Study protocol for SKIPMDD: subcutaneous ketamine infusion in palliative care patients with advanced life limiting illnesses for major depressive disorder (phase II pilot feasibility study)

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ABSTRACT

Introduction Major depressive disorder (MDD) in people with advanced life-limiting illnesses can have significant impact on the quality-of-life of those affected. The management of MDD in the palliative care setting can be challenging as typical antidepressants may not work in time nor be tolerated due to coexisting organ dysfunctions, symptom burden and frailty. Parenteral ketamine was found to exhibit effective and rapid-onset antidepressant effect even against treatment-resistant depression in the psychiatric population. However, there is currently neither feasibility study nor available prospective study available to inform of the safety, tolerability and efficacy of such for MDD in the palliative setting.

Methods and analysis This is an open-labelled, single arm, phase II pilot feasibility study involving adult patients with advanced life-limiting illnesses and MDD across four palliative care services in Australia. It has an individual dose-titration design (0.1–0.4 mg/kg) with weekly treatments of subcutaneous ketamine infusion over 2 hours. The primary outcome is feasibility. The secondary outcomes are related to the safety, tolerability and antidepressant efficacy of ketamine, participants’ satisfaction in relation to the trial process and the reasons for not completing the study at various stages. The feasibility data will be reported using descriptive statistics. Meanwhile, side effects, tolerability and efficacy data will be analysed using change of assessment scores from baseline.

Ethics and dissemination Ethics approval was acquired (South Western Sydney Local Health District: HREC/18/LPOOL/466). The results of this study will be submitted for publication in peer-reviewed journals and presented at relevant conferences.

Trial registration number Australian New Zealand Clinical Trial Registry Number: ACTRN12618001586202; Pre-results.

Strengths and limitations of this study

► This study may provide key feasibility information for a future definitive study in the palliative care setting and inform the safety, tolerability and the antidepressant activity of ketamine for this population.

► Subcutaneous ultralow-dose infusion (<0.5 mg/kg) via an individually tailored dose titration design will likely maximise acceptability and tolerability for palliative patients, though there is less evidence for this approach compared with the conventional ketamine administration regimen (intravenous 0.5 mg/kg).

► The use of Endicott criteria for the diagnosis of major depressive disorder in the palliative care setting reduces the confounding effects of symptoms of terminal illnesses.

► The use of standard psychiatry research instruments allows direct comparison of this trial with other psychiatric trials, while maintaining the use of familiar oncological and palliative care trial instruments for safety monitoring.

► Inability to inform definitive effectiveness of ketamine (not blinded randomised controlled trial).

INTRODUCTION

Major depressive disorder (MDD) is common and can be severely distressing in individuals with advanced life-limiting illnesses. It affects approximately 10%–15% of individuals in the palliative care setting.1–3 MDD can significantly impact the quality-of-life of those affected and may be associated with a sense of worthlessness and the desire for hastened death.4–7

The assessment and management of MDD can be challenging in the palliative care setting, particularly in the presence of substantial medical comorbidities when the prognosis is limited to only days to weeks.
The symptoms of advanced-life limiting illnesses can confound the assessment of MDD. Patients may develop severe fatigue, delirium or pain, inhibiting comprehensive psychiatric assessment and engagement with psychotherapeutic interventions. Pharmacologically, typical antidepressants may take up to 4 weeks to see the clinical benefit. Even psychostimulants such as methylphenidate with faster onset of actions provide limited clinical utility due to the inability to administer these medications orally towards the end-of-life.

Ketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist known for its anaesthetic and analgesic use. Recently, there is a growing evidence that subanaesthetic doses of ketamine can also provide antidepressant effects with rapid onset, even against treatment-resistant MDD. The proposed mechanism of action has involved increasing synaptogenesis and neural plasticity secondary to the rapid rise in the brain extracellular glutamate level. Additionally, it may induce alpha-amino-3-hydroxy-5-methyl-isoxazolepropionic acid receptor activation and brain-derived neurotrophic factor in the prefrontal cortex and hippocampus. The onset of its antidepressant effect may be as rapid as 2 hours after administration and can potentially last for up to 1 week after a single bolus dose. With repeated boluses, the effects may last up to 12 weeks. According to the meta-analysis, the response rate of ketamine has been high with OR of 9.1 (95% CI 4.28 to 19.34) at 24-hours post-intervention. Meanwhile, it is generally well tolerated in the general psychiatric population, who are younger with fewer comorbidities compared with the palliative population. Although there were reports of mild transient psychotomimetic and dissociative symptoms, and the potential for the acute elevation of blood pressure, which mostly resolves within 4 hours of administration, ketamine has not been associated with significantly serious immediate or short-term adverse effects.

Despite the evidence for treatment of MDD in general psychiatry, the antidepressant effect of ketamine has not been well studied in the palliative care population. To date, there are only case reports and case series of intramuscular and intravenous ketamine, an open-label proof-of-concept trial using oral ketamine and a retrospective study by Iglewicz (2015), demonstrating its effect in the hospice setting. There has been no randomised controlled trial (RCT) to inform the definitive effectiveness of ketamine as an antidepressant to treat MDD in the palliative care population. The reasons may be manifold. Participant recruitment towards the end-of-life may be challenging due to competing priorities of managing difficult physical symptoms and other life priorities. The effects of advanced life-limiting illnesses and anhedonia from depression might limit potential participants’ ability to engage with or even consent to the trial. Despite the psychiatric evidence, the pharmacological profile of ketamine for depression in the context of very poor functional status and organ dysfunction is not well understood. Not only are participants at risk of intolerance, the efficacy of ketamine at doses that might improve tolerability (ultralow doses of <0.5 mg/kg) in this population is also uncertain. Furthermore, clinicians’ general tendency to under-recognise, underassess and undertreat depression in advanced life-limiting illnesses can make conducting a definitive RCT of ketamine for depression in this setting challenging.

Given these potential challenges of conducting a definitive RCT of ketamine as a rapid-onset antidepressant in this population, a feasibility study is required to inform the acceptability, safety, tolerability and activity of subanaesthetic doses of ketamine. These piloting data may serve as foundations for the larger RCT using an individually tailored dosing approach of ketamine.

AIM AND OBJECTIVES

The primary objective of this study is to determine the feasibility of ketamine subcutaneous (SC) infusion for MDD in palliative setting, measured by the numbers of consented patients who have been screened, treated and completed the study (ie, received weekly dosing of SC ketamine and assessment up to 8 weeks). The secondary objectives are to determine the safety, tolerability, acceptability and efficacy of the treatment using an individually tailored dose titration approach.

METHODS AND ANALYSIS

Study design

The study is a pilot phase 2 multicentre feasibility study. It has an open-labelled, individual dose-titration design with all participants receiving ketamine SC infusion. The rationale for this design is discussed below.

Population and eligibility criteria

The target population involves patients with advanced life-limiting illnesses and MDD in the acute hospital, palliative care units and the community of the following Australian palliative care services: Liverpool Hospital, Braeside Hospital, Calvary/St George Hospitals and Sacred Heart/St Vincent Hospitals. The inclusion criteria are: (1) adults (≥18-year old), (2) known to palliative care services with palliative intent of treatment for irreversible life-limiting illnesses, (3) Patient Health Questionnaire-2 (PHQ-2) score ≥3 on screening, (4) MDD diagnosed by Endicott criteria (table 1) diagnosed by trained personnel, (5) clinically significant depression severity defined by Montgomery-Asberg Depression Rating Scale (MADRS) Depression Severity Score ≥16, (6) willing and able to comply with all study requirements and (7) signed, written informed consent for the study.

The exclusion criteria will be:

- Australian-modified Karnofsky Performance scale (AKPS) score=10.
- Methylphenidate use in the last 4 weeks.
- Changes to antidepressant doses in the last 2 weeks before the commencement of ketamine.

### Table 1 DSM-IV symptoms of major depressive disorder and Endicott substitute symptoms (Endicott criteria)

<table>
<thead>
<tr>
<th>DSM-IV symptoms</th>
<th>Endicott substitute symptoms</th>
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<tr>
<td>Depressed mood most of the day*</td>
<td>Depressed appearance</td>
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<tr>
<td>Marked diminished interest or pleasure in all, or almost all, activities most of the day (Anhedonia)*</td>
<td>Social withdrawal or decreased talkativeness</td>
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<td>Weight loss or gain (&gt;5% body weight in a month)/change in appetite</td>
<td>Brooding, self-pity or pessimism</td>
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<td>Insomnia or hypersomnia</td>
<td>Lack of reactivity; cannot be cheered up</td>
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<td>Psychomotor agitation or retardation</td>
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<td>Fatigue or loss of energy</td>
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<td>Feeling of worthlessness or excessive or inappropriate guilt</td>
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<td>Diminished ability to think or concentrate, indecisiveness</td>
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<tr>
<td>Recurrent thoughts of death, or suicidal ideation or planning, or a suicide attempt</td>
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*One of these symptoms must be present for a diagnosis of major depressive disorder. Each symptom must also meet severity criteria of 'most of the day' or 'nearly every day' with a duration of greater than 2 weeks. The symptoms must cause clinically significant distress or impairment. They are not due to a physiological effect of a medication or general medical condition, and must not be accounted for bereavement.

- Ketamine use in the last 4 weeks.
- Previous significant adverse effect or hypersensitivity to ketamine.
- Concurrent phenobarbitone use.
- Factors of increased risk of intracranial pressure:
  i. Recent ischaemic or haemorrhagic cerebral vascular accident in the last 1 month.
  ii. Brain tumours with symptoms and signs of increased intracranial pressure.
  iii. Seizure in the last 6 months.
  iv. Head trauma with symptoms of increased intracranial pressure.
  v. Hydrocephalus.
  vi. Uncontrolled nausea, vomiting and headache (eg, from cerebral metastases, trauma), ≥ grade 3 nausea despite one line of antiemetics.
- Factors of increased risk of sympathomimetic response (hypertension and tachycardia) with associated complications
  i. Uncontrolled hypertension with systolic blood pressure ≥160.
  ii. Tachycardia with heart rate ≥120/min.
  iii. Symptomatic ischaemic heart disease (eg, exertional angina) and decompensated heart failure with New York Heart Association (NYHA) class III and IV symptoms.
  iv. Uncontrolled hyperthyroidism (low Thyroid Stimulating Hormone [TSH] with high T3 and/or T4).
  v. Diagnosis and history of porphyria.
- Factors of increased risk of intraocular pressure with its complications
  i. Glaucoma.
  ii. Open eye injury/acute globe injury.
- Severe hepatic impairment: bilirubin ≥three times upper limit of normal; Aspartate aminotransferase (AST) and/or Alanine transaminase (ALT) > five times upper limit of normal—clinically determined to be due to hepatic impairment.
- Severe renal impairment (creatinine clearance <15 mL/min by Cockroft Gault equation).
- Other mental disorders apart from major depression (lifetime history schizophrenia/bipolar/mania).
- Recent substance misuse as determined by the treating and research clinicians.

To screen for MDD in the palliative care population, PHQ-2 will be used to minimise the burden of administration to participants while maintaining a relatively high level of sensitivity and specificity. This will be followed by a diagnostic interview using Endicott criteria. The substitute approach is to replace the four somatic items of Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria with other more depression specific items, potentially reducing the chance of misattribution of the symptoms of terminal illness as MDD. Although DSM-5 is currently available, the psychometric property of Endicott criteria has not been established using DSM-5 but DSM-IV in the oncology population. As a result, Endicott criteria based on DSM-IV will be used.

Furthermore, the MADRS score will be performed to assess depression severity. This tool has been widely used and accepted as a standard to measure the antidepressant response of ketamine in the psychiatric literatures. A usual cut-off of MADRS ≥20 indicates moderate severity depression. Nonetheless, the inclusion criteria of this study have been broadened to include depression of milder severity. It is thought that ketamine may still benefit participants with milder depression when prognoses are too short for meaningful effectiveness from the typical antidepressants. Consequently, the threshold of MADRS ≥16 has been selected in this protocol to ensure participants with

clinically significant depressive symptoms are recruited, which is in congruent with Pezzella et al.61 Palliative trials of ketamine generally have a stringent set of exclusion criteria, excluding conditions commonly encountered in the palliative setting (eg, cardiac failure and intracerebral mass). The thresholds of many exclusion criteria were largely from physician’s assessments rather than based on absolute values.23–25 However, absolute thresholds for a number of these exclusion criteria have been made for reproducibility. To assimilate the clinical population who often have significant organ dysfunctions and comorbidities, efforts have been made to ensure that the exclusion criteria are relatively inclusive as shown above. Some examples include: setting a very low score of AKPS of 10 as exclusion criteria; not excluding individuals with brain metastases unless there are concurrent symptoms or signs of increased intracranial pressure; lenient exclusion criteria for systolic blood pressure and pulse rate and only excluding the severe spectrums of hepatic and renal impairments adapted from the National Cancer Institute—sponsored Organ Dysfunction Working Group62 63 and American Society of Clinical Oncology for Anti-cancer Therapies,64 respectively. The renal impairment exclusion has been lowered to exclude only those with a creatinine clearance of <15mL/min, given the ultralow initial dose (0.1 mg/kg over 2 hours) of ketamine and the mild effects of its active metabolite on renal function.65 The exclusion of ketamine use in the last 4 weeks has also been chosen as ketamine’s antidepressant effect might last up to this time.66

Interventions

The study intervention involves the initial SC infusion of 0.1 mg/kg ketamine given over 2 hours. If there is a lack of response from the previously administered dose, further dosing escalation at 0.1 mg/kg increment on a weekly interval may be given (figure 1). Participants are allowed up to four doses (4 weeks) with the maximal dose of 0.4 mg/kg. After this treatment phase, participants are monitored for another 4 weeks to make up a total of 8 weeks as planned for the study.

The SC route of administration has been chosen as it yielded comparable efficacy to the conventional intravenous infusion and resulted in less cardiovascular, psychotomimetic and dissociative side effects.60 66 This is possibly related to the halved peak plasma concentration...
associated with the SC route, compared with the intravenous route. The use of slow infusion subcutaneously rather than boluses may further minimise the risk of toxicity. Reports have shown that intravenous ketamine infusion over 100 mins exhibited less toxicity with comparable antidepressant effect relative to the standard infusion over 40 mins. Additionally, the psychotomimetic effects might be spared if ketamine is commenced at ultralow dose infusion equivalent to 0.1–0.2 mg/kg/hour, even in the cancer setting. Since prior studies have shown that participants’ responses were observed at different dose levels even below the dose of 0.5 mg/kg, the individually tailored dose-titration approach is implemented. In addition, a weekly dosing interval is scheduled as the peak response of ketamine may take up to 3 days to occur.

After the initiation of ketamine infusion, if it is deemed appropriate for the participant’s clinical needs (eg, for neuropathic pain titration), a typical antidepressant of choice at the discretion of the treating clinician can be commenced or have its dose changed 48 hours apart from the ketamine administration. There is a concern regarding the confounding antidepressant effect from allowing the introduction or dose change of the typical antidepressants during the study. However, to be in compliance with the human research ethics requirement, the enrolled participants should not be disadvantaged from the benefits of the typical antidepressants while participating in the trial, especially when the prognosis is uncertain. Furthermore, the participation does not negatively impact on their physical symptom control (eg, restricting typical antidepressants dose-titration for managing neuropathic pain or anorexia). Given the slow onset of action of the typical antidepressant (i.e. ≥4 weeks), and the contrasting rapid onset and offset effects of ketamine (within days), the antidepressive effect of ketamine may still be differentiated from that of the typical antidepressant.

To determine not only short-term (<1 week) but also the medium-term responses of ketamine (1 to 8 weeks), this study includes a 4-week ketamine administration period and another 4-week follow-up period. This duration has been chosen as a balance between acquiring adequate short-term and mid-term safety and efficacy data while maintaining the study’s feasibility with a potentially high attrition rate, which is expected due to the progressive nature of terminal illnesses.

Comparator
A control arm has not been included as the primary research question is feasibility—having a control arm would further lower the study feasibility.

Outcome measures
The primary outcome is feasibility, measured as absolute numbers (including accrual rate of multiple centres) and proportions of palliative care patients, who have consented, been screened for MDD, met the study eligibility criteria, treated with SC ketamine, followed up and completed the study. A priori ‘stop-go’ criteria for the future definitive study have been set. The use of individually tailored dose-titration SC ketamine will be worthy of further evaluation in the future definitive study if: (1) the steady-state recruitment rate is 1.25 participants per month or higher up to 24 months, but not if it is 0.5 participants per month or lower and (2) the proportion of treated participants with a positive response (≥50% reduction in MADRS score) in symptoms is 30% or higher, but not 10% or lower.

Secondary outcomes and endpoints that correspond to the secondary objectives are listed according to the various assessment time points in table 2. For measuring side effects and tolerability, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) will be used to measure the general nonpsychiatric adverse events. The participating sites’ familiarity with its use from running the previous ketamine trial for pain may expedite the detection of potential adverse events in this vulnerable population. Nonetheless, NCI CTCAE is unable to capture the psychotomimetic and dissociative symptoms of ketamine comprehensively. The standard tools of Brief Psychiatric Rating Scale (BPRS), Clinician Administered Dissociative States Scale (CADSS) and MADRS will be used for consistency with the other available ketamine literatures in psychiatry. Positive response will be defined as MADRS score reduction of ≥50% from baseline and remission as MADRS score ≤9. Relapse is defined as MADRS ≥16 after a prior remission. The time points for MADRS measurements are chosen to capture the initial time to response (as quick as within 6 hours), the time to maximal response (usually between 1 and 3 days) and the duration of response (averaging around 7 days). Since the MADRS depression score may be affected by uncontrolled pain, concurrent pain level will be assessed using Numeric Pain Rating Scale and correlation between these factors explored.

Time—study duration
The recruitment will occur for up to 2 years.

Study procedure
The study procedure is illustrated in figure 1. This study will be overseen and coordinated by the Australian Palliative Care Clinical Studies Collaborative (PaCCSC) Trial Management Committee (TMC). The TMC consists of chief study investigators and key members of the PaCCSC group not involved in this study. They oversee the trial governance through PaCCSC Standard Operating Procedures, providing the trial infrastructure.
Table 2  Assessment schedule

<table>
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<tr>
<th>Assessments</th>
<th>Eligibility</th>
<th>Baseline (0 min)</th>
<th>30 min</th>
<th>1 hour</th>
<th>1.5 hours</th>
<th>2 hour (infusion complete)</th>
<th>4 hours</th>
<th>6 hours</th>
<th>1 day</th>
<th>2 days</th>
<th>3 days</th>
<th>7 days</th>
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AKPS, Australia-modified Karnofsky Performance Scale; BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative States Scale; EUC, electrolyte urea creatinine; FBC, full blood counts; LFT, liver function test; MADRS, Montgomery-Asberg Depression Rating Scale; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NPRS, Numeric Pain Rating Scale; PHQ-2, Patient Health Questionnaire-2; Q-LES-Q-SF, Quality-of-life Enjoyment and Satisfaction Questionnaire - Short Form; SKIPMDD, subcutaneous ketamine infusion in palliative care patients with advanced life limiting illnesses for major depressive disorder; TFT, thyroid function test.
for data collection, management, analysis and monitoring processes.

Under the guidance of BD and CL (psychiatrists in the team), the coordinating principal investigator, WL, attended training by psychiatry teams to perform psychiatric assessments. WL then provides site initiation and ongoing training to the rest of the research team members (study nurse, site coordinator and investigators).

Although the screening of depression has been recommended in the palliative population due to its high prevalence, screening is not yet a routine practice at participating sites. Therefore, it is an ethical requirement to obtain consent from potential participants before screening for MDD and assessing for eligibility criteria.

As patients with MDD may have impaired capacity to provide consent, research clinicians will use the MacArthur Competence Assessment Tool for Clinical Research to assess and confirm the capacity to consent.81–83 Due to feasibility concerns for using this tool in those with significant frailty and symptom burden, rather than using the full 21-item assessment tool, the four overarching principles of the assessment tool in assessing consent capacity will be used. These are understanding; appreciation; reasoning and expressing or evidencing a choice.81–83 Only individuals who are able to provide informed consent will be included.

Eligible participants will then undergo 4 weeks of ketamine treatment (week 1–4). During this period, the participants’ responses to ketamine will be regularly monitored at a predetermined schedule (table 2). The day-7 response (MADRS score and tolerability) determines the subsequent titration of ketamine dosing (figure 1). After the initial 4 weeks, the participants then undergo the follow-up phase, in which they are monitored weekly (week 5–8). Given there is no long-term safety data of ketamine use as an antidepressant in the palliative care population, there will be no ongoing provision of ketamine for depression after the study.

Investigators will report all serious adverse events to the PaCCSC Trial Coordinating Unit, who will then liaise with the assigned medical monitor. When appropriate, the Human Research Ethics Committee will also review the safety information of ketamine. Given the feasibility nature of this study, a medical monitor rather than the data monitoring committee will be used. The investigators will stop the study if adverse event reporting indicates safety concerns.

Each participant will be allocated a unique identification number. All trial data will be recorded on the study case report forms and entered by the research nurses into Research Electronic Data Capture—a centralised electronic database protected via Secure Sockets Layer encryption.84 All source documents and the master list linking identifying participant information and identification numbers will be stored in a locked cabinet at each site. All information will only be accessible to those who are directly involved in conducting the study. There is no anticipated sharing of data past the investigator group. Study records will be maintained for 15 years after study completion in secure archiving facilities in compliance with National Health and Medical Research Council and the Good Clinical Practice guidelines.85 86 Data confidentiality, accuracy and protocol compliance will be monitored by members of TMC or their delegates, audited on an ad hoc basis. The study is also subjected to inspection by regulatory bodies (eg, Therapeutic Goods Administration).

**Data analysis**

The sample size of 32 over 2 years is projected to be an appropriate number to inform study feasibility.87 The primary analysis will be concentrated on the feasibility metrics and adherence outcomes, which will be analysed with frequencies and percentages. The change of assessment score from baseline for side effects, tolerability and efficacy data will be analysed: percentage change for MADRS and absolute change for BPRS, CADSS, Quality-of-life Enjoyment and Satisfaction Questionnaire—Short Form and haemodynamic observations. Dependent on the nature of the data found, normally distributed data will be summarised with mean and SD and non-normal data with medians and interquartile ranges. Statistical analyses will be performed using IBM SPSS Statistics V.24.0 (IBM, Armonk, New York).

**ETHICS AND DISSEMINATION**

This study was approved by South Western Sydney Local Health District (reference number: HREC/18/LPOOL/466) on the 18 February 2019. Minor administrative amendments were approved on the 26 May 2020 (protocol V.1.2). Reporting of this protocol is compliant with the Standard Protocol Items: Recommendations for Interventional Trials guideline.88 The results of this study will be submitted for publication in peer-reviewed journals and presented at relevant conferences.

**Trial status**

This trial has been registered in the Australian New Zealand Clinical Trial Registry, with recruitment commenced on the 29 July 2019. Due to COVID-19, this trial was suspended on 24 March 2020 and gradually recommenced with all sites recruiting on the 17 August 2020.

**Patient and public involvement**

There is no patient and public involvement in the protocol design.

**Strengths of the current study design**

This protocol’s strength is that it provides key information about the feasibility of a future definitive study while exploring the safety, tolerability and efficacy of ketamine for MDD in the palliative population for up to 8 weeks. Meanwhile, the diagnosis of MDD using Endicott criteria reduces the confounding effects of the symptoms of terminal illnesses.8 55 The use of standard psychiatry
research instruments (eg, MADRS, CADSS and BPRS) allows direct comparison of this trial with other psychiatric trials, while maintaining the use of familiar oncological and palliative care trial instruments for safety monitoring (eg, CTCAE). In particular, the use of BPRS and CADSS allows for better characterisation of the side effect of confusion caused by ketamine into various psychotomimetic and dissociative symptoms than the sole use of NCI CTCAE. Importantly, ketamine will be administered in an individually tailored dose titration design using SC infusion, likely maximising tolerability while maintaining the antidepressant efficacy.

**Limitations of the current study design**

This study’s key limitation is its inability to inform definitive effectiveness of ketamine (not blinded RCT). Additionally, severely depressed patients who cannot consent are excluded. Due to the lack of feasibility data, the use of proxy or surrogate decision-maker for consent cannot yet be justified. Allowing typical antidepressants to be used in the study and titration of these medications for pain and other purposes due to ethical considerations may create confounding effects. However, as mentioned above, this issue may potentially be addressed by relying on the known rapidly wax-and-wane antidepressant effect of ketamine as compared with the gradual changes from typical antidepressants that take weeks to months.

Finally, the ketamine dose in this study is not escalated to the conventional level of 0.5 mg/kg, which has been well established for the general population with MDD due to safety / tolerability concerns.

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**Contributors**

WL and CS started the study concept. Under the supervision of DCC, MA, and BD and the inputs of CL, CS, RC, and SC, WL designed the study protocol. WL with the assistance of all the authors prepared, edited and finalised the manuscript.

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**Competing interests**

CL has served on an Advisory Board for Janssen-Cilag and as a consultant for Douglas Pharmaceuticals.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not required.

**Provenance and peer review**

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