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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 anti-depressants may not work in time nor be tolerated due to co-existing organ dysfunctions, symptom burden and frailty. Parenteral ketamine was found to exhibit effective and rapid-onset anti-depressant effect even against treatment-resistant depression in the psychiatry population. However, there is currently no prospective study available to inform of the safety, tolerability, and efficacy of such for MDD in the palliative setting, not even a prospective feasibility study.

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 (0.1-0.4mg/kg) with weekly treatments of subcutaneous ketamine infusion over two hours. The primary outcome is feasibility. The secondary outcomes relate to the safety, tolerability, and anti-depressant efficacy of ketamine, participants' satisfaction in relation to the trial process, and the reasons for inability to complete various study stages. The feasibility data will be reported using descriptive statistics. Side effect, 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.

Australian New Zealand Clinical Trial Registry Number: ACTRN12618001586202

Strengths and Limitations of this study

- This study may provide key feasibility information for a future definitive study in the palliative care population, and inform the safety, tolerability, and anti-depressant activity of ketamine in this population.
- Subcutaneous ultralow-dose infusion (0.1-0.4mg/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 to the conventional ketamine administration regimen (intravenous 0.5mg/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 & 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 around 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.[8] Patients may be too unwell with fatigue, delirium, or pain, inhibiting comprehensive psychiatric assessment and engagement with psychotherapeutic interventions.[9, 10] Pharmacologically, typical anti-depressants may be too slow for effect, often taking up to four weeks to see the clinical benefit.[11-13] Even for psychostimulants (e.g. methylphenidate) with faster onset of actions,[14-20] clinical utility is often limited due to the inability to administer these medications orally towards the end-of-life.[9]

Ketamine is a non-competitive N-methyl-D-aspartate receptor antagonist known for its anaesthetic and analgesic use[21-25] In the psychiatric literature, there is growing evidence that sub-anaesthetic doses of ketamine can also act as an effective, rapid-onset anti-depressant, even against treatment-resistant MDD.[26-35] Its mechanism of action may include increasing synaptogenesis and neural plasticity secondary to the rapid rise in the brain extracellular glutamate level, inducing alpha-amino-3-hydroxy-5-methyl-4isoxazeolepropionic acid (AMPA) receptor activation and brain-derived neurotrophic factor (BDNF) in the pre-frontal cortex and hippocampus.[36] The onset of the anti-depressant effect can be as rapid as two hours after administration.[37] The effect can potentially last for up to one week after a single bolus dose or up to 12 weeks after repeated boluses.[27, 30-34, 36, 37] Ketamine's response rate has been high from a meta-analysis (odds ratio of 9.1 [95% CI 4.28–19.34] at 24-hours post-intervention).[29] It is generally well-tolerated in the general psychiatric population, who are younger with fewer comorbidities compared to the palliative population.[26, 28, 33, 34] Apart from some mild transient psychotomimetic and dissociative symptoms, and the potential for the acute elevation of blood pressure that mostly resolves within four hours of administration, ketamine has not been associated with significant immediate or short-term adverse effects.[26, 27, 33-35, 38]

Despite the evidence for treatment of MDD in general psychiatry, the anti-depressant 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.[27, 39-43] There has been no randomised controlled trial (RCT) to inform the definitive effectiveness of ketamine as an anti-depressant 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.[44] 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 (ultra-low doses of 0.1-0.5mg/kg) in this population is also uncertain.[25] Furthermore, clinicians' general tendency to under-recognise, under-assess, and under-treat depression in advanced life-limiting illnesses can make conducting a definitive RCT of ketamine for depression in this setting challenging.[45-48]

Given these potential challenges of conducting a definitive RCT of ketamine as a rapid-onset anti-depressant in this population, a feasibility study is required to inform the acceptability, safety, tolerability, and activity of sub-anaesthetic doses of ketamine.

AIM & OBJECTIVES

The study aims to determine the feasibility, safety, tolerability, acceptability, and activity of subcutaneous ketamine as a treatment for MDD in patients with advanced life-limiting illnesses and to generate pilot data on ketamine's anti-depressant effectiveness to inform a larger RCT, using an individually tailored approach to dosing.

The primary objective is to determine feasibility, measured as the numbers and proportions of palliative care patients, who consented, are screened for depression, meet the study eligibility criteria, are treated with subcutaneous ketamine, and complete the study with weekly dosing and assessment up to eight weeks.

The secondary objectives are to determine:

1. Frequency and severity of adverse events (National Cancer Institute Common Terminology Criteria for Adverse Effect 4.03 - NCI CTCAE 4.03)[49]
2. Frequency and severity of psychotomimetic (Brief Psychiatric Rating Scale - BPRS)[50, 51] and dissociative symptoms (Clinician-Administered Dissociative State Scale - CADSS)[52, 53]
3. Improvement in depression symptoms over the study period (Montgomery-Asberg Depression Rating Scale - MADRS)[54]
4. Pain (Numerical Pain Rating Scale – NPRS)[55, 56]
5. Change in quality-of-life ratings (Quality-of-life Enjoyment and Satisfaction Questionnaire Short Form - Q-LES-Q-SF)[57, 58]
6. Reasons potential participants are unable to complete each of the study stages after consent.
7. Participants' satisfaction with ketamine as an anti-depressant and the SKIPMDD trial process (SKIPMDD two-item questionnaire)
8. Associations between baseline characteristics and clinical outcomes

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. The rationale for this design is discussed below.

Population & 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) Major Depressive Disorder (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 four weeks
- Changes to anti-depressant doses in the last two weeks before the commencement of ketamine
- Ketamine use in the last four 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 one month
  ii. Brain tumours with symptoms and signs of increased intracranial pressure
  iii. Seizure in the last six months
  iv. Head trauma with symptoms of increased intracranial pressure
  v. Hydrocephalus
  vi. Uncontrolled nausea, vomiting and headache (e.g. from cerebral metastases, trauma), ≥ grade three 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 per minute.
  iii. Symptomatic ischaemic heart disease (e.g. exertional angina) and decompensated heart failure with NYHA class III and IV symptoms
  iv. Uncontrolled hyperthyroidism (Low 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; AST and/or ALT > five times upper limit of normal - clinically determined to be due to hepatic impairment
- Severe renal impairment (Creatinine clearance <15ml/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

For the screening of 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.[59-61] This will be followed by diagnosing MDD through an interview using Endicott Criteria. This is a substitute approach replacing 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.[8, 62-64] Despite DSM-V is currently available, as the psychometric property of Endicott Criteria has been established using DSM-IV but not DSM-V in the oncology population, Endicott Criteria based on DSM-IV is used for the current protocol.[65] After making the diagnosis, the MADRS score will be performed to assess for depression severity. This tool has been widely used and accepted as the standard of measuring anti-depressant response in ketamine RCTs in the psychiatric literature.[33, 66-69] A usual cut-off of MADRS $\geqslant$ 20 indicates moderate severity.[33, 66-69] Nonetheless, the inclusion criteria for MADRS has been broadened to include depression of milder severity ($\geqslant$16). It is thought that ketamine may still benefit participants with milder depression when prognoses are too short for effectiveness from other pharmacological treatments. However, to ensure that only participants with clinically significant depressive symptoms who may benefit from ketamine (rather than only needing non-pharmacological interventions) are recruited, the threshold of MADRS $\geqslant$ 16 has been selected, assimilating the study by Pezzella et al (2001).[70]

Table 1: DSM-IV Symptoms of Major Depressive Disorder and Endicott Substitute Symptoms (Endicott Criteria)

DSM-IV Symptoms	Endicott Substitute Symptoms
Depressed mood most of the day*	
Marked diminished interest or pleasure in all, or almost all, activities most of the day (Anhedonia)*	
~~Weight loss or gain (>5% body weight in a month) / change in appetite~~	Depressed appearance
~~Insomnia or hypersomnia~~	Social withdrawal or decreased talkativeness
Psychomotor agitation or retardation	
~~Fatigue or loss of energy~~	Brooding, self-pity or pessimism
Feeling of worthlessness or excessive or inappropriate guilt	
~~Diminished ability to think or concentrate, indecisiveness~~	Lack of reactivity; cannot be cheered up
Recurrent thoughts of death, or suicidal ideation or planning, or a suicide attempt	

*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 the duration of greater than two weeks. The symptoms must cause clinically significant distress or impairment and are not due to a physiological effect of medication or general medical condition. They must not be better accounted for by bereavement.

Palliative trials of ketamine generally have a stringent set of exclusion criteria, excluding conditions commonly encountered in the palliative setting (e.g. cardiac failure and intracerebral mass). The thresholds of many exclusion criteria were largely physician assessed rather than based on absolute values.[23-25] However, absolute thresholds for a number of these exclusion criteria have been

made for reproducibility. Importantly, 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. 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 Group[71, 72] and American Society of Clinical Oncology for Anti-cancer Therapies[73] respectively. The renal impairment exclusion has been lowered to exclude only those with a creatinine clearance of <15ml/min, given ketamine's active metabolite is only mildly affected by renal function and the initiation dose is ultra-low (0.1mg/kg over 2 hours).[74] The exclusion of ketamine use in the last four weeks has been chosen as ketamine's anti-depressant effect might last up to this time.[36]

Interventions

The study intervention involves individually tailored subcutaneous infusions of ketamine, with the first infusion of 0.1-mg/kg given over 2 hours. If required, further doses may be given at weekly intervals with the dosage increased by 0.1 mg/kg on each occasion due to the previous dose's lack of response (Figure 1). Participants are allowed up to four doses (four weeks) with the maximal dose of 0.4mg/kg. A four weeks follow-up period follows.

The subcutaneous route has been chosen as it yielded comparable efficacy to the conventional intravenous route and resulted in less cardiovascular, psychotomimetic, and dissociative side effects.[69, 75] This possibly related to the halved peak plasma concentration associated with the subcutaneous route, compared to the intravenous route.[69] The decision for subcutaneous infusion rather than subcutaneous bolus further minimises the risk of toxicity: 1) there is evidence of intravenous ketamine infusion over 100mins exhibiting less toxicity while producing comparable anti-depressant effect when compared to the standard infusion over 40mins;[76, 77] 2) psychotomimetic effects might be spared if ketamine is commenced at ultra-low dose infusion equivalent of 0.1-0.2mg/kg per hour, even in the cancer setting.[22-24, 78] The individually tailored dose-titration approach is based on prior studies showing that participants required different dose levels for response, which often occurred below the dose of 0.5mg/kg.[68, 69, 75] A weekly dosing interval will be used as the peak response may occasionally take up to three days to occur.[34, 68]

After starting the ketamine infusion, if it is deemed appropriate for the participant's clinical needs (e.g. for neuropathic pain titration), a typical anti-depressant 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 anti-depressant effect from allowing the introduction or dose change of typical anti-depressants during the study. The reason for this is to ensure that the study complies with the human research ethics requirement that: participants are not disadvantaged from the benefits of typical anti-depressants while participating in the trial, especially when the prognosis is uncertain; and the participation does not negatively impact on their physical symptom control (e.g. restricting typical anti-depressants dose-titration for managing neuropathic pain or anorexia).[79,80] Given the slow onset of typical anti-depressant action (i.e. ≥ four weeks),[13] and the contrasting rapid onset and offset effects of ketamine (within days of

administration), the anti-depressant effect of ketamine may still be differentiated from that of the typical antidepressant.[26-35, 69, 76,77,81] The minimum of 48 hours gap set between the administration of a typical anti-depressant and ketamine infusion will allow for better recognition of the potential adverse effects of ketamine (likely onset is within hours of infusion with duration of less than a day) before potentially commencing on a typical antidepressant.[35, 69]

To determine not only short- (< one week) but also the medium-term responses of ketamine (within weeks), this study includes a four-week ketamine administration period and another four-week follow-up period. This study duration has been chosen as a balance between acquiring adequate short- and mid-term safety and efficacy data while maintaining the study's feasibility – a high attrition rate 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 are consented, screened for MDD, meet the study eligibility criteria, treated with subcutaneous ketamine, followed up and complete the study. A priori "stop-go" criteria for the future definitive study have been set. The use of individually tailored dose-titration subcutaneous 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; 2) the retention rate is < 50% in two weeks; and 3) 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, NCI CTCAE[49] will be used to measure the general non-psychiatric 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.[25] Nonetheless, NCI CTCAE[49] is unable to capture the psychotomimetic and dissociative symptoms of ketamine comprehensively. Consistent with the psychiatry ketamine literature,[30, 33, 69, 75, 82] the standard tools of BPRS[50, 51], CADSS[52, 53], and MADRS[54] will be used for assessments to allow for comparison. Positive response will be defined as MADRS score reduction of ≥ 50% from baseline and remission as MADRS score ≤9.[35, 69] Relapse is defined as MADRS ≥ 16 after a prior remission, in keeping with the inclusion criterion of what constitutes a clinically significant depressive score. The time points for MADRS measurements are chosen to capture the initial time to response (as quick as within six hours), the time to maximal response (usually between one to three days), and the duration of response (averaging around seven days).[27, 30-34, 36, 37, 76] As the MADRS depression score

might be affected by pain, concurrent pain level will be assessed using NPRS, and correlation between MADRS and NPRS will be explored.

Having the total assessment period of up to eight weeks informs the short-term (within days) and the currently unknown medium-term (weeks to early months) effects of ketamine while exploring the feasibility of having such a length of assessment period for the palliative population of interest.

Time - Study Duration

The recruitment will occur for up to two years.

Study Procedure

The study procedure is illustrated in Figure 1. This study will be overseen and coordinated by the Australian national 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 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, [1, 3, 83] 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 consent to research participation, research clinicians will use the MacArthur Competence Assessment Tool for Clinical Research to assess and confirm the capacity to consent.[84-86] 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.[84-86] Only persons able to provide informed consent will be included.

Eligible participants will then undergo four weeks of ketamine treatment (Week 1-4). During this period, the participants' responses to ketamine will be regularly monitored at scheduled time points (Table 2). The day-7 response (MADRS score and tolerability) determines the subsequent titration of ketamine dosing (Figure 1). After the initial four 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 anti-depressant in the palliative care population, there will be no ongoing provision of ketamine for depression after the study.

Table 2. Assessment Schedule

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
Informed consent	X	X (Re-affirm)											
PHQ-2	X												
Endicott Criteria	X												
AKPS	X	X							X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X					
ECG		X											
Bloods (FBC/LFT/EUC /TFT)	X												
MADRS[54]	X	X						X	X	X	X	X	X
BPRS[50, 51]		X				X	X	X					
CADSS[52, 53]		X				X	X	X					

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
NPRS[57, 58]		X						X	X	X	X	X	X
Adverse Events (NCI CTCAE 4.03)[49]		X	X	X	X	X	X	X	X	X	X	X	X
Q-LES-Q-SF[57, 58]		X									X	X	
Concomitant medications		X									X	X	X
SKIPMDD Participant Satisfaction Questionnaire													X (only at the end of the study – study completion or withdraw)

Abbreviations: AKPS - Australia-modified Karnofsky Performance Scale; BPRS - Brief Psychiatric Rating Scale; CADSS - Clinician Administered Dissociative States Scale; ECG – Electrocardiogram; 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

Investigators will report all Serious Adverse Events to the PaCCSC Trial Coordinating Unit, who will then liaise with the assigned medical monitor, and, if appropriate, the Human Research Ethics Committee to 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 (CRFs) and entered by the research nurses into Research Electronic Data Capture (REDCap) - a centralised electronic database protected via Secure Sockets Layer encryption.[87] 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.[88,89] 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 subject to inspection by regulatory bodies (e.g. Therapeutic Goods Administration).

DATA ANALYSIS

The sample size of 32 over two years is projected to be an appropriate number to inform study feasibility.[90] 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, Q-LES-Q-SF, and haemodynamic observations. Dependent on the nature of the data found, normally distributed data will be summarised with mean and standard deviations and non-normal data with medians and interquartile ranges. Statistical analyses will be performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA).

ETHICS AND DISSEMINATION

This study was approved by South Western Sydney Local Health District (reference number: HREC/18/LPOOL/466) on the 18th of Feb 2019. Minor administrative amendments were approved on the 26th of May 2020 (protocol version 1.2). Reporting of this protocol is compliant with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline.[91] 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 (ACTRN12618001586202), with recruitment commenced on the 29th of Jul 2019. Due to COVID-19,

this trial was suspended on the 24th of Mar 2020, and gradually recommenced with all sites recruiting on the 17th of Aug 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 key 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 eight weeks. Meanwhile, the diagnosis of MDD using Endicott Criteria reduces the confounding effects of the symptoms of terminal illnesses.[8, 64] The use of standard psychiatry research instruments (e.g. MADRS, CADSS and BPRS) allows direct comparison of this trial with other psychiatric trials, while maintaining the use of familiar oncological & palliative care trial instruments for safety monitoring (e.g. 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 subcutaneous infusion, likely maximising tolerability while maintaining the anti-depressant 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 anti-depressants to be used in the study and allowing titration of these medications for pain and depression purposes (for 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 anti-depressant effect of ketamine as compared to the gradual changes from typical anti-depressants that take weeks to months.[13] Lastly, the study drug is not dosed to the conventional 0.5mg/kg psychiatric dose that has well-established evidence for effectiveness in the generally well population with MDD (due to safety /tolerability concerns).

Authors' Contributions

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

Data Sharing

There is no anticipated sharing of data past the investigator group.

Funding Statement & Sponsorship

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Competing Interests Statement

Prof Loo (CL) has served on an Advisory Board for Janssen-Cilag and as a consultant for Douglas Pharmaceuticals. Other authors declare that there are no competing interests.

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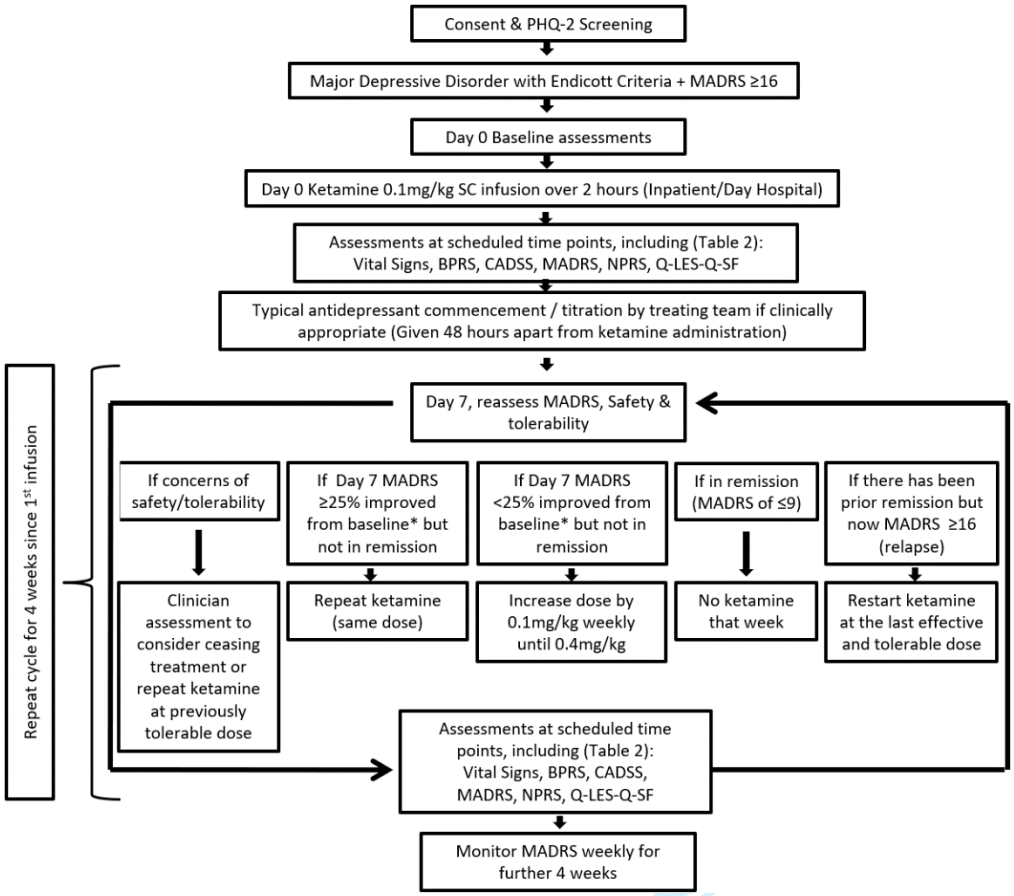
Figure Legend

Figure 1. SKIPMDD Study Procedure.

Figure 1. SKIPMDD Study Procedure.



Abbreviations: BPRS - Brief Psychiatric Rating Scale; CADSS - Clinician Administered Dissociative States Scale; MADRS - Montgomery-Asberg Depression Rating Scale; NPRS -Numeric Pain Rating Scale; PHQ-2 - Patient Health Questionnaire-2; Q-LES-Q-SF - Quality-of-life Enjoyment and Satisfaction Questionnaire - Short Form.

*Baseline MADRS score is the MADRS score prior to the last ketamine dose (default) if relapse (MADRS of ≤9) has not occurred. If relapse has occurred, the MADRS score at relapse becomes the baseline.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	Item No	Description	Page Location
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	14
	2b	All items from the World Health Organization Trial Registration Data Set	14
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8, 14-15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5, 6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, 12-15
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A (feasibility study)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A (feasibility study)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8-9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial intervention or trial conduct	7-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8-9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	10

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attachment
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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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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 anti-depressants may not work in time nor be tolerated due to co-existing organ dysfunctions, symptom burden and frailty. Parenteral ketamine was found to exhibit effective and rapid-onset anti-depressant effect even against treatment-resistant depression in the psychiatric population. However, there is currently no 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 (0.1-0.4mg/kg) with weekly treatments of subcutaneous ketamine infusion over two hours. The primary outcome is feasibility. The secondary outcomes relate to the safety, tolerability, and anti-depressant 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.

Australian New Zealand Clinical Trial Registry Number: ACTRN12618001586202

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 anti-depressant activity of ketamine for this population.
- Subcutaneous ultralow-dose infusion (< 0.5mg/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 to the conventional ketamine administration regimen (intravenous 0.5mg/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 & 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.[8] Patients may develop severe fatigue, delirium, or pain, inhibiting comprehensive psychiatric assessment and engagement with psychotherapeutic interventions.[9, 10] Pharmacologically, typical anti-depressants may take up to four weeks to see the clinical benefit.[11-13] 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.[9, 14-20]

Ketamine is a non-competitive N-methyl-D-aspartate receptor antagonist known for its anaesthetic and analgesic use.[21-25] Recently, there is a growing evidence that sub-anaesthetic doses of ketamine can also provide anti-depressant effects with rapid onset, even against treatment-resistant MDD.[26-35] The proposed mechanism of action has involved increasing synaptogenesis and neural plasticity secondary to the rapid rise in the brain extracellular glutamate level.[36] Additionally, it may induce alpha-amino-3-hydroxy-5-methyl-4isoxazeolepropionic acid (AMPA) receptor activation and brain-derived neurotrophic factor (BDNF) in the pre-frontal cortex and hippocampus.[36] The onset of its anti-depressant effect may be as rapid as two hours after administration, and can potentially last for up to one week after a single bolus dose.[37] With repeated boluses, the effects may last up to 12 weeks.[27, 30-34, 36, 37] According to a meta-analysis, the response rate of ketamine has been high with odds ratio of 9.1 (95% CI 4.28–19.34] at 24-hours post-intervention.[29] Meanwhile, it is generally well-tolerated in the general psychiatric population, who are younger with fewer comorbidities compared to the palliative population.[26, 28, 33, 34] 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 four hours of administration, ketamine has not been associated with significantly serious immediate or short-term adverse effects.[26, 27, 33-35, 38]

Despite the evidence for treatment of MDD in general psychiatry, the anti-depressant 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.[27, 39-43] There has been no randomised controlled trial (RCT) to inform the definitive effectiveness of ketamine as an anti-depressant 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.[44] 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 (ultra-low doses of < 0.5mg/kg) in this population is also uncertain.[25] Furthermore, clinicians' general tendency to under-recognise, under-assess, and under-treat depression in advanced life-limiting illnesses can make conducting a definitive RCT of ketamine for depression in this setting challenging.[45-48]

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

AIM & 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 (i.e received weekly dosing of SC ketamine and assessment up to eight 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 & 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) Major Depressive Disorder (MDD) diagnosed by Endicott Criteria (Table 1) diagnosed by trained personnel;[8, 49] 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 four weeks
- Changes to anti-depressant doses in the last two weeks before the commencement of ketamine
- Ketamine use in the last four 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 one month
  ii. Brain tumours with symptoms and signs of increased intracranial pressure
  iii. Seizure in the last six months
  iv. Head trauma with symptoms of increased intracranial pressure
  v. Hydrocephalus
  vi. Uncontrolled nausea, vomiting and headache (e.g. from cerebral metastases, trauma), ≥ grade three 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 per minute.
  iii. Symptomatic ischaemic heart disease (e.g. exertional angina) and decompensated heart failure with NYHA class III and IV symptoms
  iv. Uncontrolled hyperthyroidism (Low 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; AST and/or ALT > five times upper limit of normal - clinically determined to be due to hepatic impairment
- Severe renal impairment (Creatinine clearance <15ml/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.[50-52] 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.[8, 53-55] 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.[56] 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 anti-depressant response of ketamine in the psychiatric literatures.[33, 57-60] A usual cut-off of MADRS ⩾ 20 indicates moderate severity depression.[33, 57-60] Nonetheless, the inclusion criteria of this study has 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 (2001).[61]

Table 1: DSM-IV Symptoms of Major Depressive Disorder and Endicott Substitute Symptoms (Endicott Criteria)

DSM-IV Symptoms	Endicott Substitute Symptoms
Depressed mood most of the day*	
Marked diminished interest or pleasure in all, or almost all, activities most of the day (Anhedonia)*	
Weight loss or gain (>5% body weight in a month) / change in appetite	Depressed appearance
Insomnia or hypersomnia	Social withdrawal or decreased talkativeness
Psychomotor agitation or retardation	
Fatigue or loss of energy	Brooding, self-pity or pessimism
Feeling of worthlessness or excessive or inappropriate guilt	
Diminished ability to think or concentrate, indecisiveness	Lack of reactivity; cannot be cheered up
Recurrent thoughts of death, or suicidal ideation or planning, or a suicide attempt	

*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 two 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.

Palliative trials of ketamine generally have a stringent set of exclusion criteria, excluding conditions commonly encountered in the palliative setting (e.g. 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 Group[62, 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 ultra-low initial dose (0.1mg/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 four weeks has also been chosen as ketamine's anti-depressant effect might last up to this time.[36]

Interventions

The study intervention involves the initial subcutaneous infusion of 0.1mg/kg ketamine given over two 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 (four weeks) with the maximal dose of 0.4mg/kg. After this treatment phase, participants are monitored for another four weeks to make up a total of eight weeks as planned for the study.

The subcutaneous 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 subcutaneous route, compared to the intravenous route.[60] The use of slow infusion subcutaneously rather than boluses may further minimise the risk of toxicity. Reports have shown that intravenous ketamine infusion over 100mins exhibited less toxicity with comparable anti-depressant effect relative to the standard infusion over 40mins.[67, 68] Additionally, the psychotomimetic effects might be spared if ketamine is commenced at ultra-low dose infusion equivalent to 0.1-0.2mg/kg per hour, even in the cancer setting.[22-24, 69] Since prior studies have shown that participants' responses were observed at different dose levels even below the dose of 0.5mg/kg, the individually tailored dose-titration approach is implemented.[59, 60, 66] In addition, a weekly dosing interval is scheduled as the peak response of ketamine may take up to three days to occur.[34, 59]

After the initiation of ketamine infusion, if it is deemed appropriate for the participant's clinical needs (e.g. for neuropathic pain titration), a typical anti-depressant 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 anti-depressant effect from allowing the introduction or dose change of the typical anti-depressants 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 anti-depressants while participating in the trial, especially when the prognosis is uncertain. Furthermore, the participation does not negatively impact on their physical symptom control (e.g. restricting typical anti-depressants dose-titration for managing neuropathic pain or anorexia).[70, 71] Given the slow onset of action of the typical anti-depressant (i.e. ≥ four weeks),[13] and the contrasting rapid onset and offset effects of ketamine (within days), the anti-depressive effect of ketamine may still be differentiated from that of the typical antidepressant.[26-35, 60, 67, 68, 72] Additionally, the minimum of 48 hours gap set between the administration of a typical anti-depressant and ketamine infusion will allow for better recognition of the potential adverse effects of ketamine, which likely occur within hours of infusion with duration of less than a day.[35, 60]

To determine not only short-term (< one week) but also the medium-term responses of ketamine (one to eight weeks), this study includes a four-week ketamine administration period and another four-week follow-up period. This duration has been chosen as a balance between acquiring adequate short- 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 subcutaneous 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 subcutaneous 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)[73] will be used to measure the general non-psychiatric 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.[25] Nonetheless, NCI CTCAE[73] is unable to capture the psychotomimetic and dissociative symptoms of ketamine comprehensively. The standard tools of Brief Psychiatric Rating Scale (BPRS),[74, 75] Clinician Administered Dissociative States Scale (CADSS),[76, 77] and MADRS[78] will be used for consistency with the other available ketamine literatures in psychiatry.[30, 33, 60, 66, 79] Positive response will be defined as MADRS score reduction of ≥ 50% from baseline and remission as MADRS score ≤9.[35, 60] 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 six hours), the time to maximal response (usually between one to three days), and the duration of response (averaging around seven days).[27, 30-34, 36, 37, 66] Since the MADRS depression score may be affected by uncontrolled pain, concurrent pain level will be assessed using Numeric Pain Rating Scale (NPRS), and correlation between these factors explored.

Time - Study Duration

The recruitment will occur for up to two years.

Study Procedure

The study procedure is illustrated in Figure 1. This study will be overseen and coordinated by the Australian national 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 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, [1, 3, 80] 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 four weeks of ketamine treatment (Week 1-4). During this period, the participants' responses to ketamine will be regularly monitored at a pre-determined schedule (Table 2). The day-7 response (MADRS score and tolerability) determines the subsequent titration of ketamine dosing (Figure 1). After the initial four 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 anti-depressant in the palliative care population, there will be no ongoing provision of ketamine for depression after the study.

Table 2. Assessment Schedule

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
Informed consent	X	X (Re-affirm)											
PHQ-2	X												
Endicott Criteria	X												
AKPS	X	X							X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X					
ECG		X											
Bloods (FBC/LFT/EUC /TFT)	X												
MADRS[78]	X	X						X	X	X	X	X	X
BPRS[74, 75]		X				X	X	X					
CADSS[76, 77]		X				X	X	X					

Assessments	Eligibility	Baseline (t0 min)	30 min	1hr	1.5hr	2hr (infusion complete)	4hr	6hr	1 day	2 days	3 days	7 days	Weekly (day 7) if no repeat ketamine infusion (up to 8 weeks from initial dose)
NPRS[84, 85]		X						X	X	X	X	X	X
Adverse Events (NCI CTCAE 4.03)[73]		X	X	X	X	X	X	X	X	X	X	X	X
Q-LES-Q-SF[84, 85]		X									X	X	
Concomitant medications		X									X	X	X
SKIPMDD Participant Satisfaction Questionnaire													X (only at the end of the study – study completion or withdraw)

Abbreviations: AKPS - Australia-modified Karnofsky Performance Scale; BPRS - Brief Psychiatric Rating Scale; CADSS - Clinician Administered Dissociative States Scale; ECG – Electrocardiogram; 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

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 (CRFs) and entered by the research nurses into Research Electronic Data Capture (REDCap) - a centralised electronic database protected via Secure Sockets Layer encryption.[86] 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.[87, 88] 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 subject to inspection by regulatory bodies (e.g. Therapeutic Goods Administration).

DATA ANALYSIS

The sample size of 32 over two years is projected to be an appropriate number to inform study feasibility.[89] 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, Q-LES-Q-SF, and haemodynamic observations. Dependent on the nature of the data found, normally distributed data will be summarised with mean and standard deviations and non-normal data with medians and interquartile ranges. Statistical analyses will be performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA).

ETHICS AND DISSEMINATION

This study was approved by South Western Sydney Local Health District (reference number: HREC/18/LPOOL/466) on the 18th of Feb 2019. Minor administrative amendments were approved on the 26th of May 2020 (protocol version 1.2). Reporting of this protocol is compliant with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline.[90] 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 (ACTRN12618001586202), with recruitment commenced on the 29th of Jul 2019. Due to COVID-19,

this trial was suspended on the 24th of Mar 2020, and gradually recommenced with all sites recruiting on the 17th of Aug 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 eight 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 (e.g. MADRS, CADSS and BPRS) allows direct comparison of this trial with other psychiatric trials, while maintaining the use of familiar oncological & palliative care trial instruments for safety monitoring (e.g. 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 subcutaneous infusion, likely maximising tolerability while maintaining the anti-depressant 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 anti-depressants 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 anti-depressant effect of ketamine as compared to the gradual changes from typical anti-depressants that take weeks to months.[13] Lastly, the ketamine dose in this study is not escalated to the conventional level of 0.5mg/kg which has been well-established for the general population with MDD due to safety /tolerability concerns.

Authors' Contributions

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

Data Sharing

There is no anticipated sharing of data past the investigator group.

Funding Statement & Sponsorship

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Competing Interests Statement

Prof Loo (CL) has served on an Advisory Board for Janssen-Cilag and as a consultant for Douglas Pharmaceuticals. Other authors declare that there are no competing interests.

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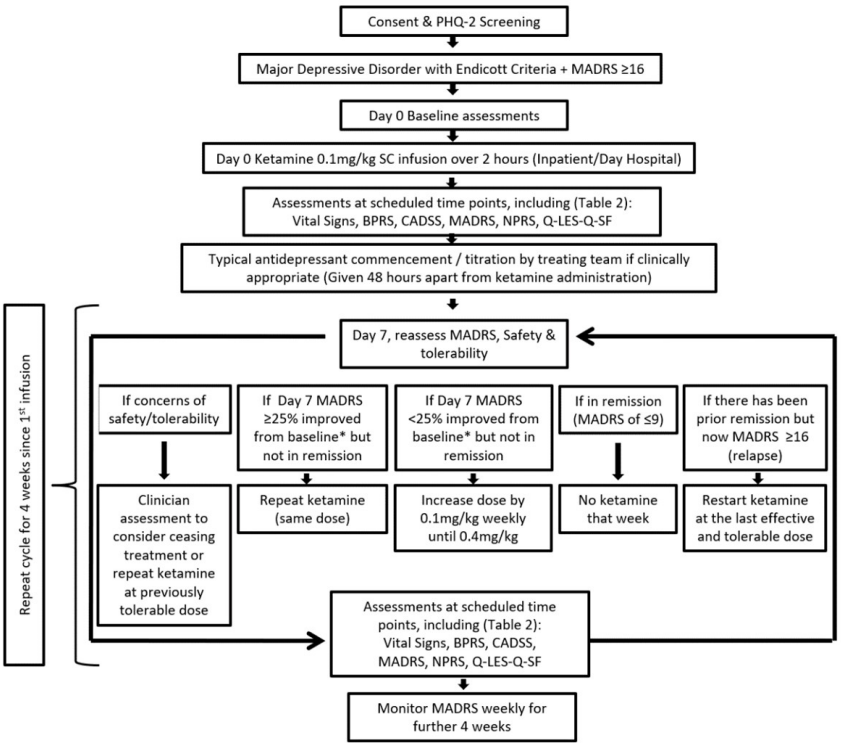
FIGURE CAPTION

Figure 1. SKIPMDD Study Procedure.

Abbreviations: BPRS - Brief Psychiatric Rating Scale; CADSS - Clinician Administered Dissociative States Scale; MADRS - Montgomery-Asberg Depression Rating Scale; NPRS -Numeric Pain Rating Scale; PHQ-2 - Patient Health Questionnaire-2; Q-LES-Q-SF - Quality-of-life Enjoyment and Satisfaction Questionnaire - Short Form.

*Baseline MADRS score is the MADRS score prior to the last ketamine dose (default) if relapse (MADRS of ≤9) has not occurred. If relapse has occurred, the MADRS score at relapse becomes the baseline.



Abbreviations: BPRS - Brief Psychiatric Rating Scale; CADSS - Clinician Administered Dissociative States Scale; MADRS - Montgomery-Asberg Depression Rating Scale; NPRS -Numeric Pain Rating Scale; PHQ-2 - Patient Health Questionnaire-2; Q-LES-Q-SF - Quality-of-life Enjoyment and Satisfaction Questionnaire - Short Form.
*Baseline MADRS score is the MADRS score prior to the last ketamine dose (default) if relapse (MADRS of ≤9) has not occurred. If relapse has occurred, the MADRS score at relapse becomes the baseline.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	Item No	Description	Page Location
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	14
	2b	All items from the World Health Organization Trial Registration Data Set	14
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8, 14-15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5, 6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, 12-15
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A (feasibility study)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A (feasibility study)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8-9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial intervention or trial conduct	7-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8-9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	10

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attachment
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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