Finnegan M, Bayazit H, Cronin T, Guler K, Galligan T, Karababa FI, McLoughlin DM (2018) Towards international standards: East meets West. Journal of ECT (in press)

Submitted papers

Finnegan M, O'Connor S, McLoughlin D. Involuntary and voluntary electroconvulsive therapy: a case-control study (submitted to Brain Stimulation)

Finnegan M, Galligan T. Ryan K, Shanahan E, Harkin A, Daly L, McLoughlin DM. Ketamine vs midazolam for depression relapse prevention following successful electroconvulsive therapy: a randomised controlled pilot trial (submitted to Contemporary Clinical Trials)

Appendix 1 Participant demographic and background information

KEEP WELL study demographic information

KEEP WELL

NAME OF RESEARCHER: _____ PARTICIPANT PROTOCOL NO: _____

DATE: DD / MM / YY VISIT NO: _____

NAME: _____ DOB: DD / MM / YY

GENDER: M / F Weight: ____ kgs Height: ____ m

Address: _____ Phone: _____

NEXT OF KIN

Name: _____

Relation to patient: _____

Phone: _____

Address: _____

ETHNICITY:
- ☐ Irish
- ☐ Irish Traveller
- ☐ African
- ☐ Chinese
- ☐ Other (including mixed background)
- ☐ Any other white background
- ☐ Any other black background
- ☐ Any other Asian background

MARITAL STATUS: ☐ Married/Co-habiting ☐ Single ☐ Divorced ☐ Widowed

EMPLOYMENT: ☐ Employed ☐ Unemployed ☐ Retired

OCCUPATION: _____ EDUCATION IN YEARS: _____

SOCIOECONOMIC STATUS (PLEASE CIRCLE):
1 Professional
2 Managerial/Technical
3 Skilled Occupations Non-Manual
4 Partly Skilled
5 Unskilled occupations

LEVEL OF EDUCATION: ☐ Primary ☐ Secondary ☐ Tertiary ☐ Quarternary

PATIENT GROUP

ICD-10 Dx: F XX . X Date of Admission: DD / MM / YY Previous ECT: Y / N

Duration of current depressive episode: DAYS I WEEKS I MONTHS Date of last ECT: DD / MM / YY

Insight: Y / N Psychosis: Y / N Catatonia: Y / N

Smoker: Y / N History of substance abuse: Y / N History of alcohol abuse: Y / N

Family history of alcohol dependency: Y / N If yes, relation to patient: _____

History of physical illness: _____

Previous surgical treatments: _____

Current medications: _____

Other therapies: _____

Appendix 2 Structured Clinical Interview for DSM-IV Disorders: Current Mood Episode

? = inadequate information 1 = absent or false 2 = subthreshold 3 = threshold or true

SCID (DSM-IV) VERSION 2.0
A. Mood Episodes

MOOD EPISODES A.1

KEEP WELL

Name of Researcher:		**Participant Protocol No:**	
Date:	DD / MM / YY	**Time:**	: AM/PM

Current Major Depressive Episode	**MDE Criteria:** **A) 5 of the following symptoms** during the **same two week period** and represent a **change** from previous functioning. At least one is **depressed mood** or **loss of interest or pleasure.** Check if symptoms persist for most of the day/nearly every day – subjective or observation by others				
In the last month has there been a period of time when you were feeling depressed or down most of the day nearly every day? (what was it like?) (Y)How long did it last? (Y)Was it nearly every day? (Y) For as long as two weeks?	**(1) Depressed mood** most of the day, nearly every day. (Subjective or observation by others)	?	1	2	3
	(2) Markedly **diminished interest or pleasure** in all, or almost all activities.	?	1	2	3
For the following questions: Focus on the worst two weeks in the past month (or past two weeks if equally depressed for entire month)					
During this two week period did you lose or gain any weight? (Y)How much weight? Were you trying to lose weight? How was your appetite? (Compared to usual?) Did you have to force yourself to eat? (Y)Was that nearly every day?	**(3) Significant weight loss** when not dieting, or weight gain (5% change within a month) or decrease/increase in appetite. Check if: Weight loss or decreased appetite ___ Weight gain or increased appetite ___	?	1	2	3
How were you sleeping? (Trouble falling asleep, waking frequently, trouble staying asleep, waking too early, OR sleeping too much? How many hours a night compared to usual? Was that nearly every night?)	**(4) Insomnia or hypersomnia** Check if: Insomnia ___ Hypersomnia ___	?	1	2	3
Were you feeling fidgety or restless that you were unable to sit still? (N) Talking or moving more slowly than usual?	**(5) Psychomotor agitation or retardation** nearly every day (observable by others, not merely subjective feelings or restlessness or being slowed down)	?	1	2	3

Note: When rating the following items, code "1" if clearly due to a general medical condition, or to mood incongruent delusions or hallucinations

Participant Protocol No: _____ **Date:** _____ **Page 1**

? = inadequate information **1 = absent or false** **2 = subthreshold** **3 = threshold or true**

	Note: Consider behaviour during the interview Check if: Psychomotor retardation ___ Psychomotor agitation ____				
What was your energy like?	**(6) Fatigue or loss of energy nearly every day**	**?**	**1**	**2**	**3**
During this time, how did you feel about yourself? (N)What about feeling guilty about things you had done/not done?	**(7) Feelings of worthlessness or excessive or inappropriate guilt** (which may be delusional) nearly every day (not merely self-reproach or guild about being sick) Note: Code 1 or 2 if only low self-esteem Check if: Worthlessness ___ Inappropriate guilt ___	**?**	**1**	**2**	**3**
Did you have trouble thinking or concentrating? (N) Was it hard to make decisions about everyday things?	**(8) Diminished ability to think/concentrate**, or indecisiveness, nearly every day (either by subjective account or as observed by others) Check if: Diminished ability to think ___ Indecisiveness ___	**?**	**1**	**2**	**3**
Were things so bad that you were thinking a lot about death or that you would be better off dead? What about thinking of hurting yourself? (Y) Did you do anything to hurt yourself?	**(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation** without a specific plan or a suicide attempt or a specific plan for committing suicide. Note: Code "1" for self-mutilation w/o suicidal intent Check if: Thoughts of own death ___ Suicidal Ideation ___ Specific plan ___ Suicide attempt ___	**?**	**1**	**2**	**3**

At least 5 of the above SXS are coded "3" and at least 1 of these is item (1) or (2)		**1**	**3**
(C) The symptoms cause **significant distress or impairment in social, occupational or other important areas of functioning**?		**1**	**3**
(D) Not better accounted for by **bereavement,** i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.		**1**	**3**

Note: When rating the following items, code "1" if clearly due to a general medical condition, or to mood incongruent delusions or hallucinations

Participant Protocol No: _____ **Date:** _____ **Page 2**

? = inadequate information **1 = absent or false** **2 = subthreshold** **3 = threshold or true**

Major Depressive Episode criteria A, C and D are coded "3"					**1**	**3**
How many separate times in your life have you been (depressed/own words) nearly every day for at least two weeks and had several of the symptoms that you described?, like (SXS of worst episode)	Total number of Major depressive episodes, including current.					
With postpartum onset: If unknown: When did these depressive SXS start?	Onset of episode within 4 weeks postpartum	**?**			**1**	**3**
With catatonic features: By observation or history	**Catatonia features criteria: At least 2 of the following.**					
	(1) Motoric immobility as evidences by catalepsy (including waxy flexibility) or stupor Describe specific behaviour:	**?**	**1**	**2**	**3**	
	(2) Excessive motor activity (that is apparently purposeless and not influenced by external stimuli) Describe specific behaviour:	**?**	**1**	**2**	**3**	
	(3) Extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism Describe specific behaviour:	**?**	**1**	**2**	**3**	
	(4) Peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate of bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing Describe specific behaviour:	**?**	**1**	**2**	**3**	
	(5) Echolalia (the pathological parrotlike and apparently senseless repetition of a word or phrase just spoken by another person) or **echopraxia** (the repetitive imitation of the movements of another person Describe specific behaviour:	**?**	**1**	**2**	**3**	
At least two items are coded "3"					**1**	**3**
		1: Melancholic features			3: With catatonic features	
With melancholic features: If unknown: during (period of current episode), when were you feeling the worst?	**Melancholic features criteria:** **A) Either of the following** occurring during the most severe period of the current episode.					
During that time that you were feeling the worst… Code based on response to item A(2) on first section only if worst time corresponds to	**(1) Loss of pleasure in all, or almost all activities**					

Note: When rating the following items, code "1" if clearly due to a general medical condition, or to mood incongruent delusions or hallucinations

Participant Protocol No: _____ **Date:** _____ **Page 3**

? = inadequate information **1 = absent or false** **2 = subthreshold** **3 = threshold or true**

period enquired about on first section.		
	(2) Lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens)	? 1 2 3 If neither A(1) or A(2) are coded 3 go to atypical features
During time when you were feeling the worst.	**B) Three (or more) of the following:**	
Was your feeling of (own words for depressed mood) different from the kind of feeling you would get if someone close to you dies? (or something else bad happened to you?) (Y) How is it different?	**(1) Distinct quality of depressed mood** (i.e the depressed mood is perceived as distinctly different from the kind of feeling experiences after the death of a loved one)	**? 1 2 3**
Did you usually feel worse in the morning?	**(2) The depression is regularly worse in the morning**	**? 1 2 3**
What time do you wake up in the morning? How much earlier is it than your usual time (before you were depressed)?	**(3) Early morning awakening** (at least 2 hours before usual time of awakening)	**? 1 2 3**
	(4) Marked psychomotor retardation or agitation	**? 1 2 3**
Code based on A3 if current month is worst period	**(5) Significant anorexia or weight loss**	**? 1 2 3**
If unclear: Were you feeling guilty about things you have done or not done? (Y) Tell me about that.	**(6) Excessive or inappropriate guilt**	**? 1 2 3**
	At least three B items are coded "3"	**1 3** Go to atypical features
	Criteria A and B are coded "3"	**1 3** With melancholic features

If current episode has melancholic or catatonic features, check here.		
With atypical features: **In the past 2 weeks**	**Atypical features criteria:** the following features must predominate during the most recent two weeks of the Major Depressive Episode.	
Code based in previous question for melancholic Sx.	**A) Mood reactivity** (i.e. mood brightens in response to actual or potential positive events.)	**? 1 2 3**
	B) Two (or more) of the following features.	
Code based on A3 section 1	**(1) Significant weight gain or increase in appetite**	**? 1 2 3**
How many hours (in a 24 hr period do you usually sleep, including naps)?	**(2) Hypersomnia** Note: Code "3" if more than 10 hours a day	**? 1 2 3**
Do your arms or legs often feel heavy (as though they were full of lead?)	**(3) Leaden paralysis** (i.e. heavy, leaden feeling sin arms and legs)	**? 1 2 3**
Are you especially sensitive to how others treat you?	**(4) Long standing pattern of interpersonal rejection sensitivity**	**? 1 2 3**

Note: When rating the following items, code "1" if clearly due to a general medical condition, or to mood incongruent delusions or hallucinations

Participant Protocol No: _____ **Date:** _____ **Page 4**

? = inadequate information **1 = absent or false** **2 = subthreshold** **3 = threshold or true**

What happens to you when someone rejects, criticizes or slights you? (Do you get very down or angry? For how long? How has this affected you? Is your reaction more extreme than most people's?) Have you avoided doing things or being with people because you were afraid of being criticised or rejected?	(not limited to episodes of mood disturbance) that results in significant social or occupational impairment				
	At least two "B" criteria are coded "3" **C. Criteria are not met for "With melancholic features" or "With catatonic features" during the same episode.** **Criteria A, B and C are coded "3"**		**1** **1** **1** With atypical features		**3** **3** **3**

Psychotic and associated symptoms					
If already has acknowledged psychotic SXS: You've told me about (SXS). Now I'd like to ask you about other experiences like that. If no acknowledgement of psychotic SXS so far: Now I'd like to ask you about unusual experiences that people sometimes have.	**Delusions:** Code overvalued ideas (unreasonable and sustained beliefs that are maintained with less than delusional intensity) as "2"				
Has it ever seemed like people were talking about you or taking special notice of you? (Y) were you convinced they were talking about you or did you think it might have been your imagination? What about receiving special messages from the TV, radio or newspaper, or from the way things were arranged around you?	**Delusions of reference**, i.e. events, objects, or other people in the individual's immediate environment have a particular or unusual significance. Describe:	**?**	**1**	**2**	**3**
What about anyone going out of their way to give you a hard time, or trying to hurt you?	**Persecutory delusions**, i.e the individual (or his/her group) is being attacked, harassed, cheated, persecuted, or conspired against.	**?**	**1**	**2**	**3**
Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people could do?	**Grandiose delusion**, i.e. content involves exaggerated power, knowledge or importance, or a special relationship to a deity or famous person Describe:	**?**	**1**	**2**	**3**
Did you ever feel that something was very wrong with you physically even though your doctor said nothing was wrong…like you	**Somatic delusion**, i.e. content involves change or disturbance in body or functioning.	**?**	**1**	**2**	**3**

Note: When rating the following items, code "1" if clearly due to a general medical condition, or to mood incongruent delusions or hallucinations

? = inadequate information **1 = absent or false** **2 = subthreshold** **3 = threshold or true**

had cancer or some other terrible disease? Have you ever been convinced that something was very wrong with the way a part or parts of your body looked?	Describe:	
(Did you feel that something strange was happening to parts of your body)		
(Did you have any unusual religious experiences? Did you feel that you had committed a crime or done something terrible for which you should be punished?)	**Other delusions** Check if: Religious delusions_____ Delusions of guilt_____ Jealous delusions_____ Erotomanic delusions_____ Describe:	**? 1 2 3**
	If never had a delusion and there is no suspicion of any psychotic feature, check here ____ and go to auditory hallucinations.	
Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against your will? (Did you ever feel that certain thoughts that were not your own were put into your head? What about taken out of your head?)	**Delusion of being controlled**, i.e, feelings, impulses, thoughts, or actions are experienced as being under control of some external force Check if: Thought insertion____ Thought withdrawal____ Describe:	**? 1 2 3**
Did you ever feel as if your thoughts were being broadcast out loud so that other people could actually hear what you were thinking? Did you ever feel that someone could read your mind?	**Thought broadcasting**, i.e. the delusion that one's thoughts are audible to others Describe:	**? 1 2 3**
How do you explain (content of delusion)?	**Bizarre delusion**, i.e. involving a phenomenon that the individual's subculture would regard as totally implausible (e.g., the person's brain has been removed and replaced with someone else's brain) Describe:	**? 1 2 3**
Auditory hallucinations	**Hallucinations (psychotic)** A sensory perception that has the compelling sense of reality of a true perception but occurs without external stimulation of the relevant sensory organ. (Code "2 for hallucinations that are so transient as to be without diagnostic significance)	**? 1 2 3**

Note: When rating the following items, code "1" if clearly due to a general medical condition, or to mood incongruent delusions or hallucinations

Participant Protocol No: _____ **Date:** _____ **Page 6**

? = inadequate information **1 = absent or false** **2 = subthreshold** **3 = threshold or true**

Did you ever hear things that other people couldn't, such as noises, or voices of people whispering or talking? (Y) Were you awake at the time? (Y) What did you hear? How often did you hear it?					
If voices: Did they comment on what you were doing or thinking?	A voice keeping up on a running commentary on the individual's behaviour of thoughts as they occur.	**?**	**1**	**2**	**3**
How many voices did you hear? Were they talking to each other?	Two or more voices conversing with each other	**?**	**1**	**2**	**3**
Visual hallucinations					
Did you have visions or see things that other people couldn't see? (Y)Were you awake at the time? Note: Distinguish from an illusion, i.e. misperception of a real external stimulus	**Visual hallucinations** Describe:	**?**	**1**	**2**	**3**
What about strange sensations in your body or on your skin?	**Tactile hallucinations** e.g., electricity	**?**	**1**	**2**	**3**
What about smelling or tasting things that other people couldn't smell or taste?	**Other hallucinations, e.g. gustatory, olfactory** **Check if:** **Gustatory____** **Olfactory____** Describe:	**?**	**1**	**2**	**3**

Tick if any of the following are coded 3:

☐ Major Depressive Episode

Severity ☐ Mild
☐ Moderate
☐ Severe

☐ Psychotic Symptoms – Delusions

☐ Psychotic Symptoms – Hallucinations

☐ Postpartum onset

☐ Catatonic Symptoms

Note: When rating the following items, code "1" if clearly due to a general medical condition, or to mood incongruent delusions or hallucinations

? = inadequate information **1 = absent or false** **2 = subthreshold** **3 = threshold or true**

- ☐ Melancholic Symptoms
- ☐ Atypical features
- ☐ Total no. of depressive episodes
- ☐ With full interepisode recovery
- ☐ Without full interepisode recovery

Note: When rating the following items, code "1" if clearly due to a general medical condition, or to mood incongruent delusions or hallucinations

Appendix 3 Maudsley Staging Method for Treatment Resistance in Depression

A MULTIDIMENSIONAL TOOL TO QUANTIFY TREATMENT RESISTANCE IN DPERESSION: THE MAUDSLEY STAGING METHOD

Fekadu, A, Wooderson, S, Donaldson, C, Markopoulou, K, Masterson ,B, Poon, L , Cleare, AJ (2009) A multidimensional Tool to Quantify Treatment Resistance in Depression: The Maudsley Staging Method, Journal of Clinical Psychiatry, 70(2), p.177 - 184.

Name of Researcher:	_____	**Participant Protocol No:**	_____
Date:	DD / MM / YY	**Visit No:**	_____

Table 1. Maudsley Staging Parameters and Suggested Scoring Conventions

Parameters/Dimension	Parameter Specification	Score	
Duration	Acute (≤ 12 months)	1	☐
	Sub-acute (13 – 24 months)	2	☐
	Chronic (>24 months)	3	☐
Symptom severity (at baseline)	Subsyndromal	1	☐
	Syndromal		
	Mild	2	☐
	Moderate	3	☐
	Severe without psychosis	4	☐
	Severe with psychosis	5	☐
Treatment failures			
Antidepressants	Level 1: 1 – 2 medications	1	☐
	Level 2: 3 – 4 medications	2	☐
	Level 3: 5 – 6 medications	3	☐
	Level 4: 7 – 10 medications	4	☐
	Level 5: > 10 medications	5	☐
Augmentation	Not used	0	☐
	Used	1	☐
Electroconvulsive therapy	Not used	0	☐
	Used	1	☐
Total		(15)	

Staging of resistance can also be presented in 3 severity categories:
mild (scores = 3 – 6)
moderate (scores = 7 – 10)
severe (scores = 11 – 15).

Appendix 4 National Adult Reading Test

KEEP WELL

NATIONAL ADULT READING TEST (NART)

Answer Sheet

Name of Researcher:		**Participant Protocol No:**	
Date:	DD / MM / YY	**Visit No:**	
Time point:			

□ CHORD	□ SUPERFLUOUS
□ ACHE	□ SIMILE
□ DEPOT	□ BANAL
□ AISLE	□ QUADRUPED
□ BOUQUET	□ CELLIST
□ PSALM	□ FACADE
□ CAPON	□ ZEALOT
□ DENY	□ DRACHM
□ NAUSEA	□ AEON
□ DEBT	□ PLACEBO
□ COURTEOUS	□ ABSTEMIOUS
□ RAREFY	□ DETENTE
□ EQUIVOCAL	□ IDYLL
□ NAIVE	□ PUERPERAL
□ CATACOMB	□ AVER
□ GAOLED	□ GAUCHE
□ THYME	□ TOPIARY
□ HEIR	□ LEVIATHAN
□ RADIX	□ BEATIFY
□ ASSIGNATE	□ PRELATE
□ HIATUS	□ SIDEREAL
□ SUBTLE	□ DEMESNE
□ PROCREATE	□ SYNCOPE
□ GIST	□ LABILE
□ GOUGE	□ CAMPANILE

NART total errors:

	Obtained IQ	*NART Predicted IQ*	*Predicted-obtained IQ*	*Abnormality (%)*
Full Scale IQ				
Verbal IQ				
Performance IQ				

Appendix 5 Edinburgh Handedness Inventory

EDINBURGH HANDEDNESS INVENTORY (revised)

Name of Researcher:	_____	**Participant Protocol No:**	_____
Date:	DD / MM / YY	**Visit No:**	_____

Please mark the box that best describes which hand you use for the activity in question					
	Always Left	*Usually Left*	*No Preference*	*Usually Right*	*Always Right*
Writing					
Scissors					
Toothbrush					
Knife (without fork)					
Spoon					
Match (when striking)					
Computer mouse					

In Likert fashion, the responses are coded "-50" (always left), "-25" (usually left), "0" (no preference, or blank row), "25" (usually right), "50" (always right). Then the eight rows are summed, giving a score *LQ** between -400 and +400. Dividing by 4 gives an Edinburgh-like *LQ* ranging from -100 (complete left handedness) to +100 (complete right handedness). With *LQ**mixed handedness becomes -200 to +200. From my everyday observations over a number of years, it is possible that the mixed handedness group divides into two :- a clumsy and a co-ordinated group. At a first guess the clumsy group would be defined as LQ* = -200 to -1 and the co-ordinated group as *LQ**= 0 to 200.

Appendix 6 Hamilton Rating Scale for Depression – 24-item

KEEP WELL

HRSD 24

HRSD 24 (modified from Williams SIGH-D 1998) with 3 items taken from W. Guy – ECDEU Manual for assessment in psychopharmacology NIMH 1976

Name of Researcher: _____ Participant Protocol No: _____
Date: DD / MM / YY Assessment No: _____
Time point: _____
☐ I have completed this participant's HRSD graph and placed a sticker in their clinical notes.

1. DEPRESSED MOOD		
What's your mood been like this past week? Have you been feeling down or depressed? Sad? Hopeless? In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day? Have you been crying at all? (1 – 4) How long have you been feeling this way?	0	Absent
	1	Indicated only on questioning
	2	Spontaneously reported verbally
	3	Communicated non-verbally (facial expression, posture, voice, tendency to weep)
	4	Virtually only communicates about being depressed (spontaneous verbal and non-verbal communication)

2. WORK ACTIVITIES		
How have you been spending your time this past week? Have you felt interested in doing (those things) or so you feel you have to push yourself to do them? Have you stopped doing anything you used to do? Y) Why? Is there anything you look forward to? (At follow-up: Has your interest come back to normal?)	0	No difficulty
	1	Thoughts and feelings of incapacity, fatigue, weakness, related to activities, work or hobbies (MORE than 3h DAY)
	2	Loss of interest in activity by direct report OR indirectly feeling she has to push herself (MORE than 3h DAY)
	3	Decreased ACTUAL time spent or productivity (Less than 3 hrs at groups or work)
	4	Bed rest in hospital OR only watching TV without leaving the ward. Stopped working, no activities at home except TV.

3. SOMATIC SYMPTOMS (GI)		
What has your appetite been this past week? (What about compared to your usual appetite?)	0	No loss of appetite
	1	Loss of appetite but eating without encouragement
	2	Difficulty eating without urging

Participant Protocol No: _____ Date: _____ Page 1

KEEP WELL

4. SOMATIC SYMPTOMS (Gen)		
How has your energy been this past week? Have you been tired all the time? This week, have you had any backaches, headaches, muscle aches? This week, have you felt any heaviness in your limbs, back or head?	0	None
	1	Loss of energy OR FATIGUE OR Heaviness in limbs/back/head or non-specific symptoms
	2	PAIN OR any clear-cut symptom (Something the patient can point to)

5. WEIGHT LOSS		
Have you lost any weight wince this past week (Y) How much? Do you think your clothes are any looser on you? At f/up: Have you gained any of the weight back?	0	Less than 1lb loss in week
	1	More than 1lb loss in week
	2	More than 2lb loss in week

6. GENITAL SYMPTOMS (LIBIDO)		
How has your interest been in sex this week? Has there been any change in your interest in sex from where you were not depressed? Is it something you have thought about much? (NO) Is that unusual for you?	0	Absent
	1	Mild
	2	Severe

7. INSOMNIA EARLY		
How have you been sleeping over the last week? Have you had any trouble falling asleep at the beginning of the night? (Y) Right after you go to bed, how long has it taken you to fall asleep? How many nights this week have you had trouble falling asleep?	0	No difficulty falling asleep
	1	Complains of occasional difficulty falling asleep (> 1/2 an hour) 3 OR LESS NIGHTS
	2	Complains of *nightly* difficulty falling asleep 4 OR MORE NIGHTS

8. INSOMNIA MIDDLE (UP TO 4 A.M.)		
During the past week, have you been waking up in the middle of the night? (Y) Do you get out of bed? What do you do? (Only go to bathroom?) When you get back to bed, are you able to fall right back asleep? Have you felt your sleeping has been restless or disturbed some nights?	0	Absent or habitual waking only to void bladder
	1	Wakes once or twice during the night but falls asleep again without undue delay
	2	Wakes frequently OR wakes occasionally but has difficulty (more 1/2 hr) falling asleep again

Participant Protocol No: _____ Date: _____ Page 2

KEEP WELL

9. INSOMNIA LATE (BEFORE 8 H/1 NIGHT SUFFICIENT)		
What time have you been waking up in the morning for the last time, this past week? What time do you usually wake up (before you got depressed)? IF EARLY: is it the alarm or do you wake up yourself?	0	No difficulty
	1	Waking in early hours but goes back to sleep
	2	Unable to fall sleep again

10. FEELINGS OF GUILT		
Have you been especially critical of yourself this past week, feeling you have done things wrong, or let others down? (Y) What have your thoughts been? Have you been feeling guilty about anything that you have once done or not done? Have you thought that you have brought this illness on yourself in some way? Do you feel you are being punished by being sick?	0	Absent
	1	Self-reproach OR feels he has let people down
	2	Ideas of guilt or ruminations over past errors or sinful deeds
	3	Present illness is a punishment. Delusions of guilt
	4	Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

11. SUICIDE		
This past week have you had thoughts that life is not worth living? Or that you would be better off dead? What about having thoughts of hurting or even killing yourself? (Y) What have you thought about? Have you actually done anything to hurt yourself?	0	Absent
	1	Feels life is not worth living, no plan
	2	Wishes he was dead or any thoughts of possible passive death of self
	3	Suicidal ideas or gesture, active
	4	Attempts at suicide

12. ANXIETY PSYCHIC		
Have you been feeling especially tense or irritable this past week? Have you been worrying a lot about little unimportant things, things that you would not ordinarily worry about? (Y) Like what, for example?	0	No difficulty
	1	Subjective tension and irritability
	2	Worrying about minor matters
	3	Apprehensive attitude apparent in face or speech
	4	Fears expressed without questioning

KEEP WELL

13. ANXIETY SOMATIC		
This past week, have you had any of these physical symptoms? Dry mouth ___ Gas___ Indigestion__ Diarrhoea___ Cramps____ Heart palpitations___ Headaches___ Hyperventilating___ Having to urinate frequently__ Sighing___ Sweating__ How much have these things been bothering you this past week? How bad have they gotten? How much of the time, or how often have you got them?	0	Absent
	1	Mild
	2	Moderate
	3	Severe
	4	Incapacitating

14. HYPERCHONDRIASIS		
In the last week, how much have your thoughts been focussed on your physical health, or how your body is working? Do you complain much about how you feel physically? Have you found yourself asking for help with things that you could really do yourself? (Y) Like what, for example? How often has that happened?	0	Not present
	1	Self-absorption
	2	Preoccupation with physical health
	3	Frequent complaints OR requests for help
	4	Hypochondriacal Delusions

15. INSIGHT		
Based on observation	0	Acknowledges being depressed and ill OR not currently depressed
	1	Acknowledges illness but attributes cause to food/climate/overwork/virus/stress, etc.
	2	Denies being ill at all

16. PSYCHOMOTOR RETARDATION		
Psychomotor slowing manifested in difficulty speaking, impaired ability to concentrate, decreased motor activity?	0	Normal speech and thought
	1	Slight retardation at interview or slowed movements
	2	Obvious retardation at interview – response time to questions increased
	3	Interview difficult to complete
	4	*Complete* stupor

KEEP WELL

17. AGITATION		
Based on observation	0	None
	1	Fidgetiness
	2	Playing with hands / hair – stays seated
	3	Moving about, cannot sit still – gets out of chair
	4	Hand wringing, nail biting, hair-pulling, biting of lips

18. DIURNAL VARIATION				
This past week, have you been feeling better or worse at any particular time of day – morning or evening?	**A**	Time	**B**	Severity
	0	No variation OR not depressed	0	None
	1	Worse in AM	1	Mild
(Y) How much worse do you feel? A little bit or a lot worse?	2	Worse in PM	2	Severe

19. DEPERSONALISATION OR DEREALISATION		
In the past week, have you ever suddenly had the feeling that everything is unreal, _____ or you are in a dream, ____ or cut off from other people in some strange way? ___	0	Absent
	1	Mild – one event in the last week or recurrent very mild events
	2	Moderate – one event per day or sever less frequently
(Y) How bad has that been?	3	Severe – severe events most days
	4	Incapacitating – actually requiring bed rest
(Y) How often this week has that happened?		

20. PARANOID SYMPTOMS		
This past week, have you felt that anyone was trying to give you a hard time or to hurt you?	0	None
	1	Suspicious
	2	Ideas of reference
(Y) Tell me about it.	3	Delusions of reference or persecution

21. COMPULSIVE SYMPTOMS		
In the past week, have there been things you have had to do over and over again, like checking the locks on the door several times?	0	Absent
	1	Mild
	2	Severe
(Y) Can you give me an example?		

KEEP WELL

22. HELPLESSNESS		
In the past week, did you feel you had trouble coping with routine activities? Were there times when you felt overwhelmed? (Y) Were these feelings so bad that you would say you felt helpless? (Y) Did other people have to urge you to tend to your responsibilities? Did you need the physical help of others to complete simple activities like grooming, dressing or eating?	0	Absent
	1	Subjective feelings indicated only on questioning
	2	Spontaneously reported helpless feelings verbally
	3	Objectively requires urging, guidance and reassurance to complete tasks or self-care
	4	Objectively requires physical assistance to complete tasks or self-care

23. HOPELESSNESS		
This past week, were you optimistic or pessimistic about the future? Do you doubt that things will improve for you? (Y) Do you have this doubt all the time? When people tell you will be well (or stay well), do you feel reassured? (N) If you doctor told you s/he was optimistic about your prospects, would you feel reassured?	0	Absent
	1	Intermittently doubts that things can improve but can be reassured
	2	Consistently feels "hopeless" but can be reassured
	3	Expresses feelings of discouragement, despair, pessimism, which cannot be dispelled
	4	Spontaneously reports and inappropriately perseverates feelings of hopelessness

24. WORTHLESSNESS		
During the last week, have you felt that you are as good as other people whom you know and respect? Have you felt that others are better than you? (Y) Did you feel that you are "no good" or "inferior"? (Y) How often did you feel this way in the past week? Do you feel you are worth nothing at all, either to yourself or others?	0	Absent
	1	Indicates loss of self-esteem on questioning
	2	Spontaneously indicated loss of self-esteem
	3	Volunteers that he is no good or inferior – differs from 2 by degree
	4	Delusions of worthlessness

Total Score	

Appendix 7 Clinical Global Impression

Clinical Global Impression (CGI)

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Appendix 8 Standardised Mini Mental State Exam

Affix
Addressograph
Here

KEEP WELL

St Patrick's
Mental Health Services

DATE: _____/_____/_____ *TIME POINT:*_____
RESEARCHER: _____ *PARTICIPANT PROTOCOL NO:*_____

STANDARDIZED MINI-MENTAL STATE EXAMINATION (SMMSE)

	QUESTION	TIME ALLOWED	SCORE
1	***What year is this?***	10 seconds	/1
	Which season is this?	10 seconds	/1
	What month is this?	10 seconds	/1
	What is today's date?	10 seconds	/1
	What day of the week is this?	10 seconds	/1
2	***What country are we in?***	10 seconds	/1
	What province are we in?	10 seconds	/1
	What city/town are we in?	10 seconds	/1
	IN HOME – What is the street address of this house? ***IN FACILITY – What is the name of this building?***	10 seconds	/1
	IN HOME – What room are we in? ***IN FACILITY – What floor are we on?***	10 seconds	/1
3	**SAY:** ***I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.*** Say the following words slowly at 1-second intervals **- ball/ car/ man**	20 seconds	/3
4	***Spell the word WORLD. Now spell it backwards.***	30 seconds	/5
5	***Now what were the three objects I asked you to remember?***	10 seconds	/3
6	**SHOW** wristwatch. **ASK:** ***What is this called?***	10 seconds	/1
7	**SHOW** pencil. **ASK**: ***What is this called?***	10 seconds	/1
8	**SAY:** ***I would like you to repeat this phrase after me: No ifs, ands or buts.***	10 seconds	/1
9	**SAY:** ***Read the words on the page and then do what it says.*** Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes	10 seconds	/1
10	**HAND** the person a pencil and paper (or use space on page 2). **SAY:** ***Write any complete sentence on that piece of paper.*** (Note: The sentence must make sense. Ignore spelling errors)	30 seconds	/1
11	**PLACE** design (page 2), eraser and pencil in front of the person. **SAY**: ***Copy this design please.*** Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.	1 minute	/1
12	**ASK** the person if he is right or left-handed. Take a piece of paper and hold it up in front of the person. **SAY**: ***Take this paper in your right/left hand*** (whichever is non-dominant), ***fold the paper in half once with both hands and put the paper down on the floor*** . Score 1 point for each instruction executed correctly: • Takes paper correctly in hand • Folds it in half • Puts it on the floor	30 seconds	 /1 /1 /1

TOTAL TEST SCORE	**/30**

CLOSE YOUR EYES

****

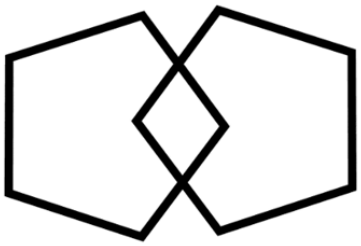
10. ***Please write any complete sentence***

_____

_____

****

11. ***Please copy the drawing***



NAME:_____ SIGNATURE:_____
(BLOCK CAPITALS)

Appendix 9 Digit span – forward and backward

Digit Span Test—Instructions and Scoring

1. General Information

- This test is modelled on the Digit Span subtest of the WAIS-R. The method of administration and scoring are the same.

2. **Digits Forward**

Instructions

- Start with item 1, say—

  I am going to say some numbers. Listen carefully, and when I have finished say them right after me.

- The digits should be given at the rate of 1 per second. Let the pitch of the voice drop on the last digit. in the same order
- Administer both trials of each item, even if the subject passes Trial 1.
- Discontinue after failure on both trials for any one item level.

Scoring

- Subject's response must be exactly correct for the trial to be passed.
- Score 1 point for each trial passed. Each item, can therefore have a score of 0 (no trials passed) 1 (one trial passed) or 2 (both trials passed).
- Record Maximum Forward Span—item level at which one or more trials passed.
- Calculate Total Score by summing scores for each item level.

2. **Digits Backward**

Instructions

- Start with item 1, say—

  Now I am going to say some more numbers, but this time when I stop I want you to say them backwards. For example if I say 7—1—9, what would you say?

- Pause for the subject to respond. If the subject responds correctly (9—1—7) say— *That's right.*
- As with Digits Forward, read the digits at a rate of one per second. Administer both trials of each item, even if the subject passes Trial 1.
- If the subject fails the practice item, say—

  No, you would say 9—1—7. I said 7—1—9, so to say it backwards you would say 9—1—7. Now try these numbers. Remember, you are to say them backwards. 3—4—8

- Whether the subject succeeds or fails on the second example (8—4—3), proceed to item 1. Give no help on this second example, or on any of the items that follow.
- Discontinue after failure on both trials for any one item level.

Scoring

- Subject's response must be exactly correct for the trial to be passed.
- Score 1 point for each trial passed. Each item, can therefore have a score of 0 (no trials passed) 1 (one trial passed) or 2 (both trials passed).
- Record Maximum Backward Span—item level at which one or more trials passed.

Calculate Total Score by summing scores for each item level.

Digit Span Test (Form I)

Note—Discontinue after failure on both trials of any one level. Administer both trials, even if subject passes first trial.

Forward Span	pass/fail	score (0,1,2)
8—1—5		
2—5—9		
4—9—6—1		
5—3—9—1		
3—8—6—2—7		
7—6—2—3—8		
4—2—6—7—3—8		
9—3—1—6—8—7		
3—5—4—8—9—6—2		
1—5—8—7—2—3—9		
7—1—6—8—2—4—3—5		
8—6—5—9—1—4—2—7		
5—3—8—7—1—2—4—6—9		
3—1—7—9—5—4—8—2—6		
Maximum Forward Span		
Total Score Forward		

Backward Span	pass/fail	score (0,1,2)
5—1		
6—9		
5—8—2		
1—7—4		
7—2—9—5		
9—7—3—5		
5—6—8—9—1		
7—1—9—4—8		
1—5—3—2—9—6		
4—1—7—8—3—9		
3—7—1—6—9—4—8		
9—1—3—4—8—7—2		
4—8—5—6—3—1—2—9		
2—5—8—4—3—7—6—1		
Maximum Backward Span		
Total Score Backward		

Appendix 10 Trails A and B

Trail Making Test (TMT) Parts A & B

Instructions:

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

Step 1:	Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.
Step 2:	Demonstrate the test to the patient using the sample sheet (Trail Making Part A – *SAMPLE*).
Step 3:	Time the patient as he or she follows the “trail” made by the numbers on the test.
Step 4:	Record the time.
Step 5:	Repeat the procedure for Trail Making Test Part B.

Scoring:

Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

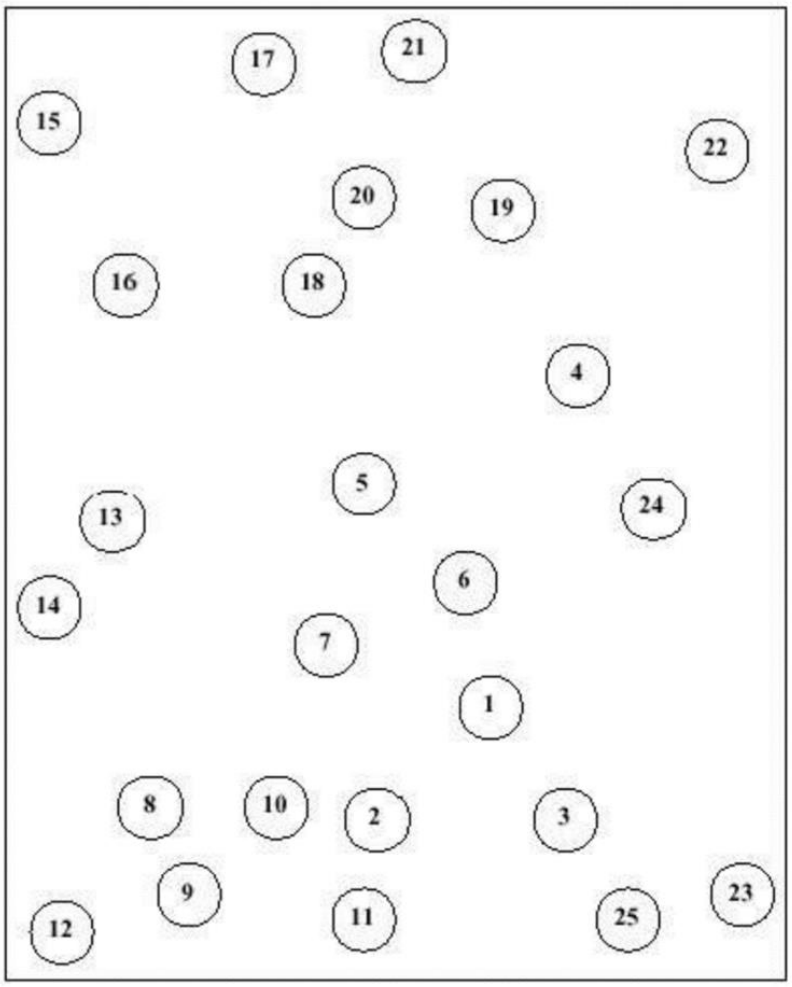
	Average	**Deficient**	**Rule of Thumb**
Trail A	29 seconds	> 78 seconds	Most in 90 seconds
Trail B	75 seconds	> 273 seconds	Most in 3 minutes

Sources:

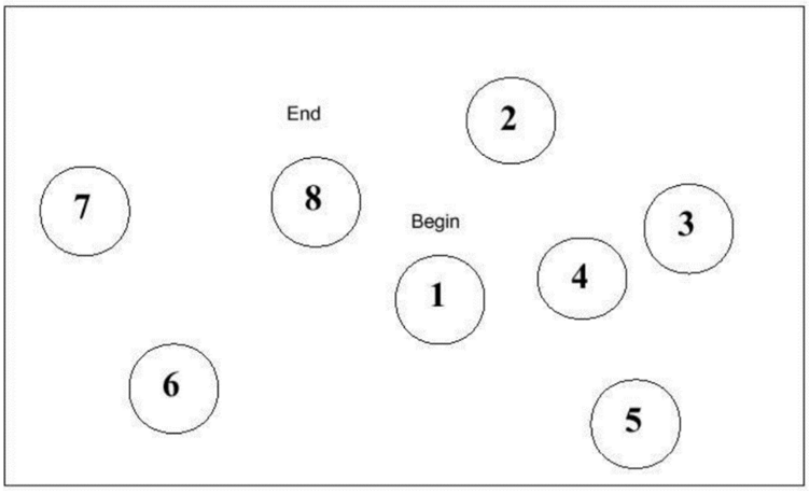
- Corrigan JD, Hinkeldey MS. Relationships between parts A and B of the Trail Making Test. *J Clin Psychol*. 1987;43(4):402–409.
- Gaudino EA, Geisler MW, Squires NK. Construct validity in the Trail Making Test: what makes Part B harder? *J Clin Exp Neuropsychol*. 1995;17(4):529-535.
- Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. 4th ed. New York: Oxford University Press; 2004.
- Reitan RM. Validity of the Trail Making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.

Trail Making Test Part A

Patient's Name: _____ Date: _____

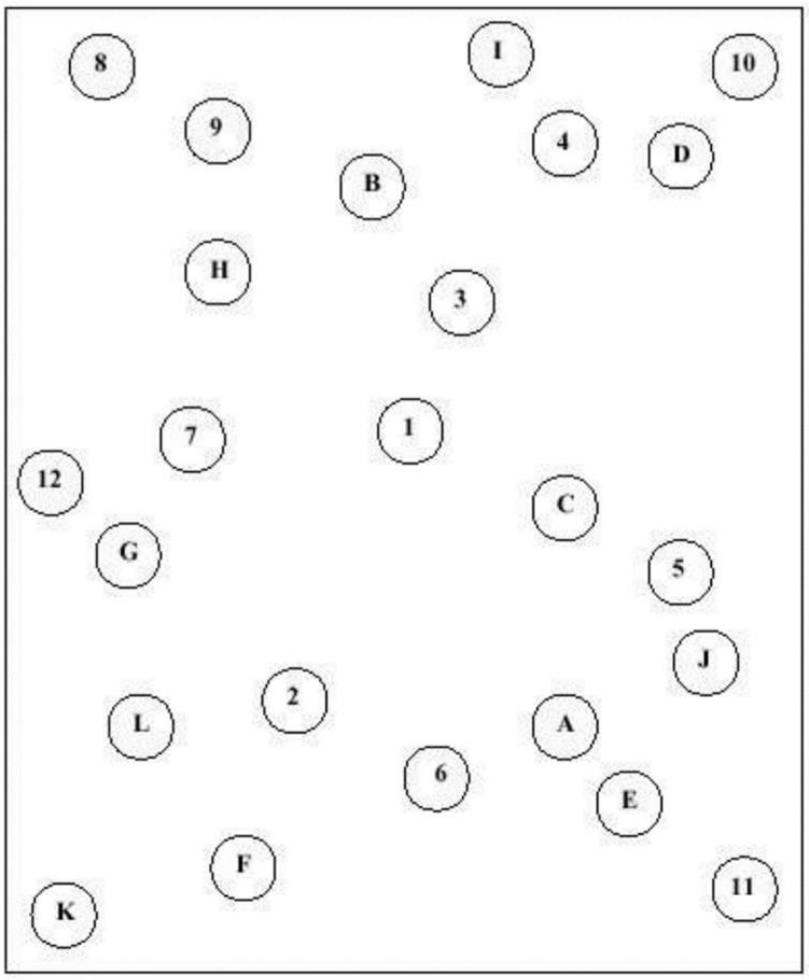


Trail Making Test Part A – *SAMPLE*

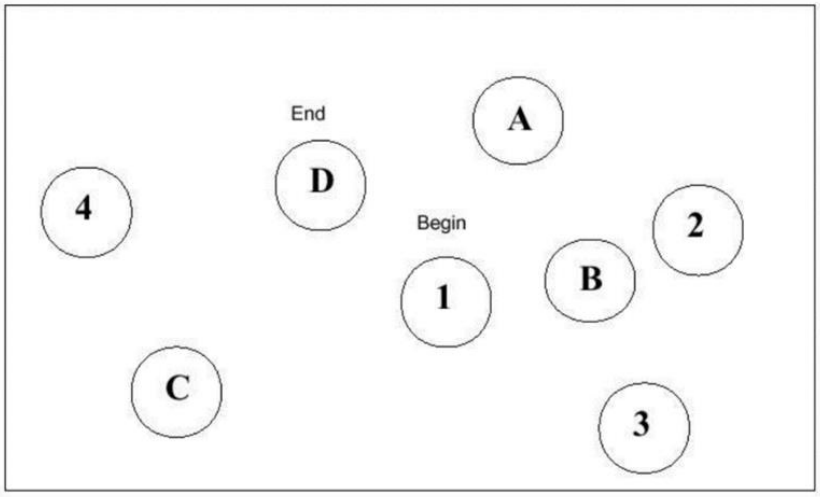


Trail Making Test Part B

Patient's Name: _____ Date: _____



Trail Making Test Part B – *SAMPLE*



Appendix 11 Addenbrooke's Cognitive Examination (III) modified version

ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III

English Version A (2012)

Name: _____ Date of testing: DD / MM / YY

Date of Birth: _____ Tester's name: _____

Hospital No. or Address: _____ Age at leaving full-time education: _____

_____ Occupation: _____

Time point: PRE ☐ POST ☐ Handedness: _____

FLUENCY

➢ **Letters**

Say: 'I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, I give you the letter "C", you could give me words like "cat, cry, clock" and so on. But, you can't give me words like Catherine or Canada. Do you understand? Are you ready? You have one minute. The letter I want you to use is the letter "P".

Fluency [Score 0 - 7] ☐

				>18	7
				14 - 17	6
				11 – 13	5
				8 – 10	4
				6 – 7	3
				4 – 5	2
				2 – 3	1
				0 - 1	0
				total	Correct

➢ **Animals**

Say: 'Now can you name as many animals as possible. It can begin with any letter."

Fluency [Score 0 - 7] ☐

				>22	7
				17 – 21	6
				14 – 16	5
				11 – 13	4
				9 – 10	3
				7 – 8	2
				5 – 6	1
				<5	0
				total	Correct

MEMORY

➢ Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."

Score only the third trial.

Memory [Score 0 – 7] ☐

	1st Trial	*2nd Trial*	*3rd Trial*
John Walsh 13 Nenagh Rd Adare Co. Limerick	_____ _____ ___ ___ ___ _____ _____	_____ _____ ___ ___ ___ _____ _____	_____ _____ ___ ___ ___ _____ _____

MEMORY

- Ask "Now tell me what you remember about that name and address we were repeating at the beginning"

John Walsh 13 Nenagh Rd Adare Co. Limerick	……. …… …… ……. ……. …… ……	**Memory** [Score 0-7]

MEMORY

- This test should be done if the subject failed to recall one or more items above. It all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right hand side; and then test not recalled items by telling the subject "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point, which is added to the point gained by recalling.

Memory
[Score 0-5]

John Walsh		Mary Fitzgerald		Peter Flynn		recalled	
13 Nenagh Rd		82 Oak Grove		42 Dublin Rd		recalled	
Adare		Castlemartyr		Navan		recalled	
Co. Limerick		Co. Cork		Co. Meath		recalled	

MEMORY

- Ask: 'Which 3 words did I ask you to repeat and remember?'
  BALL, CAR, MAN

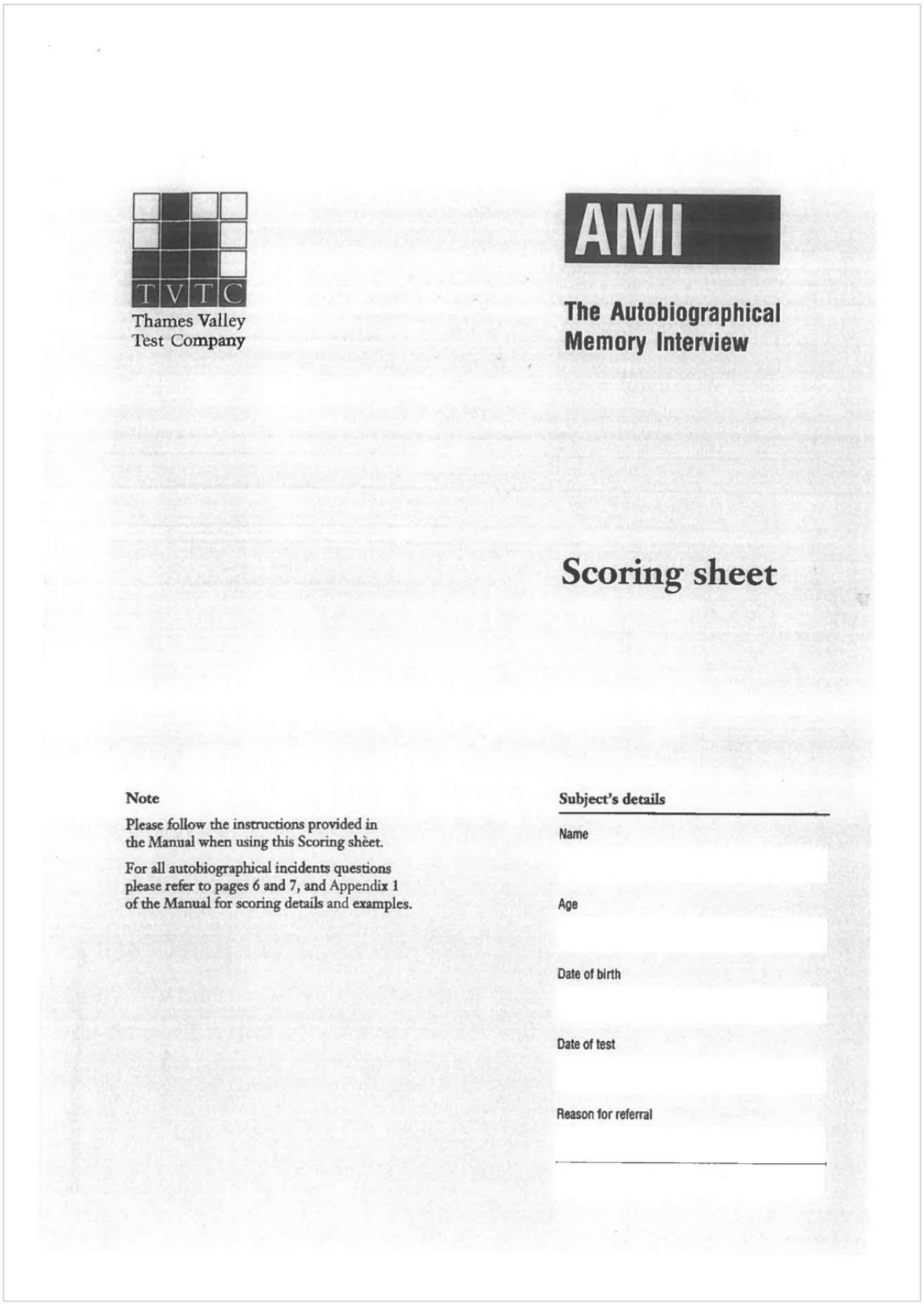
Memory
[Score 0-3]

MEMORY

Name of the current Prime Minister……
Name of the woman who was Prime Minister ……
Name of the USA president……
Name of the USA president who was assassinated in the 1960s……

Memory
[Score 0 – 4]

Appendix 12 Kopelman Autobiographical Memory Interview



TVTC
Thames Valley
Test Company

AMI

The Autobiographical
Memory Interview

Scoring sheet

Note

Please follow the instructions provided in the Manual when using this Scoring sheet.

For all autobiographical incidents questions please refer to pages 6 and 7, and Appendix 1 of the Manual for scoring details and examples.

Subject's details

Name

Age

Date of birth

Date of test

Reason for referral

Question	Scoring details	Max score	Score

Section A: Childhood

Part 1: Period before school

1.1 Subject's address before going to school

Correct = 2
Street and town only = 1
Town or street only = ½

2

1.2 Names of three friends or neighbours from the period before the subject went to school

Each correct = 1
Each first name only = ½

3

Maximum = 5

Total

A1 Recall of an incident from the period before the subject went to school
(*Prompts:* 'Your first memory?', 'Involving a brother or sister?')

3

Question	Scoring details	Max score	Score
Part 2: First school (i.e. 5–11 years)			
2.1 Name of first school	Correct = 1	1	
2.2 Location of this school	Town or city = 1	1	
2.3 Subject's age when starting at this school	Correct =1	1	
2.4 Subject's address when starting at this school	Correct = 2 Street *and* town only = 1 Town *or* street only = ½	2	
2.5 Names of three teachers or friends from this school (*Prompts:* 'The headteacher?', 'Your form teacher?', 'A friend?')	Each correct name = 1 Each first name only = ½	3	
	Maximum = 8	**Total**	
A2 Recall of an incident occurring while at primary school (age 5–11 years) (*Prompts:* 'Involving a teacher?', 'Involving a friend?')		3	

Question	Scoring details	Max score	Score
Part 2: First school (i.e. 5–11 years)			
2.1 Name of first school	Correct = 1	1	
2.2 Location of this school	Town or city = 1	1	
2.3 Subject's age when starting at this school	Correct =1	1	
2.4 Subject's address when starting at this school	Correct = 2 Street *and* town only = 1 Town *or* street only = ½	2	
2.5 Names of three teachers or friends from this school (*Prompts:* 'The headteacher?', 'Your form teacher?', 'A friend?')	Each correct name = 1 Each first name only = ½	3	
	Maximum = 8	**Total**	
A2 Recall of an incident occurring while at primary school (age 5–11 years) (*Prompts:* 'Involving a teacher?', 'Involving a friend?')		3	

Question	Scoring details	Max score	Score

Part 3: Main secondary or high school (i.e. 11–18 years)

3.1 Name of secondary (or high) school

Correct = 1 — Max score: 1

3.2 Location of this secondary (or high) school

Town or city = 1 — Max score: 1

3.3 Number and level of examinations obtained at secondary school

Correct number and level of qualifications = 1
Level only = ½ — Max score: 1

American users: Year of graduation or year of leaving high school

Correct year = 1

3.4 Subject's address whilst attending secondary (or high) school

Correct = 2
Street and town only = 1
Town or street only = ½ — Max score: 2

3.5 Names of three teachers or friends from secondary (or high) school
(*Prompts:* 'The headteacher?', 'Your form teacher?', 'A friend?')

Each correct name = 1
Each first name only = ½ — Max score: 3

Maximum = 8 — **Total**

A3 Recall of an incident while at secondary (or high) school (age 11–18 years)
(*Prompts:* 'Involving a teacher?', 'Involving a friend?')

Max score: 3

Childhood section summary	Personal semantic		Autobiographical incidents	
Part 1: Period before school	Maximum = 5		Maximum = 3	
Part 2: First school	Maximum = 8		Maximum = 3	
Part 3: Main secondary (or high) school	Maximum = 8		Maximum = 3	
	Maximum total = 21		**Maximum total = 9**	

Question	Scoring details	Max score	Score

Section B: Early adult life

Part 4: Career

4.1 Qualification(s) obtained after leaving school

Correct recall of qualifications or stating 'No qualifications' = 1
'Don't know' or inaccurate response = 0 — Max score: 1

4.2 **Either** If qualification(s) obtained: name of course and educational institution

Course

Institution

Name of course = 1
Name of institution = 1 — Max score: 2

Or If no qualifications obtained: first job

Correct = 1

and name of firm or organisation

Correct = 1

4.3 Subject's address while obtaining qualification(s) or in first job

Correct = 2
Street and town only = 1
Town or street only = ½ — Max score: 2

4.4 Names of three friends or colleagues from this period
(*Prompts:* 'The Principal' *or* 'The boss?', 'The tutor' *or* 'Your foreman?', 'Any class-mates' *or* 'Any work-mates?')

Each correct name = 1
Each first name only = ½ — Max score: 3

Maximum total = 8 — **Total**

A4 Recall of an incident from college or the first job
(*Prompts:* 'Your first day at work or college?', 'An incident with a friend?')

Max score: 3

Question	Scoring details	Max score	Score

Part 5: Wedding

5.1 **Either** if married in the late teens, twenties or early thirties:
date when subject was married

Correct = 1
Year only = ½
2

and place where this marriage was held

Town or city = 1

Or if not married in this time period:
name of someone else whose marriage the subject attended

Correct = 1

and place where this marriage was held

Town or city = 1

5.2 Subject's address before this wedding

Correct = 2
Street and town only = 1
Town or street only = ½
2

5.3 Subject's address after this wedding

Correct = 2
Street and town only = 1
Town or street only = ½
2

5.4 Name of best-man from this wedding (or any guest)

Correct name = 1
First name only = ½
1

5.5 Name of bridesmaid from this wedding (or a guest)

Correct name = 1
First name only = ½
1

5.6 Bride's (or own) maiden name (or a guest)

Correct name = 1
First name only = ½
1

Maximum total = 9
Total

A5 Recall of an incident from this wedding
(*Prompts:* 'An incident involving a guest at the wedding?', 'An incident at the reception?')

3

Question	Scoring details	Max score	Score
Part 6: Children and meeting someone new in the subject's twenties			
6.1 Name of subject's first child (or a nephew, niece or child of a close friend)	Correct = 1	1	
6.2 Date of birth of this child (or age of a nephew, niece or child of a close friend)	Correct year = ½	½	
6.3 Place of birth of this child	Town or city = ½	½	
6.4 Name of subject's second child (or another nephew, niece or child of a close friend)	Correct = 1	1	
6.5 Date of birth of this child (or age of a nephew, niece or child of a close friend)	Correct year = ½	½	
6.6 Place of birth of this child	Town or city = ½	½	
	Maximum total = 4	**Total**	
A6 Recall of a first encounter with someone while the subject was in his or her twenties (*Prompts:* 'Meeting someone in an interview?', 'Meeting someone on holiday or at work?')		3	

Early adult life section summary	Personal semantic		Autobiographical incidents	
Part 4: Career	Maximum = 8		Maximum = 3	
Part 5: Wedding	Maximum = 9		Maximum = 3	
Part 6: Children and meeting someone new	Maximum = 4		Maximum = 3	
	Maximum total = 21		**Maximum total = 9**	

Question	Scoring details	Max score	Score

Section C: Recent life

Part 7: Present hospital or institution

7.1 Name of hospital or place where seen	Correct = 1	1	
7.2 Location of this hospital or institution	Town or city = 1	1	
7.3 Date of arrival at this hospital or institution	Month or year = 1	1	
7.4 Subject's current address	Correct = 2 Street and town only = 1 Town or street only = ½	2	
7.5 Names of three staff members or fellow patients from this hospital or institution (or three current neighbours or colleagues)	Each correct name = 1 Each first name only = ½	3	
	Maximum total = 8	**Total**	

A7 Recall of an incident which has occurred at this hospital or institution (*Prompts:* 'Involving the other patients?', 'To do with the doctors or nurses?' *or two other appropriate prompts e.g.:* 'Involving the warden?', 'Involving the daily care staff?', 'Involving the social worker?', 'Involving the psychologist?') — 3

Question	Scoring details	Max score	Score

Part 8: Previous hospital or institution

8.1 Name of previous hospital or institution, or name of last hospital visited (which must be from the last 5 years)

Correct = 1 | 1 |

8.2 Location of this hospital or institution

Town or city = 1 | 1 |

8.3 Date of arrival (or visit) at this hospital or institution

Month or year = 1 | 1 |

8.4 Subject's address when attending (or visiting) this hospital or institution

Correct = 2
Street and town only = 1
Town or street only = ½ | 2 |

8.5 Names of three friends, colleagues or acquaintances connected with this hospitalisation (or three people who have visited in the last year)

Each correct name = 1
Each first name only = ½ | 3 |

Maximum total = 8 | **Total** |

A8 Recall of an incident involving a relative or visitor in the last year
(*Prompts:* 'A visit by or to a relative?', 'Involving some news about a relative?')

| 3 |

Question	Scoring details	Max score	Score

Part 9: Last Christmas or Thanksgiving

9.1 Place where subject spent last Christmas or Thanksgiving

Correct = 1 | 1 | [ ]

9.2 Name of a person with whom subject spent last Christmas or Thanksgiving

Correct name = 1
First name only = ½ | 1 | [ ]

Maximum total = 2 | **Total** | [ ]

Part 10: Holiday or journey

10.1 Place where subject visited on a holiday or a journey in the last year (or holiday or journey within the last 5 years)

Correct = 1 | 1 | [ ]

10.2 Month (or year) in which this holiday or journey took place

Month or year = 1 | 1 | [ ]

10.3 Name of a person with whom the subject went on this holiday or journey

Correct name = 1
First name only = ½ | 1 | [ ]

Maximum total = 3 | **Total** | [ ]

A9 Recall of an incident which took place while on any holiday or journey within the last 5 years (*Prompts:* 'At the place you visited?, 'Involving someone you met?')

3 | [ ]

Recent life section summary	Personal semantic		Autobiographical incidents	
Part 7: Present hospital or institution	Maximum = 8	[ ]	Maximum = 3	[ ]
Part 8: Previous hospital or institution	Maximum = 8	[ ]	Maximum = 3	[ ]
Part 9: Last Christmas or Thanksgiving	Maximum = 2	[ ]		
Part 10: Holiday or journey	Maximum = 3	[ ]	Maximum = 3	[ ]
	Maximum total = 21	[ ]	**Maximum total = 9**	[ ]

Appendix 13 Childhood and Recent Traumatic Events Questionnaire

Childhood Traumatic Events Scale

For the following questions, answer each item that is relevant. Be as honest as you can. Each question refers to any event that you may have experienced **prior to the age of 17**.

1. Prior to the age of 17, did you experience a death of a very close friend or family member?_____ If yes, how old were you?_____

   If yes, how traumatic was this? (using a 7-point scale, where 1 = not at all traumatic, 4 = somewhat traumatic, 7 = extremely traumatic)_____

   If yes, how much did you confide in others about this traumatic experience at the time? (1 = not at all, 7 = a great deal)_____

2. Prior to the age of 17, was there a major upheaval between your parents (such as divorce, separation)?_____ If yes, how old were you?_____

   If yes, how traumatic was this? (where 7 = extremely traumatic)_____

   If yes, how much did you confide in others? (7 = a great deal)_____

3. Prior to the age of 17, did you have a traumatic sexual experience (raped, molested, etc.)?_____ If yes, how old were you?_____

   If yes, how traumatic was this? (7 = extremely traumatic)_____

   If yes, how much did you confide in others? (7 = a great deal)_____

4. Prior to the age of 17, were you the victim of violence (child abuse, mugged or assaulted -- other than sexual)?_____ If yes, how old were you?_____

   If yes, how traumatic was this? (7 = extremely traumatic)_____

   If yes, how much did you confide in others? (7 = a great deal)_____

5. Prior to the age of 17, were you extremely ill or injured?_____ If yes, how old were you?_____

   If yes, how traumatic was this? (7 = extremely traumatic)_____

   If yes, how much did you confide in others? (7 = a great deal)_____

6. Prior to the age of 17, did you experience any other major upheaval that you think may have shaped your life or personality significantly?_____ If yes, how old were you?_____

   If yes, what was the event?_____

   If yes, how traumatic was this? (7 = extremely traumatic)_____

   If yes, how much did you confide in others? (7 = a great deal)_____

Recent Traumatic Events Scale

For the following questions, again answer each item that is relevant and again be as honest as you can. Each question refers to any event that you may have experienced **within the last 3 years**.

1. Within the last 3 years, did you experience a death of a very close friend or family member? _____

   If yes, how traumatic was this? (1 = not at all traumatic, 7 = extremely traumatic)_____

   If yes, how much did you confide in others about the experience at the time? (1 = not at all, 7 = a great deal)_____

2. Within the last 3 years, was there a major upheaval between you and your spouse (such as divorce, separation)?_____

   If yes, how traumatic was this?_____

   If yes, how much did you confide in others?_____

3. Within the last 3 years, did you have a traumatic sexual experience (raped, molested, etc.)?_____

   If yes, how traumatic was this?_____

   If yes, how much did you confide in others?_____

4. Within the last 3 years, were you the victim of violence (other than sexual)?_____

   If yes, how traumatic was this?_____

   If yes, how much did you confide in others?_____

5. Within the last 3 years, were you extremely ill or injured?_____

   If yes, how traumatic was this?_____

   If yes, how much did you confide in others?_____

6. Within the last 3 years, has there been a major change in the kind of work you do (e.g., a new job, promotion, demotion, lateral transfer)?_____

   If yes, how traumatic was this?_____

   If yes, how much did you confide in others?_____

7. Within the last 3 years, did you experience any other major upheaval that you think may have shaped your life or personality significantly?_____

   If yes, what was the event?_____

   If yes, how traumatic was this?_____

   If yes, how much did you confide in others?_____

Appendix 14 Standardised Assessment of Personality – Abbreviated Version

KEEP WELL

SAPAS-SR

THE SELF-REPORTED STANDARDIZED ASSESSMENT OF PERSONALITY-ABBREVIATED SCALE: PRELIMINARY RESULTS OF A BRIEF SCREENING TEST FOR PERSONALITY DISORDERS

Sara Germans, Guus L. Van Heck, Paul Moran and Paul P. G. Hodiamont

Name of Researcher: _____ **Participant Protocol No:** _____
Date: DD / MM / YY **Visit No:** _____

Table 2: Factor loadings for principal component extraction (pattern matrix) and oblimin rotation on the Self-Report Standardized Assessment for Personality-abbreviated Scale

Item	*yes* (= 1)	*no* (= 0)	F_1	F_2	F_3
1 In general, do you have difficulty making and keeping friends?	□	□	**0.79**	-0.05	-0.09
2 Would you normally describe yourself as a loner?	□	□	**0.72**	0.02	0.07
4 Do you normally lose your temper easily?	□	□	0.30	**0.64**	0.03
5 Are you normally an impulsive sort of person?	□	□	-0.33	**0.67**	-0.16
3 In general, do you trust other people?	□	□	0.44	**0.51**	0.06
8 In general, are you a perfectionist?	□	□	-0.08	-0.13	**0.71**
7 in general, do you depend on others a lot?	□	□	0.17	-0.10	**0.66**
6 Are you normally a worrier?	□	□	0.15	0.41	**0.62**

Note: Factor loadings $> \pm 0.30$ are presented in bold.
Factor loadings of factors belonging to each of the three factors presented in bold.

Appendix 15 Young Mania Rating Scale (mood item)

Young Mania Rating Scale (YMRS)

Name of Researcher:	_____	**Participant Protocol No:**	_____
Date:	DD / MM / YY	**Time:**	: AM/PM
Time point:	-60/+20/+240		

Item 1: Elevated Mood

0 Absent
1 Mildly or possibly increased on questioning
2 Definite subjective elevation: optimistic, self-confident; cheerful; appropriate to content
3 Elevated, inappropriate to content; humorous
4 Euphoric, inappropriate laughter singing

Appendix 16 Patient-rated Inventory of Side Effects

5896525651

STAR ★D PRISE

For office use only:

☐ Spanish ☐ By phone ☐ Ad hoc visit

☐ update **PRS**

Level

Week in level

Patient ID _____ Date ___/___/____ (MM DD YYYY)

Please indicate all symptoms you have experienced in the past week. These symptoms may or may not have been caused by your treatment.

1. GASTROINTESTINAL

1.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Diarrhea
- ☐ Constipation
- ☐ Dry mouth
- ☐ Nausea/vomiting
- ☐ No symptoms in this category

1.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

2. HEART

2.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Palpitation (skipping a beat)
- ☐ Dizziness on standing
- ☐ Chest pain
- ☐ No symptoms in this category

2.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

3. SKIN

3.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Rash
- ☐ Increased perspiration
- ☐ Itching
- ☐ Dry skin
- ☐ No symptoms in this category

3.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

4. NERVOUS SYSTEM

4.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Headache
- ☐ Tremors
- ☐ Poor coordination
- ☐ Dizziness
- ☐ No symptoms in this category

4.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

5. EYES/EARS

5.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Blurred vision
- ☐ Ringing in ears
- ☐ No symptoms in this category

5.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

6. GENITAL/URINARY

6.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Difficulty urinating
- ☐ Painful urination
- ☐ Frequent urination
- ☐ Menstrual irregularity
- ☐ No symptoms in this category

6.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

CRC ID _____

9932525656

STAR ★ D PRISE

☐ update **PRS**

Patient ID ___ ___ ___ ___ ___ ___ ___ ___ ___ Date ___ / ___ / ___ ___ ___ ___

Level ___ ___

Week in level ___ ___

7. SLEEP

7.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Difficulty sleeping
- ☐ Sleeping too much
- ☐ No symptoms in this category

7.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

8. SEXUAL FUNCTIONING

8.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Loss of sexual desire
- ☐ Trouble achieving orgasm
- ☐ Trouble with erections
- ☐ No symptoms in this category

8.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

9. OTHER

9.1 Check **ALL** symptoms that you have experienced during the past week regardless of cause:

- ☐ Anxiety
- ☐ Fatigue
- ☐ Poor concentration
- ☐ Decreased energy
- ☐ General malaise
- ☐ Other _____
- ☐ Restlessness
- ☐ No symptoms in this category

9.2 If you had any symptoms over the last week, how bad was your WORST symptom?

- ☐ Tolerable
- ☐ Distressing

Appendix 17 Clinician-administered Dissociative States Scale

KEEP WELL

The Clinician Administered Dissociative States Scale (CADSS)

J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Name of Researcher:		**Participant Protocol No:**	
Date:	DD / MM / YY	**Time:**	: AM/PM
Time point:			

Subjective Items:

1.	**Do things seem to be moving in slow motion?**
0	Not at all.
1	Mild, things seem slightly slowed down, but not very noticeable.
2	Moderate, things are moving about twice as slow as normally.
3	Severe, things are moving so slowly that they are barely moving.
4	Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2.	**Do things seem to be unreal to you, as if you are in a dream?**
0	Not at all.
1	Mild, things seem a little unreal, but I'm well aware of where I'm at.
2	Moderate, things seem dreamlike, although I know I am awake.
3	Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
4	Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3.	**Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?**
0	Not at all.
1	Mild, I feel a little bit separated from what is happening, but I am basically here.
2	Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
3	Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
4	Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.
4.	**Do you feel as if you are looking at things from outside of your body?**
0	Not at all.
1	Mild, I feel somewhat disconnected from myself, but I am basically all together.
2	Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
3	Severe, I feel like I am twenty feet or more away from my body, looking down from above.
4	Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.

KEEP WELL

5.	**Do you feel as if you are watching the situation as an observer or a spectator?**
0	Not at all.
1	Mild, I feel slightly detached from what is going on, but I am basically here.
2	Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
3	Severe, I feel very much as if I am an observer or a spectator, but I am still here in this room.
4	Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.
6.	**Do you feel disconnected from your own body?**
0	Not at all.
1	Mild, I feel a little bit disconnected from myself, but I am basically all here.
2	Moderate, I feel somewhat detached from my own body, but I am basically all together.
3	Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
4	Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.
7.	**Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?**
0	Not at all.
1	Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
2	Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
3	Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
4	Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.
8.	**Do people seem motionless, dead, or mechanical?**
0	Not at all.
1	Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
2	Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
3	Severe, people seem to be barely moving, or barely alive, or very mechanical.
4	Extreme, it's as if everyone were frozen or completely like machines.
9.	**Do objects look different than you would expect?**
0	Not at all.
1	Mild, things seem slightly different than normal, although it is barely perceptible.
2	Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
3	Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
4	Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.
10.	**Do colours seem to be diminished in intensity?**
0	Not at all.
1	Mild, things seem slightly paler than usual if I think about it.
2	Moderate, colours are somewhat diminished, but still recognizable.
3	Severe, colours are extremely pale, in no way as vivid as they usually are.
4	Extreme, as if everything is in black and white, or all the colours have been washed out.

KEEP WELL

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?	
0	Not at all.
1	Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
2	Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
3	Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
4	Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.
12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?	
0	Not at all.
1	Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
2	Moderate, it seems as if this interview has gone on for at least two hours.
3	Severe, it seems as if at least ten hours have gone on since the start of the interview.
4	Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.
13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?	
0	Not at all.
1	Mild, things are happening slightly faster than normal.
2	Moderate, things seem to be happening at least twice as fast as normal.
3	Severe, things seem to be happening at least 10 times faster than normal.
4	Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.
14. Have there been things which have happened during this interview [assessment] that now you can't account for?	
0	Not at all.
1	Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
2	Moderate, at least once there were things which happened which now I can't account for.
3	Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
4	Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.
15. Have you spaced out, or in some other way lost track of what was going on during this experience?	
0	Not at all.
1	Mild, I have had some episodes of losing track of what is going on, but I have followed everything for the most part.
2	Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3	Severe, I have lost several segments of time of one minute or more.
4	Extreme, I have lost large segments of time of at least 15 minutes or more.

KEEP WELL

16. Have sounds almost disappeared or become much stronger than you would have expected?	
0	Not at all.
1	Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2	Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3	Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4	Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.
17. Do things seem very real, as if there is a special sense of clarity?	
0	Not at all.
1	Mild, things seem to be a little bit more real than normal.
2	Moderate, things seem to be more real than normal.
3	Severe, things seem to be very real or have a special sense of clarity.
4	Extreme, things seem to have an incredible sense of realness or clarity.
18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?	
0	Not at all.
1	Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2	Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3	Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4	Extreme, I cannot make anything out around me.
19. Do colours seem much brighter than you would have expected?	
0	Not at all.
1	Mild, colours seem a little bit brighter than normal, but not more than twice as bright.
2	Moderate, colours seem brighter, about twice as bright as normal.
3	Severe, colours seem very bright, at least five times as bright as normal.
4	Extreme, colours seem extremely bright, almost fluorescent, at least 10 times as bright as normal.
20. Do you feel confused about who you really are?	
0	Not at all.
1	Mild, I feel a little bit confused about who I am.
2	Moderate, I feel confused about who I am, but I basically know who I am.
3	Severe, I feel very confused about who I am, and at times I wonder if I am a person, or if I am many people.
4	Extreme, I feel as if there were two or more sides to myself.
21. Do you feel like there are different parts of yourself which do not fit together?	
0	Not at all.
1	Mild, I feel like there are different sides of myself, but they're basically part of myself.
2	Moderate, I feel like I have different parts which don't quite fit together.
3	Severe, there are two or more sides to myself which have unique characteristics.
4	Extreme, I have two or more parts to myself with unique personality characteristics.

KEEP WELL

22. Do you have gaps in your memory?
0 Not at all.
1 Mild, there are some recent things which I cannot remember.
2 Moderate, there have been a few gaps in my memory which lasted a few minutes.
3 Severe, there have been large gaps in my memory which lasted for more than a few minutes.
4 Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.
23. Do you feel like you have more than one identity?
0 Not at all.
1 Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
2 Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
3 Severe, I have two or more personalities, although they are not fully developed as distinct entities.
4 Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

Appendix 18 Brief Psychiatric Rating Scale (psychosis subscale)

KEEP WELL

Brief Psychiatric Rating Scale (BPRS)
Expanded Version (4.0)

Name of Researcher:	_____	**Participant Protocol No:**	_____
Date:	DD / MM / YY	**Time:**	: AM/PM
Time point:	_____		

9. SUSPICIOUSNESS
Expressed or apparent belief that other persons have acted maliciously or with discriminatory intent. Include persecution by supernatural or other non-human agencies (e.g., the devil). Note: ratings of 3 or above should also be rated under Unusual Thought Content.

2 **Very mild** Seems on guard. Reluctant to respond to some `personal' questions. Reports being overly self-conscious in public.

3 **Mild** Describes incidents in which others have harmed or wanted to harm him/her that sound plausible. Individual feels as if others are watching, laughing or criticising him/her in public, but this occurs only occasionally or rarely. Little or no preoccupation.

4 **Moderate** Says other persons are talking about him/her maliciously, have negative intentions or may harm him/her. Beyond the likelihood of plausibility, but not delusional. Incidents of suspected persecution occur occasionally (less than once per week) with some preoccupation.

5 **Moderately Severe** Same as 4, but incidents occur frequently, such as more than once per week. Individual is moderately preoccupied with ideas of persecution OR individual reports persecutory delusions expressed with much doubt (e.g., partial delusion).

6 **Severe** Delusional - speaks of Mafia plots, the FBI or others poisoning his/her food, persecution by supernatural forces.

7 **Extremely Severe** Same as 6, but the beliefs are bizarre or more preoccupying. Individual tends to disclose or act on persecutory delusions.

"Do you ever feel uncomfortable in public? Does it seem as though others are watching you? Are you concerned about anyone's intentions toward you? Is anyone going out of their way to give you a hard time, or trying to hurt you? Do you feel in any danger?"
[If individual reports any persecutory ideas/delusions, ask the following]: "How often have you been concerned that [use individual's description]? Have you told anyone about these experiences?"

10. HALLUCINATIONS
Reports of perceptual experiences in the absence of relevant external stimuli. When rating degree to which functioning is disrupted by hallucinations, include preoccupation with the content and experience of the hallucinations, as well as functioning disrupted by acting out on the hallucinatory content (e.g., engaging in deviant behaviour due to command hallucinations). Include thoughts aloud (`gedenkenlautwerden') or pseudohallucinations (e.g., hears a voice inside head) if a voice quality is present.

2 **Very mild** While resting or going to sleep, sees visions, smells odours or hears voices, sounds, or whispers in the absence of external stimulation, but no impairment in functioning.

3 **Mild** While in a clear state of consciousness, hears a voice calling the individual's name, experiences non-verbal auditory hallucinations (e.g., sounds or whispers), formless visual hallucinations or has sensory experiences in the presence of a modality relevant stimulus (e.g., visual illusions) infrequently (e.g., 1-2 times per week) and with no functional impairment.

KEEP WELL

4 **Moderate** Occasional verbal, visual, gustatory, olfactory or tactile hallucinations with no functional impairment OR non-verbal auditory hallucinations/visual illusions more than infrequently or with impairment.

5 **Moderately Severe** Experiences daily hallucinations OR some areas of functioning are disrupted by hallucinations.

6 **Severe** Experiences verbal or visual hallucinations several times a day OR many areas of functioning are disrupted by these hallucinations.

7 **Extremely Severe** Persistent verbal or visual hallucinations throughout the day OR most areas of functioning are disrupted by these hallucinations. "Do you ever seem to hear your name being called?"

"Have you heard any sounds or people talking to you or about you when there has been nobody around?
[If hears voices]:
"What does the voice/voices say? Did it have a voice quality?"
"Do you ever have visions or see things that others do not see? What about smell odours that others do not smell?"
[If the individual reports hallucinations, ask the following]:
"Have these experiences interfered with your ability to perform your usual activities/work? How do you explain them? How often do they occur?"

11. UNUSUAL THOUGHT CONTENT

Unusual, odd, strange, or bizarre thought content. Rate the degree of unusualness, not the degree of disorganisation of speech. Delusions are patently absurd, clearly false or bizarre ideas that are expressed with full conviction. Consider the individual to have full conviction if he/she has acted as though the delusional belief was true. Ideas of reference/persecution can be differentiated from delusions in that ideas are expressed with much doubt and contain more elements of reality. Include thought insertion, withdrawal and broadcast. Include grandiose, somatic and persecutory delusions even if rated elsewhere. Note: if Somatic Concern, Guilt, Suspiciousness or Grandiosity are rated 6 or 7 due to delusions, then Unusual Thought Content must be rated 4 or above.

2 **Very mild** Ideas of reference (people may stare or may laugh at him), ideas of persecution (people may mistreat him). Unusual beliefs in psychic powers, spirits, UFOs, or unrealistic beliefs in one's own abilities. Not strongly held. Some doubt.

3 **Mild** Same as 2, but degree of reality distortion is more severe as indicated by highly unusual ideas or greater conviction. Content may be typical of delusions (even bizarre), but without full conviction. The delusion does not seem to have fully formed, but is considered as one possible explanation for an unusual experience.

4 **Moderate** Delusion present but no preoccupation or functional impairment. May be an encapsulated delusion or a firmly endorsed absurd belief about past delusional circumstances.

5 **Moderately Severe** Full delusion(s) present with some preoccupation OR some areas of functioning disrupted by delusional thinking.

6 **Severe** Full delusion(s) present with much preoccupation OR many areas of functioning are disrupted by delusional thinking.

7 **Extremely Severe** Full delusion(s) present with almost total preoccupation OR most areas of functioning disrupted by delusional thinking.

"Have you been receiving any special messages from people or from the way things are arranged around you? Have you seen any references to yourself on TV or in the newspapers?"
"Can anyone read your mind?"
"Do you have a special relationship with God?"
"Is anything like electricity, X-rays, or radio waves affecting you?"
"Are thoughts put into your head that are not your own?"
"Have you felt that you were under the control of another person or force?"
[If individual reports any odd ideas/delusions, ask the following]:

"How often do you think about [use individual's description]?"
"Have you told anyone about these experiences? How do you explain the things that have been happening [specify]?"
Rate items 12 on the basis of individual's self-report and observed behaviour.

KEEP WELL

12. BIZARRE BEHAVIOUR

Reports of behaviours which are odd, unusual, or psychotically criminal. Not limited to interview period. Include inappropriate sexual behaviour and inappropriate affect.

2 **Very mild** Slightly odd or eccentric public behaviour, e.g., occasionally giggles to self, fails to make appropriate eye contact, that does not seem to attract the attention of others OR unusual behaviour conducted in private, e.g., innocuous rituals, that would not attract the attention of others.

3 **Mild** Noticeably peculiar public behaviour, e.g., inappropriately loud talking, makes inappropriate eye contact, OR private behaviour that occasionally, but not always, attracts the attention of others, e.g., hoards food, conducts unusual rituals, wears gloves indoors.

4 **Moderate** Clearly bizarre behaviour that attracts or would attract (if done privately) the attention or concern of others, but with no corrective intervention necessary. Behaviour occurs occasionally, e.g., fixated staring into space for several minutes, talks back to voices once, inappropriate giggling/laughter on 1-2 occasions, talking loudly to self.

5 **Moderately Severe** Clearly bizarre behaviour that attracts or would attract (if done privately) the attention of others or the authorities, e.g., fixated staring in a socially disruptive way, frequent inappropriate giggling/laughter, occasionally responds to voices, or eats non-foods.

6 **Severe** Bizarre behaviour that attracts attention of others and intervention by authorities, e.g., directing traffic, public nudity, staring into space for long periods, carrying on a conversation with hallucinations, frequent inappropriate giggling/laughter.

7 **Extremely Severe** Serious crimes committed in a bizarre way that attract the attention of others and the control of authorities, e.g., sets fires and stares at flames OR almost constant bizarre behaviour, e.g., inappropriate giggling/laughter, responds only to hallucinations and cannot be engaged in interaction.

"Have you done anything that has attracted the attention of others?"
"Have you done anything that could have gotten you into trouble with the police?"
"Have you done anything that seemed unusual or disturbing to others?"

Appendix 19 Case Report Form contents for KEEP-WELL Trial participants

Case Report Form contents and structure for KEEP-WELL pilot trial participants

Case Report Form: Visit	Item
Screening Visit:	Monitoring Phase eligibility checklist and decision point
	CRF Checklist
MONITORING PHASE	
Recruitment visit:	Signed consent form
	Recruitment visit checklist
	Demographic and Clinical Data Sheet
	Structured Interview for Diagnosis - DSM IV
	Hamilton Rating Scale for Depression24 (HRSD-24)
	Standardised Assessment of Personality, abbreviated (SAPAS)
	Childhood and Recent Traumatic Events Questionnaire (CTREQ)
	Maudsley Staging Method for Treatment Resistance in Depression (MSMTRD)
	Verbal Fluency: letter and category
	Verbal Learning (modified ACE-III)
	Trail-Making Test A; Trail-Making Test B
	Digit Span: forward and backward
	Standardised Mini Mental State Exam (sMMSE)
	National Adult Reading Test
	Edinburgh Handedness Questionnaire
	Autobiographical Memory Interview (AMI): Transcript (copy 1)
	AMI Independent scoring 1 (copy 2)
	AMI Independent scoring 2 (copy 3)
	Sticker sheet for Monitoring Phase
	Monitoring Phase HRSD-24 results graph for clinical notes
Weekly, Weeks 1-6	HRSD-24
	Complete graph in clinical notes
	Complete sticker for clinical notes
Post ECT visit:	HRSD -24
	Verbal Learning (modified ACE-III)
	Verbal Fluency: letter and category
	Digit Spans
	Trail-Making Test A; Trail-Making Test B
	sMMSE
	AMI Transcript
	AMI Independent scoring 1
	AMI Independent scoring 2
	Eligibility Checklist for Treatment Phase and reaffirmed consent
TREATMENT PHASE	
Infusion Clinics 1-4	Infusion clinic arrival checklist: fasting, consent, driving
	Anaesthetist blinded checklist, Anaesthetist unblinded checklist
	Phlebotomy checklist
	HRSD-24 -60
	Patient Rated Inventory of Side Effects PRISE -60
	Young Mania Rating Scale YMRS -60
	Clinician Administered Dissociative States Scale CADSS -60

Case Report Form contents and structure for KEEP-WELL pilot trial participants

	Brief Psychiatric Rating Scale BPRS -60
	Physical Health Monitoring Sheet
	PRISE +20 mins
	CADSS +20 mins
	YMRS +20 mins
	BPRS +20 mins
	HRSD +240 mins
	PRISE +240 mins
	YMRS +240 mins
	CADSS +240 mins
	BPRS +240 mins
	HRSD-11 +240 mins
	Clinic departure checklist and participant sign out
	24-hour post clinic checklist
Infusion clinic 4: additional	sMMSE
	Verbal Fluency: letter and category
	Verbal learning : modified ACE III
	Trail-Making Test A; Trail-Making Test B
	AMI Transcript
	AMI Independent scoring 1
	AMI Independent scoring 2
	Digit Span: forward and backward
	24 hour post clinic Checklist
FOLLOW UP PHASE	
Follow-up weeks 6, 8, 12, 20,	Relapse checklist
	HRSD-24
Final follow-up week 26	Relapse checklist
	HRSD-24
	Verbal Fluency: letter and category
	sMMSE
	Verbal learning
	Trail-Making Test A; Trail-Making Test B
	Digit Span: forward and backward
	AMI Transcript
	AMI Independent scoring 1
	AMI Independent scoring 2
	Check all items on CRF checklist

Appendix 20 Pharmacy Dispensing and Return Protocol for the KEEP-WELL Trial

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

St Patrick's
Mental Health Services
Empowering recovery

Pharmacy Dispensing and Return Protocol: Investigational Medicinal Products

Ketamine for depression relapse prevention following ECT:

a randomised pilot trial (The KEEP WELL Study)

Version 2.0

Date: 09.1.17

Investigational Medicinal Products (IMP):

Ketamine - Ketalar 10mg/ml x 20ml Solution for Injection/Infusion

Midazolam - Hypnovel 10mg/5ml solution for injection

1. Dr Enda Shanahan to check randomisation list (independently prepared at CSTAR and kept in locked cabinet in ECT suite) on Tuesday (one day prior to ketamine clinic)
2. Request completed in MDA book by Dr Shanahan for each named-patient infusion – ketamine or midazolam
3. MDA book delivered to pharmacy on Tuesday by Dr Shanahan
4. Dispensing record completed on a named patient basis by Pharmacy Department
5. Ketamine or Midazolam vials delivered to out-of-hours room by Pharmacist on Tuesday
6. Dr Shanahan to collect prescribed medications from out-of-hours room on Wednesday morning prior to Ketamine Clinic
7. Infusions prepared in ECT treatment room, labelled "Trial Infusion". Only Dr Shanahan present in treatment room during this time.
8. Infusions administered in ECT recovery area with monitoring as per Trial Protocol
9. Dr Shanahan to complete "Infusion Checklist" during trial infusion preparation and administration e.g. drug date checked, name of patient checked etc. This contains **blinded information only** and can be stored in the Case Report File.
10. "IMP Administration Record" - for **unblinded staff only**, to be completed by Dr Shanahan and securely stored with MDA book and dispensing/return check and randomisation list. These are stored in a locked cupboard in the ECT department for the purposes of access by clinical staff in the event of an emergency, in order to check which IMP was administered.
11. Following clinic, ketamine and midazolam vials returned to pharmacy by Dr Shanahan for safe disposal. In the pharmacy department, "IMP Administration Record" checklist of infusion dose, date and person completed by Dr Shanahan double-checked with Pharmacist
12. IMP Return record kept by Pharmacy Department

Appendix 21 Patient Participant Information Leaflet

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

St Patrick's
Mental Health Services

Participant Information Sheet

Using ketamine to prevent relapse of severe depression in people who have had electroconvulsive therapy

"Ketamine for depression relapse prevention following ECT: a randomised pilot trial with blood biomarker evaluation"

Study Site: St Patrick's University Hospital, St James' St, Dublin 8 and Trinity College Dublin

Registration number (EudraCT): 2014-004262-14

Principal Investigator: Professor Declan McLoughlin

Telephone: 01 2493385

Email: d.mcloughlin@tcd.ie

You are being invited to take part in a study. Before you decide, it is important for you to understand why the study is being done and what it will involve. This Participant Information Sheet will tell you about the purpose, risks and benefits of this study. If you agree to take part, we will ask you to sign a Consent Form. If there is anything you are unclear about, we are happy to explain it to you. Please take as much time as you need to read this. You should only consent to take part in this study when you feel that you understand what is being asked of you, and you have had enough time to make your decision. Thank you for reading this.

Purpose of the Study

Electroconvulsive therapy (ECT) is a safe, effective treatment for severe depression. About 500 people have this treatment per year in Ireland. Unfortunately some people who recover from depression by having ECT, quickly become unwell again, even while taking antidepressants. There is an urgent need to find better treatments to prevent relapse. One possibility is the commonly used anaesthetic drug ketamine. Unlike other antidepressants which may take weeks to have effect, ketamine has been shown to have a strong, rapid antidepressant effect at low doses.

The **purpose** of this study is to examine whether repeated low doses of ketamine are better than a placebo drug at preventing relapse of depression after ECT. We will also study the **biology of depression** by comparing proteins in the blood, called **"biomarkers"**, between people who have severe depression and are having ECT, and people who are healthy. We will look at some specific messenger chemicals involved in depression, and other chemicals that help maintain healthy genes, to see if these are changed by depression and treatment. This is

important because we do not yet know exactly how ECT treats depression. Ketamine is known to have effects on substances involved in **"neuroplasticity",** the process of change in pathways between our brain cells. We will examine these neuroplasticity biomarkers in blood tests of people having ketamine and people having the placebo drug to try to better understand how ketamine has an antidepressant effect.

Why have I been chosen?

You have been asked to participate as you have been referred for ECT for treatment of depression. We will also be inviting volunteers who do not have depression to take part as a control group. In total, we hope to have over 150 people taking part in this study, but only 20 of these will receive the drug ketamine.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this Information Sheet to keep and a copy of your Consent Form**. If you decide to take part, you can withdraw at any time without giving a reason.** A decision to withdraw or not take part will not affect your rights or treatment in any way.

What will happen if I decide to take part?

If you are about to start ECT treatment – If you decide to take part, you will be asked to complete a full interview with a trained researcher before you start treatment and at the end of your course of treatment, and shorter interviews every week while you are having ECT. You will also be asked to provide **blood tests** on two occasions.

We hope that you will feel much improved after your ECT treatment. In this case you may be invited to take part in the **second part** of the study. If you decide to take part in Phase II, you will be asked to complete a full interview before you go home from hospital. If you are happy to go ahead and there is no reason why you should not have the additional treatment, a computer programme will allocate you at random to one of two groups – a group having four infusions of low-dose ketamine (the drug we are studying) or low-dose midazolam (a placebo drug). Neither you nor the researchers will know which group you are in. However, the doctor who gives you the medication infusion will know which drug you are getting. **You will continue to take your other medications as usual.**

You will have four 40-minute intravenous infusions of either ketamine or midazolam. The first infusion will take place within a week of the end of your ECT treatment. Each infusion will be one week apart. We will monitor your vital signs (heart rate, blood pressure etc.) and ask you questions regularly before, during and after each infusion, to monitor for side effects. During the first infusion, you will be asked to have four blood tests for biomarkers which might help us understand how ketamine has an antidepressant effect. For the other three sessions, you can travel from home. In total you will be at the hospital for approximately four hours each time. We will pay for your travel expenses and meals on these occasions. After the four sessions are over, you will be asked to complete follow-up interviews five times over six months.

We will make every effort to minimise any inconvenience to you and to run the study to high scientific standards. The blood samples you give will be examined by research scientists at our laboratory in Trinity College Dublin. These staff will only know the identity of your blood

sample by a code number and the key to this code and any personal information will be kept confidentially by Professor Declan McLoughlin at St. Patrick's Hospital, Dublin.

How long will my part in the study last?

If you are taking part as a person undergoing ECT, the first part of the study will involve two full interviews and several shorter ones, and will take five hours of your time in total. If you decide to also take part in the second phase of the study, this will involve fifteen separate interviews spread out over between seven and eight months. You can withdraw from the study at any time.

What do I have to do?

If you are having medication infusions in the second part of the study, it is recommended that you **do not drive or drink alcohol for 24 hours** after each of the four infusions. It is also important that you have a responsible adult who can stay with you for 24 hours after your medication infusions. Aside from these times, you can do everything as normal.

If you are a woman, **it is important that you do not get pregnant** while having the infusions. We cannot say for certain that the medication is safe for the unborn child. Pregnant women must therefore not take part in the study, and women who do take part are required to ensure they use adequate contraception during the study. Women aged 18-50 who take part in the second phase of the study may be asked to have a pregnancy test. Any woman who finds that she is pregnant while taking part in the study should immediately tell her research doctor. Men who take part are asked to share this information with their partner and ensure they are using adequate contraception during the study.

What is the medication being tested?

Ketamine is an anaesthetic medication, commonly used in children's surgery or for pain relief. It works by blocking the effect of glutamate, one of the major chemical messenger systems in the brain. This is different to the ways current antidepressants work. At high doses ketamine can cause a "high", and so it has been abused as a recreational drug. At low doses it is very safe. In this study we will use lower doses than those used to put people to sleep. The placebo drug, midazolam, is a sedative drug similar to ketamine.

What are the possible benefits of taking part?

Taking part in the study will not benefit you directly, but everyone who decides to participate will contribute to scientific knowledge about depression. Some people may benefit from learning more about their memory or mental health during the interviews. People who go on to take part in the second part of the study may benefit from having the additional treatment; however there is no guarantee of this. The individual results of the tests for biomarkers will not be available to you, and we will not be performing genetic screening in this study. We can send you a copy of the six-monthly newsletter about the progress of the study if you would like.

What are the possible disadvantages or risks of taking part?

The study includes a questionnaire about your mental health and memory. You could find you would like to talk to someone about any issues it raises, we would be happy to recommend someone to you. Other possible risks are those associated with having a blood sample

taken. This is a routine and safe procedure and you will probably already have experience of blood tests. Occasionally, minor bruising around the site from which the blood was drawn may occur, but this will quickly disappear. Very rarely, the site may become infected, but this is easily treated. A possible disadvantage to you is the time it takes to be interviewed, completing questionnaires and assessments. To minimise any discomfort, multiple breaks can be taken.

If you are having ECT you will have spoken to your doctor about the risks of the treatment, we would be happy to go over these again with you. If you decide to also take part in the second part of the study, there are other things to be aware of.

Many people find the effects of ketamine to be unpleasant. However, there are no reports of persistent side effects of ketamine at the dose used in this study, although many people experience some symptoms during the infusions and for up to one or two hours afterwards. We will therefore monitor your mental and physical health constantly during the infusions and for over three hours afterwards. The commonest of these transient symptoms during ketamine infusions are: changes in mood or anxiety, unusual sensations such as feeling outside one's body, feeling intoxicated or confused, and unusual perceptions. There are also reports of transient physical symptoms such as dizziness, headache, double vision, nausea and raised blood pressure. Some people experience memory difficulties during the infusions, but as with all the above symptoms, this resolves within two hours of the infusion. Ketamine is not addictive at the dose used in this study.

The placebo drug midazolam also acts as a sedative, and people may experience drowsiness, dizziness and poor concentration during this infusion. In some people midazolam can cause slowing of the heart and breathing rate and a decrease in blood pressure. Some people may find this type of medication makes them feel restless or anxious, and nausea, headache and blurred vision have also been reported. Symptoms such as these rarely persist beyond the infusion.

You will receive a phone number so you can always get in touch with one of our researchers if you have any concerns.

What happens at the end of the study?

The results of the study will be presented at conferences and published in scientific journals. The identity of people who have taken part will always be kept confidential. Your confidential information will be stored securely for at least five years and will be destroyed after no more than ten years in accordance with the data protection legislation at the time. As ketamine is not a routine treatment there will not be ongoing access to ketamine treatment after the study finishes.

Thank you for reading this information sheet.

If you are interested in taking part, please contact:

Prof. Declan McLoughlin

Dept of Psychiatry, Trinity College Dublin,

St Patrick's University Hospital

01 2493385 | thekeepwellstudy@gmail.com

Appendix 22 Control Participant Information Leaflet

St Patrick's Mental Health Services

TRINITY COLLEGE DUBLIN

Participant Information Sheet

Using ketamine to prevent relapse of severe depression in people who have had electroconvulsive therapy

The KEEP-WELL Study

"Ketamine for depression relapse prevention following ECT: a randomised pilot trial with blood biomarker evaluation"

Study Site: St Patrick's University Hospital, St James' St, Dublin 8 and Trinity College Dublin

Principal Investigator: Professor Declan McLoughlin

Telephone: 01 2493385

Email: d.mcloughlin@tcd.ie

You are being invited to take part in a study. Before you decide, it is important for you to understand why the study is being done and what it will involve. This Participant Information Sheet will tell you about the purpose, risks and benefits of this study. If you agree to take part, we will ask you to sign a Consent Form. If there is anything you are unclear about, we are happy to explain it to you. Please take as much time as you need to read this. You should only consent to take part in this study when you feel that you understand what is being asked of you, and you have had enough time to make your decision. Thank you for reading this.

Purpose of the Study

Depression is a major public health problem in Ireland. Electroconvulsive therapy (ECT) is a safe, effective treatment for severe depression. About 500 people have this treatment per year in Ireland. We would like to study the **biology of depression** by comparing proteins in the blood, called **"biomarkers",** between people who have severe depression and are having ECT, and people who are healthy. We will look at some specific messenger chemicals involved in depression, and other chemicals that help maintain healthy genes, to see if these are changed by depression and treatment. This is important because we do not yet know exactly how ECT treats depression.

Unfortunately some people, who recover from depression by having ECT, quickly become unwell again, even while taking antidepressants. There is an urgent need to find better treatments to prevent relapse. One possibility is the commonly used anaesthetic drug ketamine. Unlike other antidepressants which may take weeks to have effect, ketamine has been shown to

have a strong, rapid antidepressant effect at low doses. This study is part of a wider study in which we will examine whether repeated low doses of the commonly used anaesthetic drug, ketamine are better than a placebo drug at preventing relapse of depression after ECT.

Why have I been chosen?

You have been asked to participate as a healthy volunteer, i.e. you are not suffering from depression. It is important to have a "control group" of healthy people so we can compare the test results of people who have depression, with results of people who do not have depression.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this Information Sheet to keep and a copy of your Consent Form**. If you decide to take part, you can withdraw at any time without giving a reason.** A decision to withdraw or not take part will not affect your rights or treatment in any way.

What will happen if I decide to take part?

If you decide to take part as a healthy volunteer in our control group, you will be asked to complete two interviews with a trained researcher and blood tests on two occasions. Part of the interviews will involve mental health questionnaires and memory tests. The blood samples will be used to compare the levels of certain proteins in people who are depressed vs. those who are not depressed.

Other people who take part in this study may be having treatment for depression at the moment, and we will be performing the same tests and interviews with them, with some extra measures. We would be happy to tell you more about this if you would like.

We will make every effort to minimise any inconvenience to you and to run the study to high scientific standards. The blood samples you give will be examined by research scientists at our laboratory in Trinity College Dublin. These staff will only know the identity of your blood sample by a code number and the key to this code and any personal information will be kept confidentially by Professor Declan McLoughlin at St. Patrick's Hospital, Dublin.

How long will my part in the study last?

The study will take four hours of your time in total. This will be in the form of two two-hour interviews four weeks apart. You can withdraw from the study at any time.

What do I have to do?

There are no specific recommendations for taking part in this study as a healthy volunteer, apart from scheduling two interview sessions with you.

What are the possible benefits of taking part?

Taking part in the study will not benefit you directly, but everyone who decides to participate will contribute to scientific knowledge about depression. Some people may benefit from learning more about their memory or mental health during the interviews. The individual results of the tests for biomarkers will not be available to you, and we will not be performing

genetic screening in this study. We can send you a copy of the six-monthly newsletter about the progress of the study if you would like.

What are the possible disadvantages or risks of taking part?

The study includes a questionnaire about your mental health and memory. You could find you would like to talk to someone about any issues it raises, we would be happy to recommend someone to you. Other possible risks are those associated with having a blood sample taken. This is a routine and safe procedure and you will probably already have experience of blood tests. Occasionally, minor bruising around the site from which the blood was drawn may occur, but this will quickly disappear. Very rarely, the site may become infected, but this is easily treated. A possible disadvantage to you is the time it takes to be interviewed, completing questionnaires and assessments. To minimise any discomfort, multiple breaks can be taken.

You will receive a phone number so you can always get in touch with one of our researchers if you have any concerns.

What happens at the end of the study?

The results of the study will be presented at conferences and published in scientific journals. The identity of people who have taken part will always be kept confidential. Your confidential information will be stored securely for at least five years and will be destroyed after no more than ten years in accordance with the data protection legislation at the time.

Thank you for reading this information sheet.

If you are interested in taking part, please contact:

Prof. Declan McLoughlin

Dept of Psychiatry, Trinity College Dublin,

St Patrick's University Hospital

01 2493385

d.mcloughlin@tcd.ie

Appendix 23 Ethical Approval, REC of St James's and Tallaght Hospitals

SJH/AMNCH Research Ethics Committee Secretariat
Ursula Ryan Ph: 4142199
email: Ursula.Ryan1@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Professor Declan McLoughlin
St. Patrick's Mental Health Services
Department of Psychiatry & Trinity College Institute of Neuroscience
Trinity College Dublin
St. Patrick's University Hospital
James's Street
Dublin 8

19th August 2014

RE: Ketamine for Relapse Prevention Following Electroconvulsive Therapy – A Randomised Pilot Trial with Blood Biomarker Evaluation.

REC Reference: 2014-08-Chairman's Action (19) *(Please quote REC reference and EudraCT number on all correspondence)*

Dear Professor McLoughlin,

The SJH/AMNCH Research Ethics Committee decided to give ethical approval to this proposed study. Full ethical approval is now in place for this study.

Yours sincerely

Ms. Ursula Ryan
Secretary
SJH/AMNCH Research Ethics Committee

Appendix 24 Ethical Approval, REC of St Patrick's Mental Health Services

www.stpatrickshosp.ie

St Patrick's
Mental Health Services

PRIVATE & CONFIDENTIAL

October 13th, 2014

Dr Martha Finnegan
Research Registrar
St Patrick's Mental Health Services

Re: KEtamine for dEPression relapse prevention folloWing ELectronconvuLsive therapy: a randomised pilot trial with blood biomarker evaluation (The KEEP WELL Trial)
(Protocol 05/14)

Dear Dr Finnegan,

Your application was considered at the Research Ethics Committee (REC) meeting held on **September 30th, 2014**, in the Conference Room at St Patrick's University Hospital. Please accept our apologies for the delay in communicating the outcome of this review to you.

Your application was granted full ethical approval by the following committee members who were in attendance at this meeting:

Very Revd Dermot Dunne (Chair)	Prof. Jim Lucey
Mr Terence Coghlan	Ms Marie Therese Mulholland
Dr Frank Doyle	Dr Bré Sullivan
Dr Adam Kavanagh	Ms Marie Tuohy

Approval was granted subject to the following standard conditions:

1. You must adhere fully to the terms and conditions set out in your research protocol.
2. All persons involved in this research who are not employees of St Patrick's Mental Health Services are required to obtain an honorary contract from the hospital. This process should be initiated by your study supervisor. It will be your responsibility to ensure that these contracts are renewed and kept up-to-date as necessary throughout the duration of your study.
3. If there are any material changes to be made to Protocol 05/14 in the next 12 months, you must contact the Research Ethics Committee for approval.
4. You must report back to the Research Ethics Committee no later than 12 months subsequent to this approval letter (October 13th, 2015), with a summary report on the progress of this research. This report can be downloaded from the hospital website. Failure to complete this report may result in ethical approval being withdrawn for your research.
5. The committee encourages all researchers to publish the results of their study once it is completed, whether these appear to be positive or negative.
6. Please complete the attached form and send it via email to regionallibrary@hse.ie. The Directorate of Clinical and Quality Care in the HSE have requested that details of all research projects in Ireland be pooled together in one location, namely, www.lenus.ie, for the purpose of promoting a culture of research and in order to deliver evidence based clinical care. The HSE hope to gain a complete picture of the

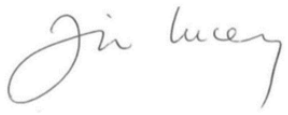
quality and quantity of healthcare and healthcare-related research in Ireland, and St. Patrick's Mental Health Services have agreed to cooperate with this process. This repository of research activity is managed by Health Librarians based in Dr Steevens' Hospital, and we thank you in advance for emailing this relatively simple form to them at your convenience.

In addition, the committee requested that the principal investigator comment on the following issues:

- Is the number of participants in this study realistic?
- Does this population have the capacity to consent? The committee are particularly interested in getting Prof. McLoughlin's comments on what constitutes valid consent.
- The timeframe of 16 months to complete all aspects of the study appears to be tight and a longer timeframe would seem reasonable.

Please can you respond to these queries **on or before October 31st, 2014**.

We wish you well in your research. With very best wishes.
Yours sincerely,



JAMES V. LUCEY MD., Ph.D., FRCPI., FRCPsych.
Secretary to the Research Ethics Committee | Medical Director
Medical Council 00646

Encl.

cc. *Prof. Declan McLoughlin, Principal Investigator and SPMHS Study Supervisor*

Appendix 25 Clinical Trial Approval, Health Products Regulatory Authority

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

23rd January 2015

St Patrick's University Hospital,
James's Street,
Dublin 8.

European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004

Re: CT Number: CT 900/559/1 - Ketamine
Case number: 2155175
EudraCT number: 2014-004262-14
Protocol number: SPMHSREC Reference 05/14
Title of trial: Ketamine for depression relapse prevention following ECT: a randomised pilot trial with blood biomarker evaluation (The KEEP WELL Study)

Dear Sir/Madam,

The Health Products Regulatory Authority has considered the application dated 23rd November 2014 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.

In accordance with Article 11 of Directive 2001/20/EC, confirmation of the authorisation of a clinical trial is mandatory for the updating of EudraCT, the EU database for clinical trials, and will be made public. Therefore, the Health Products Regulatory Authority requires that you provide the following information for this clinical trial as soon as it is available:

- Name of the responsible ethics committee
- Ethics committee opinion (favourable, not favourable, withdrawal)
- Date of the ethics committee opinion

If any changes are made to the EudraCT application form, you are reminded to provide the latest version of the XML file to the Health Products Regulatory Authority for uploading to the EudraCT database. If in future, the XML file is updated as a result of a non-substantial amendment please

An tÚdarás Rialála Táirgí Sláinte, Teach Kevin O'Malley, Ionad Phort an Iarla, Ardán Phort an Iarla, Baile Átha Cliath 2, Éire
Health Products Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland
T: +353 1 676 4971 • F: +353 1 676 7836 • info@hpra.ie • www.hpra.ie

submit the revised version of the XML file with the documentation for the next substantial amendment application.

Yours sincerely,

Sinead Murphy

Digitally signed by Sinead Murphy
DN: cn=Sinead Murphy, o=Health Products Regulatory Authority, ou=Business Process Co-Ordination Unit, email=sinead.murphy@hpra.ie, c=IE
Date: 2015.01.23 15:26:35 Z

A person authorised in that behalf
by the Board of the said Authority

Appendix 26 Publication: Clinical Trial Protocol for the KEEP-WELL Trial

Finnegan *et al. Pilot and Feasibility Studies* (2016) 2:38
DOI 10.1186/s40814-016-0080-0

Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

Ketamine for depression relapse prevention following electroconvulsive therapy: protocol for a randomised pilot trial (the KEEP-WELL trial)

Martha Finnegan[1], Karen Ryan[2], Enda Shanahan[1], Andrew Harkin[3], Leslie Daly[4] and Declan M. McLoughlin[1*]

Abstract

Background: Major depressive disorder is a common debilitating illness that is the second leading contributor to the global burden of disease. Unfortunately, about 30 % of patients do not respond to adequate trials of antidepressants and/or psychotherapies. About 45–60 % of such treatment-resistant patients will remit with electroconvulsive therapy (ECT). However, relapse rates are high following ECT—38 % after 6 months. There is a need for better relapse prevention strategies. One possibility is to use ketamine, a competitive glutamate receptor antagonist used for anaesthesia. A recent paradigm shift in treating depression and understanding its biology has been the finding that ketamine has a robust, rapid-onset, though short-lived, antidepressant effect that is possibly mediated through neuroplastic effects. However, ketamine has not previously been reported on for relapse prevention.

Methods/design: The main objective of this study is to conduct a randomised controlled pilot trial ($n = 40$) of a 4-week course of once-weekly ketamine infusions for relapse prevention following ECT for depression to assess trial procedures that will inform a future definitive trial. Participants with unipolar depression will be recruited prior to commencing ECT and be assessed weekly during the ECT course using the primary clinical outcome, the 24-item Hamilton Rating Scale for Depression (HRSD-24). Those who meet standard response criteria will be invited, on completing ECT, to be randomised in a 1:1 ratio to a course of four once-weekly infusions of ketamine or an active comparator midazolam, which mimics some of the effects of ketamine and may improve blinding over inactive placebo. Participants will be followed up over 6 months using the HRSD-24 to assess for relapse.

Discussion: This is the first registered trial (NCT02414932, https://clinicaltrials.gov/ct2/show/NCT02414932) of ketamine for depression relapse prevention, an important possible use of this agent. The primary focus of the pilot trial is on feasibility. However, a 95 % confidence interval will be determined for the difference between ketamine and midazolam groups in 6-month relapse rates to help inform a future definitive trial.

Trial registration: https://clinicaltrials.gov/ NCT02414932
Secondary Identifying numbers:
EudraCT number: 2014-000339-18
Sponsors' Reference, Sponsor: St. Patrick's Mental Health Services: 05/14
Research Ethics Committee Reference, Joint REC of St James' and Tallaght Hospitals, Dublin: 2014-08-19

Keywords: Depression, Relapse prevention, Ketamine, Electroconvulsive therapy, Pilot trial

* Correspondence: d.mcloughlin@tcd.ie
[1]Department of Psychiatry and Trinity College Institute of Neuroscience, St. Patrick's University Hospital, James' St., Dublin 8, Ireland
Full list of author information is available at the end of the article

Background

Depression, ECT and relapse

Major depressive disorder (MDD) is a debilitating mental illness with a lifetime prevalence of 12–20 % [1]. It is the most costly brain disorder in Europe, accounting for 1 % (€118 billion annually) of the total European economy [2]. Indeed, depression is currently the second largest cause globally for years lived with disability [3].

About 30 % of patients do not respond to antidepressants even after multiple trials with/without psychotherapies [4]. However, electroconvulsive therapy (ECT) offers up to 60 % of such treatment-resistant patients to complete remission [5–7]. ECT is a medically safe procedure and is more acutely effective than psychotherapy or antidepressants for severe, often treatment-resistant, depression [5]. The major concerns are cognitive side effects, but for most people, these are transient and many cognitive functions improve [8]. Treatments involve passing small electrical charges through the brain to induce a seizure lasting ~30 s under anaesthesia with a muscle relaxant. Six to 12 treatments are typically administered in a course, two to three times weekly [9]. Worldwide, 1.4 million people receive ECT annually, including nearly 260 people in Ireland [10].

In a recent meta-analysis, we found that taking antidepressants following successful ECT halves the risk for relapse (risk ratio = 0.49, $p < 0.0001$, NNT = 3.3) at 6 months from nearly 80 % [11], but mean relapse rates remain high: 27.1 % after 3 months and 37.7 % after 6 months [11]. Even continuation ECT (C-ECT), albeit mostly at non-adjustable fixed schedules, does not seem to improve 6-month relapse rates (37.2 %). Notably, these relapse rates are similar to those for patients who respond only after ≥3 antidepressant steps and most likely reflect the recurrent nature of treatment-resistant depression [4].

A major challenge now is how best to prevent relapse after successful treatment of depression with ECT. However, remarkably, the evidence base for relapse prevention in depression following any successful treatment is small. For example, the National Institute for Health and Care Excellence (NICE) in the UK have identified that evidence on relapse prevention in depression is limited and recommended research in this area. [12] To date, the reported randomised controlled trials for relapse prevention following successful antidepressant therapy have focused on the effect of 12 months' tricyclic or SSRI antidepressant therapy, showing consistent but limited reduction in relapse rates [13]. As discussed in our review [11], there have been very few randomised, controlled trials focusing on relapse prevention after ECT. One study investigated the use of nortriptyline or nortriptyline and lithium for relapse prevention following successful ECT for depression [14]. Nortriptyline-lithium combination therapy had a marked advantage in time to relapse, superior to both placebo and nortriptyline alone. Other studies have focused on fixed-schedule continuation ECT, which has a relapse prevention effect in well-chosen groups [15].

Ketamine as an antidepressant

Ketamine is a competitive glutamate *N*-methyl-D-aspartate receptor (NMDAR) antagonist with a half-life of 2–3 h. Ketamine has a remarkably rapid antidepressant effect, targeting core symptoms, in treatment-resistant depression when given as single sub-anaesthetic doses, usually a 40-min 0.5 mg/kg intravenous infusion [14]. Thereafter, robust antidepressant effects (~70 % responder rates) occur within 2–4 h and persist for a few days, i.e. beyond immediate NMDAR blockade [14]. These findings have led to the most exciting development in treating and understanding depression in over 50 years and represent a paradigm shift away from conventional slow-acting monaminergic antidepressants. Preclinical studies have shown that within just 2 h, ketamine increases synaptogenesis and spine formation in rodent prefrontal cortex and rapidly reverses chronic stress-induced depressive behaviours and prefrontal neuronal atrophy [15]. These effects are mediated, at least in part, via Akt/GSK-3/mammalian target of rapamycin (mTOR) signalling and increased dendritic translation of synaptic proteins [16], as well as deactivation of eukaryotic elongation factor 2 (eEF2) kinase, resulting in de-suppression of brain-derived neurotrophic factor (BDNF) translation [17]. BDNF mediates synaptic plasticity and is implicated in mechanisms of antidepressants and ECT [18]. Changes in blood mononuclear cell levels of phosphorylated mTOR, eEF2 and GSK-3beta have also been associated with response to ketamine [19], suggesting potential as biomarkers for response.

Ketamine is psychotomimetic, but at low dosage, it is safe, with patients and healthy controls occasionally experiencing mild dissociative and psychotic symptoms that resolve soon after finishing infusions [16–18]. To control for these effects, and also avoid "carry-over" effects in crossover studies while improving blinding, midazolam, at the sub-anaesthetic dose of 0.045 mg/kg, has been used as a control in parallel-group design trials rather than inactive placebo saline [19]. Ketamine can be a drug of abuse and chronic high-dose abuse can cause uropathy and dependency. However, repeated (e.g. 2–3/week for 2 weeks) infusions of sub-anaesthetic ketamine are safe with more sustained antidepressant effects [20, 21]. Two recent reviews of trials of ketamine for use as an antidepressant showed the most commonly used dosage is a 40-min infusion of 0.5 mg/kg [16, 22]. Bioavailability of ketamine is highest when administered intravenously [23]. In sub-anaesthetic doses, ketamine is a medically safe drug but can cause transient rises in

pulse and blood pressure during infusion and for up to 80 min afterward. However, a recent review of ketamine in depression concluded that outside recreational usage, there have been no reports of persistent adverse effects with sub-anaesthetic uses of ketamine [24].

The effect of ketamine on cognition is unclear and has only been studied in acute treatment of depression [25]. There may be changes in visual and working memory [26] and an association between baseline neurocognitive performance and response to ketamine [27]. Optimum dosing and deliver of ketamine has not been established [25]. Ketamine has been used for ECT anaesthesia and is associated with earlier improvement and possibly fewer cognitive side effects but no overall better response [16, 20, 22, 28]. There have been insufficient studies of intramuscular, oral or intranasal ketamine for depression to currently warrant studying these preparations for relapse prevention [21]. While the half-life of ketamine is 3 h, in previous studies, the antidepressant effect was maintained for up to 2 weeks [29]. No trials have yet been reported, or registered, for using ketamine as an adjunctive treatment to reduce relapse rates following successful depression treatment—a potential use of ketamine that this trial will explore.

Methods/design

Study objective

The primary objective is to conduct a randomised, controlled, patient- and rater-blinded pilot study of ketamine vs. an active comparator (midazolam) for 4 weeks following successful ECT, to assess trial process to inform a future definitive trial.

Secondary objective

To calculate a 95 % confidence interval for an unadjusted hazard ratio that will allow interpretation of statistical difference between ketamine and midazolam groups to assess ketamine for reducing 6-month relapse rates following successful ECT.

Overview

This randomised, controlled pilot trial will take place over 30 months. The study will have an open recruitment phase (phase I) followed by a randomised treatment phase (phase II). We will initially recruit patients with unipolar major depressive disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [30]) referred for ECT, who will be assessed weekly to identify those eligible to take part in the randomised controlled pilot trial in phase II. Participants who are successfully treated with ECT (phase 1) and continue to meet inclusion criteria will be randomly allocated in a 1:1 ratio to a 4-week course of either once-weekly ketamine at 0.5 mg/kg or the active comparator midazolam at 0.045 mg/kg (phase 2). The trial will take place under "real world" conditions with both groups continuing usual care (e.g. regular medications, psychological and other therapies and out-patient review) during the randomised treatment phase and thereafter. Participants will be followed up over 6 months following ECT to identify if and when relapse occurs.

Site

This single-site study will take place in St. Patrick's University Hospital, Dublin, an independent-sector 250-bed university teaching hospital that provides a national mental health service. About one third of all ECT in Ireland is administered at the centre [7, 31].

Research ethics approval

Approval for this pilot trial was obtained from the joint authorised Research Ethics Committee of St. James' and Tallaght Hospitals, Dublin. Site approval was also obtained from the relevant committee at St. Patrick's University Hospital. Authorisation for the clinical trial was obtained from the Health Products Regulatory Authority of Ireland, the relevant body under the European framework for clinical trials, EudraCT (2014-000339-18). The study will be conducted in accordance with the principles that have their origin in the Declaration of Helsinki [32], in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation [33] (ICH), and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC. The trial has been registered at clinicaltrials.gov (NCT02414932).

Recruitment

In line with recommendations for pilot studies [34], a formal sample size calculation has not been performed. Twenty participants is an acceptable total number for the purposes of a pilot trial. For this pilot trial, we aim to recruit up to 20 patients per group, a total of 40. Response rates to ECT are 40–60 % [5], so at least 66 patients need to be initially recruited. Allowing for a 15 % drop-out rate, we will therefore seek to recruit 78 patients. We expect to recruit 78 participants within 16 months, 47 of whom will meet response criteria following ECT [5], and that 40 of these will additionally consent to be randomised and participate in the pilot trial.

Consent

Written informed consent will be obtained by members of the research team using the study-specific consent form (Additional file 1). Potential participants will be provided with an information leaflet and letter of invitation (Additional file 1) and verbal information at the first point of contact with a member of the research team.

Eligibility criteria

Participants will be current inpatients in university teaching hospitals in St. Patrick's Mental Health Services, who have a diagnosis of unipolar MDD and are referred for ECT. Participants may be male or female, aged ≥18 years, and from a variety of geographical (within Ireland) and socioeconomic backgrounds. Participants will not have any medical condition that would preclude treatment with ECT or ketamine/midazolam.

To be eligible for inclusion in phase 1, each participant must meet each of the following criteria at screening and must continue to fulfil these criteria at baseline.

1. Subjects must be able and willing to give written informed consent and comply with the requirements of this study protocol.
2. Diagnosed with unipolar major depressive disorder (DSM-IV), have a 24-item Hamilton Rating Scale for Depression (HRSD-24) of ≥21 and be referred for ECT.
3. Female subjects of child-bearing potential and male subjects whose partner is of child-bearing potential must be willing to ensure that they or their partner use effective contraception during the randomised treatment phase (phase II) and for 5 weeks thereafter.

Subjects are excluded from the study if any of the following criteria are met at screening:

1. Allergy/sensitivity to study medications or their ingredients.
2. Subjects who have participated in another study and received any other investigational agent within 6 months.
3. Any condition rendering patient medically unfit for ECT; general anaesthesia; ketamine or midazolam—assessed by physical examination, routine haematology and biochemistry investigations prior to enrolment.
4. Medications that may significantly alter the pharmacokinetics of ketamine (e.g. ketoconazole, clarithromycin) are contraindicated during the trial, and participants taking any of these medications at screening will be excluded from the trial.
5. Subjects who have a history of drug or alcohol use that, in the opinion of the investigator, would interfere with adherence to study requirements.
6. Known history of, or documented positive hepatitis B or C or HIV infection, advanced malignancy or terminal illness.
7. Scheduled for non-trial procedures requiring general anaesthesia during the study.
8. Active suicidal intention.
9. Dementia, intellectual disability or a score on the standardised Mini Mental State Examination (sMMSE) of <24.
10. Lifetime history of bipolar affective disorder.
11. Current history of post-traumatic stress disorder.
12. Other axis I diagnosis (DSM-IV).
13. ECT in the 6 months prior to recruitment.
14. Currently a prisoner or residing in a nursing home.

For inclusion in the randomised controlled trial (phase 2), following successful ECT, patients must additionally have:

1. Received a significant course of ECT (i.e. at least five sessions)
2. Achieved at least response criteria (i.e. ≥60 % decrease from baseline HRSD-24 score and score ≤16 on two consecutive weekly ratings)
3. Have a nominated adult who can stay with them for 24-h on out-patient treatment days
4. sMMSE [35] score of ≥24

Assessments

The primary clinical outcome measure is the relapse rate at 6 months as measured using the objectively rated HRSD-24 [36]. To enter the study, patients must score ≥21. Subjective mood ratings will be also measured using the Quick Inventory of Depressive Symptoms, self-report version (QIDS-SR) [37]. Baseline assessment will also include diagnosis and treatment history: diagnosis of major depressive disorder will be confirmed using the mood episodes module of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) [38]. The Maudsley Staging Method for Treatment Resistant Depression (MSTRD) [39] will be used to provide a measure of treatment-resistance. Handedness will be recorded with the Edinburgh Handedness Questionnaire (EHQ) [40]. The National Adult Reading Test (NART) [41] will measure premorbid intelligence.

Additional baseline data from patient interview and case-note review will include age, sex, weight, height, occupation, educational attainment, duration of index depressive episode, number of previous depressive episodes, previous ECT, history of medical illness and surgical treatments, personal and family history of alcohol/substance dependency, presence of psychotic symptoms (detected by SCID) and current medications and other therapies. Changes in medications will be documented at follow-up interviews (Table 1, schedule of events).

Participants will be assessed weekly during ECT using the HRSD-24 and QIDS-SR. Response to ECT is defined as achieving ≥60 % decrease from baseline HRSD-24 and score ≤16 on two consecutive weekly ratings. Remission criteria are ≥60 % decrease in HRSD from baseline

Table 1 Schedule of enrolment, assessments and interventions

Assessment	Phase 1: ECT patients and healthy controls			Phase 2: ECT responders randomised to ketamine or midazolam			
	Baseline (pre-ECT)	Weekly during ECT course	End of ECT course	Pre-infusions	Infusions 1–4; weeks 1–4	Follow-ups: weeks 6, 8, 12 and 20	Final follow-up week 26
Diagnosis and treatment							
Background, SCID, NART, CTQ	✓						
Treatment review	✓		✓		✓ (1–4)	✓ (6–20)	✓
Clinical outcomes							
HDRS-24	✓	✓	✓		✓✓✓✓ (1–4)	✓ (6–20)	✓
QIDS-SR	✓	✓	✓		✓✓✓✓ (1–4)	✓ (6–20)	✓
Cognitive outcomes							
ACE-R	✓		✓		✓4th		✓
Digit spans	✓		✓		✓4th		✓
Trails A + B	✓		✓		✓4th		✓
sMMSE	✓		✓		✓4th		✓
AMI	✓		✓		✓4th		✓
Ketamine effects							
CADSS					✓✓✓✓ (1–4)		
BPRS					✓✓✓✓ (1–4)		
YMRS					✓✓✓✓ (1–4)		
PRISE					✓✓✓✓ (1–4)		
Consent							
Signed consent	✓			✓			
Verbal assent	✓	✓	✓		✓✓✓✓ (1–4)	✓ (6–20)	✓
Eligibility							
Eligibility check	✓	✓	✓	✓	✓✓✓✓ (1–4)	✓ (6–20)	✓
Randomisation							
Allocation				✓			

and score ≤10 on two consecutive weekly ratings. Those identified as being ECT responders will be invited to participate in the two-group parallel-design randomised controlled pilot trial. The advantages of randomisation and blinding in this group will also be used to perform studies of peripheral blood biomarkers as potential predictors of response to ketamine (Additional file 2). During infusion sessions in the randomised treatment phase, HRSD-24 scores will be obtained 60 min before the infusion begins and at +120 and +240 min afterwards. Baseline scores on sleep and appetite items will be maintained for repeated measures within 1 day. The +240 min HRSD-24 scores will serve as the weekly post-ECT scores up to follow-up week 4.

Ketamine psychotomimetic effects and adverse events will be assessed using the following instruments before, during (+35–40 min) and after (+240 min) infusions of ketamine or midazolam:

- Clinician-Administered Dissociative States Scale (CADSS) [42]
- Brief Psychiatric Rating Scale (BPRS; four-item positive symptom subscale) [43]
- Young Mania Rating Scale (YMRS; mood item) [44]
- Patient-Rated Inventory of Side Effects (PRISE) [45]

Participants will be followed up for 6 months following ECT with repeated questionnaires comprising treatment review plus HRSD-24 and QIDS-SR at weeks 6, 8, 12 and 20 post-ECT. Criteria for relapse are ≥10 point increase in HRSD-24 compared to baseline phase 2 score plus HRSD ≥16; in addition, increase in the HRSD should be maintained 1 week later (if indicated, additional follow-ups will be arranged). Hospital admission, further ECT and deliberate self-harm/suicide also constitute relapse. Timing of these events will be recorded. A final follow-up session in week 26 will comprise HRSD-24, QIDS-SR and cognitive outcomes.

There are no published data on effects of ketamine on cognition in ECT responders. We will use the following battery pre- and post-ECT course, after the fourth infusion and at 6 -month follow-up. The post-ECT assessment will

serve as baseline for the randomised pilot trial. Where appropriate, parallel versions will be used to reduce practice effects. Global cognition will be assessed with the sMMSE [35]. Immediate short-term memory, attention and working memory will be measured using Forward and Backward Digit Spans [46]. Motor and psychomotor speed will be assessed using the Trail Making Test (part A) [46]. Frontal-executive function will be rated by Trail Making Test (part B) [46] plus letter and category verbal fluencies [47]. Anterograde verbal memory will be tested using the verbal learning component of the Addenbrooke's Cognitive Examination III (delayed and immediate recall of a seven-item address) [48]. Retrograde amnesia for autobiographical information will be measured using the Kopelman Autobiographical Memory Interview (K-AMI) [49].

Interventions

Participants in phase I will receive ECT and usual care and will be monitored weekly using the HRSD-24 for response. ECT will be administered twice-weekly with hand-held electrodes according to Royal College of Psychiatrists' guidelines and as previously described [7, 50]. Briefly, the Mecta 5000 M device (Mecta Corporation, USA) will be used and seizure duration measured by EEG monitoring. Methohexitone (0.75–1.0 mg/kg) will be used for anaesthesia with suxamethonium (0.5–1.0 mg/kg) as muscle relaxant. Brief-pulse (1.0-ms pulse width; current amplitude 800 mA) ECT will be administered twice weekly (Mecta 5000 M device, Mecta Corp., Portland, Ore.; maximum 1200 mC), using methohexitone (0.75–1.0 mg/kg) anaesthesia and succinylcholine (0.5–1.0 mg/kg) for muscle relaxation (16, 22). Seizure threshold (ST) will be established by a method of limits, as previously described [7], at the first session, and subsequent treatments will be given at 1.5 × ST for BL ECT and 6.0 × ST for RUL ECT. Stimulus charge will be titrated upward as required during treatment courses following a standard stimulus dosing protocol. To reflect routine clinical practice, number of ECT treatments will be determined by referring physicians who will be blind to randomisation. ECT characteristics will be recorded.

Participants who have successfully responded to ECT in phase I and meet inclusion criteria to continue to the randomised controlled pilot trial in Phase II will be randomised (1:1) to receive four once-weekly infusions of either ketamine or midazolam. The regimen of four weekly infusions was chosen to facilitate subjects travelling for appointments and because ketamine has proven effects as a rapid-acting antidepressant but has not yet been studied as a series of infusions for relapse prevention. Patients and raters will be blind to treatment. The first infusion will be administered within 2 weeks of completing ECT and may be administered as an inpatient or outpatient; further infusions will take place as an outpatient. Each infusion will take 40 min, and monitoring will take place for 200 min post-commencement of infusion. Ketamine hydrochloride 10 mg/ml infusion at 0.5 mg/kg (Pfizer Healthcare Ireland) or midazolam hydrochloride (Hypnovel) 10 mg/5 ml solution at 0.045 mg/kg (Roche Products Ireland Ltd) will be made up as 50 ml colourless saline solutions and administered intravenously via an infusion pump. This dose and administration was chosen based on a previous randomised controlled trial of ketamine and midazolam in which these dosages were well-tolerated [51].

During each treatment session, participants will be monitored for heart rate, blood pressure, pulse oximetry and electrocardiogram changes. Adverse or psychotomimetic effects of either agent will be monitored using the CADSS, BPRS (four-item positive symptom subscale), YMRS (mood item) and the PRISE administered before, during and after infusions. Cognitive outcomes will be repeated in week 4. All other assessment measures will be repeated weekly, including treatment review, HRSD-24 and QIDS-SR.

Participants will be advised not to drive or operate heavy machinery for 24 h post-commencement of infusions and be provided with information on recent changes to the Road Traffic Act (Ireland) 2014, which includes provisions for roadside intoxication testing. Participants will be asked to ensure they have a nominated adult who can stay with them for 24 h on outpatient treatment days and will be contacted by a researcher 24 h after each session to enquire about side effects.

Treatment-as-usual will continue during the trial. Participants will continue to receive pharmacotherapy, psychotherapy or other therapeutic inputs as recommended by their treating team for the duration of the trial. There are no provisions for post-trial care or improving adherence due to the pilot trial design. Premature termination of the trial may take place in the event of new information regarding safety of investigative medicinal products becoming available, unsatisfactory progression of the trial, major breach of data confidentiality or if in the participants' best interests. Subjects have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason without any consequences. Subjects must discontinue the investigational medicinal product(s) and be withdrawn from the study for any of the following reasons:

- Withdrawal of consent by the subject
- Any medical condition that the investigator or sponsor determines may jeopardize the subject's safety if she or he continues receiving the study treatment
- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)

- An adverse event which requires discontinuation of the study medication
- Treatment failure and disease progression
- Lack of compliance with the study and/or study procedures (e.g. dosing instructions, study visits)
- Loss to follow-up—at least three documented attempts must be made to contact any subject lost to follow-up.

Outcomes

The focus of this study is on trial process with assessment of the primary clinical outcome being secondary. However, efficacy data will be collected in the course of the trial and will be reported as part of the study findings.

Process outcomes that will help to inform a future definitive ketamine relapse prevention trial include information on the following:

1. Recruitment methods and rate
2. Willingness of participants to be randomised
3. Willingness of participants to complete assessments
4. Randomisation
5. success of blinding of participants and raters
6. Ability to administer a course of four weekly ketamine infusions
7. Medical safety and acceptability of ketamine infusions in an ECT responder population
8. Rates of adverse dissociative and psychiatric events
9. Adherence to allocated treatment
10. Adherence to follow-up
11. Reasons for drop-out from treatment
12. Reasons for drop-out from follow-up
13. A 95 % confidence interval for the difference between the ketamine and midazolam groups in 6-month relapse rates to help inform a future definitive trial

The primary outcome relating to efficacy (the assessment of which is not a primary objective) is the relapse rate at 6 months as measured by HRSD-24. Subjective mood rating as measured by scores on QIDS-SR is a secondary efficacy outcome. The following safety evaluations will be performed during the study: adverse event monitoring, vital signs, cognitive and clinical assessments. Safety endpoints are:

(i) Tolerability of ketamine vs. midazolam in terms of cognitive outcomes
(ii) Tolerability of ketamine vs. midazolam in terms of psychotomimetic effects as measured by scores on CADSS, BPRS, YMRS and PRISE
(iii) Number of adverse effects in ketamine vs. midazolam groups

This trial has been designed and will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [52] (Fig. 1).

Allocation sequence generation and concealment

ECT responders will be randomised after post-ECT assessment. Subjects will be randomly assigned to one of

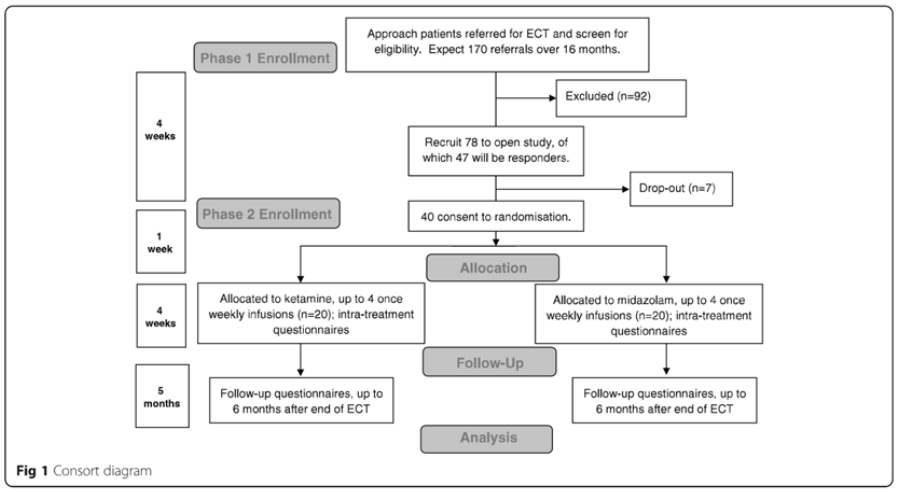


Fig 1 Consort diagram

two treatment groups in a 1:1 ratio. Computerised random allocation, using randomly permuted blocks, will be done independently by the Centre for Support and Training in Analysis and Research (CSTAR, University College Dublin, www.cstar.ie). Allocation information will be provided by means of a randomisation list prepared by CSTAR, available only to the anaesthetist to ensure allocation concealment. Researchers involved in ratings will not have access to information regarding treatment allocation.

Blinding and unblinding

To ensure patient safety during infusions and in the post-infusion period, the anaesthetist administering the ketamine/midazolam infusions will not be blinded but he will not be involved in assessments or data analysis. Patients, raters and the trial statistician will remain blinded. Success of blinding for patients and raters will be assessed after the first treatment. A set of envelopes containing allocation information will remain unopened but may be used where emergency unblinding is indicated. Unblinding for one or all participants will take place if it is in the best interests of the participants.

Statistical methods

Pilot trial data will be analysed on an intention-to-treat basis for all participants who complete at least one infusion and one post-infusion evaluation. Data analyses will be performed blinded to allocation by the trial statistician. As this is a pilot trial and small numbers of participants are involved, no missing values will be imputed. Data will be analysed using IBM PASW (SPSS) version 22 and "R" (R Foundation for Statistical Computing, Austria).

Demographic and baseline data will be summarised for each treatment group by presenting descriptive statistics. Descriptive statistics will also be used to report: rates of recruitment, willingness to be randomised, willingness to complete assessments, medical/cognitive/psychotomimetic/general adverse events between groups, adherence to allocated treatments, adherence to follow-up between groups and reasons for drop-outs between groups.

Relapse-free survival times will be compared between groups using Kaplan-Meier survival curves and log-rank test. As this is a pilot trial and insufficiently powered to achieve statistical significance, there will be no formal comparison of the two treatment groups in the pilot trial. However, Cox proportional hazard regression analysis will provide a 95 % confidence interval for an unadjusted hazard ratio for a future definitive trial.

As this is a pilot trial and small numbers of participants are involved, no missing values will be imputed. As per the pilot trial design, the primary outcomes are those relating to reasons for dropout and these will be presented using descriptive statistics.

Data management

A trial-specific operating procedure for data quality assurance will be followed by all researchers and involves eight levels of quality assurance. Researchers will be trained in administration of the primary assessment tool used in this study, the HRSD-24, and training will be repeated every 6 months to ensure good inter-rater reliability. The study will comply with the Data Protection (Amendment) Act, 2003, Ireland. All documents will be stored safely in a designated locked filing cabinet in a locked office within the Research Building at St. Patrick's University Hospital, and confidentiality will be observed at all times. With the exception of the informed consent form, subjects will be referred to only by their subject identification number on all study-specific documents, whether hard copies or electronic. Data analysis will take place in another facility (CSTAR, University College Dublin), and data will be anonymised prior to secure transfer to CSTAR for analysis.

Trial management

The Trial Steering Committee, chaired by an independent clinician and including a service user representative, will meet on a six-monthly basis. The Trial Management Group, comprising trial researchers, will meet on a weekly basis. A Data Monitoring Committee (DMC), chaired by an independent clinical researcher and comprising an independent biostatistician and independent trial methodologist, will meet every 6 months to review blinded data and reports prepared by the trial statistician. The trial results will be published and communicated to participants, and authorship eligibility guidelines of the International Committee of Medical Journal Editors (ICJME) will be followed. There is no intended use of professional authors. Important amendments to the trial protocol will be communicated to all relevant agencies. The sponsor owns the final dataset; access will be managed through the Principal Investigator. There are no contractual agreements limiting access to data for investigators. There are no plans to grant public access to the participant-level dataset or statistical code. Trial processes will not be independently audited due to the pilot trial design.

Discussion

This is the first registered trial investigating the potential use of ketamine for relapse prevention in depression and the first study to investigate intravenous ketamine for relapse prevention following successful response to ECT. Only one other registered study proposes to investigate this issue; however, that study uses intranasal esketamine (NCT02493868). Previous studies have shown that ketamine has a rapid effect in acute depression, maintained up to 2 weeks, but repeated infusions have not been studied in a recovered population for the purpose of

relapse prevention. The focus of this pilot trial is on process outcomes to help inform a future definitive trial. Strengths of the study include its double-blind design and use of independent randomisation. Notwithstanding the potential utility of the trial in assessing the safety and practicability of this treatment protocol, there are some limitations. The small number of proposed participants in this pilot trial (up to $n = 40$) limits the statistical analyses which can be confidently applied to the ones described here. The nationwide catchment area of the trial site may pose difficulties in retention of participants from phase I to phase II due to travel challenges. Treatment-as-usual will continue for all participants during the pilot trial, resulting in a heterogeneous participant group. This pragmatic design will, however, improve generalisability of the results and applicability to a future definitive trial.

Trial status

Recruitment commenced

Additional files

Additional file 1: Informed consent materials. (DOCX 26 kb)
Additional file 2: Details of biological studies. (DOCX 25 kb)

Abbreviations

Version III; BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician-Administered Dissociative States Scale; CSTAR, Centre for Support and Training in Analysis and Research, University College Dublin; CTQ, Childhood Trauma Questionnaire; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ECT, electroconvulsive therapy; EHQ, Edinburgh Handedness Questionnaire; HRSD-24, Hamilton Depression Rating Scale, 24-item version; K-AMI, Kopelman Autobiographical Memory Interview; MDD, major depressive disorder; MSTRD, Maudsley Staging for Treatment-Resistant Depression; NART, National Adult Reading Test; NMDA, *N*-methyl-D-aspartate; PRISE, Patient-Rated Inventory of Side Effects; QIDS-SR, Quick Inventory of Depressive Symptoms, Self-Report, 16-item; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; sMMSE, Standardised Mini Mental State Exam; YMRS, Young Mania Rating Scale

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Health Research Award 2014, Health Research Board, Ireland (HRA-POR-2014-604).

Ethics approval and consent to participate

Approval for this pilot trial was obtained from the joint authorised Research Ethics Committee of St. James' and Tallaght Hospitals, Dublin. Site approval was also obtained from the relevant committee at St. Patrick's University Hospital. Authorisation for the clinical trial was obtained from the Health Products Regulatory Authority of Ireland, the relevant body under the European framework for clinical trials, EudraCT (2014-000339-18). The study will be conducted in accordance with the principles that have their origin in the Declaration of Helsinki [32], in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation [33] (ICH), and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC. The trial has been registered at clinicaltrials.gov (NCT02414932).
Written informed consent will be obtained by members of the research team using the study-specific consent form (Additional file 1). Potential participants will be provided with an information leaflet and letter of invitation (Additional file 1) and verbal information at the first point of contact with a member of the research team.

Composition, roles and responsibilities

Co-ordinating centre: Single-centre trial at St. Patrick's University Hospital, Dublin
Trial Steering Committee: Composed of an independent Chair with clinical research background, trial statistician, a service user representative and investigators. The role of the TSC will be to provide overall supervision of the trial, including monitoring trial progress and conduct and advising on scientific credibility. The TSC will meet on a six-monthly basis and consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC), and will ultimately carry the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy.
Endpoint Adjudication Committee: None—for the purposes of this pilot trial, the endpoint is reached when planned recruitment is achieved.

Items from the WHO trial registration data set

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Public Title: KEtamine for dEPression relapse prevention folloWing ELectroconvuLsive therapy (The KEEP-WELL Trial)
Scientific Title: KEtamine for dEPression relapse prevention folloWing ELectroconvuLsive therapy: a randomised pilot trial with blood biomarker evaluation (The KEEP-WELL Trial)
Countries of recruitment: Ireland
Health condition or problem studied: Depression
Target sample size: No formal sample size calculation. Recruitment to cease at $n = 15$–20 per group
Recruitment status: Recruiting
Date of first enrolment: 1st April 2015
Date and version of protocol: V1.0, 22.2.15
Study type: Interventional pilot clinical trial
- Randomised
- Double-blind
- Parallel, two-arm
- Placebo-controlled

Role of sponsor and funders in study

Sponsor's role: The Sponsor has ultimate authority over the study design, trial management, data collection and analysis, interpretation of data, writing of report and submission of report. The Sponsor is directly involved in trial management by membership of the Trial Steering Committee.
Funder's role: No role in study design, data collection, trial management, analysis, interpretation of data, writing of report, submission of report.

Trial sponsor

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Appendix 27 Emergency Unblinding Protocol for the KEEP-WELL Trial

KEEP WELL

Protocol for Emergency Unblinding of Trial Participants

Version: 2.0

Date 09.1.17

TRIAL IDENTIFIER AND REGISTRY NAME:

KEtamine for dEPression relapse prevention folloWing ELectroconvuLsive therapy: a randomised pilot trial evaluation (The KEEP WELL Trial)

Date of registration: 26.1.15

EudraCT number: 2014-004262-14

Sponsors' Reference: St Patrick's Mental Health Services: 05/14

Research Ethics Committee Reference, Joint REC of St James' and Tallaght Hospitals, Dublin: 2014-08-19

The KEEP-WELL Trial at St Patrick's University Hospital is a Health Research Board-funded; Research Ethics Committee-approved double-blinded, randomised, controlled pilot trial. Participants are people with depression, referred for ECT. Participant will be monitored for response to ECT and once well, will be invited to take part in the clinical trial. Participants will be randomly allocated to receive four weekly infusions of either ketamine or midazolam in sub-anaesthetic doses and will be monitored for several hours afterwards.

Participants and researchers will now know which drug a participant has received (double-blind). The anaesthetist and pharmacist administering the drug will know the details of the agent received. To maintain good scientific practice, it is important that researchers do not at any stage become aware of which drug a participant is having.

There is a low incidence of reported side-effects of the drugs involved in this trial, both of which are proven to be safe and well-tolerated in this population. However, for safety reasons it is important that it is possible for a person or their healthcare professional to obtain information about which drug they have received (unblinding), at any time.

A set of envelopes containing treatment allocation information will remain unopened but may be used where emergency unblinding is indicated. Unblinding for one or all participants will take place if it is in the best interests of the participants. In the case of an emergency, when knowledge of the

treatment assignment is essential for the clinical management of the subject, any investigator may unblind a single subject.

This information will be stored in the locked ECT suite and will be accessible at all times by a member of staff. A researcher will be contactable on a dedicated trial number on a 24-hour basis. This protocol outlines the steps to be taken in the event of a trial participant or their healthcare professional calling to request information about their treatment in the trial.

1. All trial participants are provided with a card with the St Patrick's Hospital contact number in the event of information being required
2. Participant or healthcare professional calls the hospital (switch or ADON)
3. Telephone switch operator or ADON-on-call takes the following details:
    a. Patient name and date of birth
    b. Last trial clinic appointment
    c. Contact number
4. If call is placed to telephone switch operator, they pass this information to the ADON-on-call
5. ADON-on-call calls the dedicated trial contact number
6. Researcher directs the ADON to the emergency unblinding envelopes in the ECT suite
7. ADON opens the emergency unblinding envelope for this person only and provides this information to the patient or healthcare professional
8. Emergency unblinding information is not communicated to other staff
9. A follow-up call to the patient will be made in the next working day by the research team
10. Reporting procedures for emergency unblinding will be followed as per the Clinical Trial Protocol
11. Any breaking of the blind, whether intentional or unintentional, will be recorded and reported to the sponsor as soon as possible. Unblinding for multiple or all subjects will be discussed by the Trial Steering Committee at the next meeting. Unblinding will be recorded and justified in the final report.

Appendix 28 Charter for the Trial Steering Committee, The KEEP-WELL Trial

The KEEP-WELL Pilot Trial
Trial Steering Committee Charter

PRINCIPAL INVESTIGATOR: Prof. Declan McLoughlin

SPONSOR: St Patrick's Mental Health Services (SPMHS) as represented by Prof. James Lucey

VERSION: 1.0
DATE OF TSC CHARTER: 16.1.15

REC REFERENCE (ST JAMES AND TALLAGHT HOSPITALS REC): 2014-08-CHAIRMAN'S ACTION 19
EUDRACT NO: 2014-004262-14
HPRA Ref: CT 900/559/1, CRN 2155175

Introduction

The role of the Trial Steering Committee (TSC) is to provide overall supervision for the KEEP-WELL Pilot Trial on behalf of the Trial Sponsor (SPMHS) and to ensure that the KEEP-WELL Trial is conducted according to the guidelines for Good Clinical Practice (GCP) and all relevant regulations and local policies.

In particular, the TSC should concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question.

The TSC should provide advice, through its Chair, to the Principal Investigator, the Trial Sponsor, the Trial Funder, and the Host Institution on all appropriate aspects of the trial.

The background to this trial, its objectives, assessments, interventions, etc. is described in the trial protocol.

The purpose of this document is to define the roles and responsibilities of the TSC and to guide its activities, its relationship with other trial committees, its membership, and the format, purpose and timings of its meetings. The charter also describes the procedures for ensuring confidentiality and proper communication to and from the TSC and an outline of the content of the reports to be provided to the TSC.

Terms of reference

- To provide advice, through its Chair, to the Trial Management Group (TMG), the Sponsor and the Trial Funder on all aspects of the trial.
- To monitor and supervise the progress of the trial towards its overall objectives, review accrual and results of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the trial and the research question.
- To ensure that the rights, safety and wellbeing of the trial participants are the most important considerations and should prevail over the interests of science and society.
- To agree proposals for substantial protocol amendments and provide advice to the TMG regarding approvals of such amendments.

- To consider the recommendations of Ethics committees, the trial/study Data Monitoring Committee (DMC) and/or other trial/study committees.
- The TSC should inform the TMG if:
    - There are concerns about the safety of participants
    - Accrual is too low to provide meaningful results
    - It is evident that if the study continues it would fail to provide a clear benefit
- To recommend whether to continue or terminate the study or further adapt it based on safety and efficacy considerations.

Membership and primary responsibilities of the TSC

The KEEP-WELL TSC is a multidisciplinary group comprising of the following members who jointly have responsibility for the design, conduct and evaluation of the clinical research project.

- An independent Chair (Prof Jogin Thakore)
- Principal Investigator (Professor Declan McLoughlin)
- Co-Investigator (Prof Andrew Harkin)
- Trial Statistician (Professor Leslie Daly)
- Trial Collaborator (Dr Enda Shanahan)
- Trial Researchers (Karen Ryan, Martha Finnegan, Toni Galligan, Louise Donnelly)
- Representative of service user group (Ms Marie Tuohy)

The responsibility for calling and organising TSC meetings lies with the Principal Investigator (PI) in association with the Chair. The Chair assisted by the PI is responsible for facilitating the meetings and summarising discussions. The Chair will approve the appointment of the members of the TSC.

The TSC membership is for the duration of the trial. If any members leave the TSC the TMG should suggest replacements promptly for appointment by the Chair.

Agreements

TSC members should formally register their agreement to be a member of the committee as well as their agreement with the contents of the charter, trial protocol, confidentiality, and should declare any potential conflicts of interest.

Independent members should complete and return a signed agreement and competing interests form provided at the end of this charter.

Responsibilities

The TSC on behalf of the Sponsor and Funder will have overall responsibility for the design and conduct of the trial and for safeguarding the rights, safety and well-being of participants. Responsibilities of the TSC:

- Reviewing selection/recruitment/retention of participants and their management
- Finalising and reviewing study protocol and other study documentation.
- Determining if amendments to the protocol or changes to study conduct are required and deciding on changes to these and to study conduct in general. Any changes to trial documentation or conduct must be notified to the TSC.
- Reviewing adherence to the protocol by Investigators and participants
- Assessing the impact and relevance of external evidence
- Assessing integrity and completeness of data collected

- Monitoring the overall conduct of the trial, ensuring that it follows the standards set out in the guidelines of GCP, assessing the safety and efficacy of the interventions, recruitment figures and completion of trial assessments.
- Reviewing, commenting and making decisions on extension requests.
- Reviewing the recommendations of the DMC and other study committees and suggesting appropriate action to the TMG.
- Monitoring the progress of study/trial and deciding on appropriate action in order to maximise the chances of completing it within the agreed timelines.
- Considering new information relevant to the study e.g. results from other studies that may have a bearing to the conduct of the study and deciding on appropriate action.
- Endorsing the annual report to the funder, REC, and site

The TSC may recommend early termination of the trial or modification of the study design in the event of a clear outcome derived from accumulating data or on the basis of information available from other sources or on safety grounds.
The TSC should be available to provide independent advice as required not just when meetings are scheduled.

The TSC should maintain confidentiality of all information it receives.
Members should not discuss confidential issues from their involvement in the study until the primary results have been published.

Role of the TSC Chair

- Arrange the first meeting of the TSC, with the assistance of the PI, to agree contents of charter and set up schedule of meetings
- Establish clear reporting lines – to the Funder, Sponsor etc.
- Become familiar with the role of the DMC
- Provide an independent, experienced opinion if conflicts arise between the needs of the research team, the Funder, the Sponsor and/or any other agencies
- Leading the TSC to provide regular, impartial oversight of the trial, especially to identify and pre-empt problems
- Ensuring that changes to the protocol are debated and endorsed by other members of the TSC

For decisions to be made, at least 2 independent members of the TSC should be present (including the chair), the PI and a representative from the TMG.

TSC meetings

- The responsibility for calling and organising a TSC meeting lies with the PI in association with the TSC Chair
- Research Department administrator, Sarah Roeder, will organise these on behalf of the TSC & PI. Meetings may be by teleconference
- All TSC members will be provided with study documents (e.g. protocol, CRFs, statistical analysis plan) and the TSC report prior to the meeting
- The first TSC meeting will discuss, revise and finalise the terms of reference, agree the content of the TSC charter and sign any declaration, and agree the frequency of the meetings
- TSC will meet six-monthly
- Meetings can also be held at any time at the request of the PI or TSC chair
- The final TSC meeting will be arranged when target recruitment is completed, all data collected and cleaned and the database is locked. This final meeting will be held to

discuss final/completed data and interpretation, and publication time lines. If the study is terminated prematurely, no final study meeting is required

Attendance

Every effort will be made to ensure that all TSC members can attend the meetings. The PI or delegate should try and find a date that enables this. The PI must try to attend all meetings, especially if major actions are expected.

If the TSC is considering major actions the TSC Chair should communicate with absent members, including the PI, as soon after the meeting as possible to determine whether they all agree. If there is disagreement amongst absent members a further meeting should be arranged with the full TSC

Reporting

Prior to a TSC meeting a report will be prepared by the TMG with input from PI, statistician, etc. and circulated to TSC members at least a week before the meeting.

On consideration of the information presented at these meetings, the TSC should provide recommendations of appropriate action in writing to the TMG who will be responsible for implementing any actions. The TSC may also provide feedback to the DMC and, where appropriate, to the Sponsor/Funder.

Minutes of the meeting including key points and actions will be prepared by the research department administrator, Sarah Roeder. These minutes will describe the proceedings and include the recommendations of the TSC. All members of the TSC must agree the minutes and these will be signed off by the TSC Chair on behalf of all members. Minutes will be circulated to all TSC members, the TMG, and the Sponsor. Approved Minutes will be filed in the Trial Master File.

Decisions and recommendations by the TSC should be unanimous or, if not, a vote may be taken. The role of the Chair is to summarise discussions and encourage consensus. Therefore, it is best for the chair to give his opinion last. It is important that the implications (ethical, statistical, practical and financial) for the trial be considered before any decision is made.

Contents of the TSC Reports

An outline of the contents of the TSC report (As per section 9 above, TMG will send this report to TSC at least a week before the meeting) is given below:

- Outline of the study design, sample size sought and current available evidence
- Statistical consideration and design
- Major protocol amendments
- Patient screening
- Eligibility violations
- Protocol violations by investigators or participants
- Study accrual by month/total
- Completeness and quality of data collected/CRF return
- Quality controls
- CRF return, entry into database
- Baseline characteristics
    - Demographics

    - Clinical characteristics
    - Previous treatment
- Safety reporting
- Follow up data available
- Any matters affecting the trial
- Compliance by patients to clinic visit
- Latest DMC report and DMC recommendations

Conflicts of interest

TSC members should not have any apparent financial, scientific or intellectual conflict of interest that could prevent them from objectively reviewing the study protocol, interim and final data and giving advice to the TMG. TSC members should disclose to the Chair any other conflicts they consider relevant. Any members who develop significant conflicts of interest during the course of the trial should resign from the TSC.

Publication

Manuscripts that arise from the trial will be shared with the TSC and members will be able to comment. The TSC members and their affiliations will be acknowledged in reports of the trial. Any conditions/ limitations on publication of material from this trial by TSC members will be stated and clarified.

References:

1. MRC Guidelines for GCP in clinical trials (1998)
2. ICRIN GCP Guide (2010)

Annexe 1

Agreement and competing interests form for independent members of the KEEP-WELL Trial Steering Committee

Please complete the following document and return to

☐ I have read and understood the TSC Charter V1.0 dated 16/01/15

☐ I agree to join the TSC for this study/trial as an independent member

☐ I agree to treat all sensitive trial data and discussions as confidential

The avoidance of any perception that members of the TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests:

Table 1: Potential competing interests for independent members

1. Stock ownership in any commercial companies involved.
2. Stock transaction in any commercial company involved (if previously holding stock)
3. Consulting arrangements with any commercial company involved
4. Frequent speaking engagements on behalf of the intervention
5. Career tied up in a product or technique assessed by the trial
6. Hand-on participation in the trial
7. Involvement in the running of the trial
8. Emotional involvement in the trial
9. Intellectual conflict, e.g. strong prior belief in the trial's experimental arm
10. Involvement in regulatory issues relevant to the trial procedures
11. Investment (financial or intellectual) in competing products
12. Involvement in the publication

☐ **NO,** I have no competing interests to declare

☐ **YES,** I have competing interests to declare (please detail below)

Appendix 29 Data Quality Assurance Protocol for the KEEP-WELL Trial

Ketamine for depression relapse prevention following ECT:

a randomised pilot trial

(The KEEP WELL Study)

Data collection and quality assurance protocol

Version: 2.0

Date: 09.1.17

Data will be collected in a standardised manner in which all assessors will be trained. Once data have been collected, hard copies of assessments will be stored in secure locked filing cabinets in locked offices in the Research Department, which is accessible only by designated staff fob key. All assessments for each participant will be stored together.

There are eight levels of quality assurance for each completed assessment.

1. Each researcher corrects and reviews the assessment they have carried out on the same working day.
2. Each researcher is paired with another researcher. Once per fortnight each researcher pair will cross check each other's first level ratings for errors. Errors detected will be discussed between the researcher pair and corrected. The number of errors will be recorded.
3. Every fortnight the team leader (MF) will ensure all checks within researcher pairs have been completed and are correct. The completion of researcher pair checks, and the number of errors identified at each pair check will be recorded on the data quality assurance checklist.
4. Every month a review of the data quality assurance checklist will take place at the weekly trial management meeting. Unusual numbers of errors or late checks will be discussed.
5. The data quality assurance checklists will be presented to the independent Data Monitoring Committee at their six-monthly meeting.
6. Data entry will take place once per month in pairs. Data will be entered initially into a trial-specific secure spreadsheet and reviewed for errors.
7. Every six months, statistical analyses will be carried out to uncover any remaining input errors.
8. When researchers are unblinded, data will be examined more thoroughly for input errors. Data entry will be re-checked against original hard copies of assessments and corrected if necessary.

Please note, for the Autobiographical Memory Interview, two independent ratings of the transcript are required. The interviewer will place the transcript in the Case Report

Folder immediately upon completion of the interview and both paired raters will score the AMI separately within 48 hours using the transcript, and file their independent scores in the CRF. During fortnightly cross checks of first level ratings, a score discrepancy of more than 1 point on any item in the AMI will be discussed and a consensus mark agreed, based on the agreed "strict/conservative" marking approach.

Appendix 30 Charter for the Data Monitoring Committee, The KEEP-WELL Trial

Ketamine for depression relapse prevention following ECT:

a randomised pilot trial

(The KEEP WELL Study)

Data Monitoring Committee Charter

PRINCIPAL INVESTIGATOR: Prof. Declan McLoughlin

SPONSOR: St Patrick's Mental Health Services as represented by Prof. James Lucey

VERSION: 1.0

DATE OF DMC CHARTER: 4.2.15

TABLE OF CONTENTS

1. INTRODUCTION

This Charter is for the Data Monitoring Committee (DMC) for "Ketamine for depression relapse prevention following ECT: a randomised pilot trial (The KEEP WELL Study)". The Charter will define the primary responsibilities of the DMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMC, and an outline of the content of the Open and Closed Reports that will be provided to the DMC.

2. PRIMARY RESPONSIBILITIES OF THE DMC

The DMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMC will provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the selection/ recruitment/ retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMC will be advisory to the clinical trial leadership group, referred to as the Trial Steering Committee (TSC) and usually including a sponsor representative. The TSC will be responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

3. MEMBERSHIP OF THE DMC

3.1 Members

The DMC is an independent multidisciplinary group consisting of statisticians and clinicians that, collectively, has experience in the management of patients with mood disorders and/or in the conduct and monitoring of randomized clinical trials.

DMC Chair: *Professor Colm McDonald*

Email: colm.mcdonald@nuigalway.ie

DMC Statistician: Dr Patricia Gunning

Email: patricia.gunning@nuigalway.ie

DMC Clinical Investigator: *Professor Declan Devane*

Email: declan.devane@nuigalway.ie

DMC Clinical Investigator: *Prof. David Cotter*

Email: drcotter@rcsi.ie

3.2 Conflicts of Interest

The DMC membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMC.

The DMC members should not own stock in the companies having products being evaluated by the clinical trial. The DMC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial. The DMC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMC members who develop significant conflicts of interest during the course of the trial should resign from the DMC.

DMC membership is to be for the duration of the clinical trial. If any members leave the DMC during the course of the trial, the sponsor, in consultation with the TSC, will promptly appoint their replacements.

4. TIMING AND PURPOSE OF THE DMC MEETINGS

4.1 Organizational Meeting

The initial meeting of the DMC will be an Organizational Meeting. It will be held during the final stages of protocol development, to provide advisory review of scientific and ethical issues relating to study design and conduct, to discuss the standard operating

procedures for the role and functioning of the DMC, and to discuss the format and content of the Open and Closed Reports that will be used to present trial results at future DMC meetings. The Organizational Meeting will be attended by the DMC, by a representative of the sponsor, and the Principal Investigator. The DMC will be provided the drafts of the clinical trial protocol, the Statistical Analysis Plan, the DMC Charter, and the current version of the case report forms.

4.2 Early Safety/Trial Integrity Reviews

One 'Early Safety/Trial Integrity Review' will be held during the first year of protocol enrolment, to review early safety information, to review factors relating to quality of trial conduct, and to ensure proper implementation of procedures to reassess the sample size. These reviews may be held over the telephone, via the internet, or in St Patrick's University Hospital or another suitable venue. .

4.3 Formal Interim Analysis Meetings

One or more 'Formal Interim Analysis' meetings will be held to review data relating to treatment efficacy, patient safety and quality of trial conduct. These meetings may be held over the telephone or in St Patrick's University Hospital or Trinity College Institute of Neuroscience.

5. PROCEDURES TO ENSURE CONFIDENTIALITY & PROPER COMMUNICATION

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMC has sole access to evolving information from the pilot trial regarding comparative results of efficacy (a secondary outcome) and safety data, aggregated by treatment arm. Procedures will be implemented to ensure proper communication is achieved between the DMC and the trial investigators. . Blinded data will be presented to the DSMB for safety evaluation every six months. In order to ensure that the DMC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DSMB will review unblinded data on request for individual or all participants. Should unblinded data be requested and reviewed by the DMC, a Closed Session will be held during the meeting, for which only DMC members will be present.

Additionally, the DSMB may request to terminate the trial according to section 13.9 of the Clinical Trial Protocol, v4.0. The advice of the DMC will be notified upon receipt by the Sponsor to the joint REC of St. James' and Tallaght Hospitals, the REC of St Patrick's Mental Health Services, and the HPRA. With this notification a statement will be included indicating whether the advice will be followed.

5.1 Open and Closed Reports

A trial report will be provided to DMC members at least one week prior to each DMC meeting, with data on follow-up that is complete to within two months of the date of the

DMC meeting. Open Reports, available to all who attend the DMC meeting, will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up and compliance. The statistician (*Prof. Leslie Daly*) will assist in preparation of these Open Reports.

Should unblinded data be requested and reviewed by the DMC, an additional Closed Report will be provided, available only to those attending the Closed Session of the DMC meeting. This may include analyses of primary and secondary efficacy endpoints, subgroup and adjusted analyses, analyses of AEs and symptom severity, and Open Report analyses displayed by intervention group.

5.2 Minutes of the DMC Meeting

Minutes of the meetings will be prepared. Should unblinded data be requested and reviewed by the DMC, two sets of minutes will be prepared: the Open Minutes and the Closed Minutes. The Open Minutes will describe the proceedings in the Open Session of the DMC meeting, and will summarize all recommendations by the DMC. Since these minutes will be circulated immediately to the sponsor and to lead study investigators, it is necessary that these minutes do not unblind the efficacy and safety data if the DMC is not recommending early termination. The Closed Minutes will describe the proceedings from all sessions of the DMC meeting, including the listing of recommendations by the Committee. Because it is likely that these minutes will contain unblinded information, it is important that they are not made available to anyone outside the DMC. Rather, copies will be archived by the DMC chair and by the statistician preparing the interim reports, for distribution to the sponsor, lead investigators, and regulatory authorities at the time of study closure.

5.3 Recommendations to the Trial Steering Committee (TSC)

At each meeting of the DMC during the conduct of the trial, the DMC will make a recommendation to the Steering Committee to continue or to terminate the trial. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this Charter.

The TSC is jointly responsible with the DMC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the study made by the DMC will be considered and accepted or rejected by the TSC. The TSC will be responsible for deciding whether to continue or to stop the trial based on the DMC recommendations.

The DMC will be notified of all changes to the protocol or to study conduct. The DMC concurrence will be sought on all substantive recommendations or changes to the protocol or study conduct prior to their implementation. The TSC will maintain confidentiality of all information it receives other than that contained in the Open

Reports until after the trial is completed or until a decision for early termination has been made.

6. STATISTICAL MONITORING GUIDELINES

Descriptive statistics will be used to report the results of clinical monitoring (heart rate, blood pressure, pulse oximetry, and presence of ECG changes), cognitive assessments monitoring for psychotomimetic effects and adverse effects between groups in Phase II, will be presented to the DMC prior to every meeting.

7. CONTENT OF THE DMC'S OPEN AND CLOSED REPORTS

7.1 Open Statistical Report: An Outline

- One-page outline of the study design, possibly with a schema
- Statistical commentary explaining issues presented in Open Report
- DMC monitoring plan and summary of Open Report data presented at previous meetings
- Major protocol changes
- Information on patient screening
- Study accrual by month
- Eligibility violations
- Baseline characteristics (pooled by treatment regimen)
- Demographics
- Adherence to medication schedule (pooled by treatment regimen)
- Attendance at scheduled visits (pooled by treatment regimen)
- Reporting delays for key events (pooled by treatment regimen)
- Length of follow-up data available (pooled by treatment regimen)
- Participant treatment and study status (pooled by treatment regimen)

7.2 Closed Statistical Report: An Outline

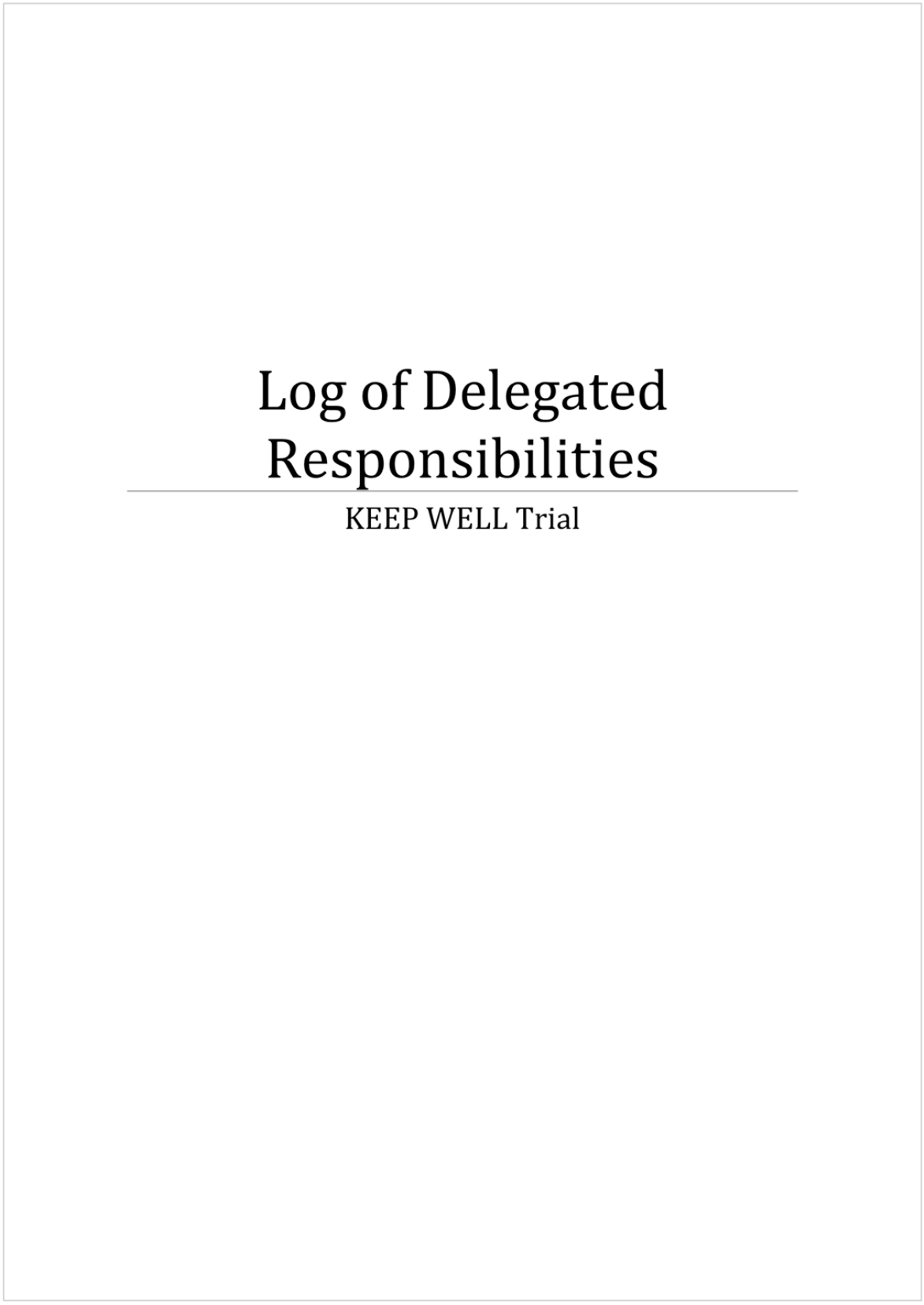
- Detailed statistical commentary explaining issues raised by Closed Report figures and tables (by coded treatment group)
- DMC monitoring plan and summary of Closed Report data presented at previous meetings
- Repeat of the Open Report information, in greater detail by treatment group
- Analyses of primary and secondary efficacy endpoints
- Subgroup analyses and analyses adjusted for baseline characteristics
- Analyses of adverse events and overall safety data

Prepared using:

Data Monitoring Committees in Clinical Trials: A Practical Perspective.

Susan S Ellenberg, Thomas R Fleming, David L DeMets

Appendix 31 Log of Delegated Responsibilities for the KEEP-WELL Trial



Name	Role	Duty
Prof Declan McLoughlin, PhD	**Principal Investigator**	Staff recruitment
		Staff line manager
		Oversight of trial governance
		Oversight of trial recruitment
		Final decisions regarding participant inclusion/ exclusion/ unblinding/ withdrawal
Dr Enda Shanahan, FCAI	**Investigator**	Oversight of physical health monitoring in infusion clinics
		Return of IMP to pharmacy and completion of Pharmacy IMP Return Checklist
		Formulation and administration of IMP according to protocol
		Completion of Randomisation list
		Provision of guidance to Investigators/ Sub-Investigators regarding AEs / ADRs
Dr Martha Finnegan, MRCPsych	**Investigator**	Data Controller
		Medical Monitor
		Safety event assessment and reporting
		IMP accountability and equipment integrity
		Assessment of inter-rater reliability and blinding
		Oversight of CRF data extraction and entry
		Co-ordination of public and site communication
		Management of Protocol and TSOPs
		Management of invoices
		Preparation of reports: HPRA, HRB, SPMHS REC, SJH REC, TSC, DMC, clinicaltrials.gov
		Co-ordination of TSC and DMC activity
		Provision of training for sub-investigators and investigators
		Co-ordination with laboratory, pharmacy, ECT
		Maintenance and review of trial documents incl. Protocol and TSOPs
		Maintenance of Staff Training Record
		Screening, recruitment and assessment of

Appendix 32 Consent form for the KEEP-WELL Trial

Consent Form Phase I
The KEEP WELL Study

Ketamine for depression relapse prevention following ECT: a randomised pilot trial with blood biomarker evaluation
EudraCT No: 2014-004262-14

Please contact Prof. Declan McLoughlin on ext 3385 for more information

The participant must complete this form herself/himself

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the attached Participant Information Leaflet….. Yes □ No □□
- I have had the opportunity to ask questions and discuss the study …… Yes □ No □
- I have received enough information about this study …… Yes □ No □
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care …….. Yes □ No □
- I agree to provide blood cells and plasma for analysis of protein expression.... Yes □ No □
- I agree to provide blood cells and plasma for the analysis of DNA and RNA, including messenger RNA and micro RNA .....Yes □ No □
- I understand that confidential anonymous data from my participation in the trial must be retained securely by the research team for at least five years and will not be retained for more than ten years.. . . . . Yes □ No □
- I agree to take part in this study of my own free will and without prejudice to my legal/ethical rights. . . . . Yes □ No □

Participant's Signature: _____ Date: _____

Participant's Name in Print: _____ Date: _____

Witness Signature: * _____ Date: _____

Witness' Name in Print: _____

Investigator's Signature: _____ Date: _____

Investigator's Name in Print: _____

Please attach the Participant Information Sheet to this Consent Form, ask the participant to sign and date it and, where appropriate, place a copy of both in the participant's case notes.

*Witness must be someone other than the Investigator

Consent Form Phase II
The KEEP WELL Study

The participant must complete this form herself/himself

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have had the opportunity to ask questions about Phase II of this study …… Yes □ No □
- I have received enough information about Phase II of this study …… Yes □ No □
- If I am invited to participate in Phase II, I agree to be randomly allocated to one of two treatment groups and I understand that I may be allocated to a placebo treatment group.....Yes □ No □
- I agree to receive four infusions of either ketamine or midazolam . . . . . Yes □ No □
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care ..…….. Yes □ No □
- I agree to provide blood cells and plasma for analysis of protein expression....Yes □ No □
- I agree to provide blood cells and plasma for the analysis of DNA and RNA, including messenger RNA and micro RNA .....Yes □ No □
- I understand that confidential anonymous data from my participation in the trial must be retained securely by the research team for at least five years and will not be retained for more than ten years.. . . . . Yes □ No □
- I agree to take part in this study of my own free will and without prejudice to my legal/ethical rights. . . . . Yes □ No □

Participant's Signature: _____ Date:

Participant's Name in Print: _____

Witness Signature: * _____ Date:

Witness' Name in Print: _____

Investigator's Signature: _____ Date:

Investigator's Name in Print: _____

Please attach the Participant Information Sheet to this Consent Form, ask the participant to sign and date it and, where appropriate, place a copy of both in the participant's case notes

Appendix 33 Publication: Editorial, Journal of ECT (in press, 2018)

Editorial

Towards international standards: East meets West

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Reprints: See corresponding author

Conflicts of interest: DMM has received a speaker's honorarium from Mecta. The other authors have no conflicts of interest to declare.

Key words: practice, Europe, depression, schizophrenia, transcultural

Abbreviations: ECT, electroconvulsive therapy

It is well-established that ECT practice, like many aspects of medicine, differs between and within countries. In particular, a pattern of distinct patient populations and ECT administration practices has been shown between high-income industrialized countries, predominantly in Europe and North America, on the one hand and middle and lower-income countries in the rest of the world on the other hand. Leiknes *et al*(1) examined 70 studies of ECT practice worldwide and found that in Western countries ECT was primarily used for depression, with older populations overall, while Asian countries utilized more ECT for schizophrenia in younger people. Similar patterns have also been shown in studies directly comparing practice between Western and Asian countries(2). Even within individual small countries like Ireland, wide regional variability in ECT use and practice can be seen(3).

To illustrate this further, we compared one year of ECT practice between two academic centers in opposite poles of Europe: Dublin in Ireland (n=125) and Sanliurfa in Turkey (n=78), which stands at the interface between traditional notions of "East" and "West". We found similar patterns. The Dublin sample was older, with a mean age of 64 years compared to 35 in the Sanliurfa sample, and had more treatment resistance and physical comorbidities.

The younger Sanliurfa sample included significantly more people with diagnoses of schizophrenia (0 in Dublin vs 5% in Sanliurfa) and mania (8.8% in Dublin vs 16.7% in Sanliurfa) and was more likely to be referred for ECT due to the need for a rapid response. The acute ECT utilization rate was high in the Sanliurfa center at 54% compared to only 3.2% in Dublin, due to availability of inpatient care only for emergencies or for ECT in Sanliurfa. When comparing courses of ECT for depression only, clinician-rated illness severity was similar in both centers. Mean charge, motor seizure duration and EEG seizure duration were all higher in the Dublin sample than the Sanliurfa sample. Those having ECT for depression in the Dublin group were significantly less likely to be the subject of an involuntary admission (13.5% of this group *vs*. 47.4% of the Sanliurfa group). The most common clinician-documented outcome at the end of ECT was recovery from depression, in 90% of those in Dublin and 52.6% in Sanliurfa, but non-recovery and withdrawal of consent were more common in the Sanliurfa sample. Although the proportion of those referred for ECT for treatment of schizophrenia in Sanliurfa (5%) was lower than the proportion of people with schizophrenia in previously reported ECT cohorts in Turkey (e.g. 52% in Canbek *et al*)(4), the overall pattern of differences in ECT practice between the countries was as expected.

It is unclear why such patterns of difference exist between countries around the world. It is likely to be a combination of factors related to the need for ECT, availability of ECT, and uptake of the treatment. We can speculate on some of these factors. Need for ECT may depend not only on the prevalence of disorders, but also on the structure and resources of mental health provision in each region. For example, emphasis on community-based treatment and early intervention may result in fewer people requiring emergency ECT and more people with treatment-resistant depression being identified and ultimately referred for ECT. A region in which resources are not available for intervention early in the illness course may report more use of emergency ECT for severe untreated illness. Similarly, where significant stigma and lack of understanding of mental illness persist, only those with severe illness may be able to access psychiatry services. Availability of ECT is in turn affected by factors such as the proportion of clinicians trained to deliver the treatment and the number of centers that are equipped to do so. Still wider factors such as geography, infrastructure, and transport, can influence clinicians' decisions to recommend ECT for people who may have to travel long distances to a center where the treatment is available. Uptake of ECT may be

influenced by the use of unmodified ECT, the level of health literacy within the community, and cultural influences such as differing thresholds for intervention.

Most importantly, clinicians worldwide are likely to be guided most strongly by evidence from their own region and by their own and their colleagues' experiences and opinions regarding use of ECT for particular indications. Guidelines in European and North American countries do not recommend ECT for schizophrenia(5,6). However, good overall outcomes are often reported in this group in studies from centers in non-Western countries(7). Therefore, clinicians in these countries may choose to prescribe ECT for patients with schizophrenia not due to a lack of resources for alternative treatments, but as a reasoned choice guided by local clinical experience and local research findings.

Although the practice of evidence-based medicine generally prefers and seeks international consensus, it is unclear whether geographical differences in ECT practice are clinically problematic. There is no evidence that outcomes for ECT are poorer in non-Western countries and most centers that use ECT for schizophrenia report positive outcomes. As there is likely to be, in fact, a spectrum of 'good' ECT practice, serving a varied global population of people with mental illness, as opposed to a single best protocol, should we bother standardizing ECT practice? Although the answer for clinical practice may be 'no', some standardization of the parameters of ECT administration in clinical research may be required. Not only are there consistent differences in terms of the populations who receive the treatment, but also in ECT treatment parameters, with wide heterogeneity in ECT administration methods in clinical trials leading to results that are not readily comparable. One area, therefore, in which consensus and international guidelines would be of benefit to all ECT clinicians, is optimal administration of ECT as well as the associated monitoring of people having ECT. At present, no such global consensus view is available.

It is unclear whether the pattern of differences in ECT prescribing and administration between Western and non-Western countries represents a problem or is merely a peculiarity. It is clear that, although global ECT practice involves a wide spectrum of people and presentations, the majority of ECT research in fact only represents the practice of a very limited number of predominantly higher-income European, North American and Australian countries, with a strong focus on ECT for depression. The established differences between Western and non-Western countries (i.e. most of the world) highlight the inequality in the evidence base of ECT for affective compared to non-affective disorders. There has not yet

been a systematic trial-based approach to determine the best method of administration of ECT for non-affective disorders. Consequently, it is uncertain whether research findings from the last number of decades on optimal administration of ECT for depression can be generalized to those operating outside of the narrow range of people who have ECT in Western countries. Do ECT guidelines, informed by a Western-centric evidence base, take into consideration the social and clinical realities experienced by the majority of clinicians administering ECT globally?

Our own data comparing practice between two centers on opposite sides of the European continent reflected the established pattern of differences between Western and non-Western countries. These differences are apparent both in terms of the populations who receive ECT, with more commonly reported use of ECT for depression in the West and more use reported for schizophrenia in the East, as well as differences in terms of ECT administration parameters, which continue to vary between reports. Differences in practice could indicate areas where clinicians in both Western and non-Western countries could improve. Given the clear evidence of the effectiveness of ECT for depression, how can early access to ECT for affective disorders be improved for people in non-Western countries? Likewise, should ECT be considered for more people with schizophrenia in Western countries? If so, more clinical trials of ECT for schizophrenia would be required to ascertain the optimal treatment parameters for this group. In both Western and non-Western countries, a great opportunity now exists to standardize ECT administration parameters and monitoring of the wide range of people across the globe who require ECT.

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Appendix 34 Publication: Book Chapter, The ECT Handbook, Royal College of Psychiatrists, 2018

Book Chapter: Royal College of Psychiatrists, Handbook of ECT, second edition (eds J Waite, N Ferrier), 2018

Cognitive side-effects of ECT: prevention and management

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IMPORTANCE OF COGNITIVE SIDE-EFFECTS

Cognitive side-effects of ECT are among the most important factors limiting prescription and uptake of ECT. Patients, families and clinicians alike share concerns about a variety of cognitive side-effects.

Factors affecting cognitive side-effects of ECT are many, and include pre-existing cognitive impairment and treatment factors such as laterality and pulsewidth (McClintock *et al*., 2014). The effect of the combination of pre-existing depression, treatment with ECT, residual depressive symptoms, as well as individual patient factors, on cognitive performance during and after ECT has not been fully elucidated. There are few strong predictors of cognitive impairment during and after ECT and questions about the extent and persistence of some cognitive side-effects remain unanswered. There is an absence of standardised instruments designed specifically for cognitive assessment during ECT, while existing instruments may not detect subtle or patchy impairments that affect quality of life post-ECT.

TYPES OF ADVERSE COGNITIVE SIDE-EFFECTS

Cognitive side-effects can be divided into those occurring *immediately* after each treatment, those which are *subacute and longer-term* (apparent during, and at the completion of, a course of ECT), as well as *retrograde amnesia*.

BOX 1: Cognitive side-effects of ECT (Lezak, 2012)

Anterograde amnesia: impaired ability to remember new information from the time of commencing ECT onwards

Retrograde amnesia: impaired ability to remember information learned before commencing ECT

Autobiographical amnesia: impaired ability to remember events personally experienced at a particular time and place (episodic autobiographical memories e.g. something that happened

at a wedding you attended) and pieces of general information (semantic autobiographical memories, e.g. year of graduation) from one's own life

Subjective memory difficulty: the experience of feeling as though one has a problem with one's memory, regardless of performance on objective memory testing

Impaired executive function: impairment in higher brain functions such as judgement, planning and completing complex tasks

IMMEDIATE COGNITIVE EFFECTS

Acute cognitive side-effects include disorientation, impaired attention, and amnesia for the immediate time period of the ECT treatment and recovery. Disorientation is very common immediately following ECT and is transient, rarely persisting beyond 60 minutes (Sobin *et al*., 1995). Time to reorientation can be measured as the time at which correct responses to 4/5 questions about orientation to person (name, date of birth, current age), place (name of hospital) and time (day of the week) are given, with 0 minutes corresponding to when the patient resumes spontaneous breathing (Semkovska *et al*., 2016). In a trial of high-dose (6 times threshold) right unilateral ECT vs bitemporal ECT at 1.5 times threshold, median time to recovery of orientation with RUL ECT was 19 minutes *vs* 26 minutes with bitemporal ECT (Semkovska *et al*., 2016). During a course of ECT, the number of ECT treatments is associated with longer periods of disorientation in older people (Martin *et al*., 2015).

Longer time to reorientation has been reported to be associated with more persistent retrograde memory impairment following a course of ECT (Martin *et al*., 2015, Sobin *et al*., 1995) and has also been associated with better mood outcomes, though this requires further study (Bjølseth *et al*., 2016). Routine assessment of time to reorientation therefore represents a low-burden, high-yield form of cognitive assessment during the ECT course that could help guide treatment strategies to minimise cognitive problems at the end of the course.

Persistent disorientation, for example disorientation beyond 90 minutes, is difficult to accurately predict but has been associated with older age (Martin *et al*., 2015), poor cognitive function at baseline (Sobin *et al*., 1995) and presence of psychotic symptoms (Calev *et al*., 1991). Higher stimulus doses result in longer time to reorientation but may be necessary for treatment efficacy. Similarly, brief-pulse (0.5-1.0 msec) ECT is associated with longer time to reorientation but remains more effective than ultrabrief pulse (0.3 msec) ECT for depression (Tor *et al*., 2015). Persistent disorientation is more likely with bitemporal ECT, occurring in 13% of those having high-dose bitemporal ECT (at 2.5 times threshold) vs. 2% of those having high-dose right unilateral ECT (at 6 times threshold) (Sackeim *et al*., 2000).

Another potential factor which may affect time to reorientation is choice of anaesthetic agent. However, there is little high-quality evidence to guide choice of agent based on effect on time to reorientation (see Chapter 22 for discussion of anaesthetic agents).

Lithium and ECT

There is ongoing debate about the potential for lithium to contribute to cognitive side-effects, specifically acute disorientation, possibly due to lithium's anticholinergic activity. There are also reports of prolonged seizure with concurrent use of lithium and ECT (Sartorius *et al*., 2005). However, studies of lithium in combination with ECT are largely limited to retrospective or observational studies and case series (Volpe and Tavares Jr, 2012). Concerns about the combination of lithium and ECT may relate to those with higher serum lithium levels (Thirthalli *et al*., 2011). Although there is no high-level evidence to guide practice, close monitoring of serum levels should take place. For those with serum lithium above 0.8mmol/L it may be prudent to reduce to a lower therapeutic range (0.4-0.5 mmol/L) during the course of ECT.

Post-ictal delirium

There are varying estimates of the incidence of post-ictal delirium, an acute confusional state, from 12% to 65% of patients (Reti *et al*., 2014). Severe disorientation and amnesia may present as restlessness and anxiety in the recovery period. Presence of catatonia and longer seizure duration have been found to be associated with risk of delirium (Kikuchi *et al*., 2009, Reti *et al*., 2014). Reorientation and supportive nursing care will often suffice to manage patients presenting with restlessness. Agitated patients who are at risk of accidental self-injury may require further doses of intravenous anaesthetic or a benzodiazepine and subsequent airway monitoring, resulting in a longer recovery period. Where delirium persists beyond four hours after treatment, medical assessment should be performed to rule out any contributory medical illness; see Chapter 22.

SUBACUTE AND LONGER-TERM COGNITIVE SIDE-EFFECTS

Cognitive side-effects occurring during the course of ECT and resolving soon after completion include anterograde amnesia and non-memory cognitive effects, such as impaired executive function.

Anterograde amnesia

ECT does not cause impairment in the ability to learn new skills or movements (procedural memory), and other aspects of implicit memory such as perceptual priming (the ability to use cues and associations to remember multiple items) are seemingly unaffected, though not often studied (Squire *et al*., 1984, Vakil *et al*., 2000).

Anterograde amnesia during the course of ECT is common and is generally limited to a period of days to weeks after completion of the course, returning to pre-ECT baseline or improving beyond baseline two or more weeks after completion of a treatment course (Semkovska and McLoughlin, 2010). Verbal memory is more affected than visual memory, but impairment in either can result in practical difficulties for patients during the course of

ECT, such as remembering medication dose changes, names of staff, and aspects of the ECT treatment itself.

There is no evidence of cumulative cognitive impairment with repeated applications of ECT, including maintenance ECT (Brus *et al*., 2017, Petrides *et al*., 2011, Russell *et al*., 2003, Smith *et al*., 2010). The CORE studies from the USA of continuation ECT *vs* continuation pharmacotherapy after successful ECT for depression found no differences between the groups in cognitive outcomes at 24 weeks of treatment. Anterograde memory improved in both groups 12 weeks after completion of the acute ECT course, regardless of use of continuation ECT (Smith *et al*., 2010).

Non-memory cognitive side effects

Though there are case reports of a variety of non-memory cognitive adverse effects following ECT, some reporting severe and permanent loss of function and reports of personality change, there is no objective evidence of lasting impairment following ECT.

Meta-analysis showed small to medium impairments in visual episodic memory (worse for delayed visual recall than for immediate visual recall) during the course of ECT, with recovery or improvement beyond baseline by 15 days post-ECT. (Semvokska + McLoughlin) In one study, deficits were identified in visual and visuospatial memory in people having ECT, with some of these deficits persisting after one month, (Falconer et al), however ECT was administered at twice the seizure threshold, likely to amplify cognitive problems. In another study, visuospatial memory improved during the course of ECT, a finding which correlated with improvement in depression (Maric et al), but in this study ECT was administered three times per week and the finding may thus not be generalizable.

A meta-analysis concluded that deficits in executive functioning can be found soon after completing a course of ECT, suggesting these are also present during the treatment course (Semkovska and McLoughlin, 2010). However, all executive functioning measures included in the analysis showed improvement in performance at 4-15 days post ECT compared with pre-ECT baseline, and improvements continued beyond 15 days follow-up. Working memory, as measured by digit span backward, was not impaired at 0-3 days post-treatment and improved vs pre-ECT baseline at follow-up more than 15 days post-treatment (Semkovska and McLoughlin, 2010).

There is no evidence of cumulative cognitive impairment with repeated courses of ECT. In fact, in long-term follow-up, many cognitive functions improve compared to pre-ECT baseline. However, as cognitive function pre-ECT and pre-depression is not routinely measured, it is not clear whether the cognitive improvement following ECT is a return to a healthy level of normal cognitive function. Factors affecting long-term cognitive performance include age (Sackeim *et al*., 2007), severity of depression at the time of testing, and the number of days since the last ECT session. One possibility is that subtle or patchy impairments in executive function following a course of ECT are not evident on routine cognitive testing but contribute to the experience of subjective memory difficulties expressed by patients.

RETROGRADE AMNESIA

The ability to remember events from one's own life is strongly associated with identity. Thus autobiographical amnesia is distressing (Rose *et al*., 2003) and consequently is the focus of research on ECT-related retrograde amnesia. More recent memories may be more vulnerable to loss during ECT than distant memories (Lisanby *et al*., 2000).

Patient factors that confer increased risk of retrograde amnesia are estimated premorbid IQ, age (Sackeim *et al*., 2007), global cognition at baseline (Sobin *et al*., 1995), and longer time to reorientation (Martin et al., 2015). As with anterograde amnesia, retrograde amnesia is more likely with more ECT treatments. High-dose right unilateral brief-pulse ECT is associated with higher percentage recall of autobiographical information than brief-pulse bitemporal ECT (Kolshus *et al*., 2017). In turn, ultrabrief-pulse right unilateral ECT is associated with less retrograde amnesia than brief pulse right unilateral ECT, but is significantly less efficacious in treatment of depression (Tor *et al*., 2015).

Though there is no high-level evidence of persisting retrograde amnesia after ECT, this does not preclude individuals having difficulty for a longer period than research findings suggest. Some individual studies have shown persistent impairment in autobiographical memory (up to three years) and there have been case reports of profound autobiographical memory loss after ECT (Fink, 2007). There is currently no standardised instrument for assessment of this major cognitive effect of ECT (Semkovska and McLoughlin, 2013). As a result, the precise nature and extent of autobiographical retrograde amnesia post-ECT is not clear, a major gap in our knowledge and the focus of much research.

Subjective Memory Difficulty

Up to one-third of patients report persistent subjective memory difficulty post-ECT (Rose *et al*., 2003), with some reports of persistence for years. Qualitative evidence reviewed by NICE suggested that the experience of cognitive impairment was variable among those who had received ECT, but that it often outweighed the person's perception of any benefit from ECT (NICE, 2009).

Subjective memory difficulty does not correlate with objective performance on cognitive assessment or any subset of memory functions, but correlates somewhat with depression severity. Assessment tools such as the Squire Subjective Memory Assessment (Squire et al., 1979) or the Subjective Assessment of Memory Impairment (Kumar *et al*., 2016) have been used in ECT research. Remission following ECT may be associated with lower risk of subjective memory difficulty, while younger, female patients may be more at risk (Brus *et al*., 2017).

It has been variously hypothesised that persistent subjective memory difficulty after ECT represents misattribution of the effects of age, mood or somatic complaints on memory (Fink, 2007). In addition, patients may become anxious about memory after ECT and misperceive a problem where their memory function is within the normal experience (Andrade *et al*., 2016).

ASSESSMENT

Remarkably, there are no specifically designed recommended instruments for cognitive testing in ECT practice. Although NICE, along with the American Psychiatric Association (APA, 2010), recommends a documented baseline assessment of potential risks and benefits of ECT for each individual, including anticipated cognitive effects, the guidelines do not suggest instruments for testing (NICE, 2009). This absence of specific recommendations may reflect the lack of suitable instruments for assessment.

What should we do? Unfortunately, there is no simple answer. Despite limitations in existing instruments, and in line with measurement-based care, there is enough evidence to recommend the practice of performing a global assessment of cognition at baseline, during the course of ECT (e.g. after six treatments), at a set time after ECT, e.g. within three days after the last ECT treatment, and after 1-2 months.

Ideally an assessment would include a measure of: immediate and delayed verbal recall, attention, working memory, autobiographical memory, and at least one aspect of executive function.

Though use of the standardised Mini Mental State Exam (sMMSE) (Molloy *et al*., 1991) has become common, it is inadequate for monitoring adverse cognitive side-effects of ECT. The sMMSE is a screening tool for dementia that is insensitive to change, does not assess executive function, and can only detect substantial impairment (Tombaugh and McIntyre, 1992).

Although no purposely designed instrument for assessment of cognition before and after ECT exists, global cognitive assessments that incorporate measures of executive function are available, and screening batteries have been suggested (Martin *et al*., 2013). The Montreal Cognitive Assessment (MoCA) (Nasreddine *et al*., 2005) and the Addenbrooke's Cognitive Assessment Version III (ACE-III) (Hodges and Larner, 2017, Hseih *et al*, 2013)) have the advantages of being sensitive to minor impairment as well as change. The ACE-III takes longer than the MoCA to administer but has high sensitivity to cognitive deficits, is freely available and does not require specialised training. Parallel, validated versions of both the MoCA and ACE-III are available for retesting during and after ECT. For more detailed cognitive assessment, a battery of assessments such as the CANTAB® (Cognitive assessment software, Cambridge Cognition 2017) can identify more subtle or discrete impairments in specific cognitive functions (Falconer *et al*., 2010, J Fray *et al*., 1996, Tsaltas *et al*., 2011).

Detailed repeat cognitive assessment is burdensome for patients and may not be practical in routine practice and is thus usually only performed as part of a research study. However, one could well argue that it should be part of regular ECT practice!

Based on meta-analytical evidence (Semkovska and McLoughlin, 2010), acute impairments in most cognitive domains should resolve within 15 days or more of completion of ECT, so we recommend that deficits persisting beyond one month after completing ECT require further assessment.

Retrograde amnesia assessment

The assessment of retrograde autobiographical amnesia is particularly difficult. Inability to retrieve information, whether on free or cued testing, indicates that memory decay has occurred over time (i.e. forgetting). Some memory decay is actually normal. It cannot be assumed that reduced consistency of recall is unique to depressed people treated with ECT, or to depressed people. Recall of autobiographical information normally declines over time in non-depressed people and consistency of recall in healthy controls declines even after an interval of two months (Semkovska *et al*., 2012). Estimates of normal rate of loss of autobiographical memories range from 27% after 6 weeks (Talarico and Rubin, 2003) to 31–42% after 2 months (Anderson *et al*., 2000).

It is difficult to separate the effect of ECT from the effect of change in depression severity on the normal rate of loss of previously reported memories. To do so would require robust normative information on the performance of:

- non-depressed people,
- depressed persons not treated with ECT,

on the instruments used for retrograde memory assessment in ECT, before and after an interval of weeks. Unfortunately, this is not currently available.

Depression is associated with impaired ability to identify separate incidents from one's own life experience (reduced specificity of episodic autobiographical memory, or over-generalisation) and poor recollection of detail of the identified events. These are consistent findings across several types of assessment (Jelovac *et al*., 2016). Reduced specificity in depressed patients prior to ECT (compared with non-depressed controls) was shown to persist at three months after ECT regardless of treatment response (Jelovac *et al*., 2016). Thus depressed patients may score poorly on episodic autobiographical memory assessment even when their semantic autobiographical memory may seem unimpaired (Verwijk *et al*., 2015). Testing retrograde memory is challenging for depressed patients experiencing reduced memory specificity and may result in patients providing information that is very limited or over-general.

The ideal instrument for assessment of retrograde autobiographical amnesia would be short and simple to administer and would provide scores for memory detail (semantic and episodic)

as well as a consistency score on retesting after ECT. Results could be measured against the general population (and also depressed persons not treated with ECT) at baseline and after several weeks of normal life. Unfortunately, currently used instruments for retrograde amnesia, e.g. the Columbia University Autobiographical Memory Interview (CUAMI, or the short form CUAMI-SF) (McElhiney *et al*., 2001, McElhiney *et al*., 1995) and the Kopelman Autobiographical Memory Interview (Kopelman *et al*., 1989), do not fulfil all these criteria. For a more detailed account of these issues see the following correspondence (Sackeim, 2014, Semkovska and McLoughlin, 2013, 2014).

The Columbia University Autobiographical Memory Interview is the most widely used instrument for assessment of autobiographical amnesia in ECT research (Sackeim *et al*., 2000). However, normative data for comparison of both healthy controls and depressed people not having ECT are not available (Semkovska and McLoughlin, 2013). Episodic recall is not measured separately to semantic recall, and the short form still takes 20-25 minutes to administer. Another disadvantage to the CUAMI-SF is that only information provided in the initial assessment is retested for consistency of recall. Therefore, scores cannot improve and the percentage recall score may be based on successful recall of very little information, i.e. a floor effect. Despite these drawbacks, the CUAMI has been useful in showing differences in retrograde amnesia associated with different ECT treatment modalities, such as laterality and pulse-width (Kolshus *et al*., 2017, Sackeim *et al*., 2000, Sackeim *et al*., 2008); see 'Prevention' below.

The Kopelman Autobiographical Memory Interview was originally designed for assessment of amnestic patients but has also been used in ECT research (Sienaert *et al*., 2010). It assesses both semantic and episodic autobiographical memory separately, with items scored on specificity and detail. It does not provide a measure of recall consistency and caution is required due to suggestions of a lack of sensitivity of the instrument to ECT-related retrograde amnesia (Jelovac *et al*., 2016). It is long (+25 minutes) and burdensome for depressed patients to complete. However, some normative data on the performance of healthy controls is available, and the instrument allows for improvement of scores on retesting should memory improve during or after a course of ECT.

PREVENTION

There is good evidence that modification of ECT treatment factors (laterality, pulsewidth, frequency) can help reduce the occurrence and severity of cognitive side-effects. Higher electrical stimulus (in relation to seizure threshold), though important for antidepressant effect, is associated with greater effect on cognition (Sackeim *et al*., 1993). More frequent ECT treatment (thrice-weekly vs twice-weekly) is associated with greater cognitive impairment (Lerer *et al*., 1995), and, though now unused, sine-wave stimulation resulted in more severe and persistent effects on cognition than contemporary brief-pulse stimuli (Sackeim *et al*., 2007).

Right unilateral (RUL) ECT is consistently associated with less severe and persistent cognitive effects (Sackeim *et al*., 1993, Sackeim *et al*., 2007). Antidepressant efficacy equal

to bitemporal ECT can be preserved by administering RUL ECT at six times threshold dose (Kolshus *et al*., 2017).

Trials of ultrabrief pulse (UBP) ECT have shown a cognitive advantage over brief pulse (BP) ECT (Tor *et al*., 2015, Verwijk *et al*., 2012). Global cognition, anterograde memory (learning and recall) and retrograde memory were less affected by high-dose RUL UBP than RUL BP ECT (Tor *et al*., 2015). Although the cognitive benefit of UBP over BP ECT is consistent, UBP ECT is significantly less efficacious in treating depression than BP ECT and requires more treatments to achieve remission (Tor *et al*., 2015).

Meta-analysis of bifrontal *vs* bitemporal ECT suggested bifrontal ECT may have slightly less impact on global cognitive function (as represented by decline in MMSE score) than bitemporal ECT (Dunne and McLoughlin, 2012), but there is currently not enough evidence to recommend routine use of bifrontal ECT with regards to its having substantial cognitive advantages over bitemporal or unilateral ECT.

Primary prevention

Modification of treatment parameters associated with less cognitive impact should be considered for those identified as being at higher risk. Those who are older, have baseline cognitive impairment or a history of cognitive difficulties following ECT should be considered at risk.

If recovery from depression is an urgent concern and the person is at high risk of cognitive side-effects, brief pulse high-dose unilateral ECT may be used. If rate of recovery is less urgent, ultrabrief pulse unilateral ECT may be considered. In addition, it would seem good practice to avoid unnecessary use of anticholinergic agents (e.g. atropine) during ECT administration. Further detail on anaesthetic agents is in Chapter 22.

Most of the patient-related risk factors for adverse cognitive effects are not malleable, e.g. age, cerebrovascular disease. However, clinical common sense indicates that physical condition should ideally be optimised pre-ECT, in particular with regards to cardiovascular, cerebrovascular and respiratory risk factors.

Preparation for the possibility of adverse cognitive side-effects and practical support during the treatment course may contribute to a positive experience that could help patients to avoid prematurely discontinuing a course of ECT due to distress. It is crucial that patients and their family, or advocates involved in the consent process, are adequately informed of the common occurrence of cognitive side-effects despite best treatment, and the effect this can be expected to have on their day-to-day activities during and for a limited time after ECT. In particular, patients should be informed that they should not drive during a course of ECT (https://www.gov.uk/government/publications/assessing-fitness-to-drive-a-guide-for-medical-professionals).

Secondary prevention

There are no guidelines to inform clinicians about at what stage and under which conditions treatment should be changed. However, if cognitive effects become apparent during the course of ECT, treatment factors can be modified as above to utilise a form of treatment less likely to impair cognition.

Research focusing on reducing the frequency and severity of adverse cognitive effects of ECT has resulted in trials of ketamine anaesthesia for ECT (McGirr *et al,* 2017) and augmentation of ECT with cognitive training (Choi *et al*., 2017), although neither of these has led to clearly improved cognitive outcomes. Acetylcholinesterase inhibitors have been found to result in significantly better performance in cognitive testing after ECT although there is large heterogeneity between studies (Henstra *et al*., 2017) and their use remains experimental. More research is likely to emerge on this topic.

Key points

- Adverse cognitive side-effects are common and important to patients, families and clinicians and may contribute to premature discontinuation of treatment or lack of use of ECT where it is indicated
- Cognitive side-effects include anterograde and retrograde amnesia, as well as impaired executive function
- Most short-term effects will resolve within weeks of the last ECT treatment and there is no objective evidence of persisting anterograde memory impairment
- The extent and duration of retrograde amnesia remains unclear and difficult to assess, with no ideal tool currently available for assessment
- There is no evidence of cumulative cognitive impairment with repeated courses of ECT
- Prevention of adverse cognitive side-effects is primarily through identifying patients at higher risk and modifying treatment factors such as laterality, pulse-width, frequency of treatment, and stimulus dose
- High-dose brief-pulse right unilateral ECT is equivalent to bitemporal brief-pulse ECT in antidepressant efficacy and is associated with better cognitive outcomes; ultrabrief pulse unilateral ECT is associated with less cognitive impact than brief pulse unilateral ECT but is less effective
- Cognitive function should be assessed prior to, during and post- ECT with suitable assessments: the sMMSE is inadequate, while the MOCA or ACE-III could be considered for routine practice where it may not be feasible to perform preferably more detailed cognitive testing
- Time for recovery to orientation should be routinely assessed as it is relatively straightforward and may have predictive value for retrograde amnesia

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