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STUDY PROTOCOL

REVISED Recommendations and Alerting for Delirium Alleviation in Real-Time (RADAR): Protocol for a pilot randomized controlled trial [version 2; peer review: 2 approved]

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v2 **First published:** 24 Sep 2019, **8**:1683
https://doi.org/10.12688/f1000research.20597.1
Latest published: 01 Sep 2020, **8**:1683
https://doi.org/10.12688/f1000research.20597.2

Abstract

Background: Delirium is a common and serious complication of major surgery for older adults. Postoperative social and behavioral support (e.g., early mobilization, mealtime assistance) may reduce the incidence and impact of delirium, and these efforts are possible with proactive patient-care programs. This pilot trial tests the hypothesis that a multicomponent decision support system, which sends automated alerts and recommendations to patient-care programs and family members for high-risk patients, will improve the postoperative environment for neurocognitive and clinical recovery.

Methods: This will be a randomized, controlled, factorial pilot trial at a large academic medical center. High-risk, non-cardiac surgery patients (≥70 years old) will be recruited. Patients will be allocated to a usual care group (n=15), Hospital Elder Life Program (HELP)-based paging system (n=15), family-based paging system (n=15), or combined HELP- and family-based system (n=15). The primary outcome will be the presence of delirium, defined by positive long-form Confusion Assessment Method screening. Secondary outcomes will include additional HELP- and family-based performance metrics along with various neurocognitive and clinical recovery measures. Exploratory outcomes include the incidence of positive family-based delirium

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 01 Sep 2020	✓ report	✓ report
version 1 24 Sep 2019	? report	✓ report

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Any reports and responses or comments on the

assessments post-discharge, 36-item Short Form Survey, PROMIS Cognitive Function Abilities Subset 4a, and 30-day readmission rates.
Ethics and dissemination: This trial has received approval by the University of Michigan Medical Institutional Review Board (IRBMED). Dissemination plans include presentation at scientific conferences, publication in medical journals, and distribution via educational and news media.
Registration: ClinicalTrials.gov Identifier NCT04007523, registered on 7/3/2019.

Keywords
Clinical Trial Protocol, Decision Support Systems, Delirium, Feasibility Studies, Perioperative Care

article can be found at the end of the article.

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Competing interests: No competing interests were disclosed.

Grant information: The RADAR Trial is supported by the University of Michigan Claude D. Pepper Older American Independence Center (P30AG024824), Michigan Institute for Clinical and Health Research (UL1TR002240), and Department of Anesthesiology, University of Michigan Medical School.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Vlisides PE, Ragheb JW, Leis A *et al.* **Recommendations and Alerting for Delirium Alleviation in Real-Time (RADAR): Protocol for a pilot randomized controlled trial [version 2; peer review: 2 approved]** F1000Research 2020, **8**:1683 https://doi.org/10.12688/f1000research.20597.2

First published: 24 Sep 2019, **8**:1683 https://doi.org/10.12688/f1000research.20597.1

REVISED **Amendments from Version 1**

This version includes additional details regarding the usual HELP care group, power calculation considerations, and limitations not previously stated. This version also states that team members will follow institutional guidelines for conducting clinical research during the COVID-19 pandemic.

Any further responses from the reviewers can be found at the end of the article

Introduction

Delirium is a distressing and common surgical complication, affecting approximately 20–50% of older surgical patients[1,2]. Postoperative delirium is associated with increased mortality[3] and cognitive and functional decline[4–6], and healthcare resource utilization[7,8]. Of the diverse prevention strategies that have been tested with variable success[7,9], one notable proactive patient-care program, the Hospital Elder Life Program (HELP), has been shown to reduce delirium incidence through social and behavioral interventions (e.g., mealtime assistance, support with visual/hearing aids)[10]. However, substantial resources are needed for program sustainment, and delirium still persists in high-risk patients[11–13]. In 2018, we found that <50% of surgical patients ≥70 years old at Michigan Medicine were officially enrolled in the program by the end of the second postoperative day. Furthermore, the average length of cumulative therapeutic activity was only 10 minutes across the first three postoperative days. This is pertinent given that the peak incidence of postoperative delirium occurs within the first 48 hours[2,14]. As such, complementary strategies that improve patient triage and support may lead to earlier identification and therapeutic intervention for high-risk patients.

Clinical decision support systems can serve as a candidate strategy for mitigating delirium risk. Such systems provide targeted patient- and disease-specific information, presented in a timely manner, for improving healthcare quality[15,16]. In the context of delirium, automated pages could be sent to supportive healthcare services, such as HELP, along with family members and caretakers, with alerts and targeted recommendations. An alert page could be sent to HELP program officials on the first postoperative morning requesting early evaluation and enhanced treatment protocols. This may improve high-risk patient triage, early resource allocation, and cumulative therapeutic time spent with patients. A similar paging system could be implemented for family members and caretakers, as family-based interventions may provide additional support for patients at risk for delirium. Feasibility has been demonstrated with family-based protocols for hospitalized medical patients, with therapeutic focus on re-orientation, visual and hearing aid assistance, and conversational stimulation[17]. Similar protocols could be adapted for surgical patients, as surgery is generally a predictable event (and thus possibly amenable to familial planning), and family support may correlate with overall postoperative recovery[18]. A recent systematic review also demonstrated that *family-performed* delirium screens demonstrated improved psychometrics compared to *family-informed* delirium screens (i.e., those not performed by family members)[19]. Thus, family members and caretakers could be recruited to actively participate in postoperative recovery by performing family-based delirium assessments[20] and implementing therapeutic protocols. An electronic, paging-based alerting system could provide family members with reminders and alerts for conducting such a program.

The premise of this pilot proposal is thus formed by the above considerations: preliminary evidence that suggests (1) suboptimal delirium prevention resource utilization and (2) the potential role for a clinical decision support system involving HELP and family members. The primary objective of this study is to determine whether pager-based clinical decision support systems enhance HELP- and family-based therapeutic activities. A secondary objective will be to identify facilitators and barriers to delivering therapeutic interventions for both HELP and family members. Overall, this pilot trial will test the hypothesis that a multicomponent decision support system will improve the postoperative environment for neurocognitive and clinical recovery in older, high-risk surgical patients.

Methods and analysis

Study overview and design

This is a single-center, randomized, factorial pilot trial at Michigan Medicine (Ann Arbor MI, USA). Approval was obtained from the University of Michigan Medical School Institutional Review Board (HUM00165251), and the trial has been registered at www.clinicaltrials.gov (NCT04007523). This protocol is also compliant with the Consolidated Standards of Reporting Trials (CONSORT) extension for pilot and feasibility trials and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Guidelines[21,22]. Lastly, all study team members are certified in Good Clinical Practice, and the study team will follow institutional protocols for conducting clinical research during the COVID-19 pandemic.

After enrollment, patients (n=60) will be allocated (1:1:1:1), via block-randomization, stratified by gender, to one of four groups: usual care (n=15), HELP-based paging system (n=15), family-based paging system (n=15), or both HELP- and family-based paging system (n=15) (Figure 1). The randomization code will be created by the biostatistician (AL) and concealed from the rest of the research team. On the morning of surgery, allocation assignments will be delivered via sequentially numbered, opaque, sealed envelopes to unblinded research team members who will initiate arm-specific operations. The support systems will consist of automated pager alerts to the HELP program and/or family members and caretakers, depending on group allocation, for providing additional delirium evaluation and therapeutic prevention activities (see *Interventions: clinical decision support systems*). Family members in the intervention group will also be provided with preoperative education on delirium and training in the Family Confusion Assessment Method (FAM-CAM) instrument[20]. Although it will not be possible to blind patients and family members to family-based interventions, study team members performing daily assessments will remain blinded to group allocation.

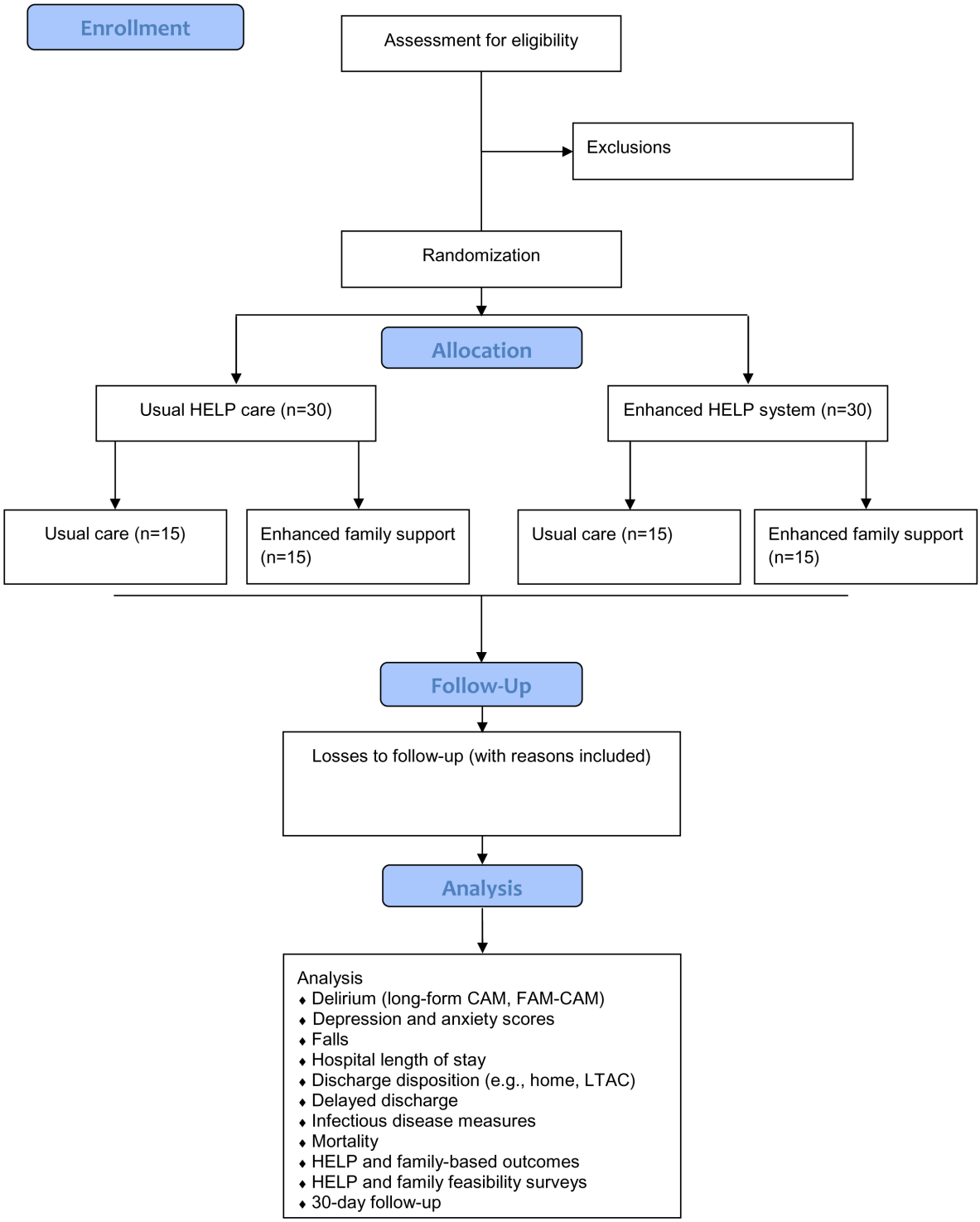

Figure 1. CONSORT study flow diagram. HELP = Hospital Elder Life program; CAM = Confusion Assessment Method, LTAC = Long-Term Acute Care.

Participants

Participants will be screened and recruited at preoperative clinics, preoperative holding areas, and surgical wards (if patients are pre-admitted). Written informed consent will be obtained from all participants and family members (or caretakers) prior to scheduled surgery. Template forms are provided as *Extended data*[23]. Supplemental recruitment materials will be distributed in conjunction with the Michigan

Institute for Clinical and Health Research, the NIH-funded Clinical and Translational Science Award Institute at the University of Michigan. Specifically, recruitment fliers will be posted throughout preoperative clinics, and informative postcards will be sent to potentially eligible patients preoperatively.

Eligibility criteria will reflect the pragmatic nature of the trial balanced with the aim of recruiting patients at high risk for postoperative delirium. Based on a validated geriatric assessment tool for predicting postoperative complications, surgical patients ≥ 70 years of age presenting for major inpatient surgery demonstrated a seven-fold increased risk of major complications, including delirium, compared to minor surgery[24]. Inclusion criteria will thus include the following: age ≥ 70 years of age; major non-cardiac, non-intracranial neurologic, and non-major vascular surgery (as defined by work-related value units suggestive of high surgical complexity), anticipated length of hospital stay at least 72 hours, and at least one family member, or caretaker, available on each of the three first postoperative days. Exclusions include emergency surgery, severe cognitive impairment (precluding ability to perform delirium assessments), planned post-operative ICU admission (HELP unavailable in the ICU), and non-English speaking.

Interventions: clinical decision support systems

This proposal will build upon previous decision support systems launched by our department for reducing intraoperative awareness and delivering protective lung ventilation strategies[25,26]. For participants randomized to the HELP-based support system, a single page will be sent to the on-call HELP staff during the first postoperative morning as the team begins ward rounds (Table 1). The page will request an enhanced treatment protocol, which includes HELP visitations three times daily. Therapeutic treatment will be administered during each visit per program protocols, which generally includes cognitive engagement, mealtime assistance, mobility and range of motion exercises, and assistance with visual and hearing aids. During the final evening visit, a sleep protocol will be implemented. For this protocol, HELP officials offer sleep and relaxation exercises, relaxation massages, and warm milk and/or tea. For the usual care group, HELP volunteers will review surgical ward censuses as able, and patients will be seen based on volunteer availability and visitation patterns. No structured, triage system will be implemented.

For participants randomized to the family-based system, family members (or caretakers) will receive preoperative education on delirium (including an educational video), a folder with an informational flyer and therapeutic activities checklists, and FAM-CAM training. Suggested therapeutic activities include daily assistance with visual and hearing aids, providing assistance with drinking and mealtime assistance, handwashing, re-orientation to time and place, and cognitive stimulation activities. Lastly, family members will also receive a pager, and automated pages will be sent twice daily with reminders to perform these activities (Table 1). Completion of activities will then be logged daily in conjunction with unblinded members of the research team. Study activities for each group are listed in Table 2.

Intervention fidelity

During this pilot phase, characterizing the success and barriers encountered with trial interventions will be essential for analyzing fidelity. As a separate, but complimentary line of investigation, facilitators and barriers to support system implementation will be characterized for both HELP personnel and family members. The following strategies for characterizing implementation efforts are driven by the Consolidated Framework for Implementation Research (CFIR)[27], which described five major domains that shape implementation effectiveness: intervention characteristics, outer setting, inner setting, characteristics of individuals involved, and the process of implementation. Survey-based questions and focus groups described below are guided by these implementation themes.

HELP-based implementation barriers will be elucidated via combination of focus groups and online surveys. This strategy has been previously used for successfully identifying facilitators

Table 1. Real-time clinical decision support – family paging system.

Days	Timing	Alphanumeric Paging Message
HELP-Based Paging System		
Postoperative day 1	Morning – 9:00 AM	*Patient LAST NAME, FIRST NAME, MRN is at high-risk for postoperative delirium. Please evaluate patient as soon as possible and enroll in the enhanced treatment protocol.*
Family-Based Paging System		
Postoperative days 1-3	Morning – 9:00 AM	*Good morning! Please complete the morning tasks listed in your folder (Morning Tasks 9:00 AM). The stimulating activity can then be performed anytime during the day. Call 734-647-8129 with questions or concerns.*
Postoperative days 1-3	Afternoon – 3:00PM	*Good afternoon! Please complete the afternoon tasks in your folder (Afternoon Tasks – 3:00 PM). After these are complete, perform a FAM-CAM. Make sure to also complete a stimulating activity today. Call 734-647-8129 with any questions.*

FAM-CAM = Family Confusion Assessment Method. MRN = Medical Record Number

Table 2. Study operations across groups.

Usual Care Group (n=15)	HELP-Based System (n=15)	Family-Based System (n=15)	Combined Systems (n=15)
Preoperative phase			
Standard Care	Standard Care	Preoperative delirium education, materials, FAM-CAM training	Preoperative delirium education, materials, FAM-CAM training
Intraoperative phase			
Standard Care	Standard Care	Standard Care	Standard Care
Postoperative care			
HELP evaluation and treatment per ward routine	HELP pager alerts	Daily family pager alerts	HELP pager alerts and associated activities
Standard care otherwise	Early evaluation request	FAM-CAM	Family pager alerts and associated activities
	Enhanced therapeutic protocol request	Family-based behavioral/social support and prevention activities	

HELP = Hospital Elder Life Program; FAM-CAM = Family Confusion Assessment Method.

and barriers to delirium prevention involving multidisciplinary bundles[28]. Prior to paging system implementation, an anonymous survey will be distributed to HELP staff members. The survey includes Likert-scale[29] questions derived from the "Safety Attitudes Questionnaire," which reports views on teamwork, safety, collaboration, resource availability, and collegiality[30]. Open-ended questions are then provided for participants to express additional thoughts and insights. These surveys will be sent again 6 and 12 months after system implementation. Within a month after each of these surveys are collected, focus groups will be held with available HELP team members. Focus groups will be tape recorded and common themes will be elicited from transcriptions[28,31]. All responses will remain anonymous from both groups and surveys. The final objective will be to delineate clear barriers and facilitators to HELP-based triage and therapy implementation strategies.

All family members will be provided with surveys (available as *Extended data*)[23] on postoperative day three (or discharge, whichever is sooner). These surveys also contain a similar combination of Likert-scale and open-ended questions to identify barriers to completing delirium screening and prevention activities.

Lastly, a sensitivity analysis will be performed, which will report daily proportions – and reasons – for missing HELP- and family-based assessments (see Sensitivity Analysis and Missing Data).

Outcomes

The primary outcome of this pilot trial will be the presence of delirium, defined by a positive long-form Confusion Assessment Method (CAM)[32] screening. The following secondary outcomes will also be collected and analyzed: delirium severity (long-form CAM severity scale), new symptoms of depression or anxiety (using the Hospitalized Anxiety and Depression Scale, HADS)[33], falls (proportion, %), length of hospital stay (days), discharge disposition (e.g., home, long-term care facility), delayed discharge due to cognitive impairment (proportion, %), incidence of any new non-surgical site infection (%), incidence of new multidrug resistant organism colonization (%), and mortality (%). Exploratory outcomes will include the incidence of positive FAM-CAM assessments (%) 30 days post-discharge, PROMIS Cognitive Function Abilities (Short Form 4a), 36-Item Short Form Survey, and 30-day readmission rates.

Protocol fidelity measures. Lastly, protocol fidelity measures will be reported for both HELP- and family-based interventions. HELP-based measures include the following: total therapeutic time spent with HELP staff during the first three postoperative days, proportion of participants visited and enrolled by HELP (%), and time to initial HELP evaluation. For family-based interventions, the following measures will be reported: cumulative time family members spent with patients, proportion of daily tasks (e.g., assistance with glasses/hearing aids, handwashing), successfully completed, length of time spent on stimulating activity, and overall agreement of the FAM-CAM with interview-rated CAM assessments.

Data collection. At Michigan Medicine, HELP data collection is standard throughout surgical and medical wards. The time at which patients are first evaluated, total therapeutic time (minutes) spent with patients, and nature of therapeutic activities (e.g., cognitive stimulation, mealtime assistance) are all collected daily and logged on computer files. Unblinded

research team will have access to these logs via secured, shared drive within the Michigan Medicine network. These research personnel will review HELP logs daily and meet with HELP leadership as needed to discuss problems that may arise regarding HELP data collection and logging.

For delirium assessment, research team members will screen for delirium using the long-form CAM[32] twice daily (once in the morning, and again in the afternoon) for the first three postoperative days. These team members will be blinded to group allocation. Our research group has extensive experience with CAM in prior trials[2,34,35], and our international group has created a program for training investigators in CAM methodology with a previously high inter-rater reliability (Fleiss kappa=0.88 [95% CI 0.85 to 0.92])[35]. Our study team members who have previously received this training will lead CAM assessment efforts for this trial. Additionally, the study PI (Vlisides), has received complementary CAM training from the NIH-funded (K07AG041835) Center of Excellence for Delirium in Aging: Research, Training and Educational Enhancement (CEDARTREE). For new team members not previously trained, the PI will lead an on-site training session using online long-form CAM training videos available from the Hospital Elder Life Program. Then, after each team member has successfully scored two non-delirious and two delirious patients identically – in terms of symptom recognition – with a previously trained study team member, the trainees will be considered independently trained for CAM assessment[2]. For those enrolled in the intervention bundle, family members (or caretakers) will perform the FAM-CAM[20] independently of the research team. FAM-CAM assessments will be requested once daily in the afternoon.

Depression and anxiety measures will take place both at preoperative baseline and during postoperative day three (or day of discharge, whichever is sooner). For assessment of falls, study team members will ask about fall occurrences during each study visit, and the medical record will also be reviewed for any falls during the study period. Additional clinical secondary outcomes described will be collected from the electronic medical record. On postoperative day three, for patients not randomized to the family-support groups, the research team will ask family members about cumulative time spent with patients, and any interactive activities performed, during the first three postoperative days for comparison to family-based intervention groups.

Finally, research data recorded on paper will be stored in participant charts that will be located in locked cabinets in the Department of Anesthesiology at Michigan Medicine. Electronic data will be de-identified and stored online using the REDCap electronic research database, which resides on a secured, password-protected network managed by the Michigan Institute of Clinical and Health Research.

Statistical analysis

Sample size and power. Given its fluctuating and recurrent nature, delirium presence will be primarily assessed over time with logistic generalized estimating equation models as we have done previously[36]. In brief, time and group will serve as fixed factors, and a group by time interaction term will be included. Interaction terms will be removed from models if no significant interaction effect is observed. These models allow for longitudinal data analysis in the setting of incomplete and missing data. Group models will be constructed individually with the control group serving as a reference, and an intention-to-treat approach will be followed. Power calculations were then conducted with generalized estimating equations by pooling intervention groups together for each calculation. For example, for detecting effects specific to the HELP intervention, the HELP arm (n=15) and combined arm (n=15) were pooled together and compared to the control arm (n=15) and family-support only arm (n=15) in a repeated-measures design with the binary outcome of delirium. Accounting for six equally spaced measurements (twice daily delirium assessments for the first three postoperative days), with an autoregressive correlation structure (baseline correlation 0.3) and linear missing data structure, a total sample size of 60 patients (n=30 in each intervention group) will provide >80% power to detect a difference in proportions of 15% (approximate Cohen's effect size difference of 0.9) for experiencing an episode of delirium between groups, assuming a baseline proportion of 20% in the control group, with α=0.05. Power analysis was conducted using PASS 16 (PASS 2019 Power Analysis and Sample Size Software [2019]. NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). As an exploratory analysis, the interaction between HELP- and family-based support groups will be assessed using a generalized estimating equations model.

Descriptive statistics will be reported for secondary and exploratory outcomes. Inferential statistics will be deferred given the small sample size and pilot nature of the trial. Rigorous statistical analysis will be deferred for planned, follow-up, large-scale investigation. However, inferential statistics will be reported for fidelity measures described previously (Outcomes – Protocol Fidelity Measures). For continuous data, the Shapiro-Wilk test will be used to assess for normal distribution, and either independent t-tests or the Mann-Whitney U-test will be used, as appropriate. For categorical data, chi-squared or Fisher's exact test will be used, as appropriate. Cohen's kappa will be used to assess agreement between research-based CAM delirium assessments and FAM-CAM assessments.

Sensitivity analysis and missing data. Missing data are anticipated for multiple outcomes described in this study. For each HELP visit, cumulative therapeutic time is routinely logged, as are reasons for deferred visits. Thus, the proportion of deferred shift visits, compared to all available shifts (excluding shifts missed due to early discharge) will be reported along with associated reasons (Table 3). Nine total visits are anticipated during the first three postoperative days – daily morning, afternoon, and evening sleep visits. Similarly, missing CAM and FAM-CAM data are expected as well. Reasons for missing assessments will be presented in conjunction with barriers that family members and caretakers report for conducting

Table 3. Anticipated reasons for missing data.

HELP Program – Reasons for deferred visits	Family and Caregivers – Reasons for deferred FAM-CAM completion
HELP staff unavailable	Family unavailable for assessment
Patient engaged with other clinical staff	Patient engaged with other clinical staff
Undergoing medical testing or procedure	Undergoing medical testing or procedure
Visitors present	Not comfortable with performing evaluation
Patient sleeping	Patient sleeping
Patient declines visit	Patient refusal
Early discharge	Early discharge
Other	Other
Not specified	Not specified

HELP, Hospital Elder Life Program; FAM-CAM, Family Confusion Assessment Method.

FAM-CAM assessments. Given the relatively small sample size and pilot nature of this trial, imputation will be deferred for missing data.

Pre-specified secondary and exploratory analyses

As described, a complementary line of analysis will focus on facilitators and barriers to implementing therapeutic protocols described, both from HELP- and family-based perspectives. Results will be used to inform therapeutic protocol design for a larger, follow-up trial. Descriptive reporting, based on mixed methods and Likert scale survey methodology[29,31], will also be used to report experiences with clinical decision support systems. This sub-study analysis involving HELP staff members has received exemption from the University of Michigan Institutional Review Board (HUM00166883).

As a final exploratory line of analysis, an additional objective will be to test collect pilot data for testing differences in microbial patterns in delirious (vs. non-delirious) patients. Preliminary data suggest that colonization of multidrug-resistant organisms is common in older, hospitalized patients; furthermore, inpatient wards commonly harbor such organisms. The attendant complications of such colonization, particularly with respect to neurocognitive and clinical recovery, remain unknown. These microbial patterns will thus be tracked in enrolled patients. Trained study coordinators will collect samples from the hands and nares of enrolled patients using a culture swab during baseline enrollment, on the first postoperative morning (prior to interventions), and again on the morning of the second postoperative day. Study coordinators will also collect samples from 5 high-touch surfaces in patient's rooms (e.g., bed controls/rail, call button/TV remote, tray table, phone, and toilet seat/commode) using a culture swab. These samples will be plated onto Bile Esculin Agar containing 6 g/mL vancomycin, Mannitol Salt Agar, and MacConkey Agar, and assessed for the presence of methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, and resistant gram-negative bacilli utilizing standard microbiology testing methods previously described[37].

Pragmatic-explanatory trial continuum analysis

The RADAR Trial interventions were designed with intentions for high generalizability. HELP is now present at more than 200 hospital systems worldwide, and decision-support systems may help triage and organize support operations across such sites, particularly for those limited by personnel and/or resources. Alternatively, for hospitals without HELP, this trial will also assess the feasibility and efficacy of similar interventions administered by family members and caretakers.

To further study the pragmatic and explanatory elements of RADAR, trial members completed the PRagmatic-Explanatory Continuum Indicator Summary (PRECIS-2) toolkit[38]. This is an assessment tool that characterizes the pragmatic and explanatory elements of clinical trial design, and the results inform as to where trial design resides on the pragmatic-explanatory continuum. For PRECIS-2 assessment, nine study domains are analyzed: eligibility criteria, recruitment, setting, intervention organization, flexibility of intervention delivery, flexibility of adherence, follow up, primary outcome, and primary analysis. Raters score each domain on a scale of 1 – 5, with lower scores reflecting explanatory trial characteristics, and higher scores suggesting a more pragmatic nature. RADAR Trial members independently scored each domain using the associated instructions, and median scores are illustrated in Figure 2. Each domain received a median score of 4 or 5, reflecting a relatively pragmatic study design. Regarding (1) eligibility criteria, the trial will recruit a heterogeneous, well-rounded group of surgical patients that will receive interventions similar to those administered postoperatively.

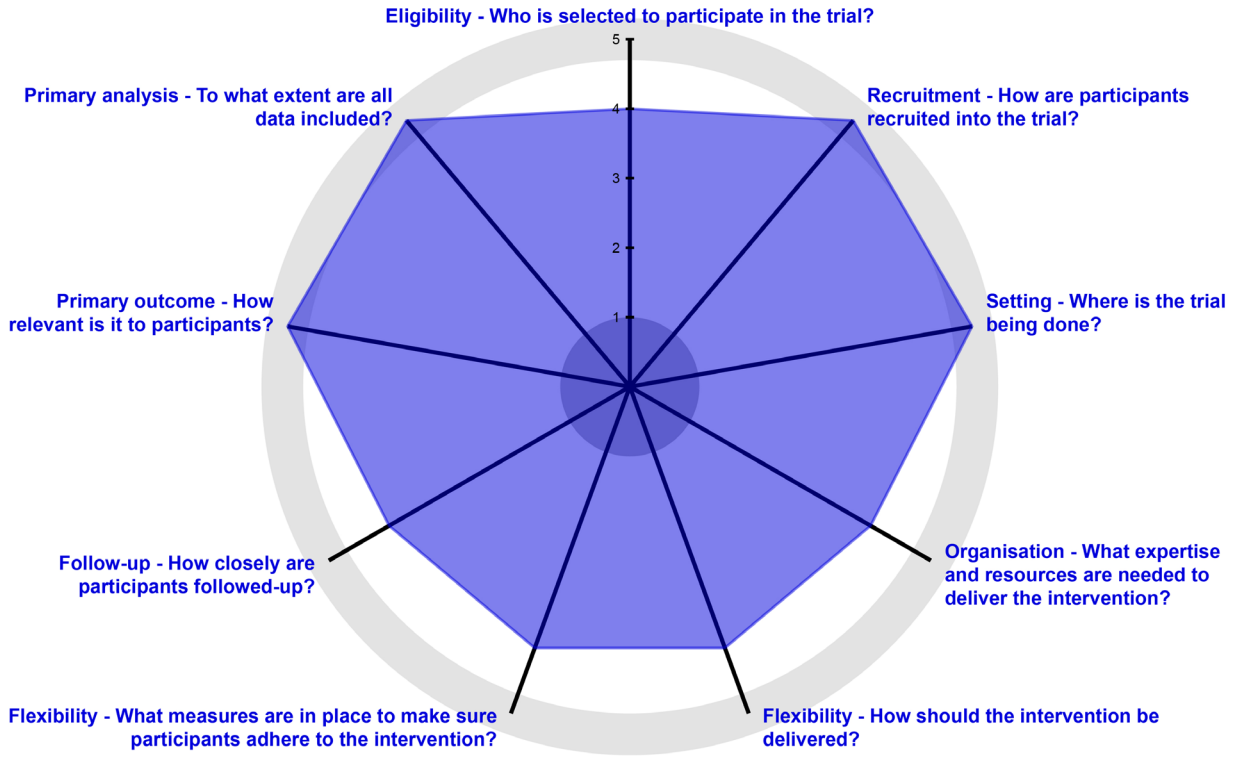

Figure 2. Pragmatic Explanatory Continuum Indicator Summary (PRECIS)-2[38] tool depicting where RADAR resides on the pragmatic-explanatory trial continuum. After reviewing training materials, members of the RADAR team independently scored each of the 9 domains included in the PRECIS-2 Toolkit. For each domain, scores range from 1 to 5, with lower scores reflecting an explanatory nature, and higher scores reflecting pragmatic characteristics. Median scores are presented from all team members (n=10) that completed the PRECIS-2 toolkit scoring. The median score for each domain was either a 4 or 5, reflecting a fairly pragmatic study design overall.

There will be some exclusions based on family and caretaker availability, cognitive function, and surgical subtype. Recruitment (2) will be conducted at regularly scheduled preoperative clinic appointments, which occur as part of routine, standard care. The setting (3) The setting will be identical to where patients otherwise receive perioperative care. Regarding (4) the expertise and resources needed to deliver the interventions, the HELP-based interventions are closely related to usual care, though they may occur sooner and more thoroughly with the pager alerting system. However, there will be some additional resources and training required, particularly for family-based interventions. For (5) flexibility of intervention delivery, pager alerts can be reliably delivered and modified as needed. There are also many opportunities throughout the day to implement clinical protocols as outlined. However, to demonstrate effectiveness, the proposed interventions likely need to occur consistently and with adherence to the protocol. In terms of flexibility adherence (6), daily pager alerts will be reliably and automatically sent to HELP and family members to enhance protocol fidelity. Checklists will also be made available to family members. Follow-up (7) for most outcomes and operations will occur in the immediate postoperative period, and many outcomes described are obtainable via chart review. However, certain follow-up measures (e.g., CAM, 30-day surveys) require prospective collection from research team members, though raters did not raters generally did not anticipate this to be particularly burdensome or prohibitive. Delirium is the primary outcome (8), which is a common and serious postoperative outcome that is relevant to surgical patients. Lastly, the primary analysis plan (9) follows an intention-to-treat approach with longitudinal modeling that accounts for missing data. Although raters generally scored the trial design as pragmatic, raters were part of the trial team, and thus not independent assessors. This may introduce bias with regards to objectively rating explanatory and pragmatic elements of a trial[39].

Data and safety monitoring plan

All participants will be monitored throughout the entire perioperative course by both the research team (including direct oversight by the PI) and clinical teams per standard care. The research team will monitor for adverse events, which will be reported per IRB guidelines. Participants will also have phone and pager numbers to the study coordinator and study PIs,

and they are encouraged to contact our study team with any concerns that arise. While admitted to the hospital, participants will otherwise undergo routine monitoring and management per standard clinical practice. There will otherwise be no additional data management committee, and no interim analyses or audits are planned for this trial. For data storage, primary source paper documents will be stored in locked files within the Department of Anesthesiology at Michigan Medicine. Electronic data will be de-identified and entered into the online REDCap, database, which is managed by the Michigan Institute of Clinical and Health Research Management Core. Lastly, all protocols and consent forms approved by the University of Michigan Medical School IRB are reviewed yearly.

Strengths and limitations

Multiple strengths of this trial are worth noting. First, trial design is relatively pragmatic, as perioperative care will be minimally altered. The HELP-based activities described already take place at Michigan Medicine; a single page will be sent to HELP to assist with triage and focus therapeutic activity on relatively high-risk patients. The system can conceivably benefit any patient regardless of surgical subspecialty, as supportive protocols outlined could be implemented – or adapted – as part of enhanced recovery protocols irrespective of surgical service. The study also offers an innovative approach to integrating family members and caretakers in the postoperative recovery process. Preliminary data suggest that family involvement is both feasible[17] and may improve clinical recovery after major surgery[18]. Thus, both HELP- and family-based support systems offered might provide an effective, practical approach to mitigating delirium risk while minimizing strain to the healthcare system.

Considerable limitations are also worth discussion. The statistical powering strategy crucially assumes there is no interaction between the interventions (e.g., HELP- and family-based support), which may not be the case. However, this pilot phase will help generate effect size and feasibility data for refining future protocols and power calculations. Next, both HELP officials and family members may be subject to the Hawthorne effect[40]. That is, individuals may modify their behavior under study conditions. Both HELP officials and family members may rigorously perform study protocols knowing that performance is being monitored. As such, protocol effectiveness will likely decrease in non-research settings. For the HELP program, performance measures will be compared to historical controls (2018 HELP records) to assess for this effect. Family members of patients not randomized to family-based support interventions may still elect to spend more time with patients after learning about the trial and proceeding with enrollment. To assess for latent family support in the control groups, the research team will ask family members about time and activities with patients for comparisons to structured family-based support allocation groups. This will be assessed on the afternoon of postoperative day three, at the end of the inpatient study window, to avoid inadvertent introduction of study-related family support interventions. Participants who are able, and motivated, to engage with HELP- and family-based support may inherently be less prone to delirium compared to those who do not adhere to study protocols. Additionally, while family members will receive basic training and education on FAM-CAM administration, they will not receive rigorous training for assessing reliability or accuracy. Such training could be pursued in a follow-up trial. Lastly, only patients with family members and/or caretakers – who will be available for the first three days of hospitalization – will be eligible for the trial. Thus, patients without such social support will be ineligible. These eligibility criteria thus exclude a group of patients who may be particularly vulnerable to delirium (i.e., less social support)[41] and reduce trial pragmatism.

Ethical considerations

Emanuel *et al.*[42] have proposed seven universal requirements, drawn from landmark codes and declarations, for comprehensively incorporating all relevant ethical considerations for clinical research, particularly in the context of aiming to improve health and/or increase understanding of human biology. These considerations are presented in question format, along with responses for this trial, in Table 4.

Dissemination

The trial will be presented at academic conferences, presentations, and medical journals. As mentioned, the trial was registered on www.clinicaltrials.gov (NCT04007523), and any protocol changes will be made publicly available on this registry. This manuscript currently reflects the 4th version of the protocol (August 21st, 2020).

If the results demonstrate improved HELP evaluation and therapeutic practices, the paging-based support intervention will be tested in a large-scale trial to assess effectiveness for reducing delirium incidence and related consequences. Family-based interventions may be included as well depending on success and feasibility with family-led delirium screening and prevention procedures described. The nature of such future interventions may be modified depending on survey results from HELP personnel and family members.

Conclusions

Delirium remains a pressing public health issue, and associated consequences bear significant morbidity. The proposed clinical decision support system has the potential to improve the environment for neurocognitive and clinical recovery for high-risk patients. The paging support system is also relatively pragmatic, and if successful, could be used across various healthcare systems and tailored accordingly. If encouraging preliminary results are demonstrated, the proposed interventions will be tested in a large-scale trial for clinical effectiveness.

Table 4. Ethical Considerations.

1. What scientific or social value will be gained from the proposed research?
The proposed clinical support system may improve neurocognitive and clinical recovery for older, vulnerable surgical patients. Given the common occurrence of delirium in this population, along with related complications (e.g., falls, delayed discharge), postoperative clinical complications may threaten the health and functional independence of older surgical patients. By aiming to provide therapeutic, supportive activity early (and frequently) during postoperative recovery, these clinical support systems may reduce the risk of delirium and associated outcomes. As such, the proposed intervention has the potential for improving health and well-being for such vulnerable patients.
2. Will accepted scientific principles and methods be used to produce reliable and valid data?
This trial incorporates multiple strategies for rigorous data acquisition and analysis. Prospective, block-stratified randomization will occur after trial enrollment. The randomized approach will mitigate selection bias during the allocation process and increase the likelihood that findings observed are attributable to the intervention. The sensitivity analysis will also provide transparency regarding missing data and challenges related to intervention fidelity. Lastly, there is a possibility of observer bias (i.e., Hawthorne effect) with HELP staff and family members, as behavior may be modified given the known presence of an ongoing trial. As such, a historical control group will be included from 2018 for determining HELP measures prior to trial initiation. Ongoing family support data will also be collected from groups not randomized to family-based support interventions.
3. Are participants selected such that stigmatized and vulnerable individuals are not targeted for risky research, and socially affluent and powerful are not targeted for beneficial research?
As outlined in the eligibility criteria, all surgical patients (≥70 years old) at high risk for postoperative complications will be eligible for enrollment, regardless of demographic or social background. In a preliminary study that predicted postoperative risk of complications in older patients, those who were ≥70 years of age presenting for major surgery had a seven-fold increased risk of major complications compared to minor surgery[23]. Thus, this study specifically aims to include this vulnerable demographic of patients for beneficial research.
4. Is there a favorable benefit-to-risk ratio for participants? Will the benefits to the participant, and/or society, outweigh any potential risk to the enrolled participants?
The risks associated with this study are minimal. Those randomized to the control group will receive standard perioperative care. If randomized to an interventional group, the patients will likely receive enhanced support from HELP staff and/or family members. Risks associated with these interventions are minimal, but may include anxiety and fatigue from cognitive and functional interventions to improve health after surgery. We feel that trial benefits outweigh these risks, particularly if the intervention reduces the risk of delirium and possible downstream consequences (e.g., falls, delayed discharge).
5. Will independent reviews take place such that a committee, with an appropriate range of expertise, will have the ability to approve, amend, or terminate the study?
The trial has been approved by the University of Michigan Medical School Institutional Review Board, and annual reviews will occur per institutional protocols. The study team will monitor for Adverse Events and Other Reportable Information or Occurrences in compliance with Institutional Review Board protocols.
6. Will informed consent be obtained from all participants prior to enrollment?
Written informed consent will be obtained from all participants prior to trial enrollment. Consent forms are written in conjunction with Institutional Review Board requirements, which require discussion of the following: purpose of the study, participant eligibility, study procedures, information about risks and benefits, ending participation, financial considerations, confidentiality, and study team contact information.
7. Does the proposed study engender respect for potential and enrolled subjects?
Patients will be free and able to withdraw from the trial at any time, and several measures will be taken to maintain participant privacy and confidentiality. If new, unanticipated risks or benefits become apparent during the course of the trial, the protocol will be amended and participants will be made aware of any new risks or benefits of study inclusion. Participant welfare will be respected and maintained throughout trial operations. Adverse events will be reported per Institutional Review Board guidelines, and clinical care will otherwise proceed per perioperative standards at Michigan Medicine.

Data availability

Underlying data

No data are associated with this article

Extended data

Open Science Framework: Recommendations and Alerting for Delirium Alleviation in Real-Time (RADAR): Extended Data. https://doi.org/10.17605/OSF.IO/UYZ92[23].

This project contains the following extended data:

- RADAR Family Consent v1.0 7-23-2019.pdf
- RADAR Subject Consent v1.0 7-23-2019.pdf
- HELP Focus Group Discussion Guide.pdf
- RADAR – HELP Facilitators and Barriers Survey.pdf
- RADAR Family Survey – Facilitators and Barriers.pdf

These data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

Data collection forms related to the Hospital Elder Life Program (e.g., Confusion Assessment Method, Family Confusion Assessment Methods) are subject to copyright restriction and are available on the Hospital Elder Life Program Website (https://www.hospitalelderlifeprogram.org/). The Hospital Anxiety and Depression Scale is also subject to copyright restriction and can be accessed at the following website: https://www.gl-assessment.co.uk/. The 36-Item Short Form Survey (SF-36) can be found on the Rand Healthcare website (https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html), and the PROMIS cognitive function assessments can also be found on the associated website (http://www.healthmeasures.net/explore-measurement-systems/promis).

Reporting guidelines

Open Science Framework: CONSORT Pilot and SPIRIT checklists, and WHO Trial Registration Data Set for 'Recommendations and Alerting for Delirium Alleviation in Real-Time (RADAR): Protocol for a pilot randomized controlled trial'. https://doi.org/10.17605/OSF.IO/UYZ92[23].

- RADAR CONSORT Pilot Checklist.doc
- RADAR SPIRIT Checklist.doc
- RADAR WHO Trial Registration Data Set.docx

Reporting guidelines are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

Acknowledgements

We would like to acknowledge George A. Mashour, MD, PhD, Sharon Inouye, MD, MPH, and Ann Kolanowski, PhD, RN, FAAN, for study design consultation. Additionally, we acknowledge the Michigan Institute for Clinical and Health Research and Michigan Medicine Office of Patient Experience for assistance with designing recruitment materials. We also acknowledge the Hospital Elder Life Program for permissions with the Confusion Assessment Method (Copyright 2003, Hospital Elder Life Program, LLC) and Family Confusion Assessment Method (FAM-CAM), Copyright 1988, 2011. Hospital Elder Life Program. Not to be reproduced without permission.

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 07 September 2020

https://doi.org/10.5256/f1000research.29050.r70561

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✔ **Nicolai Goettel**
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[2] Department of Clinical Research, University of Basel, Basel, Switzerland

The authors have addressed all comments and suggestions in this revised version. Good luck with the trial!

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Delirium, postoperative neurocognitive disorders

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

Reviewer Report 03 September 2020

https://doi.org/10.5256/f1000research.29050.r70562

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✔ **Bala Subramaniam**
Department of Anesthesiology, Harvard Medical School, Boston, MA, USA

The authors have addressed my concern. I have no reservations

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Postoperative delirium, Perioperative hemodynamics, Resilience

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

Version 1

Reviewer Report 20 August 2020

https://doi.org/10.5256/f1000research.22648.r69809

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Nicolai Goettel
[1] Department of Anesthesia, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, University of Basel, Basel, Switzerland
[2] Department of Clinical Research, University of Basel, Basel, Switzerland

Thank you for the opportunity to review this work.

Vlisides and coworkers present the protocol for a pilot randomized controlled trial (RCT) investigating the effect of a multicomponent decision support system, which sends automated alerts and recommendations to patient-care programs and family members for high-risk patients, on the incidence of postoperative delirium.

High-risk, non-cardiac surgery patients (≥70 years old) are allocated to 4 groups: (1) usual care group (n=15), (2) Hospital Elder Life Program (HELP)-based paging system (n=15), (3) family-based paging system (n=15), and (4) combined HELP- and family-based system (n=15).

Primary outcome measure is the incidence of postoperative delirium assessed by Confusion Assessment Method (CAM) screening. Secondary outcome measures are diverse performance metrics for postoperative neurocognitive disorders and clinical recovery.

The study protocol is methodologically sound and closely follows the CONSORT and SPIRIT guidelines.

Even though patients are randomly allocated to treatment groups, there is a risk of apprehension bias and the Hawthorne effect. Study participants, especially those in groups 2–4, may respond differently due to being observed, or individuals may modify an aspect of their behavior in response to their awareness of being observed.

There is also a considerable risk of compliance bias. Preventive interventions for postoperative neurocognitive disorders tend to be rather complex and time-consuming for all persons involved.

Participants compliant with the intervention may differ in some way from those not compliant, which can systematically affect the outcome of interest. In this context, one could argue that higher-functioning patients are more compliant with the intervention; hence, they may present less postoperative delirium.

Figure 1 (CONSORT flow chart): There seems to be a two-step group allocation rather than the 1:1:1:1 group allocation mentioned in the text. What is the difference between “usual HELP care” and “enhanced HELP system”?

One eligibility criterion for recruitment is a high risk for postoperative delirium. However, the inclusion criteria only partially reflect a high-risk surgical population. In other words, being 70 years of age and older and undergoing major non-cardiac, non-intracranial, and non-major vascular surgery might not be sufficient to reach a high-risk level for postoperative delirium. I would suggest to extend the inclusion criteria to participants with an even higher risk of postoperative neurocognitive disorders, such as patients with pre-existing cognitive impairment.

Given the above, the overall incidence of postoperative delirium (or other postoperative neurocognitive disorders) could potentially be quite low in the studied population, or at least not attain the 20% in the control group assumed by the authors. This would subsequently lead to statistically weak results (underpowered study).

In summary, this research is hypothesis-driven and the study is well-designed. I comment the authors for making the effort to include most (if not all) state-of-the-art nonpharmacological interventions to prevent postoperative neurocognitive disorders in a single RCT. I wish the investigators best of luck with the ongoing trial.

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

Yes

Is the study design appropriate for the research question?

Yes

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

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Delirium, postoperative neurocognitive disorders

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

Author Response 21 Aug 2020

Phillip Vlisides, University of Michigan Medical School, Ann Arbor, USA

Thank you for the opportunity to review this work.

Vlisides and coworkers present the protocol for a pilot randomized controlled trial (RCT) investigating the effect of a multicomponent decision support system, which sends automated alerts and recommendations to patient-care programs and family members for high-risk patients, on the incidence of postoperative delirium.

High-risk, non-cardiac surgery patients (≥70 years old) are allocated to 4 groups: (1) usual care group (n=15), (2) Hospital Elder Life Program (HELP)-based paging system (n=15), (3) family-based paging system (n=15), and (4) combined HELP- and family-based system (n=15).

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The study protocol is methodologically sound and closely follows the CONSORT and SPIRIT guidelines.

Even though patients are randomly allocated to treatment groups, there is a risk of apprehension bias and the Hawthorne effect. Study participants, especially those in groups 2–4, may respond differently due to being observed, or individuals may modify an aspect of their behavior in response to their awareness of being observed.

RESPONSE: We would like to thank the reviewer for the thorough, thoughtful review. We agree that apprehension bias, and the Hawthorne effect, are real possibilities with this trial. We have attempted to mitigate this bias with the following strategies (as outlined in the Strength and Limitations section):

First, we will compare HELP metrics (specifically, time to initial evaluation and cumulative time spent with patients) with this trial compared to historical controls (2018 records). If performance measures are improved in the control group compared to the 2018 historical controls, this suggests that the Hawthorne effect may be present. If performance is similar, this would weight against the presence of the Hawthorne effect.

Second, we will assess cumulative time family members spent with patients, along with any potential therapeutic activities performed, even for patients/families not randomized to family-based support interventions. We will wait to collect these data until postoperative day three, so as to not introduce the idea of providing enhanced family support during the first three postoperative days.

There is also a considerable risk of compliance bias. Preventive interventions for postoperative neurocognitive disorders tend to be rather complex and time-consuming for all persons involved. Participants compliant with the intervention may differ in some way from those not compliant, which can systematically affect the outcome of interest. In this

context, one could argue that higher-functioning patients are more compliant with the intervention; hence, they may present less postoperative delirium.

RESPONSE: **We agree that this limitation is present. Indeed, patients who are able – and motivated – to engage with HELP- and family-based support may inherently be less prone to postoperative delirium and related neurocognitive disorders. We have added this limitation to the protocol manuscript.**

Figure 1 (CONSORT flow chart): There seems to be a two-step group allocation rather than the 1:1:1:1 group allocation mentioned in the text. What is the difference between "usual HELP care" and "enhanced HELP system"?

RESPONSE: **The reviewer is correct. This two-step allocation helps to facilitate our randomization procedures, but the final 1:1:1:1 allocation remains the same.**

At our institution, with usual HELP care, the team manually reviews the census of surgical wards daily and then sees various patients throughout the day based on volunteer availability and visitation patterns. There is presently no structured triage system for prioritizing high risk patients, as outlined in the manuscript. As a result, some high risk patients may not be seen until the second or third postoperative day, as discussed in the Introduction section. This information has been included in the Interventions section of the protocol manuscript.

One eligibility criterion for recruitment is a high risk for postoperative delirium. However, the inclusion criteria only partially reflect a high-risk surgical population. In other words, being 70 years of age and older and undergoing major non-cardiac, non-intracranial, and non-major vascular surgery might not be sufficient to reach a high-risk level for postoperative delirium. I would suggest to extend the inclusion criteria to participants with an even higher risk of postoperative neurocognitive disorders, such as patients with pre-existing cognitive impairment.

RESPONSE: We agree with the reviewer that there exists a higher-risk tier, which includes patients with pre-existing cognitive impairment (along with other risk factors). Data from a frailty prediction model for surgical patients ≥70 years old, developed by our institution, suggest that high surgical complexity alone (i.e., procedure requiring considerable perioperative resources with inpatient admission) was associated with increased risk of geriatric complications, including delirium and related outcomes (AOR 12.1, 95% CI: 6.4 – 22.7; p<0.001) (Min et al., JAMA Surg. 2017 Dec; 152(12): 1126–1133). As such, for a feasibility/pilot trial, we surmised that this population would be appropriate for testing both efficacy and feasibility with such candidate interventions. Focusing on patients with prior neurocognitive impairment may be more challenging logistically, specifically with regards to determining basic barriers to implementation. However, we will certainly consider this population in the future as we continue to determine the impact and barriers with respect to such decision-support systems.

Given the above, the overall incidence of postoperative delirium (or other postoperative

neurocognitive disorders) could potentially be quite low in the studied population, or at least not attain the 20% in the control group assumed by the authors. This would subsequently lead to statistically weak results (underpowered study).

RESPONSE: Indeed, this is an important consideration with postoperative delirium. Prior trials at our institution have revealed an incidence of approximately 20% with such non-cardiac surgery populations (Avidan et al., Lancet 2017; Vlisides et al., JNA 2019). In fact, the inclusion criteria for these prior trials included patients >60 years of age. As such, we anticipate that this 20% estimate will be accurate. Nonetheless, if the incidence differs significantly in this pilot trial, these results will better inform future power calculations for subsequent trials.

In summary, this research is hypothesis-driven and the study is well-designed. I comment the authors for making the effort to include most (if not all) state-of-the-art nonpharmacological interventions to prevent postoperative neurocognitive disorders in a single RCT. I wish the investigators best of luck with the ongoing trial.

RESPONSE: We would like to thank the reviewer for the constructive, encouraging feedback.

Competing Interests: N/A

Reviewer Report 17 December 2019

https://doi.org/10.5256/f1000research.22648.r56796

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Bala Subramaniam
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The authors have designed an elegant study to maximize their ability to use existing supportive interventions in the prevention of delirium. This study is very much needed and wish the very best for the authors to complete all the elements proposed in this study.

1. The authors note this as a factorial design. In Fig. 1 this is categorized as usual HELP vs. Enhanced HELP system. The study is powered for interventions vs. controls. Enhanced HELP, Family support and HELP plus family support are all intervention groups. Is this powered to 15 vs. 45 (unbalanced)? While they note that n=30 in their power calculations. This is confusing.

2. Given 1, is factorial design the best suited for this study?

3. In the HELP group, all efforts are taken to make sure the investigators get two assessment

right before they become eligible to score CAM. Why aren't the same efforts taken for FAMCAM as well? I suppose there will be logical issues, perhaps scoring with case videos might be one option.

4. Inclusion criteria mentions high-risk group and yet age is the only one chosen to define high risk. Or have I missed other risk factors in the inclusion criteria?

5. Family support can do certain things and HELP can do certain things. I presume this will be complimentary. It will be interesting to find out the results of this study.

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

Is the study design appropriate for the research question?
Partly

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

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

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Postoperative delirium, Perioperative hemodynamics, Resilience

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 21 Aug 2020

Phillip Vlisides, University of Michigan Medical School, Ann Arbor, USA

The authors have designed an elegant study to maximize their ability to use existing supportive interventions in the prevention of delirium. This study is very much needed and wish the very best for the authors to complete all the elements proposed in this study.

The authors note this as a factorial design. In Fig. 1 this is categorized as usual HELP vs. Enhanced HELP system. The study is powered for interventions vs. controls. Enhanced HELP, Family support and HELP plus family support are all intervention groups. Is this powered to 15 vs. 45 (unbalanced)? While they note that n=30 in their power calculations. This is confusing.

RESPONSE: We would like to thank the reviewer for the thorough and thoughtful review. We can certainly understand the confusion regarding power/sample size calculations and will attempt to clarify.

The power calculations pool two intervention groups together for each calculation. For example, for detecting effects specific to the HELP intervention, the HELP arm (n=15) and combined arm (n=15) were pooled together and compared to the control arm (n=15) and family-support only arm (n=15). This strategy was also used for the family-specific intervention calculations. This is a conventional strategy for factorial trials described by Montgomery et al. (BMC Med Res Methodol. 2003; 3:26). We have added this language to the Statistical Analysis section of the manuscript.

We acknowledge that his powering strategy has shortcomings. For example, this strategy crucially assumes there is no interaction between the interventions (e.g., HELP- and family-based support), which may not be the case in this trial. However, in the context of a pilot clinical trial for generating effect size data, testing feasibility, and informing future trial protocols, we surmised that this would be a reasonable initial strategy. We have added this limitation (and additional explanation) to the protocol manuscript.

Given 1, is factorial design the best suited for this study?

RESPONSE: As discussed above, there are indeed methodological limitations with this approach. The main objective of this pilot study, however, is to determine both efficacy and feasibility with these decision-support systems for both HELP- and family-based support. The factorial design allows for separate (and combined) analyses with respect to each intervention arm. This is particularly salient given that many hospital systems do not have HELP, and such family-based support systems might be alternative supportive care options for such hospital systems. In fact, the results from this study might inform future design for separate trials (one specific to hospitals with HELP, and a separate trial for hospitals without HELP). The factorial design allows us to (1) efficiently collect initial data on these interventions simultaneously and (2) analyze effects both separately and jointly via exploratory interaction analysis.

In the HELP group, all efforts are taken to make sure the investigators get two assessment right before they become eligible to score CAM. Why aren't the same efforts taken for FAMCAM as well? I suppose there will be logical issues, perhaps scoring with case videos might be one option.

RESPONSE: The reviewer raises important points about CAM and FAM-CAM methodology. Logistical issues are indeed a concern. Family members will only be scoring their own family members, and there will be a limited number of assessments (i.e., three days) prior to discharge. Thus, training opportunities would be limited. This is nonetheless an important methodological issue. We did not incorporate case videos for family members, but this could be considered for future protocols. We have added this as a study limitation in the protocol manuscript.

Inclusion criteria mentions high-risk group and yet age is the only one chosen to define high risk. Or have I missed other risk factors in the inclusion criteria?

RESPONSE: The high-risk label is derived from one of our group's prior studies, in which patients at least 70 years of age, presenting for surgery with work-related value units suggestive of high surgical complexity were among the highest risk of perioperative complications (including delirium) regardless of comorbidity burden (JAMA Surg. 2017 152(12): 1126-1133). Patients 70 years of age presenting for major surgery were assigned nine points in the screening tool published (JAMA Surg. 2017 152(12): 1126-1133), and a score ^{3}9 points was proposed as the optimal cutoff for predicting major perioperative complications (e.g., infection, delirium, falls). We have clarified this language in the updated protocol manuscript.

Family support can do certain things and HELP can do certain things. I presume this will be complimentary. It will be interesting to find out the results of this study.

RESPONSE: The reviewer is correct – the HELP- and family-based activities will be complementary. In the future, these interventions may work in a combined, complementary manner, or they each may be suitable as an independent set of interventions. Family-based support protocols might, for example, be helpful for hospitals without HELP availability.

We otherwise thank the reviewer for the review and analysis of the protocol.

Competing Interests: N/A

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