Protocol Development for a Qualitative Methodological Study Within a Trial (Qual-SWAT): The KARMA-Dep-2 Trial [version 1; peer review: 2 approved]

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Abstract

Background: Despite methodological improvements in clinical trial design and conduct more generally, methodological limitations persist in trials concerning mental health care. A qualitative Study Within A Trial (Qual-SWAT), embedded in the KARMA-Dep-2 host trial, will be undertaken to explore and gain an understanding of two methodological questions in randomised trials specific to mental health care: (1) what are the key barriers and enablers of participation in randomised trials in mental health; and (2) how can randomised trials become part of routine mental health care. These issues will be examined from patient-participant and clinician- / researcher-participant perspectives, in alignment with PRioRiTy research themes.

Methods: A descriptive qualitative study design will be used. Data will be collected via one-to-one semi-structured interviews, conducted via Microsoft Teams. The interview data will be analysed using Braun and Clarke's Thematic Analysis approach. One-to-one interviews will be conducted with three participant groups (N = 60): 1) host trial patient-participants (n = 20); 2) eligible host trial patient-participants who refused enrolment in the host trial (n = 20); and 3) clinician- / researcher-participants who are associated with work on the host trial (n = 20).

Ethics and dissemination: Ethical approval has been granted by St. Patrick's Mental Health Services Research Ethics Committee, Ireland (Ref: Protocol 09/20). When the study is completed, a report will be prepared and submitted to the Health Research Board (HRB). Findings will be shared with the host trial team and study participants and submitted for publication.

Host trial registration: ClinicalTrials.gov (NCT04939649); EudraCT (2019-003109-92). Official title: Ketamine as an Adjunctive Therapy for Major Depression - A Randomised Controlled Trial: [KARMA-Dep (2)].
Keywords
mental health, randomised trial, recruitment and retention, study within a trial (SWAT), qualitative, trial methodology

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Author roles: McCaffrey J: Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Hunter A: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing

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Introduction

Background

Despite the increasing improvement and availability of treatments for major depression, prevalence has not decreased correspondingly, and depression remains a public health concern (i.e., treatment-prevalence paradox; Ormel et al., 2022). Debate persists about the ontology of depression and its measurement (Fried et al., 2022; McPherson & Armstrong, 2022), the types of outcome domains assessed in clinical trials and treatment (Chevance et al., 2020; Cuijpers, 2019; Krause et al., 2023), and the comparative effectiveness of different treatment modalities on patient outcomes (Cuijpers et al., 2023). Treatment-resistance also presents a complex issue to be addressed when developing clinical research studies and clinical practice guidelines (Howes et al., 2022). A lack of clarity around concepts such as treatment-resistant depression (PRD) and partially responsive depression (PRD) impedes progress in advancing clinical trial design and practice-based recommendations (Sforzini et al., 2022). Identifying methods to improve trial design and efficiency can provide guidance on addressing some of these issues, especially when exploring novel therapeutic approaches (Correll et al., 2023). Germane to this study is the clinical utility of ketamine infusion as an adjunctive therapy for major depression, based in an Irish mental health service (Gallagher et al., 2022).

Randomised controlled trials (RCTs), as they are traditionally designed and conducted, may not be suitable to address the types of research questions and treatment issues that are specific to provision of mental health care (Chevance et al., 2022; McPherson et al., 2020). Concerns about the methodological shortcomings in mental health trials go back decades (e.g., Hotopf et al., 1997). Methodological limitations can include poor trial recruitment and retention (Chevance et al., 2022; Liu et al., 2018), suboptimal sample size, statistical power and reporting bias (de Vries et al., 2022; Vrlićak Davidović et al., 2022). Significant research waste and implementation gaps also exist, with limited translation of research findings into practice (Kazdin, 2022; Minogue et al., 2022; Yordanov et al., 2015).

One approach to improving trial design, conduct, and recruitment is the use of qualitative methodologies (Hennessy et al., 2018; Kazdin, 2022; Powell et al., 2022; Tan et al., 2022). A Cochrane synthesis of qualitative studies considered factors that influence decision-making regarding trial participation, including the manner in which trial information is communicated to potential participants, how the trial is designed, how participant decision-making may be influenced by others (e.g., recruiters), and how risk-benefit perceptions and communication impact recruitment (Houghton et al., 2020). According to a recent Lancet Psychiatry review, only a relatively few qualitative research studies “have identified the barriers and facilitators for either patient participation in mental health RCTs or participant recruitment by clinicians” (Chevance et al., 2022). Although research has identified both positive and negative impacts of service user engagement in research (Happell et al., 2018; McCabe et al., 2023; Newmark et al., 2020; Russell et al., 2020; Staley et al., 2013), there is a lack of research exploring the impacts of involving mental health service users in the design and conduct of clinical trials. In addition, research is needed to identify strategies on how best to engage clinicians / healthcare professionals in conducting research activities (Yoon et al., 2023).

A promising approach to address this gap, to improve trial design and conduct, and reduce research waste, is the use of Study Within A Trial (SWAT) methodology (Ahmed et al., 2022; Allan et al., 2021; Boxall et al., 2022; Thiblin et al., 2022). A SWAT can be defined as a “self-contained research study that has been embedded within a host trial with the aim of evaluating or exploring alternative ways of delivering or organising a particular trial process” (Treweek et al., 2018). Challenges to implementing SWAT protocols within host trials have been noted, including a lack of funding and understanding about SWAT methodology, perceptions that a SWAT will add to the complexity of an already complex study process, and concerns about the increased burden placed on research participants (Arundel et al., 2023; Clark et al., 2022; Doherty et al., 2022). Additional research is needed to explore the use of SWAT methodology in clinical research generally, and in mental health research specifically.

Study aims and objectives

Currently, there is a lack of research knowledge about the feasibility and utility of using qualitative SWAT methods to explore randomised trial processes in mental health care, and this study aims to address this gap. This qualitative Study Within A Trial (Qual-SWAT) will be embedded in the KARMA-Dep-2 Trial (Ketamine as an Adjunctive Therapy for Major Depression), to address two key methodological questions relating to the design and conduct of trials as part of mental health service provision. The methodological questions proposed arise from the PRioRiTy studies (Prioritising Recruitment / Retention in Randomised Trials), which identified a list of the top ten priority research questions to be addressed concerning recruitment and retention in randomised trials (Brunsdon et al., 2019; Healy et al., 2018). The specific methodological questions guiding the development of this study are as follows:

1. How can randomised trials become part of routine mental health care and best utilise current clinical care pathways?

2. What are the barriers and enablers for clinicians / healthcare professionals in helping conduct randomised trials?

The purpose of this study is to identify the key barriers and facilitators encountered when participating in a randomised mental health trial, from a patient-participant perspective, and to gain an understanding of how randomised trials can become part of routine mental health care. This study also aims to identify key barriers and enablers to recruitment and retention in mental health trials, from a clinician perspective, in order to guide future delivery, education and research. In addition, the
study findings will be fed back to the host trial research team, to provide support for ongoing recruitment and retention within the host trial. A key objective, using both qualitative and SWAT methodology, is to contribute to the rigorous development of a participant-led understanding of the two identified PRiORiTy methodological questions. By exploring the perspectives of patients and healthcare professionals, it may be possible to develop strategies to prevent inefficiency and waste in clinical trials (Gillies et al., 2019).

Methods

Ethics

This study will adhere to the Declaration of Helsinki (World Medical Association, 2013). Ethical approval for this study has been granted by the Research Ethics Committee (REC) of St. Patrick’s Mental Health Services (Ref: Protocol 09/20). Participants will be informed of their right to withdraw from the study at any stage without penalty or consequence. As the sample will include psychiatric patients, it is important to acknowledge that they will only be included in this study if they have the ability and capacity to give fully informed consent and are stable. The research team has developed a distress protocol for the conduct of interviews, and this will be strictly adhered to during the conduct of all interviews (Draucker et al., 2009; Pinto et al., 2022; Whitney & Evered, 2022). A period of time will be given to all participants post-interview, to discuss any issues relating to the interview process that may have caused potential distress, and support will be offered if necessary.

Host trial

The host study is a pragmatic, randomised controlled, parallel-group, superiority trial, which is investigating the use of ketamine as an adjunctive therapy for major depression ((KARMA-Dep-2: ClinicalTrials.gov NCT04939649; EudraCT 2019-003109-92); see Gallagher et al., 2022, for pilot trial information).

Study design

This is a qualitative, Study Within A Trial (SWAT), embedded in the KARMA-Dep-2 trial. This qualitative SWAT (Qual-SWAT) is conducted independently from the host trial. This study will use a descriptive qualitative design, relying on purposive sampling. One-to-one semi-structured interviews will be conducted via Voice over Internet Protocol technology (VoIP; Tomás & Bidet, 2023), using Microsoft Teams.

Study participants and procedure

According to a systematic review, a sample size of 9 - 17 interviews is sufficient to achieve saturation, which is a cornerstone of rigour in qualitative research (Hemming & Kaiser, 2022). Three groups of participants will be invited to take part in qualitative interviews (N = 60). These sub-groups include: (1) participants who agree to participate in the host trial (n = 20); (2) participants who are invited to take part in the host trial and decline participation (n = 20); and (3) clinicians and researchers who are associated with work on the host trial (n = 20). To be eligible for inclusion in the Qual-SWAT, participants must be: (1) over the age of 18 years with the ability to give fully informed consent; (2) eligible for participation in the host trial; and (3) a clinician or researcher working on the host trial. Potential patient participants will be excluded from the Qual-SWAT if they are not deemed eligible for the host trial, based on trial exclusion criteria. For details on the host trial inclusion/exclusion criteria, see the trial registration (ClinicalTrials.gov NCT04939649). Clinicians and researchers who are not associated with the host trial will be excluded as potential participants in the Qual-SWAT.

Recruitment for the Qual-SWAT will be publicised, using flyers, in two clinical settings across St. Patrick’s Mental Health Services (i.e., St. Patrick’s University Hospital, Dublin, and St. Patrick’s, Lucan). An email invitation regarding the Qual-SWAT participation will be sent to the multidisciplinary team (MDT) and research staff at both clinical sites. The host trial PI / trial co-ordinator will act as gatekeeper, by identifying potential participants and distributing study information packs (i.e., invitation letter, participant information leaflet, and consent form). The host trial consent form will provide an option for participants to agree to future contact for follow-up research studies that may arise from the host trial.

Potential participants will be given a 14-day time-frame, to allow for a period of time to review and consider the study information provided, to ask any questions they have, and to make a fully informed decision with regards to their participation in the study. Following the 14-day period, arrangements will be made to proceed with the research study with those who have indicated an interest in participating. All participants in the Qual-SWAT will be asked by the PI / co-investigator to read and return a signed consent form before undertaking interview.

Interview guide

The interview guide will include questions about the experience of trial recruitment, key issues relating to participation, views on trial conduct, processes, and integration of research into day-to-day care, and views on further research in mental health care settings (Table 1). In addition, observational and field notes will be included during the interview process.

Analysis and rigour

Demographic information will be collected in order to describe sample characteristics. SPSS will be used to manage quantitative data and report on sample descriptive statistics. The Microsoft Teams interviews will be recorded and transcribed verbatim, and then analysed to determine common themes. Thematic analysis will be used to analyse interview data, using a six-stage approach (Braun & Clarke, 2006). This involves listening to recordings, reading and rereading the transcripts, coding the data, categorising the codes and finally developing themes. A computer-assisted qualitative data analysis software package (CAQDAS; e.g. NVivo) will be used to aid qualitative data management and analysis (Clarke et al., 2021; Dalkin et al., 2021; Kalpakas & Radivojevic, 2022). Data analysis will be undertaken by the Qualitative Research and
Trials Centre (QUESTS) team, who will familiarise themselves with the data, identify a thematic framework and undertake analysis to produce summary statements explaining the main themes emerging from the data.

Various methods will be used to enhance rigour, based on recommended good practice (Forero et al., 2018; Nowell et al., 2017; Patterson et al., 2023; Yadav, 2022). Data will be sourced from multiple participant groups to capture a range of perspectives and enhance data completeness (i.e., triangulation). NVivo functions (e.g., annotation) will be used to facilitate transparent decision-making processes within and between researchers (i.e., audit trail). Two researchers will complete an independent initial analysis of one transcript, and then discuss, compare and agree on initial themes (i.e., inter-coder reliability). Agreed themes will be discussed by the entire research team to enable ongoing reflexive analysis. The Standards for Reporting Qualitative Research will be used to guide reporting (SRQR; O’Brien et al., 2014).

**Data management**

This study will operate in accordance with the Data Protection Act (2018), General Data Protection Regulation (2018) and Health Research Regulations (2018) (Clarke et al., 2019; Mee et al., 2021). Participant confidentiality and anonymity will be maintained throughout the research process. Participant coding will occur on recruitment. Data anonymisation will be applied throughout data collection and analysis phases. Code

**Table 1. Interview guide.**

<table>
<thead>
<tr>
<th>Questions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opening and introduction:</strong> The aim of this interview is to further understand your experience, opinions and perceptions regarding recruitment to the KARMA-Dep (2) Trial. The interviewer should explain that this is a guided discussion to ascertain the participant’s experience. We are specifically looking for data on: why you chose to participate / decline, experience of participation and views on trial conduct and integration of research in day to day care.</td>
<td></td>
</tr>
<tr>
<td><strong>Discussion topic guide</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Experience of recruitment</strong></td>
<td></td>
</tr>
<tr>
<td>What is your experience of being recruited to the trial?</td>
<td>Had you heard about the trial on the ward? Did you discuss it with a clinician?</td>
</tr>
<tr>
<td>Why did you gain consent / refuse to participate in the trial?</td>
<td>What more could have been done to inform you?</td>
</tr>
<tr>
<td>What do you know about the process of recruitment for this trial?</td>
<td></td>
</tr>
<tr>
<td>How do you think it can be improved?</td>
<td></td>
</tr>
<tr>
<td><strong>Important issues in relation to participation?</strong></td>
<td></td>
</tr>
<tr>
<td>What issues are important to you in relation to being involved in the trial?</td>
<td>Is there a benefit just to taking part- in yourself (routine and altruism)</td>
</tr>
<tr>
<td>How did your understanding of research in inpatient settings change following agreeing to participate?</td>
<td></td>
</tr>
<tr>
<td><strong>Possible changes in Trial Process?</strong></td>
<td></td>
</tr>
<tr>
<td>What is the impact of participation on you personally? Professionally?</td>
<td></td>
</tr>
<tr>
<td>How does participation in this trial impact on your well-being? View of trial conduct?</td>
<td>Did the approach make you think about your own mental health and could being approached do harm</td>
</tr>
<tr>
<td><strong>Views on further research in Mental Health Inpatient Settings</strong></td>
<td></td>
</tr>
<tr>
<td>Did you find that the clinical staff on the ward understood and supported the research process?</td>
<td></td>
</tr>
<tr>
<td>Are there any ways to make participating in research while in hospital easier for future studies?</td>
<td>Would videos from participants discussing their experience help</td>
</tr>
<tr>
<td>Are you happy for us to contact you about future research?</td>
<td></td>
</tr>
<tr>
<td>Is there anything else that you would like to add that you think is important about your experience and/or needs?</td>
<td></td>
</tr>
<tr>
<td>• Thank everyone for participating.</td>
<td></td>
</tr>
</tbody>
</table>
numbers will be applied to all digital audio recordings and transcripts. All electronic data will be password protected and stored securely in accordance with the Data Protection Act (2018).

Dissemination
A knowledge exchange and dissemination plan will be prepared and agreed with the PI of the host trial. In consultation with the Health Research Board (HRB), a written report will be submitted to the HRB. The report will be made available to the host trial team and to research study participants. Findings will be disseminated and presented at national and international conferences, and submitted for publication to a peer-reviewed journal.

Conclusion
There is limited research exploring the impacts of involving mental health service users in the design and conduct of clinical trials. Research is also needed to identify strategies on how to engage clinicians / healthcare professionals in conducting clinical research activities, and how best to embed clinical trials into routine clinical practice. This Qual-SWAT aims to add to the evidence base, specifically by developing an understanding of the potential benefits to participation in mental health trials, as well as barriers to recruitment and retention.

Study status
Following substantial COVID-19 and post-pandemic delays in recruitment, interviews are ongoing. The host trial is currently applying for an 18-month, no-cost extension.

Data availability
No data are associated with this article.

Acknowledgments
The authors would like to thank all the trial recruiters involved in the KARMA-Dep project: Orlaith Loughran, Kelly McDonagh, Sarah McDonogh, Ellie Shackleton, Cathal McCallfrey, Masashi Terao, Ana Jelovac (Affiliation: Department of Psychiatry, Trinity College Dublin, St. Patrick’s University Hospital, Dublin, Ireland). The authors would also like to thank the Principal Investigator of the KARMA-Dep project: Declan McLoughlin (Affiliation: Department of Psychiatry, Trinity College Dublin, St. Patrick’s University Hospital, Dublin, Ireland, and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland).

References


Hennings S, Hunter A, Healy P, et al.: Improving trial recruitment processes: how qualitative methodologies can be used to address the top 10 research priorities identified within the PRIoRiTy study. Trials. 2018; 19(1): 584. PubMed Abstract | Publisher Full Text | Free Full Text


Emily Taylor
Department of Clinical and Health Psychology, The University of Edinburgh, Edinburgh, UK

This is a clearly written protocol for a well-thought through and valuable study that makes good use of a pre-existing trial. My comments below are caveated by the fact that the study is already underway.

The protocol requires a long period between invitation to participate and consent and participation, which might result in lost participants, especially in the sub-sample who have exited the host study. Reading on I was a little unclear as to whether this is a minimum or maximum time, but either way might be restrictive. Can you clarify what the 14 days refers to? If it is a minimum requirement and there is scope to reduce this, I would recommend doing so.

The multi-perspective approach will be valuable in this study. The sample size is ambitious but is presumably feasible in the context of the host study. If sub-samples are seriously unbalanced, how problematic would this be, and have the authors set some lower limits for the sub-samples to ensure that all parties are properly represented?

Is there an option to interview in-person as an alternative to Teams? Some participants may prefer this.

Is the rationale for, and objectives of, the study clearly described?  
Yes

Is the study design appropriate for the research question?  
Yes

Are sufficient details of the methods provided to allow replication by others?  
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** qualitative designs and trials in developmental trauma with care-experienced children and young people

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 16 June 2023

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The proposal is carefully written and makes the case very well, I firmly support the progress of the project. The use of qualitative research methods within a quantitative superiority RCT is of particular value in addressing well-known concerns about the potentially reductive nature of assessing mental health outcomes numerically. The choice of qualitative approach, thematic analysis, is appropriate for a sample of this size, and the formulation of the questionnaire appears to address the research questions well. The only concern I had, which is not easily addressed and not at all unique to this project, is the inevitable sample bias in trying to interview people who have already declined to take part in the larger study. However in this case I suspect declining will have been to do with not wanting to take ketamine rather than absolutely not wanting to participate in research, and getting hold of a sample could be reasonably straightforward. Additionally, understanding this group will be of particular value, especially if the host trial indicates effectiveness of ketamine.

Overall this is a strong proposal and in my view should be supported.

**Is the rationale for, and objectives of, the study clearly described?**
Yes

**Is the study design appropriate for the research question?**
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Yes

**Are the datasets clearly presented in a useable and accessible format?**
Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Mental health, psychotherapy, clinical trials, neuroscience, virtual reality, brain imaging, electrophysiology, PTSD, depression, compassion.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.