Ketamine augmentation of ECT to improve outcomes in depression

Short title: Ketamine-ECT Study

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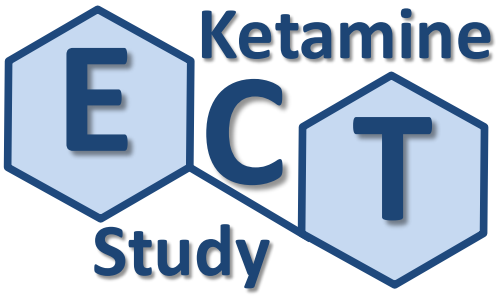

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Principal Investigator signature

I confirm that I have read and understood protocol version 8.0, dated 09.10.2014. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …… Date ……

Print Name ……

Full Site Name ……

Contents

Responsibilities

Sponsor: Manchester Mental Health and Social Care Trust will act as the sponsor for this study. Day-to-day responsibility for sponsor level activities will be delegated to the Chief Investigator and the Trial Manager.

Funder: NIHR Efficacy and Mechanism Evaluation Programme is funding this study (funder's reference: 09/90/04). Contact: Dr Jane Sinclair, Programme Manager, EME, Telephone: +44 (0) 23 8059 7502; j.sinclair@southampton.ac.uk

Trial Management: A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by the Project Manager.

Chief Investigator: The Chief Investigator (Professor Ian M Anderson) will have overall responsibility for the conduct of the study as a whole.

Clinical Principal Investigators: The Principal Investigator will have overall responsibility for the conduct of the study at a particular trial site.

Trial Management: The following functions falling under the responsibility of the sponsor will be delegated to Professor Anderson as Chief Investigator:

- Application for authorisation and Ethics Committee Opinion (including CTA request, Research Ethics Committee opinion, R&D application, including site specific assessment and local approval procedures, notification of protocol amendments and end of trial).
- Good Clinical Practice and Trial Conduct (including GCP arrangements, management of IMP, data monitoring, emergency and safety procedures).
- Pharmacovigilance (including defining and recording adverse events and reactions, reporting SUSARs, notifying investigators of SUSARs, ensuring SAEs are reviewed by an appropriate committee for safety monitoring, annual listings and safety report).
- Administration of the study budget.

Clinical Principal Investigator responsibilities:

- Study conduct and the welfare of study subjects.
- Familiarity with the use of the IMP as described in the product information, appropriate storage, administration according to the protocol and drug accountability. Ensuring that the IMP is not used for any purposes other than the conduct of the study.
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events.
- Screening and recruitment of subjects.
- Ensuring that all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care when an adverse event occurs.
- Obtaining relevant local approvals and abiding by the policies of Research Governance.
- Compliance with the Principles of GCP, Research Governance Framework and any national legislation implementing the EU Clinical Trials Directive (2001/20/EC) and subsequent amendments.
- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants prior to any study specific procedures.
- The PI should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. The Principal Investigator (PI) shall provide a current signed and dated curriculum vitae as evidence for the Trial Master File.
- Ensuring that study site team members are appropriately qualified by education, training and experience to undertake the conduct of the study.
- Availability for Investigator meetings, monitoring visits and in the case of an audit.
- Maintenance of study documentation and compliance with reporting requests -
- Maintaining an Investigator Site File, including copies of study approval, list of subjects and their signed informed consent forms.
- Documenting appropriate delegation of tasks to study personnel eg. Pharmacist, Research Assistant, Investigator(s).
- Ensuring that data collected are accurate and complete.
- Providing updates on the progress of the trial.

- Ensuring that subject confidentiality is maintained during the project and archival period.
- Ensuring archival of study documentation for a minimum of 10 years following the end of the study, unless local arrangements require a longer period.

A Trial Steering Group (TSC) has been appointed (see Appendix 1 for Terms of Reference)

A Data Monitoring and Ethics Committee (DMEC) has been appointed (see Appendix 2 for Terms of Reference)

1. Protocol Summary

Short title:	Ketamine-ECT Study
Protocol version:	8.0
Protocol date:	09.10.2014
Chief Investigator:	Professor Ian M Anderson
Sponsor:	Manchester Mental Health and Social Care Trust
Funder:	NIHR Efficacy and Mechanism Evaluation Programme
Study design:	Randomised, placebo-controlled, parallel study with blind assessment
Study Intervention:	Ketamine versus placebo (1:1 ratio)
Primary objective:	To determine whether ketamine improves cognitive outcomes after ECT
Secondary objectives:	To determine whether ketamine speeds clinical response to ECT. Elucidation of the neurobiological processes involved.
Number of study sites:	6 NHS Trusts for patient recruitment and treatment and 5 NHS Trusts for mechanistic studies (in conjuction with 2 Universities for MRI studies))
Study population/size:	100 patients, aged 18 years or older, who are receiving ECT for a primary depressive disorder. 50 healthy control subjects, aged 18 years or older with no personal or family history of mental illness.
Study duration:	42 months
Trial Duration:	34 months

2. Background

2.1. Rationale for current study

At least 3% of the UK population meet criteria for major depression at any one time(1) and the annual treatment costs for depression in 2000 were estimated at £370 million with £8.5 billion in indirect costs(2). Drug and psychological treatments outcomes are extremely disappointing; in the largest depression treatment study to date only a quarter of patients remitted after the first antidepressant and a third of patients failed to remit even after 4 treatments(3). Patients who are severely depressed and/or have failed to respond to previous treatment have the greatest mortality through suicide and morbidity due to persistent illness. Nearly one in 10 severely ill hospitalised and suicidally depressed patients will eventually commit suicide compared with one in 50 depressed outpatients(4). Failing to respond to 2-6 drug treatments results in only a 10-20% chance of significant improvement with standard care over the next 1-2 years with persistent extremely low quality of life(5). For this group of patients the National Institute for Health and Clinical Excellence (NICE) recommends consideration of ECT as a treatment option(6). In spite of ECT's superior acute efficacy its use has dramatically declined even though the needs of severely and persistently ill patients are not being met. Adverse cognitive effects are a major reason for ECT's poor acceptability and unfavourable benefit-risk balance. The key clinical rationale for this study is to determine the degree to which adjunctive ketamine prevents ECT-induced cognitive impairment. If it does to a clinically important degree then standard ECT practice will be altered nationally and internationally and the improvement of the benefit:risk balance of ECT will be a substantial benefit to patients and inform future ECT research.

The rationale for the mechanistic study is to increase understanding of the neural circuitry involved in ketamine's protective effects on cognition in ECT and to increase knowledge about the role of glutamate in the cognitive deficits associated with ECT. Brain imaging is currently of limited clinical use in psychiatric disorders and difficult to apply to very ill groups of patients. This study will allow us to evaluate the use of fNIRS as an imaging technique that could be of practical use in the future to predict outcomes and to personalise treatment.

2.2. The use of electroconvulsive therapy for the treatment of depression

Electroconvulsive Therapy (ECT) was the first effective treatment for depression discovered serendipitously in the 1930s(7). Modern ECT consists of giving brief pulses of electricity to the brain to induce a controlled seizure under a brief general anaesthetic combined with a muscle relaxant ('modified' ECT) to minimise both psychological distress and potential adverse physical complications from unmodified seizures. ECT is given twice a week in the UK (cf 3 x a week in USA(8) and Australia; Loo personal communication) with patients receiving on average 5-8 treatments(9;10) and the usual range up to 12 treatments(11). It is widely recognised as the most effective acute antidepressant treatment with a large effect size (ES) of -0.91 against sham treatment in randomised controlled trials (RCTs)(12) compared with -0.5 or less for antidepressants against placebo(6). ECT also has a much greater efficacy than pharmacotherapy (ES -0.8)(12) and achieves remission rates of 50-60% in patients who have failed to respond to drug treatment(12;13). In severely ill patients, who are suicidal or have stopped eating or drinking, ECT can be life-saving(11). It has equal efficacy in both unipolar and bipolar depressed patients(14).

2.3. Adverse cognitive effects of ECT

The number of people being treated with ECT in England has been falling, with an estimated 1,250 receiving it over a 3 month period in 2006 (30% under the Mental Health Act) compared with over twice that number in 1999(9). This has been driven in large part by concerns about a poor risk-benefit balance due to adverse cognitive side effects(15) with 1 in 5 patients in a recent study discontinuing due to confusion or cognitive impairment(8). ECT is otherwise a very safe and effective treatment(11) but its efficacy cannot be convincingly dissociated from its adverse cognitive effects(6;8). Meta-analysis confirms that ECT causes large objective impairments in cognitive function by the end of the treatment course(16) with 72% of measures showing significant worsening; the largest ES is found in word list delayed recall (-1.1) with significant impairment in all tests of anterograde memory. Executive function is also impaired (Trail Making Test B: ES -1.1; semantic, letter verbal fluency (VF): ES -0.7 to -0.8) but mostly non-significant small impairments are seen in tests involving working memory (WM) such as digit span and immediate recall (ES -0.04 to -0.21). Intermediate ES were found for the Mini Mental State Examination (MMSE, -0.28) and the Digit Symbol Substitution Test of speed of processing (-0.35). ECT therefore causes significant impairment in memory encoding and retrieval and to a lesser extent psychomotor speed. Following ECT there is a rapid reversal of deficits, with moderate to large improvements above baseline in most measures after 1-2 weeks. However some deficits may remain and spatial recognition memory was still impaired one month after the end of treatment in a recent study(17).

The meta-analysis was also not able to measure retrograde amnesia. A systematic review showed that after ECT 29-55% of patients have reported persistent, and often distressing, loss of important past memories(18). The quality of evidence examining the effect of ECT on objective measures of autobiographical memory is limited but a review concluded that impairment occurs with ECT but the degree of subsequent recovery varies between studies(19). In a recent study subjective memory impairment was associated with objective autobiographical memory impairment immediately after the ECT course, and six months later(20).

2.4. Role of glutamate in mood, cognition and the effects of ECT

The effects of ECT, and of electroconvulsive shock (ECS) in animals, range from changed neurotransmitter function to increased neurogenesis and altered gene expression(7). While the precise mechanisms underlying the effects of ECT are not fully understood, altered synaptic functioning in neural circuits involved in mood and cognition is believed to play a key role. Glutamate, an amino acid neurotransmitter with a role in both neuroplasticity and excitotoxicity, acts on a variety of receptors in the brain, most commonly N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors. These are present in approximately 70% of the synapses in the mammalian brain with high density in the cerebral cortex, hippocampus, amygdala, striatum and septum(21). Considerable preclinical evidence supports a role for glutamate in mood regulation and in the action of antidepressant treatments(21;22); in particular decreased NMDA-mediated, and increased AMPA-mediated neurotransmission has been proposed(22). Glutamate also has a central role in cognition, especially learning and memory, through its role in synaptic plasticity and the signalling pathway involved in long-term potentiation (LTP) in the hippocampus(23;24). Studies in depressed patients have found decreased frontal cortical measures of glutamate/glutamine+glutamate (Glx) measured in vivo by magnetic resonance spectroscopy (MRS) which normalises with effective treatment(21). There are similar findings with ECT; pre-treatment low Glx/glutamate concentration has been found in dorsolateral prefrontal cortex (DLPFC)(25) and anterior cingulate cortex (ACC)(26;27) which either normalised after ECT(25;27) or predicted treatment response(26). The picture is less clear in the hippocampus. A human study found ECT increased Glx concentration in unipolar but not bipolar patients in amygdala/anterior hippocampus(28) but in rats ECS decreased(29) or did not alter(30) hippocampal glutamate content. However in the latter studies ECS reduced expression/function of the regulatory NMDA receptor subunit (NMDA-NR2B) associated with memory function(29;31) and increased expression/function of the AMPA receptor(31;32). It has been proposed that the memory impairment occurring with ECT is a consequence of indiscriminate activation/saturation of glutamate receptors at the time of the seizure leading to a disruption of hippocampal plasticity involved in memory(33;34); autobiographical memory impairment may occur through disruption of the reconsolidation of 'fragile' reactivated or recalled memories(35).

2.5. Ketamine effects on mood, cognition and the effects of ECT

Ketamine is a dissociative anaesthetic, analgesic and psychotomimetic which inhibits the NMDA receptor but also stimulates glutamate release and potentiates activity at non-NMDA receptors such as AMPA receptors(36). Ketamine given acutely can cause psychological effects including dissociation, sensory distortion, anxiety or excitement(37) and cognitive impairment(38), especially in manipulating information in WM and encoding into episodic memory. Given acutely in sub-anaesthetic doses to normal volunteers ketamine increases activation in temporal and parietal cortex, mid-cingulate cortex and hippocampus while decreasing activation in subgenual cingulate(39). It acutely increases ACC and frontal cortical activation both to VF(40;41) and WM(42) tasks, implicating glutamate neurotransmission in these responses.

One of the most exciting new findings in the treatment of depression has been the replicated, very rapid, antidepressant effect after a single dose of intravenous ketamine alone, or as an adjunct to antidepressants, in both unipolar(43;44) and bipolar(45) depression. Repeated administration maintains improvement but relapse occurs very rapidly on stopping treatment(46); this, together with the rapid onset, suggest an acute pharmacological antidepressant effect, unlike the adaptive mechanisms posited with other antidepressant treatments including ECT. There is a striking similarity between the pharmacological effect of ketamine and the proposed effects of ECT on glutamate neurotransmission(22), occurring through different mechanisms(47). This may account for evidence that ketamine hastens the response to ECT but hasn't been shown to increase final efficacy(48;49) (Loo submitted).

Ketamine, in spite of its acute cognitive effects, has been shown to prevent ECS-induced impairment in LTP and in spatial memory in rats(33;50). Preliminary human data from retrospective/non-randomised studies suggests that ketamine anaesthesia improves speed of reorientation after ECT(51) and word recall measured after 6 ECT treatments(52). An RCT of adjunctive ketamine (0.5mg/kg) given during induction of anaesthesia prevented delirium and improved cognitive outcomes after cardiac surgery(53;54) supporting the hypothesis

that ketamine may be protective in situations in which excitotoxic damage might occur. A putative mechanism is that ketamine, through antagonising NMDA receptors, protects against indiscriminate stimulation by ECT.

2.6. Depression, cognitive deficits and fronto-subcortical neural circuit abnormalities

In addition to abnormal affective cognition (processing of emotionally salient information)(55), depressed patients also have deficits in non-emotional ('cold') cognitive processes, most consistently executive function, attention, psychomotor speed and memory(56;57). These deficits, together with decreased left DLPFC grey matter volume, have been associated with poorer response to antidepressants(58;59). Current neurobiological models of depression emphasise abnormalities in fronto-limbic and fronto-striatal neural circuits(60-62) and it has been proposed that mood disorders involve altered reciprocal interactions between a 'ventral circuit' including ventral prefrontal and limbic areas (involved in affective cognition, mood and autonomic/neuroendocrine function) and a 'dorsal circuit' including dorsal prefrontal, dorsal ACC and parietal cortices (involved in executive, attentional and memory functions)(61;63). In unipolar depression underactivity of the dorsal circuit and overactivity of the ventral circuit has been proposed, with recovery dependent on 'normalisation' of these circuits through modulation by the rostral ACC(61).

This hypothesis is supported by a recent meta-analysis which found significant decreases in resting cerebral blood flow (CBF)/glucose metabolism in areas corresponding to the dorsal circuit and increases corresponding to the ventral circuit(64). DLPFC decreases appear particularly related to symptom severity and psychomotor retardation/negative symptoms(65-68). Effective treatment with antidepressants has been associated with normalisation of pre-treatment abnormalities(64;69) which is supported by a recent connectivity study of treatment effects in elderly patients(70).

ECT differs from antidepressants in that it improves mood but impairs cognition. Although limited by small sample sizes, imaging studies of the effects of ECT most consistently find a reduction in cerebral metabolism in bilateral anterior and posterior frontal cortex(71). Temporal lobe and dorsal frontal lobe decreases have been associated with impairments in learning, attention, WM and autobiographical memory(72). Although the picture is less clear for mood improvement, associations have been reported with reduction in frontal blood flow(73;74) and subgenual ACC and hippocampal metabolism(75). We propose that ECT, instead of reciprocally 'rebalancing' dorsal and ventral networks as is seen with antidepressants, produces a combined suppression of both networks leading to the picture of mood improvement with impaired cognition. After the ECT course has ended the dorsal network recovers under the influence of a restored ventral network, and cognition improves.

2.7. Abnormalities in frontal cortex reactivity in depression

In addition to altered responses to emotional stimuli generally found in medial prefrontal and orbitofrontal cortex, and subcortical regions including medial temporal lobe(64), depressed patients also show altered responses to cold cognitive tasks which vary according to task and performance. We concentrate here on two types of task that consistently activate networks involving areas of the dorsal and lateral prefrontal cortex but vary in their subcortical components.

VF tasks activate predominantly left-sided areas including inferior frontal gyrus (IFG; Broca's area), premotor and medial supplementary motor areas, dorsal ACC, anterior insula, temporal and parietal cortices, caudate nucleus and hippocampus - the last especially in semantic tasks requiring associative memory(76-78). Effective connectivity analyses have emphasised interconnections between IFG and both ACC(79) and anterior insula(80). Decreased activation in regions of left lateral prefrontal cortex compared with controls has been found in most(81-86) although not all(87;88) studies in depression, with a minority of studies also showing concurrent impaired performance(82;83;88).

Tests of WM, such as the N-back task, activate a network used in maintaining task-relevant information during a delay, involving rehearsal and goal-directed attention. These include the DLPFC and ventrolateral prefrontal cortex, premotor area, dorsal ACC, parietal and temporal cortices and cerebellum(89;90). Some studies in depressed patients have found increased DLPFC/ventrolateral prefrontal activation in the absence of impaired performance(91-94), but others have found no change(95-97) or decreased(95;98) activation; the latter also associated with impaired performance. One interpretation is that depressed patients recruit more brain regions in an attempt to maintain function(91). A study using a verbal WM fMRI task showed decreased connectivity in depressed patients associated with longer delay in a prefrontal-parietal network and increased connectivity associated with shorter delay in a network involving the ACC and DLPFC(99). Greater degree of

improvement with antidepressant treatment has been associated with less DLPFC hyperactivation before treatment(92) and with the dorsal-ventral network interaction theory of antidepressant response(61).

These two types of task, both activating the prefrontal cortex and dorsal ACC, offer the opportunity to investigate overlapping networks. The WM network is predominantly cortical while the VF network includes the hippocampus involved in memory formation and recall. Encoding of memories activates bilateral IFG and left hippocampus with the left IFG playing a pivotal coordinating role in associative encoding(100). Autobiographical, episodic and semantic memory retrieval share a common functional network which includes left hippocampus, bilateral inferior frontal gyri, ACC and posterior cingulate cortex(101). We therefore propose to use VF as a functional probe of the associative memory network and fronto-hippocampal connectivity. WM provides a control task for a network functionally relatively spared by ECT.

2.8 Near infrared spectroscopy

Near infra-red spectroscopy (NIRS) is based on the principle that most biological tissues are relatively transparent to light in the infrared ranges between 700-1150nm. However chromophores such as oxygenated (oxy-Hb) and deoxygenated haemoglobin (deoxy-Hb) absorb specific wavelengths in this range offering an 'optical widow' for non-invasive assessment of these compounds in the brain. Attenuation of specific wavelengths of near infrared light transmitted through the tissue of interest allows calculation of the changes in the concentration of oxy-Hb and deoxy-Hb (in μmolar units) by applying the modified Beer Lambert law. Using multiple sources and detectors allows topographic maps of changes in oxy-Hb and deoxy-Hb to be generated across the illuminated region. In addition a spatially resolved spectroscopy (SPS) technique can be used, with a modification of diffusion equation of light transport, to provide an absolute measure of tissue oxygenation (the tissue oxygenation index; TOI). This index is the absolute percentage of total haemoglobin in the field of view which is oxygenated(102). Analogous to fMRI using blood oxygen level dependent (BOLD) changes, it is possible to use functional NIRS (fNIRS) as an index of functional activation of cortical blood flow(103;104). Preliminary evidence supports reasonable concordance between fMRI and fNIRS measures(103;105) but they are best viewed as complementary methodologies. fNIRS lacks the spatial resolution and brain coverage of fMRI and in particular it is limited to measuring superficial cortical areas close to the scalp with the depth determined by the separation between transmitter and detector. It is however a relatively cheap, portable, safe, quick and extremely well tolerated 'bedside' technology that allows imaging to be carried out when fMRI scanning is difficult or contraindicated. fNIRS provides greater temporal resolution than fMRI (data acquisition typically in the order of 10Hz) allowing more detailed analysis of the haemodynamic response function associated with neural activity, e.g. latency effects. Complementary fMRI and fNIRS studies in the same patients can therefore provide a wealth of information; structural and fMRI data can be used to inform the spatial sensitivity of fNIRS, and highly temporally resolved oxy-Hb and deoxy-Hb measures can be used to understand the physiological basis of the fMRI BOLD signal. The TOI, although used clinically in intensive care settings, has been little studied in relationship to functional disorders. Its reliability and validity has yet to be established(106), however it does provide a potential absolute measure with which to assess cerebral tissue metabolism across groups and within subjects(104).

Of relevance to this application fNIRS has been extensively used to study frontal cortex activation using VF and WM tasks with a high degree of reliability with repeated administration(103;107-110). Depressed subjects reliably demonstrate decreased lateral prefrontal cortex activation compared to controls during a VF task(81;84-86;111); WM has been less studied with a single recent study showing a decrease in prefrontal activation in depression associated with decreased performance(98). We are not aware of fNIRS studies using these tasks to examine change with antidepressant treatment.

3. Objectives

1) To find out whether adjunctive ketamine attenuates the cognitive adverse effects of ECT and speeds clinical improvement. 2) To investigate the tolerability and acceptability of adjunctive ketamine given with ECT, 3) To identify how ketamine modifies ECT's effect on fronto-subcortical neuronal circuits believed to be involved in cognitive impairment after ECT.

3.1 Clinical outcome hypotheses

Hypothesis 1 (primary). Ketamine compared with saline treatment will reduce ECT-induced cognitive impairment in anterograde verbal memory at the time of primary outcome (usually 4 ECT, see section 7). In the original protocol, autobiographical memory and VF had been included as primary outcomes, but in recognition of recruitment shortfall, a single key primary outcome (HVLT-R) was selected, with the others now secondary outcomes.

Subsidiary hypothesis 1a: Ketamine compared with saline treatment will reduce ECT-induced cognitive impairments at end of acute treatment with ECT ('end of ECT').

Subsidiary hypothesis 1b: Four months after end of ECT a significant difference between ketamine and saline groups will remain only for autobiographical memory.

Hypothesis 2. Ketamine compared with saline treatment will result in a greater decrease in depression scores after 4 ECT treatments.

Subsidiary hypothesis 2: Compared with saline, patients receiving ketamine will need fewer ECT treatments to achieve remission.

3.2 Mechanistic hypotheses

MR imaging, included in the original protocol, has been excluded due to low recruitment.

Hypothesis 3 (key mechanistic hypothesis). Ketamine compared with saline treatment will increase frontal cortex activation (as measured by fNIRS and fMRI) in response to a verbal fluency (VF), but not a working memory (WM) task, and this will relate to group differences in task performance.

Hypothesis 4. No longer included [originally: Ketamine compared with saline treatment will result in stronger frontal cortex-hippocampal connections (measured by VF task-dependent functional connectivity analysis with fMRI)].

3.3 Exploratory mechanistic hypotheses

Hypothesis 5. Ketamine augmentation compared with saline will be associated with a relative increase in frontal tissue oxygenation index (TOI) measured with spatially resolved spectroscopy NIRS at the end of ECT which will correlate with differences in performance in VF but not WM.

Hypothesis 6. No longer included [originally: Glutamate concentrations in DLPFC and ACC measured by MRS will increase during ECT and will be correlated with clinical improvement].

4. Research design

See Appendix 3 for Flow Chart

4.1 Clinical trial

A 34-month (originally 30 month) randomised placebo-controlled clinical outcome and mechanistic study of ketamine added to standard ECT during anaesthetic induction in 100 severely ill depressed patients who have been referred for ECT by their psychiatrist (revised from originally target of 160 patients). Clinical and research teams and patients will be blind to allocation but for safety reasons the anaesthetic team will not be. Success of blinding will be assessed after 4 treatments and at end of ECT.

ECT will be administered twice a week until the patient's depression has remitted. Patients will be allocated to treatment group in a 1:1 ratio according to a randomised permuted blocks algorithm, after stratification by Trust for those not undergoing MR imaging and by scanning centre for those undergoing MR imaging. The Research Ethics, Medicines and Healthcare products Regulatory Agency (MHRA) applications and relevant Pharmacovigilance activities will be undertaken by Manchester Mental Health and Social Care NHS Trust (MMHSCT) to their procedures and in accordance with statutory regulations, Research Governance Framework and Good Clinical Practice (GCP), in conjunction with the Research Trial Manager.

Data Management and Quality Assurance will be undertaken by the Christie Clinical Trials Unit (CTU) in accordance with their Standard Operating Procedures (SOPs) to ensure compliance with GCP standards.

Assessments will consist of neuropsychological, efficacy and safety assessments carried out according to the schedule described in Appendix 4

There are no planned stopping rules or interim analyses but continuation of the trial will be subject to safety findings overseen by the DMEC.

4.2 Mechanistic studies

MR imaging, included in the original protocol, has been excluded due to low recruitment.

These will be carried out on all patients as far as possible. Patients will receive fNIRS at the same time as the neuropsychological tests using a portable optical topography system to obtain minimum of 20 usable datasets (revised from original of 100).

Matched healthy controls (to obtain usable datasets for fNIRS in N=50) will be recruited to undertake identical neuropsychological and imaging tasks on a single occasion to be able to identify pre-treatment abnormalities in depression and the degree to which they normalise with ECT.

DNA samples for exploratory genetic analysis will also be collected to look for predictors of the benefit of ECT or ketamine which may be of use in personalising treatment in the future, and may help explain variation in mechanistic outcomes.

5. Study population

Hospital out- and in-patients with moderate to severe depression who have been referred for ECT treatment by their treating team, and determined to be fit for ECT treatment and ketamine administration by an anaesthetist. Matched healthy volunteers will be recruited for mechanistic studies.

5.1. Patient criteria

5.1.1 Inclusion criteria

1. Male or female aged 18 years and above;
2. Current DSM-IV diagnosis of a major depressive episode, moderate or severe as part of unipolar or bipolar disorder mood disorder diagnosed by the Mini International Neuropsychiatric Interview (MINI) (112);
3. American Society of Anaesthesiologists (ASA) score (excluding mental health considerations in the scoring) of 1, 2 or stable 3, and judged as suitable to receive ketamine by an anaesthetist;
4. Verbal IQ equivalent to ≥ 85, sufficiently fluent in English to validly complete neuropsychological testing;
5. Capacity to give informed consent;
6. Willing to undertake neuropsychological testing as part of the study.

5.1.2 Exclusion criteria

1. DSM-IV diagnosis of a primary psychotic or schizoaffective disorder, current primary obsessive compulsive disorder or anorexia nervosa;
2. History of drug or alcohol dependence (DSM-IV criteria) within the last year;
3. ECT in last 3 months (to avoid confounding the assessment of cognitive outcomes) or has previously received ECT in the current trial;
4. Known hypersensitivity or contraindication to ketamine or excipients in the injection, including significant cardiovascular disease, uncontrolled hypertension, glaucoma, cirrhosis or abnormal liver function or liver disease;
5. Known hypersensitivity or contraindication to concomitant medications used for ECT including propofol and suxamethonium or excipients in the injections;
6. Evidence of organic brain disease including dementia, neurological illness or injury, or medical illness which may significantly affect neuropsychological function;
7. Detained under the Mental Health Act (1983 as amended 2007) or unable to give informed consent;
8. Pregnancy, or at risk of pregnancy and not taking adequate contraception, breastfeeding;
9. Score < 24 on the Mini Mental State Examination (MMSE)(113);

5.2 Healthy control criteria

These will be sex, age and handedness matched as a group with patients undertaking mechanistic studies

5.2.1 Inclusion criteria

1. Aged 18 years or more;
2. Currently psychiatrically well, confirmed through MINI interview and no current psychotropic medication;
3. In good physical health.

5.2.2 Exclusion Criteria

1. Personal history of psychiatric disorder, as revealed by MINI interview;
2. First degree family history of major psychiatric illness requiring treatment;
3. Significant physical illness including organic brain disease, neurological illness or injury that could interfere with interpretation of results;
4. Psychotropic medication or other medication that could interfere with interpretation of results;
5. Score < 24 on the Mini Mental State Examination (MMSE);

5.3. Treatment and study withdrawal criteria

5.3.1 Treatment withdrawal

- The patient withdraws consent or decides to discontinue for any reason (e.g. adverse event) or simply wishes to stop without having to give a reason;
- Loss of capacity to provide continuing consent;
- Serious adverse event considered to be related to active trial medication as determined by local PI in consultation with responsible medical officer (RMO), anaesthetist and the patient;
- Local PI, RMO, anaesthetist and/or ECT consultant decision based on collaborative decision for safety reasons, adverse events or patient deterioration (for governance purposes formally decided by PI or delegee).

5.3.2 Study withdrawal

Participants can withdraw from study intervention but will remain in the study for follow-up unless consent to participate is withdrawn or lost.

6. Planned interventions

6.1 ECT

Standard ECT protocols will be agreed between centres for patient safety and trial reliability and validity and will be consistent with requirements given in the Royal College of Psychiatrists' (RCPsych) ECT Handbook(11). Oral psychotropic medication continued by the clinical team will where possible remain unchanged for the first 4 treatments and ideally until the end of ECT.

Routine clinical investigations for ECT work-up will be as clinically required by clinical protocols and include physical examination, blood pressure, pulse rate, blood tests (full blood count, renal, hepatic and thyroid function tests) and ECG which will be recorded as having been done but not specified by the trial protocol. An opinion will be recorded by the anaesthetist in the pre-anaesthetic assessment that they are not aware of contraindications to ketamine being given as specified in the trial protocol.

ECT treatments will be scheduled twice weekly. For each ECT treatment, after preoxygenation with 100% oxygen and hyperventilation, anaesthesia will consist of propofol combined with the muscle relaxant suxamethonium, and these drugs will remain the same for all the ECT treatments unless varied for clinical reasons as defined in the relevant standard operating procedure (SOP). ECT treatment will be given after motor endplate depolarisation is determined by cessation of muscle fasciculation in the feet. Electrode placement will be standard bifrontotemporal (BL) or right unilateral D'Elia (RUL) with brief pulse stimuli (0.5-1ms). Following rapid stimulus dose titration (as described in the RCPsych ECT Handbook(11)) to determine the seizure threshold in the first session, treatment doses will be 1.5-2.0 x threshold for BL, and 4-6 x threshold for RUL electrode placement (according to local clinic protocol). Stimulus parameters will remain the same at least until after the primary outcome assessment (see section 7).

Agreed guidelines will be followed to determine an adequate seizure and for restimulation and dosage adjustments later in the course as given in the RCPsych ECT Handbook(11) and specified in study SOPs.

The goal will be to treat patients to remission (Montgomery Asberg Depression Rating Scale, MADRS ≤10) in accordance with NICE guidelines(6) and the clinical team will be encouraged treat patients according to these guidelines. However the final decision to end ECT treatment will rest with the clinical team in consultation with the patient and ECT team. Factors that could influence outcome including patient illness characteristics, handedness, seizure duration, stimulus dosage and anaesthetic and other medication will be recorded.

6.2 Experimental intervention

The experimental intervention will be intravenous ketamine 0.5mg/kg or an equal volume of saline given according to the randomisation schedule by the anaesthetist as a slow bolus according to the relevant study SOP. This will usually bebefore the induction agent and suxamethonium at each ECT treatment unless it is necessary to alter the administration order for clinical reasons as defined in the SOP.

We will define someone as a study dropout) if consent for study participation is withdrawn or further assessments are not able to be carried out for other reasons which will be recorded. Intervention dropout will be defined as stopping ketamine/placebo for any reason before the end of ECT and the reason recorded

(such as withdrawn consent or an adverse event). As there is no specified length of an ECT course we will record the reason for finishing ECT treatment rather than pre-defining criteria for a dropout from ECT treatment. The end of acute treatment with ECT is defined in section 7.

7. Assessments

See Appendices 3 and 4 for flowchart and schedule. Note that the time of primary outcome assessment is defined as after 4 ECT unless unavoidably varied by ±1 ECT treatment to avoid loss of data for reasons defined in the relevant SOP. The end of acute treatment with ECT (end of ECT) is defined as the last ECT given to as part of a course of treatments to bring about clinical improvement. This will usually be the last ECT treatment received with variations described in the relevant SOP. Approximate timings of each specific research assessment involving patient time are given italicised in brackets where applicable.

7.1 Pretreatment

- Physical and psychiatric illness and medication checklist to complete Massachusetts General Hospital (MGH) (113) staging for previous treatment trials (from notes, clinical team and patient);
- Background information including demographics, ethnicity and years in full time education (from notes and patient);
- Mini Mental State Examination (MMSE)(114) *(7 minutes)*
- Mini International Neuropsychiatric Interview screen including suicidality screen *(10 minutes)*
- Mini International Neuropsychiatric Interview (MINI)(112) *(30 minutes but varies according to symptoms);*
- Wechsler Test of Adult Reading to assess premorbid intellectual functioning (WTAR)(115) *(2 minutes);*
- Modified Edinburgh Handedness Questionnaire (mEHI)(116) *(1 minute)*
- If taking part in MRI scanning substudy, a safety questionnaire to check for contraindications to MRI (local routine questionnaire at each imaging centre) *(3 minutes)*;
- Physical examination documented as done with height and weight, pulse and blood pressure to be recorded in the case report form (CRF) (carried out by treating team for ECT workup)
- ECG documented as done (carried out by treating team for ECT workup)
- Blood tests (full blood count, renal, hepatic and thyroid function) documented if done (as carried out by treating team for ECT workup).

7.2 Safety measures

The safety measures will be those applied in standard practice before and after each ECT.

- Heart rate and blood pressure.
- Peripheral oxygen saturation and capnography (during and after ECT).
- Reorientation: Number correct of 5 orientation items, (name, place, day of the week, age, and birthday)(117) 30 minutes and 60 minutes after first breath and whether oriented 60 minutes after first breath as measured as 4 or more items correct (*30 seconds).*

Occurrence of emergent agitation, psychosis or mania/hypomania will be recorded as an adverse event both within and between ECT sessions. In addition the Brief Psychiatric Rating Scale (BPRS)(118), which includes ratings of psychosis and elevated mood, will be administered at the same time as the efficacy ratings (7.4.2).

7.3 Trial blinding

Blinding will be assessed after time of primary outcome and at end of ECT by asking patients, the ECT consultant and the RAs to complete a brief questionnaire indicating their guess as to treatment allocation, how certain they are (Likert scale) and reason for their choice. The ratings will be put in a sealed envelope and sent directly to the CTU for data entry in order to minimise the risk of those involved in study ratings being influenced by others' beliefs.

7.4 Clinical outcomes (all patients)

7.4.1 Neuropsychological tests

The neuropsychological tests have been chosen to be sensitive to the effects of ECT(8;119;120) and to have a duration short enough to be acceptable to patients *(total 35-40 minutes)*.

Primary

- Hopkins Verbal Learning Test – Revised (HVLT-R)(121) (6 alternate forms) *(5 minutes)*

Secondary

- Autobiographical Memory Interview - short form (AMI-SF)(122) *(15-20 minutes)*
- Controlled Oral Word Association Test (COWAT)(123) letter and category fluency *(5 minutes)*
- Medical College of Georgia Complex Figure Test (MCG complex figure test)(124)(4 alternate forms) *(7 minutes)*
- Digit span as a test of WM(125) *(4 minutes)*
- Self-reported Global Self Evaluation of Memory (GSE-My)(126) recently reported to correlate with AMI-SF scores after ECT *(1 minute)*

7.4.2 Efficacy measures

Primary

- MADRS(127) *(10 minutes)*

Secondary

- Clinical Anxiety Scale (CAS)(128) *(5 minutes)*
- BPRS(118) to detect psychosis or manic symptoms *(8 minutes)*
- Remission at end of ECT (MADRS ≤10)
- Number of ECT treatments to achieve remission
- Response at end of ECT (≥ 50% decrease in MADRS from baseline)
- Clinical Global Impression – Severity and Improvement (CGI-S, CGI-I)(129)
- Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR)(130) *(5 minutes)*
- EuroQol (EQ-5D) (131) *(2 minutes)*
- Proportion significantly worsening after end of ECT (MADRS increase of ≥4 points + CGI-S increase of ≥1 point to CGI-S ≥3 compared with assessment at end of ECT)

7.5 Mechanistic outcomes

7.5.1 Near Infrared Spectroscopy (NIRS)

Two purpose built optical topography systems (Biomedical Optics Research Laboratory, Dept. of Medical Physics and Bioengineering, University College London (UCL)) will provide a 48 channel array for topographical coverage of bilateral DLPFC and ventrolateral prefrontal cortex. fNIRS will be used to to map the response to VF and WM tasks employing alternative versions of the fMRI tasks. Fiducial markers placed on fixed external landmarks during the MRI studies will act as reference points for array placement and co-registration markers for combined analysis of the fMRI and fNIRS data.

A measure of the absolute TOI derived by spatially resolved spectroscopy (SRS) will be compared with the CBF data acquired from ASL MRI. A mathematical model of brain circulation and metabolism developed by Elwell's group to aid the interpretation of NIRS data(132), will be used to explore the fNIRS, arterial spin labelling (ASL) and BOLD signals and in order to more fully characterize cerebral metabolism in the resting and activated brain.

7.5.2 Exploratory Genetic analysis

Blood samples will either be posted to the University of Manchester, Neuroscience and Psychiatry Unit (NPU) for storage at -20°C or will be stored at -20°C locally initially and then transferred at a later date. Handling of the sample will follow the requirements of the Human Tissue Act.. Genomic DNA will be extracted using standard methods in the NPU. Polymorphisms will be genotyped using standard highly accurate technologies routinely carried out in the Centre for Integrated Genomic Medical Research (CIGMR) or an alternative accredited laboratory.

7.6 Schedule of assessments

See Appendices 3 and 4 for flowchart and schedule. Note that assessment timings may be varied within defined parameters to ensure data capture without compromising study validity. In particular the primary outcome assessment after the 4th ECT may be varied, only if strictly necessary, to after the 5th ECT, or if only 3 ECT treatments are received, then this point will be taken as both the primary outcome and end of ECT.

7.6.1 Neuropsychological tests

Depending on the preference of the participant they can either undertake the tests in the same session following the MINI or at a further session. These will be repeated between 1-3 days after the 4th ECT (2 weeks), 1-5 days after the last ECT and 1 and 4 months after the last ECT.

7.6.2 Efficacy assessments

Ratings of mood and illness severity will be carried out at the screening/recruitment visit visit after the MINI if the patient is eligible for the study. They will be repeated after every second ECT (i.e. weekly) until the end of ECT treatment and 1 and 4 months after the last ECT by the RA.

7.6.3 Imaging

NIRS will be carried out at the same time as neuropsychological tests at baseline, mid ECT, end ECT and one month follow up..

7.6.4 Genetic analysis

A blood sample (4 ml, EDTA) will be obtained (at a suitable time during the study for patients and as a separate blood test for controls) from each participant who consents to the genetic testing.

8. Study procedures and practical issues

8.1 Patient identification

All patients receiving ECT require ECT work-up and are notified to the respective ECT Clinic manager before ECT can be undertaken. Although this should allow sufficient time for study screening and assessments, referral to the ECT Clinic is often only shortly before the first ECT. In order to prevent 'too late' referrals close liaison will be between ECT Clinic managers, referring clinical teams and RMOs, local PI, MHRN Clinical Studies Officers (CSOs) and study RAs. In addition educational events and proactive contact with clinical areas for intelligence of patients who may undergo ECT will be undertaken to encourage early referral. Patients undergoing emergency ECT will rarely be able to give informed consent. Potentially suitable patients will be approached initially through their clinical team (treating team or ECT clinic team) or local R&D approved, GCP and Caldicott Guardian compliant, methods of informing patients of research opportunities including MHRN CSOs attached to clinical teams, prior consent by patients to be involved in research such as a patient research passport or citizen scientist scheme. Involvement in the research will be subject to agreement of the treating clinical team in consultation with the patient.

Control participants will be recruited by advertisement (poster, email, website), word of mouth or interested non-blood relatives of patients undergoing ECT.

8.2 Screening

A screening log will be kept to document details of all subjects undergoing ECT not only those invited to participate in the study. Information recorded here will be sex, ethnicity, and age. For subjects who are suitable for the study but decline participation, this will also document any reasons available for non-participation.

8.3 Consent

A Research Ethics Committee-approved Participant Information Leaflet (PIL), informed by user involvement, will describe the rationale for the study and the possible benefits and risks of taking part. In seeking informed consent the clinical PI or designee will establish that the patient has capacity (in discussion with the clinical team), has read and understood the PIL and will answer any questions before the patient signs an approved informed consent form. The patient will sign that he/she understands that they may withdraw consent at any time without affecting their treatment. Written consent will be obtained prior to any study-specific procedures or activities. The taking of consent from patients will be by medical and research staff who have been trained both in GCP and sufficiently about the study to be able to explain the nature and risks involved and to answer queries about them. The research requires the ability to validly take part in neuropsychological testing including basic literacy, and adequate visual and motor abilities. A patient who is unable sign his/her name would not therefore to be able to take part in the study.

Controls will also receive an ethically-approved PIL, informed by user involvement, that will describe the rationale for the study and the possible benefits and risks of taking part. They be consented by a principal investigator or trained researcher.

The original signed consent form will be retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant. The participant will specifically consent to their GP being informed of their participation in the study. The right to refuse to participate without giving reasons will be respected.

The information sheet and consent form for the study will be available only in English as sufficiently good English is required to validly undertake the neuropsychological tests which are the primary outcome.

Separate consent forms will be used for the imaging sub-studies, and a desire not to participate in these parts of the study will not preclude the patient from taking part in the main study.

8.4 Data Handling and Record Keeping

Data will be collected on paper case report forms (CRFs) which will be sent to Christie CTU for data entry. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Non-identifiable patient data will be stored on University and personal computers, this will include anonymised imaging data. No participant identifiable data will leave the study site. Case report forms and samples will bear only the participant's unique study ID number and initials. The quality and retention of study data will be the responsibility of the Chief Investigator. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

8.5 Randomisation

Patients will be randomised in a 1:1 ratio to ketamine or saline following recruitment and before the first ECT using permuted block randomisation, stratified by inclusion by Trust.. The randomisation code will be generated by the Christie CTU and provided to the local pharmacies for drug preparation when a patient is recruited (see 8.6). For safety reasons the anaesthetist and anaesthetic team administering the anaesthetic for ECT will not be blind, and will be aware of the randomisation by being able to identify the study drug at the time of ECT in the packaging provided by pharmacy. Once allocated, the patient will continue to receive the same experimental treatment during the study.

Contact details for Randomisation: 0161 446 3311 The registration line will be open during office hours (9-5pm Monday-Friday)

8.6. Blinding and study drug dispensing

The patient, clinical team, ECT psychiatry team and investigator/assessor will be blinded to the treatment arm. Only the anaesthetist and anaesthetic team will not be blind.

Ketamine injections and sodium chloride 0.9% (normal saline) injections will be dispensed via clinical trial prescriptions by local hospital pharmacies. Investigational Medicinal Product (IMP) dispensing and storage arrangements will comply with the summary of product characteristics (see Appendix 5), local pharmacy procedures and GCP. Dispensing of the trial medication will be by prescription completed by the anaesthetist or medically qualified delegee on study-approved forms that do not identify whether the drug is ketamine or normal saline. To avoid casual unblinding of the ECT Clinic staff drug vials will be dispensed boxed in plain packaging and the packaging 'labelled' as the outer plain box will require labelling by pharmacy in line with Annex 13 (Investigational Medicinal Products) of the EU Guidelines to Good Manufacturing Practice (http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm) by the local pharmacies. Drug reconciliation will be carried out at each site to the principles of GCP. Before each ECT session the anaesthetist will draw up the ketamine or saline into a syringe for administration ensuring the non-anaesthetic team do not see the preparation of study drug. The syringe labelling will not identify which drug is being administered.

Every attempt will be made to minimise the risk that the unblinded anaesthetist transmits this information to the ECT Clinic team during ECT. However this may not be possible and the effects of ketamine may be apparent during or after the treatment. The key blinding is related to cognitive and efficacy assessments which will be done by the RA who will not attend the ECT sessions. In addition blinding checks will be carried out as in Section 7.3 to assess the degree to which unblinding has taken place.

As the anaesthetist is not blind there is no need to break blinding at the time of ECT sessions. In the unlikely event that there is the need to break the blind outside ECT session this will be discussed with the local PI or appropriate delegee and if necessary carried out through contacting the local pharmacy, or the Clinical Trials Unit, during working hours where a code will be kept securely. There is no provision for emergency or out-of-

hours code breaking, given that the anaesthetist is not blinded during the acute administration period, ketamine's short half life means that the drug is rapidly eliminated from the system and that clinical management outside the ECT session would not be altered by knowing whether or not ketamine had been received. Code breaks will not be routinely performed for patients who complete study treatment.

8.7 Study Medication

Ketamine (2-(2-chlorophenyl)-2-(methylamino)cyclohexanone) is available as its hydrochloride salt in a racaemic mixture. It is an NMDA receptor antagonist with the blockage non-competitive and use-dependent. Ketamine has also been found to bind to opioid, epecially μ receptors, and sigma receptors. Ketamine also has anticholinergic, predominantly anti-muscarinic effect and at high doses it blocks calcium channels(134).

Ketamine is available as a clear solution for infusion or injection. The ketamine product used will be one approved by the MHRA for use in the trial under a Clinical Trial Authorisation (CTA). Products will include Ketalar Injection (Pfizer). Further details related to Ketalar are given here to provide information about the clinical use of ketamine, but for other ketamine products the Summary of Product Characteristics (SmPC) for that product must be consulted. The ketamine strength to be used in the study will be 10mg ketamine base/ml, unless product availability necessitates a variation approved under the CTA. Ketamine is chemically incompatible with barbiturates and diazepam because of precipitate formation and therefore these should not be mixed in the same syringe or infusion fluid. Ketamine is contra-indicated in people in whom an elevation of blood pressure would be a serious hazard and should not be used in patients with eclampsia or preeclampsia, severe coronary or myocardial disease, cerebrovascular accident or cerebral trauma. Because of the substantial increase in myocardial oxygen consumption, ketamine should be used in caution in patients with hypovolemia, dehydration or cardiac disease, especially coronary artery disease (e.g. congestive heart failure, myocardial ischemia and myocardial infarction). In addition ketamine should be used with caution in patients with mild-to-moderate hypertension and tachyarrythmias. Elevation of blood pressure begins shortly after the injection of ketamine, reaches a maximum within a few minutes and usually returns to preanaesthetic values within 15 minutes after injection. The median peak rise of blood pressure in clinical studies has ranged from 20 to 25 percent of preanaesthetic values. For full details related to the Ketalar preparation see the SmPC in Appendix 5. SmPCs for other authorised preparations will need to be consulted if they are used in place of Ketalar.

8.8. Procedures for discontinuation of a patient

Any patient discontinued from the investigational drug will be asked, together with relevant clinical staff, about the reason(s) and the presence of any adverse event which will be recorded in the study case report form and acted on as indicated. Efforts will be made to continue to obtain follow-up data, with the permission of the patient.

8.9 Protocol violations

For protocol violations without implications for patient safety the reasons will be recorded fully and the patient continued in the study. They should be discussed with the local clinical PI and Project Manager as soon as possible to consider implications for trial management and interpretation but not recorded as an adverse event. Where protocol violations may impact on patient safety they will be recorded as an adverse event and a decision to continue with treatment or in the study made by the local PI in consultation with the ECT and clinical team and participant.

Following a protocol violation, or premature withdrawal from treatment, whether or not a patient's data will be included in the analysis will be decided on the basis of rules established in a pre-specified analysis plan. This will be designed to preserve the validity and integrity of the data and study and will be drawn up and agreed with the Data Monitoring and Ethics Committee.

9. Statistical Considerations

9.1 Study power

It is proposed to recruit patients from at least 6 NHS Trusts (serving about 5.5 million people) providing Mental Health care in the North of England.

9.1.1 Clinical outcomes

Original estimates: One hundred and sixty patients (80 per treatment arm) will be recruited. Recent studies of ECT have reported drop-out rates of between 0% and 26% of patients from treatment during the ECT course(8;136). We assume a 20% drop-out from treatment but expect to assess 95% of patients after 4 treatments, 90% at end of ECT, and 80% at 1 month and 75% at 4 months follow up. This gives 152 for the primary outcomes and 144 for the outcomes at the end of ECT.

Revised estimates September 2014 due to shortfall in recruitment: One hundred (50 per treatment arm) will be recruited. Recent studies of ECT have reported drop-out rates of between 0% and 26% of patients from treatment during the ECT course(8;136). We assume a 20% drop-out from treatment but expect to assess 95% of patients after 4 treatments, 90% at end of ECT, and 80% at 1 month and 75% at 4 months follow up. This provides 95 for the primary outcome and 90 for the outcomes at the end of ECT (see revised power calculation below).

In 2009/2010, 355 patients from the original NHS Trusts involved in the study received ECT over 12 months. Preliminary data from 2010/2011 indicated similar numbers. The most comparable recent study involving ECT in the UK(134) found that 41% of 260 assessed patients were eligible (using similar inclusion/exclusion criteria to this study) and 18% were randomised. However the study involved randomisation to ECT or transcranial magnetic stimulation and 22% of eligible patients did not want to be involved in research or were excluded due to clinical decision. As the current study offers adjunctive, rather than alternative, treatment and all patients will receive standard ECT, we were optimistic that a higher recruitment proportion can be achieved. A 22.5% recruitment rate would have resulted in 80 patients/year being recruited giving 160 patients over the 24 months planned for recruitment (see Appendix 3).

However once recruitment was underway the monthly recruitment figures varied from 0-5 and both the numbers of patients receiving ECT, and the proportion of eligible patients has been lower than predicted. A revised recruitment rate of 4-5/month from September 2014 based on 11 ECT suites is projected to achieve 90-100 patients recruited to the end of the study.

Original power calculation: The study is designed to detect a standardised effect size (ES) of 0.53 between the ketamine treatment group and the placebo group in the primary outcome variable, HVLT delayed recall, after 4 ECT sessions. A sample size of 76 assessable patients per treatment group provides 90% power to detect this ES at a 5% significance level. Assuming 95% of patients can be assessed after 4 ECTs this requires a total of 80 patients to be randomly assigned to each treatment group, or a total of 160. If only 85% of the 160 patients can be assessed then this gives 87% power to detect an ES of 0.53.

The three main cognitive interdependent measures are HVLT delayed recall, COWAT category fluency and AMI-SF. Based on a total of 76 assessable patients per group, and using a Bonferroni correction for the three outcomes, this gives 81% power to detect a standardised ES of 0.53 for all 3 outcomes assuming independence.

Revised power calculation September 2014: 90 patients (45 per treatment arm) gives 81% power to detect an ES of 0.6 for HVLT delayed recall. Depending on dropouts this will require between 90 (if 0% dropout) and 100 (if 10% dropout) patients to be recruited to achieve this at primary outcome.

9.1.2 Mechanistic outcomes

Original power calculation: For fNIRS is we aim to recruit all patients possible in Greater Manchester and Newcastle (about 60% of total, minimum N=100) and, depending on timing and resources, we will attempt to include some patients in other Trusts involved to further increase numbers. There are no informative ECT studies using fNIRS. A study in depressed subjects(81) showed an ES difference from controls of 0.8 in frontal cortex oxyHb response to a VF task. With 45 patients per group assessed at end of ECT we will be able to detect an ES of 0.6 with 80% power and two sided p=0.05.

Assuming that genetic effects will explain 1% variability, the ketamine effect will explain 5% variability (R2) and their interaction an additional 3-5% variability in treatment outcome (decrease in MADRS score or improvement in cognitive function) using independent groups (50% ketamine, 50% placebo), continuous outcome measures, dominant inheritance and a gene-environment interaction model with 160 participants the study will have 63-84% power at a 5% (two sided) significance level to detect gene x treatment interaction effect (Quanto 1.2.4, http://hydra.usc.edu/gxe, 2009).

Revised power calculations September 2014: For fNIRS a revised prediction of 20 patients only gives 10 patients per treatment arm giving an ability to detect an ES of 1.4 with 80% power and two sided p=0.05. Comparing 20 patients and 40 controls (ratio 1:2) gives an ability to detect an ES of 0.8 with 80% power and two sided p=0.05.

Revised power calculation not carried out for genetic analysis.

9.2 Statistical Analysis

There are no interim analyses planned unless requested for safety reasons by DMEC.

9.2.1 Clinical outcomes

All estimates of efficacy will be based on a modified intention to treat (ITT) analysis including patients who have received at least one ECT treatment (as this is a study of the effect of ketamine on ECT). The main statistical inference for both types of clinical outcome will be made after 4 ECT sessions. In addition, the two treatment groups will be compared at the end of acute ECT treatment and one and four months later (end of acute ECT treatment will be defined as in the relevant SOP to take account of the few patients who go on to receive continuation ECT). Efficacy measures will also be analysed weekly. Analysis methods involving linear mixed effect models taking into account missing data, stratification and other baseline factors will be fully specified in a detailed data analysis plan to be approved by DMEC.

9.2.2 Mechanistic studies

The effects of ECT treatment and the modulatory influence of ketamine or saline will be analysed using standard analysis methods for each specific technique adjusting for baseline factors where appropriate in order to explore which performance differences are explained by neuronal effects of treatment. Mechanisms (i.e. treatment-effect mediation) will be evaluated by applying methods described by Baron & Kenny(139) and instrumental variable methods (140). Comparison of NIRS and MRI/MRS data (i.e. calibrating one against the other) will be carried out using instrumental variable regression methods(141). Any modifications to the planned analysis methods will be informed by advances in statistical methodology and the particular requirements of the data sets obtained.

fNIRS data will be analysed using custom-designed software developed at University College London based on previous multichannel, maximum change algorithms to define the functional activation(142) and with HOMER2 (http://www.nmr.mgh.harvard.edu/PMI/resources/homer2/home.htm).

We will determine our candidate gene list based on previous candidate gene association studies and recent novel findings from genome-wide association studies with major depressive disorder (http://www.genome.gov/gwastudies/) and by considering relevant genes for the function of the glutamate neurotransmitter system.

10. Service user involvement

Initial discussions have been had NIHR Research Design Service for the North West Public and Patient Involvement (PPI) Team (http://www.rds-nw.nihr.ac.uk/PI/) and we will continue to seek their advice as the project develops.

The user representative collaborator and the Project Manager will act as PPI co-ordinators to facilitate user involvement, and a reference group will meet intermittently during the study period as required for input into specific aspects of the study. This will include recruitment materials, participant information and consent, and to inform a planned qualitative study design to look into the experience and views of service users and professionals, including the implications of the study for future ECT provision.

The PPI co-ordinators will produce an end of project evaluation report on the impact of user involvement. A user representative will be a member of the TSC.

11. Data Monitoring, Quality Control and Quality Assurance

11.1 Study discontinuation

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the DMEC, Trial Steering Committee (TSC), regulatory authority or ethics committee concerned.

Eleven months after the start of recruitment the TSC will review recruitment and advise on whether to continue, discontinue or extend the study (in time and/or in number of centres) and make a recommendation to the funder and sponsor. If the study is prematurely discontinued, active participants will be informed; collection of further participant data will be determined by the reason for study discontinuation and patient decision.

11.2 Monitoring, quality control and assurance

The trial will be managed by the Manchester Project Team (Professor I M Anderson and the Project Manager) in conjunction with the Sponsor and Christie CTU. The TMG will include: Chief Investigator, Project Manager, Trial Statistician, Data Manager or representative from Christie CTU, representative of MMHSCT as Sponsor, a Clinical Principal Investigator; an Imaging Principal Investigator and a User representative.

The Principal Investigators will be responsible for day-to-day study conduct at site.

The Project Manager will provide day-to-day support for the sites and provide training through Investigator meetings. Together with the Sponsor s/he will undertake site initiation visits and routine monitoring visits.

Quality control will be maintained by adherence to MMHSCT SOPs, Christie CTU SOPs, Ketamine-ECT Study SOPs, study protocol, the principles of GCP, research governance and clinical trial regulations.

A TSC will be established, to provide overall supervision of the trial; the roles and responsibilities of the TSC are set out in Appendix 1. The Committee will meet at least annually, although there may be periods when more frequent meetings are necessary.

An independent DMEC will be convened to undertake independent review. The roles and responsibilities of the DMEC are detailed in Appendix 2 and the purpose of this committee is to monitor outcome and safety endpoints. Only the DMEC will have access to unblinded study data. The Committee will meet at least annually, and more often as appropriate; and meetings will be timed so that reports can be fed into the TSC. At the first meeting (trial month 5), the DMEC will approve the analysis plan including the rules for addressing protocol violations, will discuss and advise on the inclusion of any interim analysis and possible adoption of a formal stopping rule for safety. At trial month 11 DMEC will undertake a formal safety review of the study.

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits, to ensure that the study is conducted in accordance with GCP. Study site monitoring will be undertaken by the Project Manager and Sponsor. The main areas of focus will include consent, serious adverse events, essential documents in study files and drug accountability and management.

Site monitoring will be risk-based, with a risk assessment and monitoring plan developed by the Trial Management Group at the outset of the study. It will include:

- All original consent forms, reviewed as part of the study file. The presence of a copy in the patient hospital notes will be confirmed for 100% of participants
- All original consent forms compared against the study participant identification list
- All reported serious adverse events verified against treatment notes/medical records (source data verification)
- Checking of the presence of essential documents in the Investigator Study File
- Verification of primary endpoint data at source and eligibility data for 10% of the participants entered in the study
- Checking of drug accountability and management

Central monitoring will include:

- All applications for study authorisations or submissions of progress/safety reports reviewed for accuracy and completeness, prior to submission
- All documentation essential for study initiation, reviewed prior to site authorisation

- All monitoring findings will be reported and, followed up with the appropriate persons in a timely manner.
- The study may be subject to inspection and audit by Manchester Mental Health and Social Care Trust, under their remit as Sponsor, and other regulatory bodies, to ensure adherence to GCP. The investigator(s) / institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data and documents.

12. Pharmacovigilance

These will be defined and reported according to The Medicines for Human Use (Clinical Trials) Regulations 2004 (http://www.mhra.gov.uk/Howweregulate/Medicines/ Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm#l3).

12.1 Definitions

Adverse event (AE): Any untoward medical occurrence which does not necessarily have a causal relationship with the treatment. "Treatment" includes all investigational agents (including comparative agents) administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Adverse Reaction (AR): Any untoward or unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality:
The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to ketamine (i.e definitely, probably or possibly related) are considered to be adverse reactions. If any doubt about the causality
exists, the local Principal Investigator should consult the Chief Investigator. In the case of discrepant views on causality between the Principal Investigator and others, all parties will discuss the case and will refer as necessary to the DMEC. In the event that no agreement is reached, the MHRA, main REC and other bodies will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship.
Unlikely	There is little evidence to suggest there is a causal relationship (eg. The event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (eg. The participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (eg. Because the event occurs within a reasonable time after administration of the trial medication). However the influence of other factors may have contributed to the event (eg. The participant's clinical condition, other concomitant treatment).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the casual relationship.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR):
Any untoward medical occurrence or effect that:
- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

The following are not considered to be SAEs:

- any pre-planned hospitalisations not associated with clinical deterioration;
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition;
- elective or scheduled treatment for pre-existing conditions that did not worsen during the study.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. Suicide attempts are a risk in this group of patients and a particular issue is whether or not a prevented suicide attempt is classed as an SAE/SAR. As a guide, preventative physical intervention at the time of the attempt itself would be classified as an SAE/SAR as would the need for hospitalisation to prevent a suicide attempt, whereas increased community support (including Crisis Resolution) and/or change in treatment would not.

Suspected, Unexpected Serious Adverse Reaction (SUSAR):
An adverse reaction that is both unexpected and serious. An adverse reaction is 'unexpected' if its nature or severity is not consistent with the applicable product information (see section 19.2).

12.2 Expected adverse reactions and protocol specifications

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used or to the effects of ECT.

Known mild AEs related to anaesthesia or ECT will not be recorded unless they are judged to be related to study drug, but will be if they are moderate or severe; all ARs/SAEs/SARs/SUSARs will be recorded/reported. Cognitive side-effects known to occur as a result of ECT will not be recorded as adverse effects as they are being routinely monitored as part of the outcomes and will be reviewed by DMEC. The exception will be if the PI judges that there is a causal link with the study drug when recording/reporting should be undertaken. For a full list of expected undesirable effects of ketamine, see the Summary of Product Characteristics (Appendix 5).

Timing: AEs will be recorded from randomisation until 7 days following end of treatment. ARs/SAEs/SARs/SUSARS will be recorded until exit from the study in order to monitor adverse reactions and serious adverse events/reactions throughout study participation.

12.3 Recording & Reporting Adverse Events or Reactions

Recording and reporting will comply with European Union and MHRA guidance (http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf; http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm)

All adverse events should be reported, subject to exclusions specified in 12.2, as described below. Any questions concerning adverse event reporting should be directed to the Chief Investigator or Project Manager in the first instance. ARs/SAEs/SARs/SUSARs will be followed until resolved or stabilised. Any events directly resulting in the patient being withdrawn from treatment will also followed until resolved or stabilised.

AEs/ARs: Severity will be graded on a three-point scale (mild, moderate, severe). Relation of the AE to the treatment (causality) will be assessed by the site PI. Non-serious AEs/ARs during drug treatment (subject to exclusions in 12.2) will be reported to the Project Manager and Trial Management Team within a timeframe to be agreed in study operational procedures.

SAEs/SARs including SUSARs: These will be reported to the Chief Investigator and Trial Management Team within 24 hours of the site PI becoming aware of them.

The initial report can be made by secure fax or email. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as a follow-up, on an SAE follow-up form. Causality should be assessed by the site PI and reviewed by the CI; the expected or unexpected nature of any SARs will be assigned by the CI on behalf of the Sponsor.

The CI will ensure that the Sponsor, MMHSCT is notified of any SUSARs. The MHRA (via https://esusar.mhra.gov.uk/) and REC will be notified, by the Trial Management Team, on behalf of the Sponsor, of all SUSARs occurring during the study, according to the following timelines: fatal and life-

threatening - within seven days of notification, non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study, on a case-by-case basis.

Local PIs should report any SAEs/SARs and SUSARs to their local R&D Office in line with Trust policies.

Contact details for reporting SAEs/SARs and SUSARs

Email: jo.e.lowe@manchester.ac.uk or ketECT@manchester.ac.uk

Tel: 0161 275 1727 or 0161 275 1235

13. Ethics & Regulatory Issues

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions, up to and including the April 2008 version.

Favourable ethical opinion from a Type 3 Research Ethics Committee, R&D approval via the NIHR Coordinated System for gaining NHS Permissions and Clinical Trial Authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) will be sought prior to commencement of the study. Local R&D approval will be sought before recruitment may commence at each site. The Trial Management Team will require a written copy of local approval documentation, before initiating each centre and accepting participants into the study.

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their unique study identification code (ID), and a back-up ID including patient initials in case study ID is incorrect or missing. The study will comply with the Data Protection Act, 1998. All study records, including signed consent forms and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

14. Insurance and Finance

The participating NHS Trusts have liability for clinical negligence that harms individuals toward whom they have a duty of care. Indemnity in respect of negligent harm arising from study management is provided via NHS schemes by Manchester Mental Health and Social Care Trust in its role as sponsor. Indemnity in respect of negligent harm arising from study conduct is provided by NHS schemes, via the participating NHS Trusts, covering NHS-employed staff and medical academic staff with honorary NHS contracts, who are conducting the trial. Indemnity in respect of negligent harm arising from study design or protocol authorship is provided by NHS schemes, for those protocol authors whose substantive contract of employment lies with the NHS, and via Manchester University insurance for protocol authors who have their substantive contract with the University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

The NIHR Efficacy and Mechanism Evaluation Programme (NIHR EME) is funding the study.

15. Study Report / Publications

The data will be the property of the CI and PIs. Publication will be the responsibility of the CI, in consultation with other PIs as necessary, and all use of data for publication by whatever media should be discussed with him and agreed before publication.

It is planned to publish this study in peer-reviewed journals and to present data, orally and/or in posters, at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on the Funder's web site. The Funder prior will be notified of all manuscripts, abstracts or other modes of presentation prior to publication or presentation. Individuals will not be identified from any study report.

Participants will be provided with a lay summary of the results at the end of the study at their request.

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APPENDIX 1: Trial Steering Committee Terms of Reference

TRIAL STEERING COMMITTEE (TSC) – ROLES AND RESPONSIBILITIES

The main features of the TSC are as follows:

- The TSC will provide overall supervision for the trial on behalf of the Sponsor and Funder, and will ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice. It should be noted that the day-to-day management of the trial is the responsibility of the Investigators, the Chief Investigator and the TMG.
- The TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question.
- The TSC will consider that the safety and well-being of the trial participants are the most important considerations, which should prevail over the interests of science and society.
- The TSC will provide advice, via its chair, to the Chief Investigator(s), the Sponsor, the Funder, the Host Institution and the Contractor on all appropriate aspects of the trial.
- Membership of the TSC will be limited, and on this occasion includes an independent Chair[11], an independent member, and two consumer representatives.
- The TSC shall invite representatives of the Sponsor and the Funder to all TSC meetings.
- Responsibility for calling and organising TSC meetings lies with the Chief Investigator. The TSC will meet at least annually, although there may be periods when more frequent meetings are necessary.
- There may be occasions when the Sponsor or the Funder will wish to organise and administer these meetings for particular trials. In the HTA Programme's case this is unlikely, but it reserves the right to convene a meeting of the TSC in exceptional circumstances.
- The TSC will provide evidence to support any requests for extensions, indicating that all practical steps have been taken to achieve targets.

[1] The Good Clinical Practice (GCP) guidelines define independence as: 'not involved directly in the trial other than as a member of the TSC'.

APPENDIX 2: Data Monitoring and Ethics Committee Terms of Reference

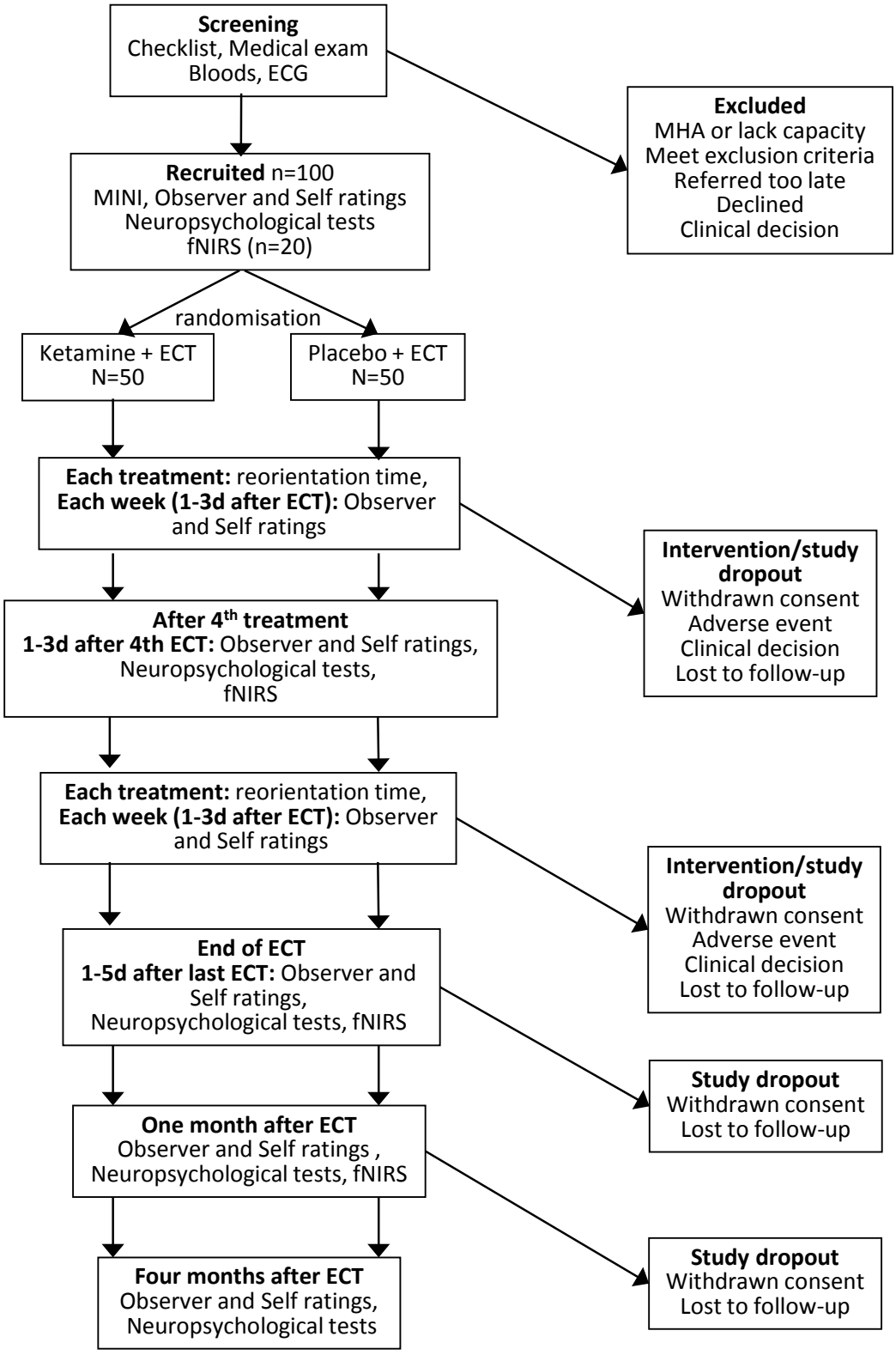
DATA MONITORING & ETHICS COMMITTEE (DMEC) – ROLES AND RESPONSIBILITIES

The main features of the DMEC are as follows:

- Access to the unblinded comparative data.
- Monitor data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue.
- Considers the safety, rights and well-being of the Trial Participants as paramount.
- Considers whether any interim analysis is necessary, consider the data from any analysis and consider requests for its release, and advise the TSC.
- The DMEC may be asked by the TSC, Sponsor or Funder to consider data emerging from other, related studies.
- If funding is required above the level originally requested, the DMEC may be asked by the Chief Investigator, TSC, Sponsor or Trial to provide advice and, where appropriate, information on the data gathered to date, in a way that will not unblind the trial.
- Membership of the DMEC is completely independent[2], small (3-4 members) and consists of experts in the field, eg. a clinician with experience in the relevant area, and expert trial statisticians.
- DMEC meetings may be split into 'open' and 'closed' elements; only members of the DMEC should attend 'closed' parts of meetings. Attendance at 'open' parts of meetings is at the discretion of the DMEC.
- Responsibility for calling and organising DMEC meetings lies with the Chief Investigator, in association with the Chair of the DMEC. The project team should provide the DMEC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMEC
- The DMEC will meet at least annually, and more often as appropriate; and meetings should be timed so that reports can be fed into the TSC.

[2] Independence, in respect of the DMEC, is defined as independent from the Chief Investigator, TSC and Host Institution.

APPENDIX 3: Study Flowchart



fNIRS: functional near-infrared spectroscopy; fMRI/MRS: functional magnetic resonance imaging/ magnetic resonance spectroscopy; MINI: Mini International Neuropsychiatric Interview; Observer ratings: Brief Psychiatric Rating Scale; Montgomery Åsberg Depression Rating Scale; Clinical Global Impression; Self ratings: EuroQoL; Quick Inventory of Depressive Symptomatology-Self Report.

APPENDIX 4: Schedule of visits

Main study visits	Screening and randomisation	Baseline			Visit 1 (week +1)			Visit 2 (week +2)			Visit 3a to Visit 3n (week +3 to week +n/2)		Visit 4 (end of ECT)	Visit 5 (4 weeks post end of ECT)	Visit 6 (16 weeks post end of ECT)
Treatments			ECT1	ECT2		ECT3	ECT4		ECT5	ECTn		final ECT			
Timing window	-4wk to -1d pre-ECT1	-2wk to -1d pre-ECT1			+1d to +3d after ECT2			+1d to +3d after ECT4 (±1 ECT if necessary)			+1d to +3d after ECT6 and even no. ECT		+1d to +5d after final ECT	+3wk to +5wk after final ECT	+12wk to +20wk after final ECT
Informed consent	X														
Pretreatment assessments (1)	X														
Safety measures (2)			X	X		X	X		X	X		X			
Trial blinding assessment							X (ECT consultant)	X (RA and patient)				X (ECT consultant)	X (RA and patient)		
Neuropsychological tests (3)		X						X					X	X	X
Efficacy Ratings (4)		X			X			X			X		X	X	X
NIRS (5)		X						X					X	X	

1 Physical and psychiatric illness and medication checklist; Mini Mental State Examination (MMSE); Mini International Neuropsychiatric Interview (MINI) screen + suicidality screen; MINI; Wechsler Test of Adult Reading (WTAR); Modified Edinburgh Handedness Questionnaire (mEHI); Physical examination (incl. ht, wt, CVS, BP); ECG; Blood tests (see 7.1)

2 HR and BP; Peripheral oxygen saturation and capnography; Time to reorientation (see 7.2)

3 Hopkins Verbal Learning Test - Revised (HVLT-R); Autobiographical Memory Interview - short form (AMI-SF); Controlled Oral Word Association Test (COWAT); Medical College of Georgia (MCG) Complex Figure Test complex figure test; Digit span; Self-reported Global Self Evaluation of Memory (GSE-My) (see 7.4.1)

4 Montgomery Asberg Depression Rating Scale (MADRS); Clinical Anxiety Scale (CAS); Clinical Global Impression, Severity and Improvement (CGI-S, CGI-I); Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR); EuroQol (EQ-5D) (see 7.4.2)

5 Verbal Fluency and Working Memory fNIRS; Tissue Oxygenation Index (see 7.5.1)

APPENDIX 5: Ketalar Injection Summary of Product Characteristics

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Summary of Product Characteristics last updated on the eMC: 03/03/2014

(electronic Medicines Compendium: http://www.medicines.org.uk/EMC/medicine/12939/SPC/Ketalar+Injection/ accessed 22-05-2014)

Ketalar 10 mg/ml Injection

Table of Contents

1. Name of the medicinal product

Ketalar 10 mg/ml Injection

2. Qualitative and quantitative composition

Each 1 ml of solution contains:

Ketalar 10mg/ml Injection: ketamine hydrochloride equivalent to 10 mg ketamine base per ml.Excipient(s) with known effect: Each 1 ml contains 2.6 mg of sodium

For the full list of excipients see section 6.1.

3. Pharmaceutical form

Solution for Injection or Infusion

A clear solution for injection or infusion.

4. Clinical particulars

4.1 Therapeutic indications

Ketalar is recommended:

As an anaesthetic agent for diagnostic and surgical procedures. When used by intravenous or intramuscular injection, Ketalar is best suited for short procedures. With additional doses, or by intravenous infusion, Ketalar can be used for longer procedures. If skeletal muscle relaxation is desired, a muscle relaxant should be used and respiration should be supported.

For the induction of anaesthesia prior to the administration of other general anaesthetic agents.

To supplement other anaesthetic agents.

Specific areas of application or types of procedures:

When the intramuscular route of administration is preferred.

Debridement, painful dressings, and skin grafting in burned patients, as well as other superficial surgical procedures.

Neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms, and lumbar punctures.

Diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions.

Note: Eye movements may persist during ophthalmological procedures.

Anaesthesia in poor-risk patients with depression of vital functions or where depression of vital functions must be avoided, if at all possible.

Orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies.

Sigmoidoscopy and minor surgery of the anus and rectum, circumcision and pilonidal sinus.

Cardiac catheterization procedures.

Caesarian section; as an induction agent in the absence of elevated blood pressure.

Anaesthesia in the asthmatic patient, either to minimise the risks of an attack of bronchospasm developing, or in the presence of bronchospasm where anaesthesia cannot be delayed.

4.2 Posology and method of administration

For intravenous infusion, intravenous injection or intramuscular injection.

NOTE: All doses are given in terms of ketamine base

Adults, elderly (over 65 years) and children:

For surgery in elderly patients ketamine has been shown to be suitable either alone or supplemented with other anaesthetic agents.

Preoperative preparations

Ketalar has been safely used alone when the stomach was not empty. However, since the need for supplemental agents and muscle relaxants cannot be predicted, when preparing for elective surgery it is advisable that nothing be given by mouth for at least six hours prior to anaesthesia.

Premedication with an anticholinergic agent (e.g. atropine, hyoscine or glycopyrolate) or another drying agent should be given at an appropriate interval prior to induction to reduce ketamine-induced hypersalivation.

Midazolam, diazepam, lorazepam, or flunitrazepam used as a premedicant or as an adjunct to ketamine, have been effective in reducing the incidence of emergence reactions.

Onset and duration

As with other general anaesthetic agents, the individual response to Ketalar is somewhat varied depending on the dose, route of administration, age of patient, and concomitant use of other agents, so that dosage recommendation cannot be absolutely fixed. The dose should be titrated against the patient's requirements.

Because of rapid induction following intravenous injection, the patient should be in a supported position during administration. An intravenous dose of 2 mg/kg of bodyweight usually produces surgical anaesthesia within 30 seconds after injection and the anaesthetic effect usually lasts 5 to 10 minutes. An intramuscular dose of 10 mg/kg of bodyweight usually produces surgical anaesthesia within 3 to 4 minutes following injection and the anaesthetic effect usually lasts 12 to 25 minutes. Return to consciousness is gradual.

A. Ketalar as the sole anaesthetic agent

Intravenous Infusion

The use of Ketalar by continuous infusion enables the dose to be titrated more closely, thereby reducing the amount of drug administered compared with intermittent administration. This results in a shorter recovery time and better stability of vital signs.

A solution containing 1 mg/ml of ketamine in dextrose 5% or sodium chloride 0.9% is suitable for administration by infusion.

General Anaesthesia Induction

An infusion corresponding to 0.5 – 2 mg/kg as total induction dose.

Maintenance of anaesthesia

Anaesthesia may be maintained using a microdrip infusion of 10 - 45 microgram/kg/min (approximately 1 – 3 mg/min).

The rate of infusion will depend on the patient's reaction and response to anaesthesia. The dosage required may be reduced when a long acting neuromuscular blocking agent is used.

Intermittent Injection

Induction

Intravenous Route

The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5mg/kg (in terms of ketamine base).The average amount required to produce 5 to 10 minutes of surgical anaesthesia has been 2.0 mg/kg. It is recommended that intravenous administration be accomplished slowly (over a period of 60 seconds). More rapid administration may result

in respiratory depression and enhanced pressor response.

Intramuscular Route

The initial dose of Ketalar administered intramuscularly may range from 6.5 mg/kg to 13 mg/kg (in terms of ketamine base). A low initial intramuscular dose of 4 mg/kg has been used in diagnostic manoeuvres and procedures not involving intensely painful stimuli. A dose of 10 mg/kg will usually produce 12 to 25 minutes of surgical anaesthesia.

Dosage in Hepatic Insufficiency:

Dose reductions should be considered in patients with cirrhosis or other types of liver impairment. (see section 4.4 Special Warnings and Special Precautions for Use)

Maintenance of general anaesthesia

Lightening of anaesthesia may be indicated by nystagmus, movements in response to stimulation, and vocalization. Anaesthesia is maintained by the administration of additional doses of Ketalar by either the intravenous or intramuscular route.

Each additional dose is from ½ to the full induction dose recommended above for the route selected for maintenance, regardless of the route used for induction.

The larger the total amount of Ketalar administered, the longer will be the time to complete recovery.

Purposeless and tonic-clonic movements of extremities may occur during the course of anaesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anaesthetic.

B. Ketalar as induction agent prior to the use of other general anaesthetics

Induction is accomplished by a full intravenous or intramuscular dose of Ketalar as defined above. If Ketalar has been administered intravenously and the principal anaesthetic is slow-acting, a second dose of Ketalar may be required 5 to 8 minutes following the initial dose. If Ketalar has been administered intramuscularly and the principal anaesthetic is rapid-acting, administration of the principal anaesthetic may be delayed up to 15 minutes following the injection of Ketalar.

C. Ketalar as supplement to anaesthetic agents

Ketalar is clinically compatible with the commonly used general and local anaesthetic agents when an adequate respiratory exchange is maintained. The dose of Ketalar for use in conjunction with other anaesthetic agents is usually in the same range as the dosage stated above; however, the use of another anaesthetic agent may allow a reduction in the dose of Ketalar.

D. Management of patients in recovery

Following the procedure the patient should be observed but left undisturbed. This does not preclude the monitoring of vital signs. If, during the recovery, the patient shows any indication of emergence delirium, consideration may be given to the use of diazepam (5 to 10 mg I.V. in an adult). A hypnotic dose of a thiobarbiturate (50 to 100 mg I.V.) may be used to terminate severe emergence reactions. If any one of these agents is employed, the patient may experience a longer recovery period.

4.3 Contraindications

Ketalar is contra-indicated in persons in whom an elevation of blood pressure would constitute a serious hazard (see section 4.8 Undesirable effects). Ketamine hydrochloride is contraindicated in patients who have shown hypersensitivity to the drug or its components. Ketalar should not be used in patients with eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident or cerebral trauma.

4.4 Special warnings and precautions for use

To be used only in hospitals by or under the supervision of experienced medically qualified anaesthetists except under emergency conditions.

As with any general anaesthetic agent, resuscitative equipment should be available and ready for use.

Respiratory depression may occur with overdosage of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to the administration of analeptics.

The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in transient respiratory depression or apnoea and enhanced pressor response.

Because pharyngeal and laryngeal reflexes usually remain active, mechanical stimulation of the pharynx should be avoided unless muscle relaxants, with proper attention to respiration, are used.

Although aspiration of contrast medium has been reported during Ketalar anaesthesia under experimental conditions (Taylor, P A and Towey, R M, Brit. Med. J. 1971, 2: 688), in clinical practice aspiration is seldom a problem.

In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

When Ketalar is used on an outpatient basis, the patient should not be released until recovery from anaesthesia is complete and then should be accompanied by a responsible adult.

Ketalar should be used with caution in patients with the following conditions:

Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

Ketamine is metabolised in the liver and hepatic clearance is required for termination of clinical effects. A prolonged duration of action may occur in patients with cirrhosis or other types of liver impairment. Dose reductions should be considered in these patients. Abnormal liver function tests associated with ketamine use have been reported, particularly with extended use (>3 days) or drug abuse.

Since an increase in cerebrospinal fluid (CSF) pressure has been reported during Ketalar anaesthesia, Ketalar should be used with special caution in patients with preanaesthetic elevated cerebrospinal fluid pressure.

Use with caution in patients with globe injuries and increased intraocular pressure (e.g. glaucoma) because the pressure may increase significantly after a single dose of ketamine.

Use with caution in patients with neurotic traits or psychiatric illness (e.g. schizophrenia and acute psychosis)

Use in caution in patients with acute intermittent porphyria.

Use in caution in patients with seizures.

Use in caution in patients with hyperthyroidism or patients receiving thyroid replacement (increased risk of hypertension and tachycardia)

Use in caution in patients with pulmonary or upper respiratory infection (ketamine sensitises the gag reflex, potentially causing laryngospasm)

Use in caution in patients with intracranial mass lesions, a presence of head injury, or hydrocephalus.

Emergence Reaction

The psychological manifestations vary in severity between pleasant dream-like states, vivid

imagery, hallucinations, nightmares and emergence delirium (often consisting of dissociative or floating sensations), In some cases these states have been accompanied by confusion, excitement, and irrational behaviour which a few patients recall as an unpleasant experience. (See section 4.8 Undesirable Effects).

Emergence delirium phenomena may occur during the recovery period. The incidence of these reactions may be reduced if verbal and tactile stimulation of the patient is minimised during the recovery period. This does not preclude the monitoring of vital signs.

Because of the substantial increase in myocardial oxygen consumption, ketamine should be used in caution in patients with hypovolemia, dehydration or cardiac disease, especially coronary artery disease (e.g. congestive heart failure, myocardial ischemia and myocardial infarction). In addition ketamine should be used with caution in patients with mild-to-moderate hypertension and tachyarrhythmias.

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

Elevation of blood pressure begins shortly after the injection of Ketalar, reaches a maximum within a few minutes and usually returns to preanaesthetic values within 15 minutes after injection. The median peak rise of blood pressure in clinical studies has ranged from 20 to 25 percent of preanaesthetic values. Depending on the condition of the patient, this elevation of blood pressure may be considered a beneficial effect, or in others, an adverse reaction.

Cases of cystitis including haemorrhagic cystitis have been reported in patients being given ketamine on a long term basis. This adverse reaction develops in patients receiving long term ketamine treatment after a time ranging from 1 month to several years. Ketamine is not indicated nor recommended for long term use.

Ketalar has been reported as being a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia, or disorientation. Cases of cystitis including haemorrhagic cystitis have also been reported. If used on a daily basis for a few weeks, dependence and tolerance may develop, particularly in individuals with a history of drug abuse and dependence. Therefore the use of Ketalar should be closely supervised and it should be prescribed and administered with caution.

4.5 Interaction with other medicinal products and other forms of interaction

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

Ketalar is chemically incompatible with barbiturates and diazepam because of precipitate formation. Therefore, these should not be mixed in the same syringe or infusion fluid.

Ketamine may potentiate the neuromuscular blocking effects of atracurium and tubocurarine including respiratory depression with apnoea.

The use of halogenated anaesthetics concomitantly with ketamine can lengthen the elimination half-life of ketamine and delay recovery from anaesthesia. Concurrent use of ketamine (especially in high doses or when rapidly administered) with halogenated anaesthetics can increase the risk of developing bradycardia, hypotension or decreased cardiac output.

The use of ketamine with other central nervous system (CNS) depressants (e.g. ethanol, phenothiazines, sedating H_1 – blockers or skeletal muscle relaxants) can potentiate CNS depression and/or increase risk of developing respiratory depression. Reduced doses of ketamine may be required with concurrent administration of other anxiolytics, sedatives and hypnotics.

Ketamine has been reported to antagonise the hypnotic effect of thiopental.

Patients taking thyroid hormones have an increased risk of developing hypertension and

tachycardia when given ketamine.

Concomitant use of antihypertensive agents and ketamine increases the risk of developing hypotension.

When ketamine and theophylline are given concurrently, a clinically significant reduction in the seizure threshold is observed. Unpredictable extensor-type seizures have been reported with concurrent administration of these agents.

4.6 Fertility, pregnancy and lactation

Ketalar crosses the placenta. This should be borne in mind during operative obstetric procedures in pregnancy. With the exception of administration during surgery for abdominal delivery or vaginal delivery, no controlled clinical studies in pregnancy have been conducted. The safe use in pregnancy, and in lactation, has not been established and such use is not recommended.

4.7 Effects on ability to drive and use machines

Patients should be cautioned that driving a car, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more after anaesthesia.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

  o The medicine has been prescribed to treat a medical or dental problem and

  o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

  o It was not affecting your ability to drive safely

4.8 Undesirable effects

The following Adverse Events have been reported:

MedDRA System Organ Class	Frequency†	Undesirable Effects
Immune system disorders	Rare	Anaphylactic reaction*
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Common	Hallucination, Abnormal dreams, Nightmare, Confusion, Agitation, Abnormal behaviour
	Uncommon	Anxiety

	Rare	Delirium* Flashback*, Dysphoria*, Insomnia, Disorientation*
Nervous system disorders	Common	Nystagmus, Hypertonia, Tonic clonic movements
Eye disorders	Common	Diplopia
	Not Known	Intraocular pressure increased
Cardiac disorders	Common	Blood pressure increased, Heart rate increased
	Uncommon	Bradycardia, Arrhythmia
Vascular disorders	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory rate increased
	Uncommon	Respiratory depression, Laryngospasm
	Rare	Obstructive airway disorder*, Apnoea*
Gastrointestinal disorders	Common	Nausea, Vomiting
	Rare	Salivary hypersecretion*
Hepatobiliary disorders	Not known	Liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Erythema, Rash morbilliform
Renal and urinary disorders	Rare	Cystitis*, Haemorrhagic cystitis*
General disorders and administration site conditions	Uncommon	Injection site pain, Injection site rash

† Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data)

* AE frequency estimated from post-marketing safety database

4.9 Overdose

Respiratory depression can result from an overdosage of ketamine hydrochloride. Supportive ventilation should be employed. Mechanical support of respiration that will maintain adequate blood oxygen saturation and carbon dioxide elimination is preferred to administration of analeptics.

Ketalar has a wide margin of safety; several instances of unintentional administration of overdoses of Ketalar (up to 10 times that usually required) have been followed by prolonged but complete recovery.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ketamine is a rapidly acting general anaesthetic for intravenous or intramuscular use with a

distinct pharmacological action. Ketamine hydrochloride produces dissociative anaesthesia characterised by catalepsy, amnesia, and marked analgesia which may persist into the recovery period. Pharyngeal-laryngeal reflexes remain normal and skeletal muscle tone may be normal or can be enhanced to varying degrees. Mild cardiac and respiratory stimulation and occasionally respiratory depression occur.

Mechanism of Action:

Ketamine induces sedation, immobility, amnesia and marked analgesia. The anaesthetic state produced by ketamine has been termed “dissociative anaesthesia” in that it appears to selectively interrupt association pathways of the brain before producing somesthetic sensory blockade. It may selectively depress the thalamoneocortical system before significantly obtunding the more ancient cerebral centres and pathways (reticular-activating and limbic systems). Numerous theories have been proposed to explain the effects of ketamine, including binding to N-methyl-D-aspartate (NMDA) receptors in the CNS, interactions with opiate receptors at central and spinal sites and interaction with norepinephrine, serotonin and muscarinic cholinergic receptors. The activity on NMDA receptors may be responsible for the analgesic as well as psychiatric (psychosis) effects of ketamine. Ketamine has sympathomimetic activity resulting in tachycardia, hypertension, increased myocardial and cerebral oxygen consumption, increased cerebral blood flow and increased intracranial and intraocular pressure. Ketamine is also a potent bronchodilator. Clinical effects observed following ketamine administration include increased blood pressure, increased muscle tone (may resemble catatonia), opening of eyes (usually accompanied by nystagmus) and increased myocardial oxygen consumption.

5.2 Pharmacokinetic properties

Ketamine is rapidly distributed into perfused tissues including brain and placenta. Animal studies have shown ketamine to be highly concentrated in body fat, liver and lung. Biotransformation takes place in liver. Termination of anaesthetic is partly by redistribution from brain to other tissues and partly by metabolism. Elimination half-life is approximately 2-3 hours, and excretion renal, mostly as conjugated metabolites.

5.3 Preclinical safety data

Preclinical safety data does not add anything of further significance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

Ketalar 10mg/ml Injection: sodium chloride, benzethonium chloride, water for injections

6.2 Incompatibilities

Ketalar is chemically incompatible with barbiturates and diazepam because of precipitate formation. Therefore, these should not be mixed in the same syringe or infusion fluid.

6.3 Shelf life

60 months.

For single use only. Discard any unused product at the end of each operating session.

After dilution the solutions should be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Do not freeze. Store in the original container. Discard any unused product at the end of each operating session.

6.5 Nature and contents of container

Ketalar 10mg/ml Injection:	25 ml white neutral glass vial with rubber closure and aluminium flip-off cap containing 20ml of solution as 10 mg ketamine base per ml.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused product at the end of each operating session.

See Section 4.2 Posology and method of administration.

7. Marketing authorisation holder

Pfizer Limited, Sandwich, Kent CT13 9NJ, United Kingdom

8. Marketing authorisation number(s)

PL 00057/0529

9. Date of first authorisation/renewal of the authorisation

1st July 2003

10. Date of revision of the text

01/2014

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