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Perioperative mental health intervention for depression and anxiety symptoms in older adults study protocol: design and methods for three linked randomised controlled trials

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ABSTRACT

Introduction Preoperative anxiety and depression symptoms among older surgical patients are associated with poor postoperative outcomes, yet evidence-based interventions for anxiety and depression have not been applied within this setting. We present a protocol for randomised controlled trials (RCTs) in three surgical cohorts: cardiac, oncological and orthopaedic, investigating whether a perioperative mental health intervention, with psychological and pharmacological components, reduces perioperative symptoms of depression and anxiety in older surgical patients.

Methods and analysis Adults ≥60 years undergoing cardiac, orthopaedic or oncological surgery will be enrolled in one of three-linked type 1 hybrid effectiveness/implementation RCTs that will be conducted in tandem with similar methods. In each trial, 100 participants will be randomised to a remotely delivered perioperative behavioural treatment incorporating principles of behavioural activation, compassion and care coordination, and medication optimisation, or enhanced usual care with mental health-related resources for this population. The primary outcome is change in depression and anxiety symptoms assessed with the Patient Health Questionnaire-Anxiety Depression Scale from baseline to 3 months post surgery. Other outcomes include quality of life, delirium, length of stay, falls, rehospitalisation, pain and implementation outcomes, including study and intervention reach, acceptability, feasibility and appropriateness, and patient experience with the intervention.

Ethics and dissemination The trials have received ethics approval from the Washington University School of Medicine Institutional Review Board. Informed consent is required for participation in the trials. The results will be submitted for publication in peer-reviewed journals, presented at clinical research conferences and disseminated via the Center for Perioperative Mental Health website.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study uniquely assesses the effectiveness of a perioperative mental health intervention with combined psychological and pharmacological components to reduce depression and anxiety in older adult surgical patients.

⇒ This intervention has been pilot tested and adapted to older adults in three surgical cohorts: cardiac, orthopaedic or oncological surgeries.

⇒ The perioperative mental health intervention is compared with enhanced usual care.

⇒ We are testing the implementation potential of a perioperative mental health intervention using a randomised controlled trial hybrid type 1 effectiveness-implementation design.

⇒ Engagement and participation in our perioperative mental health intervention may vary significantly across patients. Interventionists may find it difficult to meaningfully engage patients in the behavioural activation component after their surgery. Medication optimisation may not be possible for all patients in the study, given their reluctance to changing their medications.

Trial registration numbers NCT05575128, NCT05685511, NCT05697835, pre-results.

INTRODUCTION

Preoperative anxiety and depression symptoms contribute to poor surgical outcomes,[1] including increased rates of readmission, delirium, falls and mortality.[2–5] Among older adults, poor perioperative mental health also contributes to a decline in health-related quality of life (QoL).[6–10] Exacerbating the

mental health concerns in this population is the high rates of polypharmacy among older adults undergoing major surgical procedures.[11] Of particular concern is the use of potentially inappropriate medications, including opioids and benzodiazepines, which are harmful perioperatively, increasing falls and delirium.[12–15] These findings are observed across a range of surgical populations, and while the number of surgical procedures is increasing for all surgery types,[16] there is considerable evidence suggesting an increased prevalence of depression and anxiety among older cardiac, oncological and orthopaedic surgery patients and its deleterious effects on their recovery, as summarised below.

Orthopaedic surgery

Total hip (THA) and knee (TKA) arthroplasties are projected to exceed 4 million procedures annually in the USA by 2030.[17] Across multiple studies, the strongest and most consistent variables associated with unsatisfactory pain and functional outcomes after THA and TKA are comorbid mental health conditions, including anxiety, depression and pain catastrophizing.[18–20] Preoperative anxiety symptoms are a risk factor for newly diagnosed depression within 1 year of TKA.[21 22] Preoperative anxiety and depression symptoms are also risk factors for other complications such as persistent postsurgical pain.[23] A 2018 systematic review of psychological interventions in THA and TKA patients identified only seven randomised intervention trials, and concluded that this body of literature was 'still in its infancy'.[24]

Oncological surgery

By 2030, 17.3 million people worldwide are projected to undergo surgery for cancer each year, with two-thirds of these cases occurring in older adults.[25] Depressive symptoms are four times more common in patients with cancer than in the general population.[26] Preoperative depressive symptoms increase the risk of adverse intraoperative and postoperative outcomes, including surgical complications, delirium, persistent pain and cancer recurrence.[27–34] Oncological patients with depressive symptoms also have shorter overall survival in the setting of advanced or metastatic disease and reduced progression-free survival than those patients without depressive symptoms.[31–33] Among 1500 older adults with cancer who met the criteria for major depression, nearly 75% were untreated for depression.[35] The proportion was higher in the oldest subgroup, with 87% of patients over age 70 having untreated depressive symptoms.

Cardiac surgery

More than 80% of patients undergoing major cardiac surgeries in the USA are older adults[32 36] and account for approximately 500 000 surgeries annually. The prevalence of mental health disorders is substantially higher,[37] among older adults undergoing cardiac surgery than among community-dwelling older adults. It is estimated that between 27% and 47% of patients scheduled for cardiac surgery, and 19%–61% of patients after cardiac surgery, have depressive symptoms,[38–40] which is consistent with the 33% preoperative rate of depressive symptoms among older adults undergoing cardiac surgery in our institution. Anxiety symptom rates are similar; 34%–58% before cardiac surgery,[41] and 25%–31% postoperatively.[42 43] For older adults undergoing cardiac surgery, poor mental health preoperatively is a risk factor for poor postoperative outcomes, including increased mortality, comorbidity and a decline in health-related QoL.[6–10 44]

Comprehensive perioperative care focuses on improvements in functional recovery, including the use of preoperative physical optimisation,[45] early mobilisation[46 47] and postoperative physical rehabilitation.[48 49] Many previous efforts to improve mental health in surgical patients have not incorporated evidence-based interventions.[24] The growing recognition of the significant impact of poor mental health on the postoperative recovery serves as an impetus for promoting the holistic care of the surgical patient, including their physical, mental and cognitive health. However, there are currently no systematic efforts to identify and apply evidence-based combined behavioural and pharmacological interventions for depression and anxiety symptoms, adapt them for use in older adult surgical populations and test their effectiveness and potential for implementation in these patient populations.[24 35 37 50–52]

Previously, we enrolled 23 patients undergoing orthopaedic, oncological or cardiac surgery in an open-label feasibility study evaluating our perioperative mental health intervention and study procedures—both of which informed this current protocol.[53 54] Findings from our feasibility study demonstrated that the study procedures were feasible, with both study reach (ie, patients who agreed to participate in the study out of total eligible to participate) and intervention reach (ie, participants who completed the intervention out of participants who agreed to participate in the study) exceeding 80% of potential participants. Preliminary efficacy analysis indicated improvement in symptoms of depression and anxiety as measured by the Patient Health Questionnaire-Anxiety Depression Scale (PHQ-ADS). Qualitative interviews with patients and caregivers at the end of the study indicated positive experiences with the intervention and the interventionists, as well as improved management of their depression and anxiety symptoms. In preparation for, during and following this feasibility study, our team adapted the perioperative mental health intervention to better fit the needs of our patient populations.[55]

As a next step in this line of research, we will conduct three randomised controlled trials (RCTs) to evaluate the effectiveness and implementation of the adapted perioperative mental health intervention, consisting of a surgical wellness programme and medication optimisation that reduces depression and anxiety symptoms in three at-risk surgical populations: orthopaedic, oncological and cardiac surgeries.

METHODS AND ANALYSIS

Trial design

Three RCTs will be conducted among 100 participants from each of the three surgical cohorts (n=300): orthopaedic (NCT05697835), oncological (NCT05685511) and cardiac (NCT05575128).

The effectiveness of the perioperative mental health intervention versus enhanced usual care will be evaluated in a hybrid type 1 effectiveness-implementation trial.[56] A type 1 trial was chosen because the primary focus of the trials is on early-phase effectiveness testing while understanding the context for implementation. We will adopt a mixed methods approach[57] within this experimental study design through which we will collect quantitative outcomes to show the intervention effectiveness and gather qualitative data to ascertain patient experiences

with the intervention and other data on its implementation. We will synthesise the findings to address the study goal.

Study procedures

Figure 1 shows the study flow described in detail for each surgical cohort. Recruitment for all three cohorts is ongoing. Recruitment began for the cardiac surgery cohort in November 2022, and for the oncological and orthopaedic surgery cohorts in February 2023. The planned end date for recruitment to all three trials is August 2024.

Setting and participants

Participants include adults aged 60 years or older with a scheduled orthopaedic, oncological or cardiac surgical
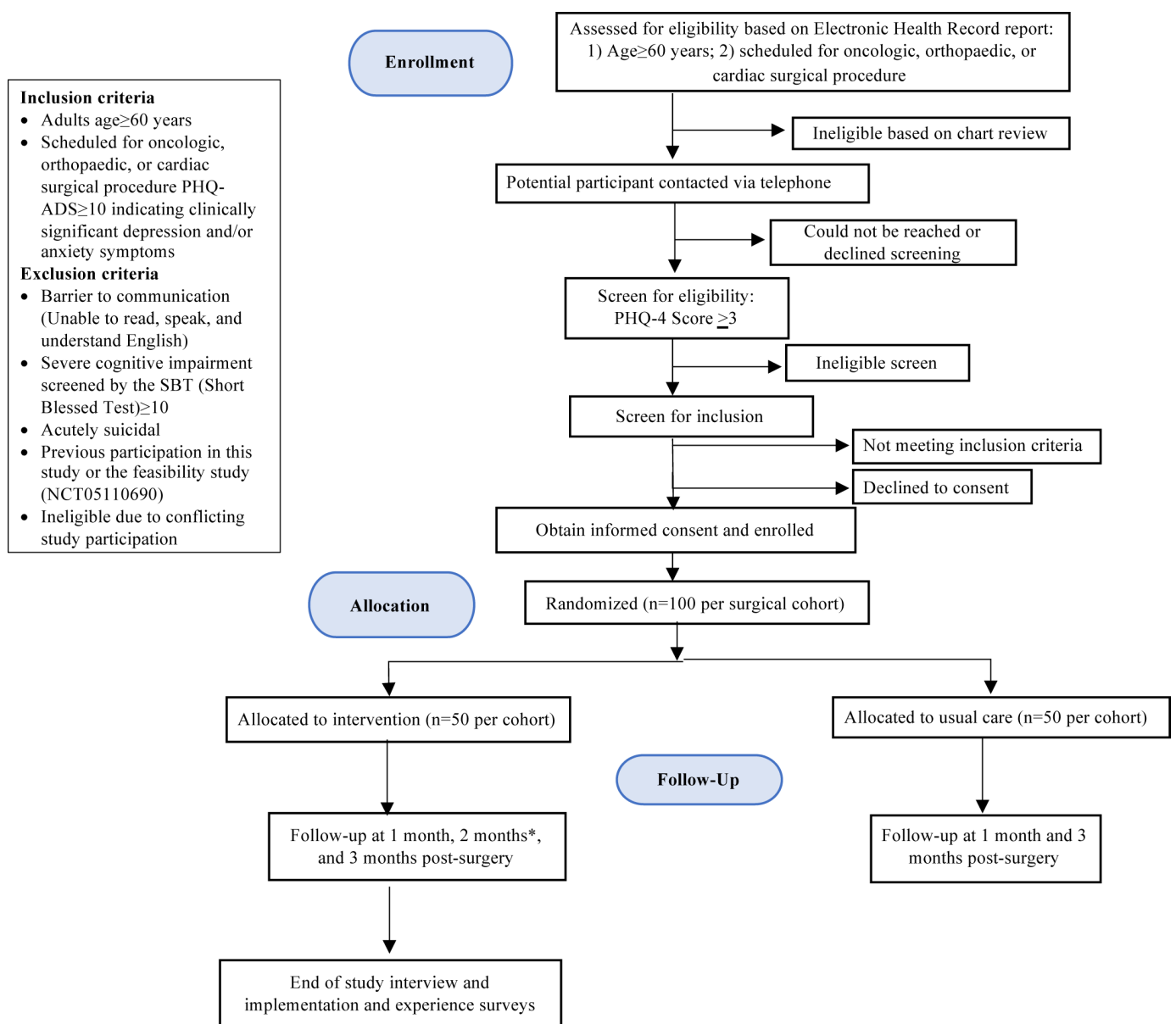
Figure 1 Study flow diagram for each surgical cohort. *Note: 2-month timepoint for intervention group is the target engagement assessment. PHQ-4, Patient Health Questionnaire-4; PHQ-ADS, Patient Health Questionnaire-Anxiety Depression Scale.

procedure at three hospitals in the Barnes-Jewish/Christian (BJC) Network. BJC hospitals encompass both academic and community practice settings and serve a diverse rural, suburban and urban population. Barnes-Jewish Hospital (BJH) will be the primary recruitment site. For the orthopaedic cohort, we will also recruit patients seen at Barnes-Jewish West County Hospital, given the high number of orthopaedic surgeries performed at that location. Similarly, in the cardiac cohort, patients seen at Missouri Baptist Medical Center will be recruited given their high rates of cardiac surgery.

BJH is a large teaching hospital serving a catchment area including both urban and rural patients in Missouri. Based on the primary catchment area for BJH, we anticipate that 48% of potentially eligible patients will be male and 52% female; 78.4% will be non-Hispanic white, 18.1% will be African-American, 1.4% Asian and 2% Hispanic/Latino of any race.[58]

These studies are approved by the Washington University School of Medicine Institutional Review Board (IRB) (202209033, 202301070, 202212097). The IRB approvals cover the three participating hospitals without the need for individual IRB approval from each hospital.

Patients will sign an informed consent document (electronic or paper), indicating their willingness to participate in the study (see online supplemental appendix A for a participant consent template).

Screening

A research coordinator will screen the orthopaedic, oncological, cardiac surgery and cardiology procedure clinic schedules, direct clinician referrals and the anesthesiology preoperative assessment clinic schedule for potential candidates.

For each cohort, a research coordinator will extract the patient's phone number, age and sex, type of surgery, the surgeon's name and planned surgery date, from their electronic health record (EHR). A research coordinator will contact potentially eligible patients to screen for inclusion criteria.

Screening: patients aged 60 years or older will be screened using the Patient Health Questionnaire-4 (PHQ-4) which consists of 4 questions from the PHQ-2 and Generalised Anxiety Disorder scale (GAD-2).[59] Scores >3 will indicate positive prescreen and the patient will be considered potentially eligible and moved to formal screening. Scores <3 indicate negative screen and the patient will be excluded due to low risk for anxiety or depression. Formal screening consists of the full 17-item PHQ-ADS, including the 4 questions with the PHQ-4.

Inclusion criteria

Each participant must meet all of the following criteria: (1) age ≥60 years at the time of scheduled surgery; (2) scheduled for oncological, orthopaedic or cardiac surgical procedure (see online supplemental appendix B for list of included procedure codes and description); (3) PHQ-ADS[60] ≥10 indicating clinically significant depression and

anxiety symptoms (the PHQ-ADS is a combination of the PHQ-9 and GAD-7).

Exclusion criteria

Additional exclusion criteria are as follows: (1) barrier to communication (unable to read, speak and understand English); (2) severe cognitive impairment screened by the Short Blessed Test[61] (SBT) ≥10; (3) acute suicidal features (assessed via a suicide safety screening. This screening is administered if the patient spontaneously reports suicidal thoughts or if the patient scores above a 0 on PHQ-9 item 9 (this item elicits information about thoughts of being dead or of hurting oneself)); (4) ineligible due to conflicting study participation as noted by the orthopaedic, oncological, cardiac surgeon or study principal investigator; or (5) previous participation in this study or the feasibility study.[53]

Baseline characterisation of participants

A brief battery of simple-to-use assessments is consistent with the pragmatic nature of these trials. *Symptoms of anxiety and depression* will be measured at screening by the PHQ-ADS tool. QoL will be assessed by the Centers for Disease Control and Prevention Health-Related Quality of Life survey (CDC HRQOL-14).[62] The questions in this patient-reported survey correspond to the QoL domains of healthy days (physical and mental health status), activity limitations and healthy days symptoms (how pain, mood, anxiety, sleep and energy levels affect their daily life). *Cognitive function* is assessed using the SBT.

Randomisation

All eligible and consented participants will be randomised in a 1:1 ratio to receive either the perioperative mental health intervention or enhanced usual care. The study biostatistician generates the randomisation table using a variable block sequence. The assignment of the treatment condition for each individual participant will be done by the REDCap randomisation module[63 64] after confirming trial eligibility. For participants assigned to the intervention, a randomisation table will be generated using a similar block sequence design, and the data manager will manually select the individual intervention team member according to the randomisation table and record that information in REDCap. This process will trigger an automatic notification via REDCap to the assigned intervention team member.

Blinding

Research coordinators responsible for collecting outcome data throughout the study will be blinded until data collection is complete. Participants are not blinded to their group assignment. At the end of the 3-month follow-up, the research coordinators will complete a blinding question to guess the arm to which each participant was allocated. This will allow the team to determine the effectiveness of the blinding procedures.[65] On completing this form, it will be locked by the data manager, and the participant's assignment will be revealed to the research

coordinators to conduct the end-of-study interviews with the participants in the intervention arm.

Enhanced usual care

Following randomisation, participants in the enhanced usual care arm will receive information (see online supplemental appendix C: Handouts for Participants) sent by a team member via mail or email, according to participant preference. The handouts include information on 'mindfulness and recovery from surgery', 'self-help for disrupted sleep', and 'training your brain' (ie, cognitive training). These materials were selected based on evidence supporting their effectiveness with older adults with anxiety and depression symptoms,[66–70] our prior study with older surgical patients and clinicians[71] and feedback from our interventionists during our intervention design studios.[55] The activities described in the handouts are self-directed which participants can choose to read and pursue if they wish. Participants in the control group have no interaction with the interventionist teams.

We chose to use enhanced usual care to provide some harmonisation between the participants in the usual care arm. Providing resources to participants in both arms increases the possibility of benefit for all participants, which may potentially improve recruitment and retention.

Intervention

Following randomisation, participants in the intervention arm will receive the same handouts provided to the enhanced usual care arm participants sent by a team member via mail or email, according to participant preference. Participants in the intervention arm will also receive a perioperative mental health intervention that integrates two main components: (1) a psychological intervention incorporating principles of behavioural activation, compassion and care coordination, and (2) medication optimisation.

Perioperative wellness programme

The psychological intervention will be described to patients as a wellness programme, based on input from our study internal advisory board (IAB) with patients, caregivers and clinicians. It is semistructured, providing opportunity for individualising the approach to meet the participant's changing needs before and after surgery. The wellness programme uses principles of behavioural activation, compassion and care coordination. The basic premise of behavioural activation is to help people with anxiety or depression symptoms engage in reinforcing or meaningful activities, guided by their values.[72] Behavioural activation techniques will be used to support the patient in an individualised, active recovery from surgery, which encourages participants to gradually re-engage in the important activities in their life and cope with the stressors of the surgical period. As such, participants can tailor the wellness programme by choosing activities that they identify as personally rewarding and meaningful. Participants

will be asked to check with their physicians if there is any question about the safety of any physical activities that are included in their behavioural activation plan.

The programme will be delivered by a masters-level social worker or counsellor, referred to as a wellness partner, with oversight from study team members, including a PhD-level clinical social worker, psychologist and a geriatric psychiatrist. The style of the wellness programme is supportive, and explicitly incorporates the principles of compassionate care (eg, validating concerns, conveying a genuine interest in the patient as a whole person, asking open-ended questions) and empathetic listening. Because the surgical period can present new challenges for patients, an important emphasis of the wellness programme is care coordination. Common types of problems during the surgical period include difficulties navigating the health system to receive needed care, trouble managing activities of daily living and financial issues. The role of the wellness partner is to actively listen and validate, while following the participant's lead when discussing potential solutions.

The wellness programme can be carried out remotely via phone or secure web conference, with optional in-person visit/s while the participant is hospitalised for their surgery. The programme will typically begin preoperatively, with sessions approximately every 2 weeks. After discharge, the wellness programme will continue for 10–12 sessions or about 3 months postoperatively. Figure 2 illustrates the intervention delivery timeline.

Medication optimisation

In clinical trials including thousands of older adults, we have developed and refined a process for assessing and optimising medications,[73 74] including adjusting suboptimal dosing of antidepressants and discontinuing or reducing dosages of medications that are harmful to brain health. This component of the intervention is optional and medication changes are only pursued if a participant is prescribed a targeted medication (see online supplemental appendix D: Targeted Harmful Medications for Optimization and E: Antidepressant Medications of Interest) and is interested in a recommended change. Medication changes will be performed collaboratively with participants and their clinicians and no new medications are introduced as part of this study.

This component of the intervention will be led by the pharmacy team consisting of clinical pharmacist specialists and pharmacy students trained in medication reconciliation and optimisation processes. One student and supervisor are assigned to each participant. The participants' home medications will first be reviewed and confirmed with the patient by a pharmacy team member before beginning medication optimisation. For participants who are prescribed at least one of the targeted medications, the following steps are taken: (1) reconciling the participant's medications listed in the EHR with the participant, (2) identifying targeted medications that impact brain health, (3) informing the participant
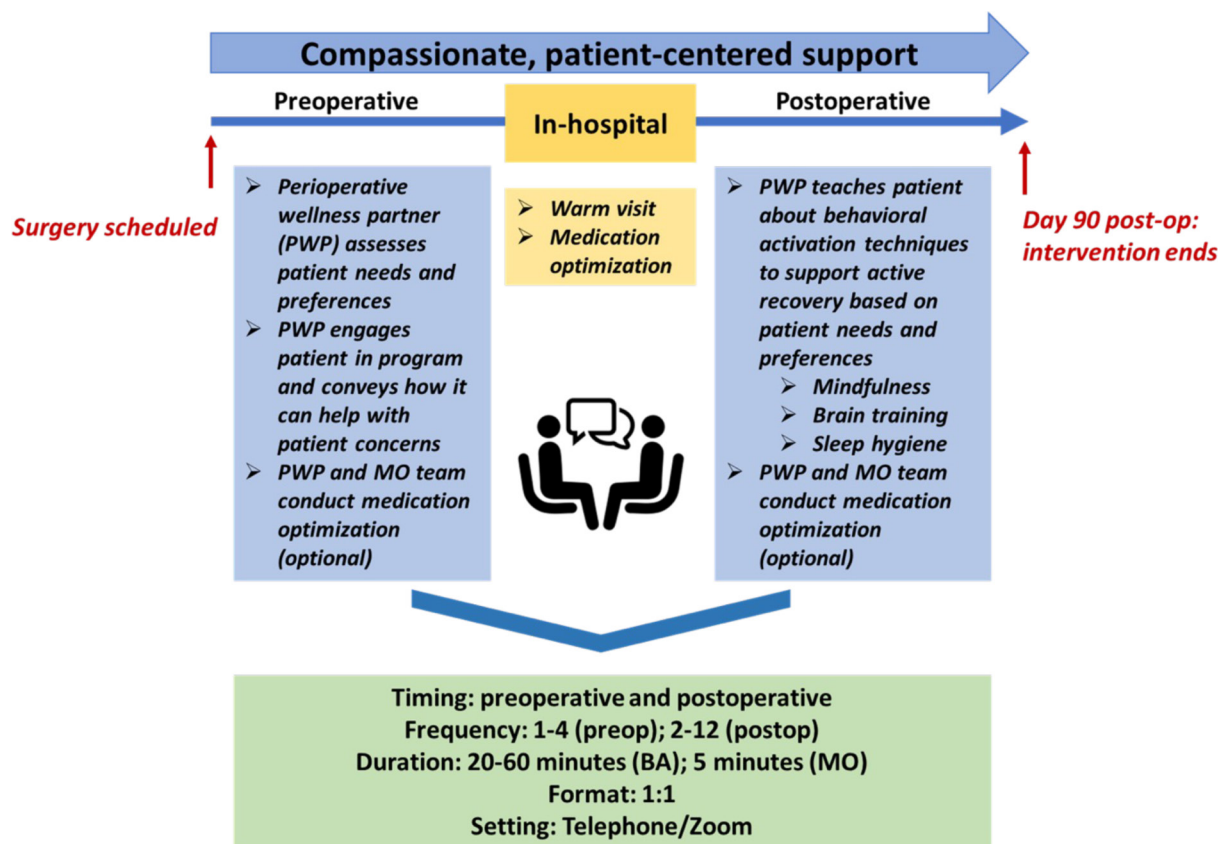
Figure 2 Timeline of the intervention delivery. BA, behavioural activation; MO, medication optimisation.

why we are focused on the specific medication(s), (4) assessing the participant's likely need for, and interest in, a medication adjustment, (5) discussing recommended change(s) with prescribing physicians when necessary, (6) implementing the adjustment and (7) assessing the response to the adjustment.

Deprescribing may consist of direct discontinuation or dose reduction and/or weaning strategies, depending on the medication and clinical context surrounding its use, with the ultimate goal of eventual discontinuation. Pharmacy team members are guided by the deprescribing resources and algorithms available on the US Deprescribing Research Network[75] and the following steps that have been used and refined by the teams' previous experiences[54 73 74 76]: (1) assess indication for use and whether the patient perceives the medication to be helpful, (2) assess duration of use and dosage change history, (3) ask about any issues with balance, cognition, sedation or confusion, (4) if the patient has been taking a centrally acting anticholinergic ask if they have been experiencing any possible anticholinergic side effects such as dry mouth or constipation, (5) assess the patient's willingness to stop taking the medication, take a lower dosage or take the medication less frequently, (6) counsel on any possible side effects of medication withdrawal that could occur from stopping or decreasing use, (7) if the patient is in agreement to discontinue or reduce the use or dosage of the medication, discuss the patient's willingness for the team to contact the prescriber to gain support, buy-in,

monitoring and follow-up, and (8) monitor the patient regularly with follow-up calls and educate patients to reach out to our pharmacy team and their prescribing physician if any symptoms of withdrawal are experienced.

While the participant is in the hospital, the study pharmacy team will coordinate with the inpatient team to ensure that medication changes that were introduced preoperatively are maintained in-hospital and that no new inappropriate medications are initiated. Additionally, the wellness partner and pharmacy team will ensure that targeted medication changes are continued after discharge and up to 3 months postoperatively.

Training for Interventionists
The wellness partners have experience in mental health treatment and training in psychological and pharmacological treatments, including behavioural activation and medication optimisation. Prior to initiating the study, the wellness partners will participate in four 1-hour weekly training sessions covering four core behavioural activation strategies using Behavioural Activation Skills Assessment training modules[72] and to orient the team members to the wellness programme manual developed by our team.

For the pharmacy team, training sessions will be led by two study team clinical pharmacy specialists with multiple weekly sessions. Session content includes good clinical practices; review of the medication optimisation intervention manual; EHR access and navigation; intervention

database navigation; and demonstrating compassion and empathy during patient communication. Students will be given supplemental readings about antidepressant dosing and potentially harmful medications.

Weekly intervention meetings will also help the wellness partners and pharmacy team to review the intervention and materials and receive continuous feedback.

Outcome measurements
Primary outcome
The primary outcome of the study is the change in PHQ-ADS from baseline to 3 months after surgery.

The PHQ-ADS was selected as a single outcome measure in these trials for several reasons: its use is consistent with our trials' pragmatic designs given that the PHQ-ADS is a simple measure that is already widely used in routine care.[77–79] In addition, measuring depressive and anxiety symptoms together in one scale is consistent with their common comorbidity, as patients frequently have both types of symptoms.[80–82] Further, mental health evaluation and treatment broadly is moving towards this combined assessment/treatment of depression and anxiety symptoms together,[83–85] and the intervention evaluated in these trials is designed to help with both depression and anxiety symptoms.

Table 1 includes a comprehensive list of all outcome questionnaires at baseline and follow-up timepoints administered in person, remotely via a web-based survey, or via telephone.

Other outcomes
Other outcomes include QoL measured via the CDC HRQOL-14[62] and other key perioperative outcomes of interest including:

(1) In-hospital: (a) delirium incidence, assessed by trained research assistants by EHR review using the Chart-based Delirium Identification Instrument method as in our prior work,[76] and (b) length of stay (hospital and intensive care unit (ICU)), assessed via a research data warehouse.

(2) Post discharge: (a) falls assessed by self-report, (b) all-cause 90-day postoperative hospitalisation, assessed by EHR review and (c) persistent postsurgical pain assessed via pain presence and severity at the site of surgery and Brief Pain Inventory[86] pain interference scale.

Implementation outcomes
For participants in the intervention arm, we will evaluate their experience using a version of the Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey which we modified to include elements about medication optimisation, behavioural activation and compassion, and using implementation surveys (Acceptability of Intervention Measure, Intervention Appropriateness Measure and Feasibility of Intervention Measure[87]) which will be administered after the intervention is complete.

Intervention measures
We will collect the following descriptive data for the wellness programme and medication optimisation components: number of wellness programme and medication optimisation sessions, duration of sessions, number of preoperative sessions and number of postoperative sessions. In both the intervention and enhanced usual care arm, all medication data available will be collected at baseline preoperatively, in the hospital, and at discharge by the pharmacy team, including information on the use of common medications for chronic pain, such as opioids, gabapentin and pregabalin. For participants in the intervention arm, the pharmacy team will review and confirm EHR medication data with the participant. For participants in the control group, these data will be collected via EHR review. For the medication optimisation component, we will collect number of medications at baseline and the number of medications eligible for optimisation (deprescribing and dose escalation).

We will assess multiple components of fidelity to the perioperative mental health intervention to examine the extent to which the intervention is carried out by our intervention team as intended and consistently across different settings. We created fidelity rating checklists that we will use to analyse treatment delivery, treatment receipt and enactment of treatment skills for both the wellness programme and medication optimisation based on the framework developed by Bellg et al[88] and Borrelli et al.[89] Patient data will be tracked, including adherence to core components of the intervention, quality of delivery and participant responsiveness which will be documented in the session documentation form and the fidelity checklist. All sessions will be audio recorded. A proportion of sessions will be reviewed and rated for fidelity by a team of researchers with training in the intervention.

Target engagement measure
We will employ a survey at 2 months after surgery to measure target engagement of our wellness programme and medication optimisation. The survey contains questions on the various components of our intervention, and includes the Behavioural Activation for Depression activation subscale,[90] the Sinclair Compassion Questionnaire[91] to evaluate the level of compassion and attention provided by the perioperative wellness partners, the MiPrep scale[92] to determine the level at which participants felt prepared for surgery, and one question to assess participants' understanding of how the study's target medications can affect their mental health, if applicable. There are five response options for each question ranging from strongly disagree to strongly agree. This survey will be used to assess the components of the intervention believed to be responsible for the change in depression and anxiety symptoms over the course of the study period.

All participants will be followed for up to approximately 3 months after their scheduled procedure. They will complete follow-up surveys at approximately 1 month, 2 months (for intervention arm only) and 3 months after

Table 1 Details on study outcomes

		Data source	Description	Data collection mechanism	Time points
Effectiveness outcomes					
Primary (clinical)	3-month change in anxiety and/or depression symptoms	PHQ-ADS[60]	A validated composite of symptoms of depression and anxiety	Patient self-report	Baseline; 3 mo
Other (clinical)	1-month and 3-month change in quality of life	CDC HRQOL-14 survey[62]	A patient-reported global health measure. The questions in this survey correspond to the QOL domains of Healthy Days (physical and mental), Activity Limitations and Healthy Days Symptoms	Patient self-report	Baseline; 1 mo and 3 mo
	In-hospital delirium incidence	Retrospective EHR chart review	The Chart-based Delirium Identification Instrument (CHART-DEL)[106] will be used by trained research assistants.	EHR report, and research team member review EHR for delirium-related information from the time of post-op inpatient stay.	In-hospital: at ICU and hospital floor
	Postdischarge falls	Patient reported falls	Modified patient reported falls survey[107]	Patient self-report	Baseline; 1mo and 3mo
	Persistent postsurgical pain	Pain presence and severity at the site of surgery, and Brief Pain Inventory (BPI)[86] pain interference scale	BPI is a well-validated measure of pain severity and pain interference items.	Patient self-report	Baseline, 1 mo, 3 mo
	Length of stay (both hospital and ICU)	Research data core	Standardised reports on research data core warehouse will generate statistics of enrolled patients regarding the length of stay, rehospitalisation, and related clinical metrics.	EHR report	In-hospital: at ICU and hospital discharge
	All-cause rehospitalisation	Research data core		EHR report	Post-op: 1 mo and 3 mo
Implementation and experience outcomes					
Reach		Enrolment Log	*Reach of the study*: proportion and representativeness of patients who agreed to participate in the study out of total eligible to participate[108] *Reach of the perioperative mental health intervention*: proportion of participants who completed the intervention out of participants who agreed to participate	EHR	EOS
Intervention acceptability*		Acceptability of Intervention Measure[87]	4-item Likert scale survey measuring whether the interventions are agreeable to surgical older patient participants	Patient self-report	EOS
Intervention feasibility*		Feasibility of Intervention Measure[87]	4-item Likert scale survey measuring whether the interventions can be successfully carried out in perioperative settings	Patient self-report	EOS

Continued

Table 1 Continued

	Data source	Description	Data collection mechanism	Time points
Intervention appropriateness*	Intervention Appropriateness Measure[87]	4-item Likert scale survey measuring the perceived fit of the interventions by the participants to address perioperative anxiety and/or depression symptoms	Patient self-report	EOS
Patient satisfaction and experience*	Modified-CAHPS[109]	The modified CAHPS asks patients about their experience with the intervention before surgery, during surgery, and after surgery.	Patient self-report	EOS

*Applicable to intervention arm participants only.
CAHPS, Consumer Assessment of Healthcare Providers and Systems survey; CDC HRQOL, Centers for Disease Control and Prevention Health-Related Quality of Life survey; EHR, electronic health record; EOS, end of study; ICU, intensive care unit; PHQ-ADS, Patient Health Questionnaire Anxiety and Depression Scale.

surgery by either web-based survey, mail or telephone interview.

End-of-study interviews

We will also obtain patient perspectives on the wellness programme and medication optimisation after the intervention period has been completed via semistructured interviews with participants in the intervention arm. Interview topics will be based on the Consolidated Framework of Implementation Research (CFIR)[93 94] which was developed to guide intervention implementation and comprises 39 constructs across five domains: intervention characteristics, inner setting, outer setting, characteristics of individuals and implementation process (see online supplemental appendix F for interview guide). The interviews will explore participant perceptions, attitudes and experiences with the components of the wellness programme and medication optimisation. The interviews will also obtain detailed accounts of participants' experiences after the intervention has been stopped, with regards to intervention sustainability and maintenance. Interviews will be conducted via Zoom or telephone and will be audio recorded and transcribed verbatim. These interviews will not be conducted for participants in the control arm as interview questions are specific to the participant's experience with the perioperative mental health intervention.

Interventionist feedback from wellness partners and the pharmacy team will be obtained through mid-point and end-of-study periodic reflection meetings.[55]

Data management

All data will be stored under lock and key (office, file cabinet) and/or in a password-protected secure REDCap database,[63 64] only accessible to the research team members. All REDCap email correspondence will be sent using secure survey links and no personal health information that may directly identify participants will be included.

Data analysis
Primary outcome

The primary outcome of the study is the change in PHQ-ADS from baseline to 3-month visit. The primary statistical model will be a mixed-model repeated measures analysis of variance (ANOVA) with a treatment group by time point design. This model is ideal because it uses all available data and is robust despite missing data. The primary statistical test is a contrast that compares the change from baseline to 3 months postsurgery in the treatment arm to the change in the enhanced usual care arm. The population used for the primary analysis is a modified Intent to Treat (mITT) group consisting of those randomised participants who actually undergo the procedure or surgery. Participants will still be included in the analysis if they died post operatively, prior to the end of the trial. Statistical significance will be set at 0.05 and relevant changes in PHQ-ADS will be estimated along with 95% CIs.

Other outcomes

Other outcomes measured on the same schedule as the PHQ-ADS will be analysed using the same mixed model described in the primary outcome analysis. For length of stay (ICU and hospital), a simple analysis of covariance will compare the two groups where we will identify the relevant covariates during the planning phase. Delirium and rehospitalisation will use a corresponding generalised linear model with a logistic link function and appropriate covariates. Falls data will be analysed using an extension of the Cox model when there may be multiple events with appropriate covariates.[95] For all analyses, we will examine the potential moderating effect of patients' sex. The

statistical analysis plan will be finalised prior to the analysis of the trials.

Interview data will be analysed using an inductive-deductive thematic analysis.[96 97] After reading the transcripts multiple times for familiarity, research team members will openly code using data-driven codes and then use the CFIR to code the data. Codes will be compared across the data to identify repeated and inter-related concepts and categories, and subthemes will be formed. Similar subthemes will be grouped over multiple rounds of review to generate overarching themes about patients' experiences with the intervention, interactions with their interventionists and implementation strategies. The study team has conducted substantial pilot work with older adult surgery patients,[54 55 71] through which we have refined our approach to qualitative analysis, including a foundational codebook developed and refined during our prior work to inform our analysis.

Similar to other hybrid effectiveness-implementation RCTs,[98–101] the qualitative assessments will be used to help provide context to the quantitative findings in order to draw conclusions about reach, implementation, acceptability, feasibility and appropriateness of the intervention.

Implementation outcomes

For the implementation outcomes, we will present the means and SD for each of the implementation surveys (acceptability, feasibility and appropriateness of the interventions) and the CAHPS patient experience survey. Study reach will be presented as the proportion of patients who agreed to participate in the study out of the total eligible patients to participate. Intervention reach will be reported as the proportion of participants who completed the perioperative mental health intervention out of participants who agreed to participate.

Intervention measures

We will report the following averages: number of wellness programme sessions, duration of sessions, number of preoperative sessions and number of postoperative sessions. Additionally, we will report averages for number of medications at baseline and the number of medications eligible for optimisation (deprescribing and dose escalation). We will report summary information for outcomes of optimisation. Regarding the intervention fidelity, we will report summary results of the fidelity checklist in the areas of treatment delivery, treatment receipt and enactment of treatment skills for both the wellness programme and medication optimisation, including the proportion of participants who followed the components of the intervention as intended.

Sample size and power of primary analysis

To estimate the power of the primary outcome analysis, we examined the manuscript that provided the original validity and reliability studies for the PHQ-ADS[49] and one of the trials which provided data for that study (Stepped Care to Optimize Pain care Effectiveness (SCOPE)).[84 85]

The PHQ-ADS authors estimate the minimal clinically important difference from the SE of measure as 3–4 points.[49] Since the SCOPE trial was a pain relief study without a requirement for anxiety or depression, we conducted a blinded sample size reassessment after 125 participants had completed the 3-month assessment in one of the three cohorts. The average change in the PHQ-ADS was 6.7 with a SD of 8.8. These 125 participants were from 135 in the mITT group, or 7% dropout. With the chosen sample size of 50 mITT participants in each group, we estimated the power for a simple t-test between the two groups of size 46, a 2-tailed significance level of 0.05, and a difference between the two groups of >4 points as shown in figure 3. These power calculations are somewhat conservative since they are based on a simple t-test and we will be using a repeated measures ANOVA for the actual analysis.

Ethics and dissemination

The trials have received ethics approval from the Washington University School of Medicine IRB and were considered to be minimal risk to participants. Unlikely but potential risks include increased risk of depression or anxiety symptoms, or medication withdrawal symptoms, and breach of confidentiality. Participants will be assessed for suicide risk throughout the study, and study personnel will follow an operationalised protocol (adapted from Belnap et al[102]) to respond appropriately to varying levels of suicide risk in collaboration with the study psychiatrist (EJL). The risk of medication withdrawal (ie, from the deprescribing of benzodiazepines) will be mitigated by slowly tapering rather than stopping these medications. Informed consent is required for participation in the trials. The PIs and senior study coordinator monitor for breaches of confidentiality on an ongoing basis. Study-related adverse events will be reported per IRB guidelines. All serious adverse events will be recorded and adjudicated by the PIs and reported per IRB guidelines. This plan is consistent with the National Institute of Mental Health Guidance on Risk-Based Monitoring[103] for a study that is not significantly greater than minimal risk.

The results will be submitted for publication in peer-reviewed journals, presented at clinical research conferences, and disseminated to study participants and the general public via the Center for Perioperative Mental Health website (perioperativewellness.wustl.edu).

Patient and public involvement

In preparation for these trials, we convened an IAB. The IAB comprised patients and caregivers from each targeted surgical cohort, surgeons and nurses from each surgical specialty, community social workers/interventionists, pharmacists, health information technology administrators, hospital patient experience representatives and research team members. The patients on our IAB have experience with surgery and history of depression and/or anxiety diagnoses. Patients and caregivers were recruited through word of mouth and advertisements at the
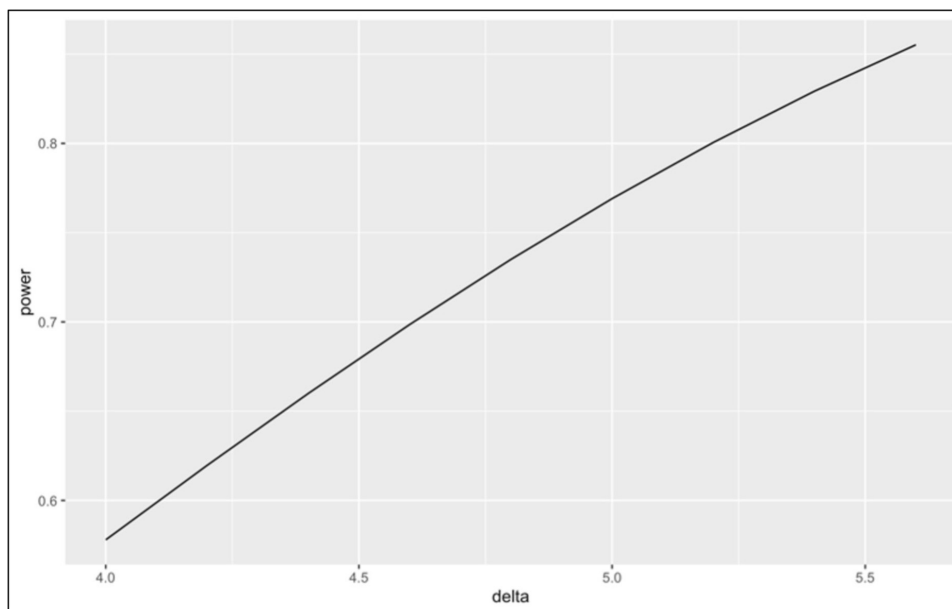
Figure 3 Revised power calculation for 46 participants in each group for a 2-sided t-test at alpha=0.05 and within group SD of 8.8.

academic medical centre and compensated for their time. Thus far, we have convened the IAB four times. Our next meeting will occur when the study data have been analysed to seek their feedback on the dissemination of our results. Our findings from these meetings are described in detail elsewhere.[55] Their primary feedback has centred on using plain and more patient-friendly terminology, shortening the recruitment script, and emphasising the benefits of the study early in the recruitment process. The IAB members also helped us identify barriers and facilitators to intervention implementation and brainstormed adaptations to address these. An example of their feedback was to provide handouts to the participants in both arms and to refer to the interventionists as perioperative wellness partners. They emphasised the need to build rapport with the wellness partner in the initial sessions and we modified those sessions to focus on building trust and introducing the patient more slowly to the intervention.

DISCUSSION

Improving perioperative mental health could be highly impactful, with benefits for both patient QoL and key surgical outcomes such as postoperative complications and rehospitalisation. In three hybrid type 1 effectiveness-implementation RCTs, we aim to test the effectiveness of a perioperative mental health intervention with both psychological and pharmacological components for reducing symptoms of depression and anxiety in older patients undergoing orthopaedic, oncological or cardiac surgical procedures, compared with enhanced usual care. The intervention has been refined and adapted for older adults in the perioperative setting based on the results of a feasibility study.[54] The intervention is patient centred in order to fit the needs of the different surgical settings and

populations of patients. It can be tailored to each participant based on the activities they choose and whether they decide to implement the medication optimisation recommendations.

A hybrid type 1 was chosen to test both the effectiveness of the intervention and implementation outcomes such as reach, fidelity, feasibility, adoption and acceptability. In particular, this study can help us uncover implementation strategies that will address any contextual barriers that may affect its large-scale implementation and sustainability. Evaluating our intervention in three complex surgical settings at the same time may allow us to have a more generalisable intervention from the beginning.[104] To this end, we will explore differences in the outcomes among the three surgical cohorts. As indicated by results of our feasibility study,[54] we anticipate that one primary difference between the cohorts will be the duration of the preoperative period, which ranges from months (in orthopaedic populations) to days (in cardiac populations). A single trial for these three different surgical populations would be problematic, as the perioperative period differs for the three types of surgery. This will influence the goals of the preoperative sessions of our perioperative mental health intervention. Other sources of heterogeneity could include the recovery goals of each population, the willingness of patients to undergo a mental health intervention, the typical patient goals, illness severity and the usual care that is provided. These sources of heterogeneity explain why we did not propose a single trial of all surgical populations.

Another study-related challenge regards the medication optimisation component of our intervention as we will not be managing every medication that a patient is taking at home (prescription and OTC) and there are

other medications that may be considered potentially inappropriate that may not be deprescribed through this study. Although we have data monitoring and follow-up plans for patients accepting a deprescribing recommendation, this process is dependent on being able to successfully contact patients and their prescribing physicians. A further limitation of this study is the use of an enhanced usual care group, which will not allow us to adequately control for placebo effects. Though participants in the control group do not interact with a wellness partner, they do receive resources related to mental health. This approach was selected to increase the possibility of benefit for all participants with symptoms of depression and anxiety.

Despite the heterogeneity of the surgical cohorts and the challenges this may pose, the proposed study will allow us to identify and test core components of the perioperative mental health intervention that is applicable to a broad range of surgical patients, while allowing us to adapt and test flexible components of the intervention personalised according to patient preferences, needs and constraints as well as the specific surgical context—leading to a feasible and scalable perioperative mental health intervention that can be sustained in the real-world setting. Homogeneity in outcomes and core components of the intervention will allow us to design a meta-analysis of the three RCTs, and to examine the implications of their heterogeneity in a data-driven manner. This will test whether we have developed a simple model that is amenable and adaptable for use across a broad spectrum of clinical phenotypes. Furthermore, findings from our target engagement measure will determine how patient participation in our perioperative mental health intervention may impact their depression and anxiety symptoms. Notably, while this additional follow-up survey is only employed in the intervention group, we do not anticipate that this extra study assessment will impact the primary outcome[105] as it will be primarily distributed as an electronic survey vs study visit, unless the participant prefers to complete the survey via telephone. In this case, the survey is administered by an independent study team member and not their interventionist.

The contributions from this study could substantially improve our understanding of how we can adapt established behavioural and pharmacological interventions to meet older patient preferences and mental health needs in perioperative settings. The results of this study will provide critical data for designing a multicentre trial that will examine the effectiveness and implementation strategies of an optimised perioperative mental health intervention in a larger cohort of high-risk older adults undergoing surgery. Any modification to the protocol will be presented to the ethics committee. Abstracts will be submitted to relevant national and international conferences. The results will be submitted to peer-reviewed journals and disseminated via a public website.

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