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BEHAVIORAL ACTIVATION AND MEDICATION OPTIMIZATION FOR PERIOPERATIVE MENTAL HEALTH FEASIBILITY STUDY

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1 Background and Significance

Inadequate management of preoperative mental health disorders often contributes to poor postoperative outcomes [1], including increased rates of readmission, delirium, falls, and mortality [2-5]. However, very little work has been done to improve perioperative mental health. In particular, there has been limited systematic efforts that identify evidence-based behavioral and pharmacological strategies that were originally developed for depression and anxiety in otherwise medically well psychiatric patients. A mental health intervention bundle, composed of behavioral and pharmacological strategies, can mitigate anxiety and depression symptoms during the perioperative period [6]. However, we currently lack conclusive evidence on effectiveness of such an intervention bundle focused on the delivery of perioperative mental health care in older surgical patients. Towards this end, we will develop and test an intervention bundle that encompasses: (1) behavioral activation, and (2) medication optimization (*see* more details on the intervention bundle in section 4.2).

2 Objectives

The study will address the following objectives: (1) demonstrate the feasibility of our study procedures including patient recruitment, screening and outcome measures, and feasibility of adapting our intervention bundle and its intervention delivery process within three older surgical patient populations (i.e., orthopedic, oncologic, and cardiac); (2) empirically test the effectiveness of our adapted perioperative mental health intervention bundle with clinically significant symptoms of depression and/or anxiety; and lastly (3) identify implementation strategies to ensure acceptability, feasibility, and adoption of our intervention bundle by patient and clinician stakeholders. Insights gained from this pilot study will inform the design of three clinical trials that are planned to start in Jan 2023. This project is led by research team members of the newly established Center for Perioperative Mental Health https://perioperativewellness.wustl.edu/ that strives to improve perioperative mental health and well-being for older adults.

3 Study Setting and Participants

The study will be conducted at Barnes-Jewish Hospital and Washington University School of Medicine locations, including Siteman Cancer Center and Barnes-Jewish West County Hospital. Participants will include patients and caregivers. We expect to recruit and enroll up to 70 participants total in this study: up to 45 patients, up to 12-15 in each of 3 surgical cohorts; up to 25 caregiver participants.

3.1 Patient Participants

3.1.1 Inclusion criteria

Patients will be included if they meet **all** of the following eligibility criteria:

1. Age ≥60 years on the day of surgery;
2. Scheduled major orthopedic surgery, or major surgical resection of a thoracic or abdominal malignancy, or major cardiac procedure;
3. Clinically significant depression or anxiety symptoms screened by the PHQ-ADS (Patient Health Questionnaire Anxiety and Depression Scale) ≥10 [7].

3.1.2 Exclusion criteria

Patients will be excluded from the study if they meet **any** of the following:

1. Estimated life expectancy < 12 months;
2. Unable to read, speak, and understand English;
3. Current alcohol or other substance abuse;
4. Severe cognitive impairment screened by the SBT (Short Blessed Test) ≥10;
5. Acutely suicidal (*see* instruments in Appendix A).

Data related to patient inclusion and exclusion will be gathered either via EHR chart review, and/or clinical PI discretion, and/or self-reported by patient during telephone screening process. Eligible patients will be offered the opportunity to participate in the study regardless of gender or minority status. Thus, the sample composition will reflect the composition of community-living older adults in the St. Louis area. All of our studies actively encourage the participation of minorities in the research.

3.2 Caregiver participants

Caregivers offer a unique perspective on a patient's mood and health status, and can be in a position to help effect change, engagement in activities and potentially our intervention bundle. Patient caregivers will be identified by the patient as a family member or friend who cares for the patient as needed to support health and safety, and often have additional care-related responsibilities in the perioperative period.

3.3 Participant Recruitment and Screening

We have outlined our multi-pronged approach to recruit patients, caregivers and clinicians for this study.

3.3.1 Patient recruitment

In all three cohorts, patients may be contacted by the study team and invited to screen if interested. Prospective patients will be identified by Epic workbench reports customized to limit results to those at least 60 years of age with an eligible surgery scheduled at BJH/WUSM. For the WUSM Orthopedic Surgery clinics, patients complete a PROMIS questionnaire as standard routine practice at appointment check-in. Given that the PROMIS scores are available for the orthopedic surgical patients, the EHR report will be further customized as needed based on PROMIS scores.

Initial contact by research coordinator may be made by phone, or in-person if the patient is on campus for a clinical visit in one of the collaborating departments. We will use an information sheet or phone script (see Appendix A) to introduce the goals of the center and the study. Additionally, recruitment flyers (see Appendix B) will be utilized to invite interested patients to contact the study team to screen. The IRB-approved flyers will be distributed to the waiting rooms and clinical offices of the clinicians seeing our target population, as well as the CPAP which many surgical patients visit prior to scheduled surgery. Lastly, patients can also be referred to the study by their clinician, either by offering a recruitment flyer to any patients who meet our inclusion criteria, or by the clinic team at the time of their clinic visit. Clinical teams may refer patients to the study team for screening, some by phone, or email to study team members, or email to cpmh@wustl.edu. Some prospective participants may have clinic visits at the included Departments' satellite sites, and some orthopedic procedures scheduled through Washington University take place at Barnes-Jewish West County Hospital, where those patients may also be enrolled and have study visits. However, the majority of consenting and study procedures will take place within the WUSM and BJH Medical Center Campus.

3.3.2 Patient screening

We will then screen the patients who are interested to proceed in the study and provide a verbal consent. (Appendix A) The screening checklist (also in Appendix A) will be based on our eligibility criteria (see criteria above). To avoid burdening patients with the full PHQ-ADS at the time of screening, patients will first be asked to complete the brief PHQ-4 (i.e., first 4 questions of PHQ-ADS related to anxiety and depression) Patients who score ≥3 will continue with the remaining questions in the PHQ-ADS. Patients with a total score of PHQ-ADS ≥10, and a SBT (Short Blessed Test) score of ≤ 9 will be invited to consent to participate in the study (Table 1). This will be completed at the time of recruitment by a trained member of the research team, and the screener can be collected by phone or in person per patient preference.

Table 1. Scored Instruments for Screening (see details in Appendix A)

Screening Instrument	Eligibility Criteria	Cut-off for Eligibility	Source
PHQ-4	Pre-screen Depr/Anx sx	Inclusion $\geq$ 3	Self-report in screening instrument
PHQ-ADS	Clinically Significant Sx	Inclusion $\geq$ 10	Self-report in screening instrument
SBT	Cognitive health	Exclusion $\geq$ 10	Self-report in screening instrument

3.3.3 Caregiver recruitment

Patients may refer their caregivers (e.g., spouse, partner, children, friend) to contact the study team if interested, or if they prefer to share the caregiver's phone number, the study team contact them by phone and invite them. With the patients' consent, patients' caregivers are also invited to participate by phone, or mail. They will participate in a brief REDCap survey to report any changes related to confusion or delirium in the patient once *before* surgery, and once per week for 4 weeks *after* surgery (FAM-CAM attached). Additionally, some patients' caregivers (up to 25) will be invited to participate in a semi-structured interview (see Appendix J) after the patient's participation in the intervention has been completed.

3.4 Participant Consenting and Enrollment

3.4.1 Patient consent

Patients will be invited to read, discuss, review and ask any questions they may have about study participation with a study team member, and then complete the Informed Consent Form (Appendix C). The informed consent will be available either via a paper collected by mail or in person, or by secure REDCap link to e-consent, as per patient preference. Patients who meet all eligibility criteria in 3.1 and provide consent may be enrolled into the study per PI discretion. Some patients who meet the eligibility criteria but who may require additional clinical input before enrolling them into the study, will be discussed with the study team clinicians and the PI.

3.4.2 Caregiver consent

Caregivers will be invited to participate in semi-structured interviews about the intervention bundle that can be conducted via Zoom/Phone or in-person depending on participant convenience and choice. Hence, they will be consented verbally or with a written consent depending on their participation. If they consent to a semi-structured interview (Appendix J). The interviews with study patient caregivers, will provide valuable feedback on the intervention bundle. Caregivers may also consent verbally to participate in the FAM-CAM confusion and delirium assessment via phone, mail, or email link to REDCap survey.

4 Study Design

This is a feasibility study utilizing mixed methods. All eligible and consenting patients will receive the intervention bundle and will undergo a standard battery of assessments prior to the intervention and will be followed for approximately 3 months in the postoperative period. In conjunction with the

quantitative data collected, qualitative methods will be employed to evaluate acceptability, implementation and practicality of the intervention.

4.1 Assessments

At enrollment, a research coordinator will administer a battery of baseline assessments (see Appendix D) to characterize patient participants. Patient participants will complete these baseline assessments after consent:

- Demographics survey
- Medical History of Comorbidities
- Brief Pain survey
- BADS (Behavioral Activation Depression Scale)
- Brief survey of Patient Reported Falls past 3mo
- VR-12 Quality of Life survey
- SDM-4 (Shared Decision Making)
- PHQ-ADS (Patient Health Questionnaire Anxiety and Depression Scale, collected at screening in Appendix A)
- SBT (Short Blessed Test, collected at screening in Appendix A)
- Review of Medication list (at initial intervention visit) Ultra Brief Confusion Assessment Method (and 3D-CAM if UB-CAM is positive) or FAM-CAM, and/or delirium may be assessed by EHR review using the CHART-DEL [23] method (Appendix M).

Anxiety and depression assessment will use the PHQ-ADS, as described above. The use of this tool for this population is supported by a recent meta-analysis suggesting that the PHQ9 (on which this tool is based) has good sensitivity and specificity in the diagnosis of depression in older adults [9]. *Quality of Life* (QoL) will be assessed using the Veterans RAND 12 Item Health Survey (VR-12) [10]. The questions in this patient-reported survey correspond to the QoL domains of general health perceptions, physical functioning, role limitations due to physical and emotional problems, bodily pain, energy/fatigue levels, social functioning and mental health. *Cognitive function* assessment will be performed using the Short Blessed Test (SBT) as described above. The SBT is a reliable test for characterizing cognitive functioning in this setting [22]. *Falls* data will be collected by monthly Patient-Reported Falls Questionnaire, which will be collected
by phone with other assessments or via a REDCap survey which can be emailed to participants one time per month asking about any falls over the last month.

4.2 Perioperative Mental Health Intervention Bundle

Our intervention bundle will be initiated prior to surgery and continue postoperatively, and will span for approximately 3 to 4 months across the perioperative period (including pre- and 3 month post-operative periods). The personalized intervention bundle is comprised of behavioral activation and medication optimization, both facilitated by specially trained interventionists on the research team.

4.2.1 Behavioral Activation

The behavioral intervention will consist of *behavioral activation* (BA), the basic premise of which is to help people with mental health problems to engage in activities that are reinforcing or meaningful and guided by their personal values [13]. The interventionists in this component of the intervention bundle, Perioperative Wellness Partners, are qualified social workers and therapists with relevant mental health experience, in addition to specific training to implement this intervention. Patients will be asked to check with their physicians if there is any question about the safety of any physical activities that are included in the behavioral activation plan. Behavioral activation as the core intervention allows for uniformity across participants from each cohort, yet enough flexibility for the actual components of behavioral activation to be individually adapted based on patient preferences. In a recent meta-analysis, behavioral activation programs improved depression and anxiety [14], as well as disability in older adults [15]. In addition, BA delivered by telehealth to older adults was cost-effective and lowered health care utilization costs over 1 year [16]. In addition to the core intervention of behavioral activation, study participants will be able to adapt the intervention by choosing activities, per their preference, with demonstrated benefit in improving depression and anxiety symptoms in older adults [17, 18]. BA will span across approximately 3 months postoperatively and will begin pre-operatively, with sessions approximately weekly or biweekly, depending on patient preference and health condition. For example, participants with hospital stays >1 week, behavioral intervention may continue weekly in the hospital setting, if the patient chooses. Finally, after discharge during the postoperative period, the behavioral intervention will continue for the remaining months/sessions. The timing, format and frequency of the behavioral activation sessions will be adapted and tailored based on patient preferences and needs. The behavioral activation process will be guided by the internal study team manual,(Appendix F) which will be adapted and calibrated as needed throughout this feasibility study, along with the adaptations to the BA patient worksheets (see Appendix H) which the patient and perioperative wellness partners may use to guide these intervention sessions and activities. We will track all adaptations to BA conduct and content during this study for our future intervention study.

4.2.2 Medication Optimization

Medications will be *reviewed and optimized*, as appropriate, by our team of interventionists including a psychiatrist, pharmacologist, perioperative wellness partners, and pharmacists. In several clinical trials including thousands of older adults, we have developed and refined a process for this review and medication optimization, including adjusting suboptimal dosing for anti-depressants and discontinuing medications that are harmful for brain health (such as anticholinergics [19]). Medication optimization consists of a simple set of principles: reconcile patient's medications, identify the patient's likely need for, and interest in, a medication adjustment, make the adjustment, and assess the response to that adjustment. Benzodiazepines, non-benzodiazepine sedatives, strong centrally acting anticholinergics, and antihistamines may be deprescribed as they increase the risk for falls and delirium. We will follow the principles of shared decision-making with patients for medication changes, identifying DEMS (deprescribing eligible medications) which worsen functional recovery, impair cognitive function, and increase medical risks like falls, delirium, and bleeding With the patients' consent, we will initiate communication with the prescribing provider regarding any changes to medications (DEMs in particular) which they have prescribed. While the participant is in-hospital, the interventionist's role will include coordinating with the hospital team to ensure that medication changes that were introduced preoperatively are maintained in-house and that no new inappropriate medications are initiated. We will give voice to patient and family concerns by helping

them communicate with the hospital (and subsequent transitional) provider team. After discharge, and up to approximately 3 months postoperatively, the interventionist will ensure that medication changes are reconciled during transitions of care. The interventionists will ensure the agreed-upon changes are implemented, or an alternative course of action is justified. The internal study team manual for medication optimization will be updated as needed in the feasibility study. Please see Medication Optimization SOP in Appendix F.

4.3 Evaluation Measures and Outcomes

Preoperative assessments along with preoperative and postoperative surveys (assessments described in 4.1 above) regarding quality of life, depression, and anxiety will be obtained from all study participants. Study participants will be followed for approximately 3 months after their scheduled procedure. They will complete follow-up surveys at approximately 1 month and approximately 3 months after surgery by either web-based survey, mail, or via a telephone interview (or in person if the visit coincides with a clinic visit). Collection of falls data will occur approximately monthly for 3 months by phone with study coordinator, or REDCap, or in person. The results of follow-up surveys will be obtained via secure REDCap e-mail link, mail, or telephone survey. Rehospitalizations will be obtained from patient self-report and/or EHR at the end of study follow-up. Please see Table 2.1 for list of outcomes and details.

Additional pre-operative data related to patient medical, social and surgical history, problems, diagnosis and medication lists will be retrieved from the patient electronic health record using the research data core (RDC). Post-operative data including post-operative acute diagnoses (e.g., complications), additional procedures, postoperative opioid use, pain scores will also be retrieved.

4.3.1 Primary Feasibility Outcomes

Reach of the study: patients who agreed to participate in the study out of total eligible to participate.
Reach of the intervention bundle: patients who completed the interventions out of patients who agreed to participate in the pilot.

4.3.2 Secondary Feasibilty Outcomes

Completeness of planned RCT primary outcome data collection at specified timepoints

4.3.2.1 Potential Study Primary Outcomes for Planned RCT

Effectiveness outcomes will include the primary outcome measure of PHQ-ADS, a validated composite scale of depression and anxiety symptoms [7] measured at baseline, 1, and 3 months after surgery. The Behavioral Activation for Depression Scale, or BADS (activation subscale), is our primary measure of target engagement. BADS is a sensitive and pragmatic assessment of the mechanism of change in Behavioral Activation. Approximately three months post-operative is the primary endpoint.

4.3.2.2 Potential Study Secondary Outcomes for Planned RCT

The secondary outcomes will include QoL measured via the VR-12 Health Survey, and other perioperative outcomes of interest, nominated by our stakeholders as key outcomes of interest, including:

1. In-hospital: (i) Delirium incidence, assessed by trained research coordinators using the Ultra Brief and 3-D Confusion Assessment Method, [20] as in our prior work [19], and/or Delirium incidence may be assessed by EHR review using the CHART-DEL [23] method ; (ii) Length of Stay (hospital and ICU), assessed by EHR review.
2. Post-discharge: (i) Falls, prospectively assessed monthly falls reported by patients. (ii) All-cause rehospitalization out to approximately 3 months postoperative, assessed from EHR report, supplemented by review with patient and caregiver.
3. Process outcomes: Shared Decision Making (modified collaboRATE) 3 item survey will be administered at post-end of study. CAHPS modified survey will be administered after the intervention is complete, as part of post-end of study surveys.
4. Implementation-potential surveys: Acceptability of Intervention Measure, Intervention Appropriateness Measure, Feasibility of Intervention Measure.

4.3.3 Exploratory Feasibilty Outcomes

Impletmentation potential

Completeness of planned RCT primary outcome data collection at specified timepoints

Table 2. Feasibility study outcomes and potential study primary and secondary outcomes for planned RCT. Note: The surveys and questionnaires will be administered via email or research coordinators over the telephone.

Outcomes	Specific measure: description	Source	Timepoint
Reach *(Primary)*	Reach of the study: patients who agreed to participate in the study out of total eligible to participate Reach of the intervention bundle: patients who completed the interventions out of patients who agreed to participate in the pilot	Electronic Health Record, Research data warehouse	End of Study
Completeness of planned RCT primary outcome data collection at specified timepoints *(Secondary)*	Defined as a percentage of instrument or data fields completed for- Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS)[62]: 16-item scale with components of the Patient Health Questionnaire-9 and Generalized Anxiety Disorder Scale (collected at baseline; 1 mo; 3 mo)	Research data warehouse	End of Study
Implementation-Potential *(Exploratory)*	Acceptability, appropriateness and feasibility of the interventions: The Acceptability of Intervention Measure (AIM), the Intervention Appropriateness Measure (IAM), and the Feasibility of Intervention Measure (FIM).[77] Each survey has 4 items in a Likert scale ranging from completely disagree to completely agree.	Surveys	End of Study

Completeness of planned RCT secondary outcomes data collection at specified timepoints *(Exploratory)*	We will be measuring the completeness of data collection for the following potential secondary outcomes for the planned RCT secondary outcomes: • Quality of Life (collected at baseline; 1 mo; 3 mo) • In-hospital delirium incidence (collected at baseline; in-hospital/postoperatively) • Post-discharge falls (collected at baseline; 1 mo; 2 mo; 3 mo) • Medication optimized and adherence to medications(collected at baseline; 1 mo; 3 mo) • Length of stay (both hospital and ICU) • All-cause rehospitalization (collected in the hospital/postoperatively; 1 mo; 3 mo) • Persistent postsurgical pain (collected at 1 mo; 3 mo) • Patient experience (collected at end of study) • Shared decision making (collected at end of study)	Research data warehouse	End of Study

Table 2.1 Details on Potential Study Outcomes for Planned RCT

Effectiveness Outcomes		**Data Source**	**Description**	**Data Collection Mechanism**	**Time points (Baseline, 1, 2, 3 month-post-op or EOS)**
Primary *(Clinical)*	Anxiety and Depression	Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS)	A validated composite of symptoms of depression and anxiety	Patient Self-Report	Baseline; 1 mo and 3 mo
Primary *(Target Engagement measure)*	Anxiety and Depression / Target Engagement	Behavioral Activation for Depression Scale (BADS)	A validated scale utilized to measure target engagement in studies of geriatric depression	Patient Self-Report	Baseline; 1mo; 2mo; 3mo
Secondary (Clinical)	Quality of Life	The Veterans RAND 12 Item Health Survey (VR-12)[43]	A patient-reported global health measure. The questions in this survey correspond to the QOL domains of general health	Patient Self-Report	Baseline; 1 mo and 3 mo

			perceptions, physical functioning, role limitations due to physical and emotional problems, bodily pain, energy/fatigue levels, social functioning and mental health.		
	In-hospital delirium incidence	Ultra Brief CAM to screen for 3D CAM, and if UBCAB positive, then 3D CAM Confusion Assessment Method[44]	UB-CAM and 3D CAM are standardized, evidence-based interview that enables researchers and clinicians, following structured training, to reliably and reproducibly identify the four cardinal features of delirium.	UB-CAM and 3D CAM Research Coordinator-Administered	Baseline/pre-op; In-hospital: During post-op hospital stay; up to twice daily for 3 days; if not in person, UB-CAM may be collected by phone.
	Family Confusion Assessment Method	FAM-CAM	The FAM-CAM is intended to evaluate for evidence of delirium based on observations from family members or caregivers. The instrument facilitate and educate caregivers to pick up acute changes in mental status, and the earliest signs of cognitive changes in frail or cognitively impaired older persons.	Survey or phone	Baseline/pre-op; post-op, once every week for 4 weeks.
	Post-discharge falls	Patient Reported Falls	A Patent Reported Falls survey will be collected monthly either by phone or REDCap link, at follow-up clinic appointments.	Patient Self-Report	Baseline; 1mo; 2mo; 3mo
	Medication list	Data collection Appendix D; Appendix G	Review of all patient medications, confirming accuracy of EHR med list, number of medications optimized and medication adherence	Patient Self-Report/ study team member verifies EHR meds list with patient	Baseline, initial intervention visit; approximately 1mo; approximately 3mo at end of

					intervention.
	Length of stay (both hospital and ICU)	Research Data Core	Standardized reports on the research data core (RDC) warehouse will generate statistics of enrolled patients regarding the length of stay, rehospitalization, and related clinical metrics.	EHR report	In-hospital: at ICU and hospital discharge
	All-cause rehospitalization	Research Data Core		EHR report	Post-op: 1 mo and 3 mo
Secondary ***(Process)***	Patient experience	Modified-Consumer Assessment of Healthcare Providers and Systems (CAHPS)[45]	The modified CAHPS asks patients about their experience before surgery, during surgery, and after surgery.	Patient Self-Report	Post-EOS
	Shared decision making	Shared decision making process CollaboRATE modified	A 3-item survey modified to measure shared decision making, following a encounters with study interventionists and perioperative wellness partners	Patient Self-Report	Post-EOS
Implementation Outcomes		**Data Source**	**Description**	**Data Collection Mechanism**	**Time points**
	Implementation-Potential (I)	Acceptability of Intervention Measure, Intervention Appropriateness Measure, Feasibility of Intervention Measure	Acceptability, Feasibility and Appropriateness 4-item Likert scale survey	Patient Self-Report	Post-EOS

In addition to these outcomes, we will also be assessing fidelity of our intervention bundle which will assess the extent to which an intervention bundle is carried out by our perioperative wellness partner, as intended and consistently across different settings, and patients. To track this, we will observe and take notes on the patient and the perioperative wellness partner during the behavioral intervention and medication optimization sessions with the patient and clinician. Observations will involve a member of the research team observing the wellness partner over a period of time or number of intervention sessions. We will capture data on patient interactions with the wellness partner, their delivery of the intervention bundle, any observed barriers and facilitators to the intervention adherence, acceptance and fit within the perioperative workflow. These observation sessions of patients and their wellness

partners will be selected based on a convenience sample. If the patient agrees to audio/video recording, the intervention sessions will be audio recorded (or audio/video if the patient prefers to meet by Zoom teleconference). The observations may be made by a member of the research team reviewing the recorded sessions.

Lastly, we will also obtain various stakeholder perspectives on the intervention bundle after the intervention period has been completed using semi-structured interviews. We will conduct interviews with patients, and caregivers, and the topics of discussions will be guided by an implementation science framework referred to as CFIR (Consolidated Framework of Implementation Research). The interviews will explore the participants' perceptions, attitudes, experiences with the intervention bundle, intervention bundle acceptability and detailed accounts of participants' experiences after the intervention has been stopped with regards to intervention sustainability and maintenance. These insights will inform whether the intervention bundle needs to be changed or adapted before our future trials (*see* interview guides in Appendix J). Interviews will be conducted via Zoom or telephone and will be digitally recorded and transcribed verbatim.

5 Data Analysis

The quantitative data will be used to provide baseline and post-intervention comparisons on a number of outcome variables relevant to the intervention, with the hypothesis that performance on these measures will improve post intervention. These data will also be used to estimate effect sizes for further trials so that these are suitably powered. Quantitative data will be tabulated for descriptive purposes. Given the small sample size, a non-parametric approach will be used to calculate effect size data ($r = Z/\sqrt{(N)}$), where Z is the standardized test-statistic from a Wilcoxon signed-rank test and N is the sample size, along with the associated 95% confidence interval. The r values will be calculated for the timepoint as compared to baseline.

The observation data will be analyzed using open coding and FRAME analytic framework that helps track any adaptations to intervention bundle and delivery. The interview data will be analyzed using thematic analysis [8].

Table 3. Study Calendar

	Time 0	Baseline/ Time 1	In-Hospital / Post-Op	1 mo follow up	2 mo follow up	3 mo follow up	Post-EOS
Patient Consent	X						
Patient Screening (Appendix A)	X						
Patient Baseline surveys (Appendix D)		X					
Caregiver Consent		X					X
Patient Delirium Assessment (Appendix K) pt UB/ 3-D CAM ; & Caregiver if applicable, FAM-CAM		X (pt)	X(pt) twice daily x 3	FAM-CAM if applicable			

1x weekly for 4 weeks.			days post-op	(weekly x 4wks)			
Patient Follow-up 1 & 3 mo Surveys (Appendix G)				X		X	
Patient Monthly Surveys (Appendix L)				X	X	X	
Patient Post-EOS Surveys (Appendix I)							X*
Patient Semi-Structured Interview (Appendix J)							X*
Caregiver Semi-Structured Interview (Appendix J)							X*
Behavioral Activation and Medication Review Intervention Sessions			Approximately 6-12 sessions as needed (per Pt preference) from Baseline, continuing for up to approximately 3 months post-op during study data collection, until EOS.				

*Post-End of Study (EOS) implementation surveys and semi-structured interviews will be completed approximately 2 weeks after EOS assessment.

6 Patient Participant Retention

Participant retention strategies will include flexibility in scheduling follow-up visits and coordination of research (both data collection and intervention) visits with the clinical visits. Remuneration for each data collection study visit will be provided after the final follow-up visit to encourage retention as well. For patients who are difficult to reach by phone, we may utilize a reminder, the *Attempting to Reach You Letter* (Appendix N) to remind them to contact either the Perioperative Wellness Partner or the Study Coordinator for a study session.

7 Protection of Human Subjects

The study will be conducted under appropriate Washington University Institutional Review Board guidance, and use only IRB-approved study procedures and instruments. The study team will follow the protocol under the supervision of the PI, a mentor with several years of experience in the conduct of human volunteer studies, and co-Investigators with extensive expertise in human subject research. All members of the study team are IRB-approved and trained in Good Clinical Practice and Human Subjects Research education.

8 Data Management for Participant Privacy

A unique patient number (UPN) will be assigned at enrollment and used wherever possible on the case report forms (CRF) to identify data, minimizing use of patients' names or personal identifiers in data.

All paper data will be stored under lock and key (two locked doors, e.g., office, file cabinet) and all electronic data will be hosted on a password-protected, firewall-secured server that is only accessible to the research team through password-protected departmental computers. Surveys that are completed electronically will be administered via the Research Electronic Data Capture (REDCap) server. All REDCap email correspondence will be sent using secure survey links. Similarly, interview data from caregivers will follow the same security and storage policies.

8.1 List of Protected Health Information collected for study

For Patient and Caregiver Participants, the HIPAA-protected identifiers that will be collected for this study include:

- Name
- Date of birth
- Contact information
- Mailing address
- Phone number
- Electronic mail address
- SSN for the purpose of remuneration

For Patient Participants only, these additional HIPAA-protected identifiers will also be collected for study:

- Dates of services (surgical procedure, hospitalization)
- Medical record number

9 Potential Risks

This study involves minimal risk to subjects. Unlikely but potential risks include errors in medication recommendations or medication withdrawal symptoms, and breach of confidentiality. The risk of medication withdrawal (i.e., from benzodiazepines) is mitigated by slowly tapering rather than stopping these medications. Patients who are identified as being acutely suicidal will be excluded from the study. Nevertheless, since the rate of completed suicide in the USA remains high (i.e., about twice the rate of homicide) and most Americans who commit suicide suffer from depression, all participants eligible to participate in this study are statistically at a relatively higher risk for suicide than the general population. However, the participants' absolute risk for completing suicide during this brief study remains very low (i.e., about 1 in 3,000 to 10,000) and participation in the study does not create or increase the risk of completed suicide; rather, most experts believe that one of the most efficient ways to decrease suicidal risk in older depressed individuals is to treat their depression. Furthermore, all participants will be formally assessed frequently throughout the study. If the study personnel identify that a participant has become acutely suicidal, this participant will be referred to a mental health professional for further evaluation and treatment (see section: Procedures to Minimize Risks). This may lead to a clinical intervention that is lifesaving and may not have occurred had the participant not been participating in the study.

10 Adverse Experiences

Based on the nature of this study, which involves surveys, a cognitive test, and a behavioral intervention, adverse events are exceedingly unlikely. The principal investigator and study coordinator will monitor for breaches of confidentiality and other adverse events on an ongoing basis. If the PI or study coordinator becomes aware of a reportable adverse event, the event will be reported to HRPO according to institutional guidelines.

11 Procedures to Minimize Potential Risks

Professor Eric Lenze, MD (PI on the Center for Perioperative Mental Health; Co-I on this study) will manage the oversight of the interventions making medication optimization recommendations to reduce the risk of medication error or medication withdrawal symptoms. Algorithms for tapering medications that should not be abruptly discontinued will be employed. We have carried out this deprescribing protocol in several large RCTs and have not seen any problems occur.

Suicide Risk Management: As discussed above, at each assessment point, the research staff will assess for passive death wish, and suicidal ideation, intent or plan when they administer the PHQ-ADS. If a participant endorses suicidal ideation, intent, or plan, the rater will be trained to follow an operationalized protocol (Appendix E) that has been developed to manage high-risk participants in other studies of depressed participants potentially at risk for suicide. This protocol has already been used successfully by Dr. Lenze's team to manage acutely suicidal patients. Briefly, the protocol entails a specific determination of the suicidal risk and prescribes a set of actions. If a participant is determined to be at high and immediate risks, the rater is instructed to stay with the participant until he or she has contacted a study psychiatrist (Dr. Lenze) to discuss the situation and to devise a plan. In case of extreme emergency, raters are instructed to call their hospital security team or 911 for immediate help and to initiate commitment proceedings.

Patients will be encouraged to check with their physician if there is any question about the safety of any physical activities that are included in the behavioral activation plan. It is possible that the participant may feel uncomfortable completing the surveys or participating in the study sessions. The study sessions and interview can be discontinued at any time, and the patient may refuse to answer any questions that s/he does not wish to answer.
To minimize the risk of breach of confidentiality, we will ensure that protected health information will only be shared with members of the research team. Only data necessary to complete the study will be collected. Data will be coded with UPN wherever possible, and the master list linking names to UPNs will be securely accessible only to the PI, Co-Investigators, data analyst, and primary research coordinator. Electronic data will be stored as detailed in section 8.

12 Data and Safety Monitoring Plan

The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the studies planned. Given the nature of the protocol, the risks are likely limited to breach of confidentiality. Data will be monitored and protected as described in Section 8, with PI oversight of data management.

Participation in this study does not entail any physical or medical risks that are greater than those ordinarily encountered in daily life. It is possible that the participant may feel uncomfortable completing the questionnaires. If a participant becomes upset, the PI will talk to the participant either

at that time or will contact the participant by telephone. If any further referrals are deemed necessary (i.e., social work or psychiatry), these referrals will be made in collaboration with the patient's primary medical team.

There is also a risk of breach of confidentiality. All reasonable steps will be taken to ensure that patient privacy is maintained. Hard copy data (i.e. signed informed consent forms) will be maintained in a locked office within a locked suite. Electronic data will be stored on a Washington University password-protected server and never stored on a portable hard drive or laptop computer. Patient data will be identified by a study ID only, with a master key linking patient names with study IDs kept in a separate file accessible only to the Primary Investigator and Research Study Assistant.

The only interventions outside the standard of care for management of the patient's diagnosed condition in this study are the administration of questionnaires, a cognitive test, and medication optimization. We expect that the occurrence of a serious adverse event as it relates to these study interventions to be extremely rare. If a breach of confidentiality were to occur, it would be reported to QASMC and HRPO within 10 days of notification.

The study principal investigator and study coordinator will monitor for breaches of confidentiality and other adverse events on an ongoing basis. Once the PI or study coordinator becomes aware of a reportable adverse event, the event will be reported to HRPO and QASMC according to institutional guidelines. This study does not require QASMC audit or submission of DSM reports.

13 Premature Discontinuation

Subjects will be withdrawn if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study. As part of the informed consent process, patients will be notified they may choose to not participate in the study or withdraw at any time with no penalty, and no effect on the standard care they receive.

14 Potential Benefits of the Proposed Research to Participants and Others

Although the study is designed to improve symptoms of depression and anxiety and other outcomes of care, there is no guarantee that the study participants will receive any clinical benefits by participating in the study. This may lead to a clinical intervention that is lifesaving and may not have occurred had the participant not been participating in the study. Given the undertreatment of depression and anxiety in older adults, the minimal risks are acceptable in comparison to the potential benefits in improving the mental health of older adults undergoing surgery.

15 Remuneration

It will not cost the patient anything to participate in the study, and with the flexible design allowing for phone visits, they will not be required to make any extra study visits to the medical center (some visits may be concurrent with a clinic or procedure appointment). Patients will receive remuneration by debit card of $25 for completion of each data collection study visit at Baseline, 1, 2, 3 month post-op, Post-EOS data collection surveys, and semi-structured interview, up to $125 after completion of their participation.

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17 References

1. Mangusan, R.F., et al., *Outcomes associated with postoperative delirium after cardiac surgery.* Am J Crit Care, 2015. **24**(2): p. 156-63.
2. Blumenthal, J.A., et al., *Depression as a risk factor for mortality after coronary artery bypass surgery.* Lancet, 2003. **362**(9384): p. 604-9.
3. Connerney, I., et al., *Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study.* Lancet, 2001. **358**(9295): p. 1766-71.
4. McKenzie, L.H., J. Simpson, and M. Stewart, *A systematic review of pre-operative predictors of post-operative depression and anxiety in individuals who have undergone coronary artery bypass graft surgery.* Psychol Health Med, 2010. **15**(1): p. 74-93.
5. Takagi, H., et al., *Perioperative depression or anxiety and postoperative mortality in cardiac surgery: a systematic review and meta-analysis.* Heart Vessels, 2017. **32**(12): p. 1458-1468.
6. Abraham, J., et al., *A Qualitative Study of Perioperative Depression and Anxiety in Older Adults.* Am J Geriatr Psychiatry, 2020.
7. Kroenke, K., et al., *Patient Health Questionnaire Anxiety and Depression Scale: Initial Validation in Three Clinical Trials.* Psychosom Med, 2016. **78**(6): p. 716-27.
8. Ritchie, J. and J. Lewis, *Qualitative research practice: a guide for social science students and researchers*. 2003, London: Sage Publications.
9. Levis, B., et al., *Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis.* BMJ, 2019. **365**: p. l1476.
10. Selim, A.J., et al., *Updated U.S. population standard for the Veterans RAND 12-item Health Survey (VR-12).* Qual Life Res, 2009. **18**(1): p. 43-52.
11. Arias, F., et al., *Rapid In-Person Cognitive Screening in the Preoperative Setting: Test Considerations and Recommendations from the Society for Perioperative Assessment and Quality Improvement (SPAQI).* Perioper Care Oper Room Manag, 2020. **19**.
12. Vila, M.R., et al. *Cognitive flexibility and persistent post-surgical pain: the FLEXCAPP prospective observational study*. British Journal of Anaesthesia, 2020.
13. Puspitasari, A.J., et al., *A randomized controlled trial of an online, modular, active learning training program for behavioral activation for depression.* J Consult Clin Psychol, 2017. **85**(8): p. 814-825.
14. Stein, A.T., et al., *Looking beyond depression: a meta-analysis of the effect of behavioral activation on depression, anxiety, and activation.* Psychol Med, 2020: p. 1-14.
15. Choi, N.G., et al., *Improving Social Connectedness for Homebound Older Adults: Randomized Controlled Trial of Tele-Delivered Behavioral Activation Versus Tele-Delivered Friendly Visits.* Am J Geriatr Psychiatry, 2020.
16. Egede, L.E., et al., *Cost-Effectiveness of Behavioral Activation for Depression in Older Adult Veterans: In-Person Care Versus Telehealth.* J Clin Psychiatry, 2018. **79**(5).
17. Farhang, M., et al., *Impact of mind-body interventions in older adults with mild cognitive impairment: a systematic review.* Int Psychogeriatr, 2019. **31**(5): p. 643-666.
18. Lenze, E.J., et al., *Mindfulness-based stress reduction for older adults with worry symptoms and co-occurring cognitive dysfunction.* Int J Geriatr Psychiatry, 2014. **29**(10): p. 991-1000.

19. Wildes, T.S., et al., *Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES Randomized Clinical Trial.* JAMA, 2019. **321**(5): p. 473-483.
20. Inouye, S.K., et al., *Clarifying confusion: the confusion assessment method. A new method for detection of delirium.* Ann Intern Med, 1990. **113**(12): p. 941-8.
21. Lamb, S.E., et al., *Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus.* J Am Geriatr Soc, 2005. **53**(9): p. 1618-22.
22. Katzman R, Brown T, Fuld P. Validation of a short orientation-memory-concentration test of cognitive impairment. Am J Psychiatry. 1983; 140:734–9.

23. Xu G, Fong TG, Yee J, Inouye SK. Delirium Identification: A training guide to a chart-based delirium instrument. 2011; Hebrew Rehabilitation Center, Boston, MA.