Integration of Machine Learning and Clinical Decision Support to Prevent Postoperative Delirium in Patients With Cognitive Impairment
NCT05777187
PI: Ira Hofer, MD
Document Date: 9-14-2023

INTEGRATION OF MACHINE LEARNING AND CLINICAL DECISION SUPPORT TO PREVENT POSTOPERATIVE DELIRIUM IN PATIENTS WITH COGNITIVE IMPAIRMENT

Principal Investigator:

Ira Hofer, MD

Associate Professor, Department of Anesthesiology and Medicine

Icahn School of Medicine at Mount Sinai

Supported by:

The National Institute on Aging

FY22_Demo1_Hofer

(Any modification to the protocol should be annotated on the coversheet or in an appendix. The annotation should note the exact words that are changed, the location in the protocol, the date the modification was approved by the Executive Committee, and the date it became effective.)

Version 3 *(Please change version number with each amendment)*
09/14/2023

Summary of Changes Version 3

The use of strictly Physician Assistants to complete the 4AT post-operative delirium screen was changed to include any medical provider that may be on the care team. This was done to increase the post-operative screens being done so the primary endpoint could be reached in a timely manner. Previously, using only the PA providers did not allow for comprehensive post-operative delirium screening for all study participants due to the difference in services that the patients were on. It was noted that many patients were on medical services rather than surgical services where the PA providers were available.

Page/Section	Description of Change	Rationale
Page xii/Design and Outcomes	Changed "physician assistant (PA)" to "medical provider" under secondary outcomes in the following sentence: "The impact of 4AT screening prompts on medical provider post-operative care practices"	Replaced physician assistant with medical provider to broaden use of clinic care team to complete 4AT assessments.
Page 3/1. Study Objectives/1.2 Secondary Objectives	Changed "physician assistant (PA)" to "medical provider" in bullet point e) "The impact of 4AT screening prompts on medical provider post-operative care practices"	Same as above
Page 6/3. Study Design	Changed "PAs" to "medical provider" and corrected spelling of second use of the word "notification" in sentence "Postoperatively, for patients in both groups the medical providers caring for the patients will receive a notification to screen the patient for POD, and if the screen is positive a notification to screen the patient on each subsequent day until the delirium resolves."	Same as above and correction of spelling.
Page 8/4. Selection and Enrollment of Participants/4.1 Inclusion Criteria	Changed sentence "For providers, all anesthesia providers (anesthesiologist, resident, and nurse anesthetist and PAs on the surgical services in all the hospitals will be included in the study." to "For providers, all anesthesia providers (anesthesiologist, resident, and nurse anesthetist and medical providers completing the 4AT screens, including PAs on the surgical services, in all the hospitals will be included in the study"	This sentence was changed to add all medical providers completing post-operative delirium screens in addition to surgical physician assistants to the inclusion criteria for assessing clinical care.
Page 11/5. Study Interventions/5.4 Adherence Assessment	Changed sentence "For the notification of the PAs we will examine postoperative length of stay as a time series before and after the intervention and for enrolled patients as opposed to patients who are unenrolled because they have had a prior surgical procedure during the study period" to "For the post-operative delirium screen (4AT)	This sentence was changed to remove the mention of PA (physician assistant) specifically and focus directly on the 4AT assessment done by any medical provider on the care team.

	notifications we will examine postoperative length of stay as a time series before and after the intervention and for enrolled patients as opposed to patients who are unenrolled because they have had a prior surgical procedure during the study period."	
Page 13/6 Study Procedures/6.2 Description of Evaluations/6.2.3 Follow-up Visits	Changed sentence "Patients will have routine postoperative care with the addition of 4AT assessments by the physician assistant on each postoperative day as part of routine care." to "Patients will have routine postoperative care with the addition of at least one 4AT assessment by a medical provider on the care team". Added sentence "If post-operative delirium is present in the screen, providers will be encouraged to re-screen the following day, but only one assessment is needed for the present study's primary end point."	Replaced PA with medical provider to broaden use of clinic care team to complete 4AT assessments. Additional sentence added to clarify amount of 4AT screens, and what is needed for primary outcome purposes as oppose to clinical.
Page 17/9.4 Outcomes/9.4.2 Secondary Outcomes	Replaced "physician assistant staff" with "medical providers".	Replaced PA with medical provider to broaden use of clinic care team to complete 4AT assessments.
Page 18/9.5 Data Analyses	Under bullet point d), changed "physician assistant" to "medical provider" in first sentence in paragraph: "Analysis of delirium screening prompt on medical provider post-operative care practices". Changed "the PAs" to "a medical provider" and "surgical service" to "care team" in second sentence: "At present not all patients with CI are screened for POD by their providers. Part of our intervention will be ensuring that all these patients are screened for POD by a medical provider on their care team."	Replaced PA with medical provider to broaden use of clinic care team to complete 4AT assessments. Replaced surgical service with care team to ensure accuracy of provider. Not only surgical services are part of patient's care team.

Summary of Changes Version 2: The use of the Confusion Assessment Method (CAM) was transitioned to the use of the 4 A's Test. These tests are similar both are reliable in measuring post-operative delirium. Anywhere in the protocol where CAM was previously named was changed to 4AT.

Rationale
Use of the CAM was changed to use of the 4AT for logistic reasons in the study.
Change in use of CAM to 4AT. It was noted that the impact that the alert for need for screening may impact PA behavior.
Same as above.
Stratification of patients changed from risk grouping to by surgical service in conjunction with change of staff assessing delirium changing from nursing staff to PA staff.

Same as above.
Misspelling.
Including additional detail to asses adherence.
Change in use of CAM to 4AT.
Change in use of CAM to 4AT as well as specifiying that PA staff will complete post-operative delirium assessments.
Change in use of CAM to 4AT.
Change in use of CAM to 4AT and added description and justification for use of 4AT.
Addition of measurement on PA care management as related to the study.
The CAM no longer being used for study, and the 4AT is able to assess patients that are unable to respond due to drowsiness or sickness.
It was noted that the impact that the alert for need for screening may impact PA behavior.

TABLE OF CONTENTS

Page

PRÉCIS

Over one million surgical procedures are performed annually on patients with cognitive impairment (CI) in the United States. Up to 50% of these patients will develop postoperative delirium (POD) – a fluctuating disturbance in attention, altered level of consciousness and disorganized thinking lasting up to one-week post-procedure. POD is associated with in-hospital complications, longer hospitalization, post-discharge worsening of functional and psychological health, progressive cognitive decline, dementia, and death.

It is estimated that 30-40% of POD cases are preventable and optimal perioperative management is associated with POD prevention. For example, glycemic control, medication management, blood pressure titration and anesthetic depth have all been associated with POD. Thus, anesthesiologists have an opportunity to improve safety in an area that is "directly attributable to anesthesia" with a serious impact on patient outcomes. While these studies demonstrate the potential for perioperative interventions to prevent POD, providers often struggle to identify at risk patients and ensure that the increasing number of best practice guidelines are consistently applied to each patient.

The modern electronic health record (EHR) provides an unprecedented opportunity to address this shortcoming. However, a key challenge in applying best practice guidelines to patients is often patient identification. While clinicians struggle to read and absorb all the data in the EHR, computers excel at consistently and accurately processing large amounts of data. Clinical decision support (CDS) pathways have been demonstrated to be highly effective at identifying at risk patient populations and increasing anesthesiologist adherence to best practices such as glucose control, blood pressure, anesthetic management, lung protective ventilation, thereby improving postoperative outcomes.

We have extensive experience in the pathogenesis and prevention of POD, EHR data, integrating risk stratification systems into the EHR to identify patients with CI, and providing perioperative decision support. We propose leveraging our experience in informatics and POD research to perform a prospective randomized controlled trial (RCT) that will test the effectiveness of a CDS system to promote adherence to best with the goal of decreasing POD in patients with baseline CI.

In particular the protocol will involve 1) identifying patients with baseline cognitive impairment (CI) scheduled for surgery 2) randomizing these cases to a) CDS prompts to the anesthesiologist regarding 12 perioperative best practices or b) no prompts (controls) and measuring the efficacy of the protocol at reducing POD as measured by the "4 A's Test" (4AT).

Study Title

Integration of Machine Learning and Clinical Decision Support to Prevent Postoperative Delirium in Patients with Cognitive Impairment

Objectives

The primary objective of this pilot study is to increase adherence to best practices by anesthesia providers in order to reduce postoperative delirium (POD) in patients with underlying cognitive impairment. In order to accomplish this goal, we will identify patients with baseline cognitive impairment undergoing surgery using structured data from the electronic health record (EHR) and an existing natural language processing (NLP) model. Patients will then be randomized to usual care or clinical decision support (CDS) alerts directed at the anesthesia provider for 12 perioperative best practices.

Design and Outcomes

Design: Prospective Stage IV pragmatic randomized controlled trial
Setting: Mount Sinai Health System – four hospitals
Population: Patients with baseline cognitive impairment undergoing surgery.
Intervention: 12 clinical best practices in 5 domains (see subsequent slides)
Outcomes:
Primary outcome:
Postoperative delirium as measured by the 4 A's Test (4AT)
Secondary outcomes:
The ability of CDS prompts to increase best practice adherence
The impact of individual and overall practice adherence on POD prevention
The efficacy of this tool in various sociodemographic subgroups to ensure that it is equitable.
The impact of 4AT screening prompts on medical provider post-operative care practices

Interventions and Duration

In order to accomplish our study goal, we will identify patients with baseline cognitive impairment undergoing surgery using structured data from the electronic health record (EHR) and an existing natural language processing (NLP) model. Patients will then be randomized to usual care or clinical decision support (CDS) alerts directed at the anesthesia provider for 12 perioperative best practices.

The study will run for 12 months.

Sample Size and Population

Study population (estimated): 12,000 prospectively and 12,000 patients as historical controls.
We will identify patients with baseline cognitive impairment undergoing surgery using structured data from the electronic health record (EHR) and an existing natural language

processing (NLP) model. Patients will be randomized to usual care or clinical decision support (CDS) alerts directed at the anesthesia provider for 12 perioperative best practice.

STUDY TEAM ROSTER

Principal Investigator: **Dr. Ira Hofer**
One Gustave L. Levy Place,
New York, NY, 10029
212-241-7473
Email address: ira.hofer@moungsinai.org
Main responsibilities: Dr. Hofer will be responsible for study design, coordinating meetings with the other investigators, and overseeing study execution. /Key roles: Principal Investigator

Co-Principal Investigator: **Dr. Susana Vacas, MD PhD**

5 Fruit Street, Gray Bigelow 444-K
Boston, MA 02114
310-562-9407
Main responsibilities: Dr. Vacas will be responsible for CDS pathway design and statistical analysis. Her role will not require IRB oversight /Key roles: Co-Investigator

Co-Investigators: **Dr. Girish Nadkarni**

One Gustave L. Levy Place, Box 1243
New York, NY, 10029
Telephone: 212-241-1385
Fax: 212-987-0389
Email address: girish.nadkarni@mountsinai.org
Main responsibilities: Dr. Nadkarni will be responsible for deployment of the NLP algorithm into clinical care. /Key roles: Co-Investigator

Dr. Matthew Levin

One Gustave L. Levy Place,
New York, NY, 10029
Telephone: 212-241-8382
Email address: matthew.levin@mssm.edu
Main responsibilities: Dr. Levin will be responsible for deployment of the NLP algorithm into clinical care and CDS implimentation/Key roles: Co-Investigator

Dr. Alex Federman

17 East 102nd Street, 7th Floor
New York, NY 10029

Telephone: 212-659-8551
Email address: alex.federman@mountsinai.org
Main responsibilities: Dr. Federman will be responsible for designing the tools to identify patients with CI. /Key roles: Co-Investigator

PARTICIPATING STUDY SITES

Catherine Sarkisian, MD

200 Medical Plaza Driveway Suite 365
Los Angeles, CA 90095
(310) 206-8272
Main responsibilities: Dr. Sarkisian will be responsible for assisting with the clinical trial design. There is no need for IRB oversight in her role. /Key roles: Co-Investigator

1 STUDY OBJECTIVES

1.1 Primary Objective

The primary objective of this pilot study is to increase adherence to best practices by anesthesia providers in order to reduce postoperative delirium (POD) in patients with underlying cognitive impairment. In order to accomplish this goal we will identify patients with baseline cognitive impairment undergoing surgery using structured data from the electronic health record (EHR) and an existing natural language processing (NLP) model. Patients will then be randomized to usual care or clinical decision support (CDS) alerts directed at the anesthesia provider for 12 perioperative best practices.

1.2 Secondary Objectives

The secondary objective is to measure:

- a) The ability of CDS prompts to increase best practice adherence
- b) The impact of individual and overall practice adherence on POD prevention
- c) The efficacy of this tool in various sociodemographic subgroups to ensure that it is equitable.
- e) The impact of 4AT screening prompts on medical provider post-operative care practices

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Over one million surgical procedures are performed annually on patients with cognitive impairment (CI) in the United States[1,2]. Up to 50% of these patients will develop postoperative delirium (POD)[3,4] – a fluctuating disturbance in attention, altered level of consciousness and disorganized thinking lasting up to one week post-procedure.[5,6] POD is associated with in-hospital complications, longer hospitalization, post-discharge worsening of functional and psychological health, progressive cognitive decline, dementia, and death.[1,7-11]

It is estimated that *30-40% of POD cases are preventable[12,13] and optimal perioperative management is associated with POD prevention.[14-19]* For example, glycemic control[20], medication management[21], blood pressure titration[16,17,22] and anesthetic depth[23] have all been associated with POD. Thus, anesthesiologists have an opportunity to improve safety in an area that is "directly attributable to anesthesia" with a serious impact on patient outcomes. While these studies demonstrate the potential for perioperative interventions to prevent POD, providers often struggle to identify at risk patients and ensure that the increasing number of best practice guidelines are consistently applied to each patient.

The modern electronic health record (EHR) provides an unprecedented opportunity to address this shortcoming. However, a key challenge in applying best practice guidelines to patients is often patient identification. While clinicians struggle to read and absorb all the data in the EHR, computers excel at consistently and accurately processing large

amounts of data. Clinical decision support (CDS) pathways have been demonstrated to be highly effective at identifying at risk patient populations and increasing anesthesiologist adherence to best practices such as glucose control[24-27], blood pressure[28-30], anesthetic management[28,31], lung protective ventilation[32], thereby improving postoperative outcomes.

We have extensive experience in the pathogenesis and prevention of POD, EHR data, integrating risk stratification systems into the EHR to identify patients with CI, and providing perioperative decision support. *We propose leveraging our experience in informatics and POD research to perform a prospective randomized controlled trial (RCT) that will test the effectiveness of a CDS system to promote adherence to best with the goal of decreasing POD in patients with baseline CI.*

2.2 Study Rationale

1. Preventing POD is one of the most important priorities for patients with cognitive impairment (CI). Adults over 65 years of age are 16% of the United States population and 40% of surgical volume. Nearly 30% of this population has preoperative CI. Patients with CI have an overall incidence of postoperative delirium (POD) of 30-50% and an incidence as high as 70% depending on existing comorbidities or type of surgery. POD increases all-cause mortality by 10-20% for every 48 hours of delirium and is associated with increased duration of postoperative mechanical ventilation, ICU and hospital length of stay. POD is linked to long-term cognitive decline, including an 8-fold amplified risk for dementia, and intensified functional decline. It is estimated that worsening long-term cognitive dysfunction occurs in more than 10% of older non-cardiac surgical patients. The annual costs associated with POD are estimated to be over $150 billion. National associations, including the American Geriatrics Society (AGS) and the American Society of Anesthesiologists (ASA), have issued calls to action to prevent POD.

2. Intraoperative best practices are efficacious in prevention of POD. 30-40% of POD cases are preventable and intraoperative management is critical to POD prevention. Inappropriate medications (defined by The Beers criteria) have been linked to POD and glycemic control (avoiding both hypoglycemia and hyperglycemia) has been shown to prevent POD. Several studies have also found an association between intraoperative hemodynamic management with the incidence of POD. Given the disruptive effect of anesthetics on the brain, some have hypothesized that anesthetics might contribute to POD directly – it has been shown that titrating anesthetic dose to age-adjusted anesthetic concentrations or to the electroencephalogram (EEG) reduces the incidence of POD and improves cognitive function at one year.

3. Multipronged interventions are more effective at preventing postoperative complications. Several studies have demonstrated the ability of enhanced recovery after surgery (ERAS) pathways to improve perioperative outcomes. The studies span a variety of surgical procedures and patient populations and have consistently shown that multi-intervention pathways are more successful at improving outcomes than singular interventions. To date there have been no ERAS pathways to prevent POD studied prospectively.

4. Perioperative providers struggle to identify patients at risk of POD. POD develops through an interaction of predisposing patient vulnerabilities and precipitating factors that occur throughout the perioperative period. While CI and similar cognitive features are risk factors for POD, other risk factors such as metabolic derangements, polypharmacy, and poorly controlled pain are not directly related to cognition. Similarly, precipitating factors such as surgical duration, invasiveness of surgery, and some medications can directly and indirectly trigger neurological change. Several perioperative risk stratification instruments for POD have been published, however, they are based on small studies, limited predictive features, and narrow inclusion criteria, thereby limiting generalizability. Further, work by our group has shown that anesthesiologists often struggle to assimilate all of the information scattered throughout the modern electronic health record (EHR), leading them to underestimate patient risk. As a result, providers at the point of care – the operating room – often fail to identify patients at risk of POD. The struggle to apply the diverse array of existing risk instruments is exacerbated by the fact that anesthesiologists are often unaware that patients had POD, as it occurs well after their contact with the patient, making their "clinical intuition" less relevant.

5. Clinical Decision Support (CDS) has been shown to increase provider awareness of risk and adherence to best practices. CDS refers to alerts imbedded in an EHR at the point of care to modify provider behavior. While CDS has shown mixed results in other settings it has been extremely effective at modifying perioperative provider behavior. Institutions have successfully used perioperative CDS to in areas such as glycemic control, postoperative nausea and vomiting66, anesthetic depth blood pressure control, and antibiotic prophylaxis. However, too many CDS alerts can cause burnout amongst providers and decrease effectiveness making generalized CDS alerts less effective than those targeted to high-risk patients. Thus, integrating risk-stratification targeting high-risk patients with CDS prompts to adhere to best practices carries the potential to be more effective for the patient and the provider's well-being and practice.

6. Overall Clinical Significance: POD is a major cause of morbidity in patients with CI, and perioperative management is implicated in the incidence of POD. Implementation of the various perioperative best practice guidelines for the prevention of POD remains inconsistent due to challenges of identifying patients at risk for POD and the rapid nature of perioperative care. This proposal will prevent POD by identifying patients with CI by performing a stage IV effectiveness randomized controlled trial using CDS to promote provider adherence to perioperative best practices while measuring the effectiveness of the CDS on reducing POD.

3 STUDY DESIGN

Location: The trial will be conducted at the Mount Sinai Health System (MSHS) in Manhattan, containing one of the most diverse populations in the world, with 130 operating rooms across four hospitals, performing more than 100,000 surgical procedures each year.

Identification of patients with CI: Patients will be identified as having CI if the established NLP model yields a positive prediction or if the patient has structured data in the EHR indicative of cognitive impairment (i.e. Mini-Mental score exam <24, ICD codes for CI,

etc.). The use of multiple criteria is crucial because our previous work has shown that using multiple techniques to identify clinical phenotypes is superior to any single technique independently. These models and techniques already exist at MSHS and the NLP model is currently under peer review.

Randomization and risk stratification: In the perioperative period an anesthesia attending supervises multiple junior providers in pairings that change daily. Thus, randomization at the level of the provider is impossible and patients will be randomized at the level of the surgical procedure. In order to avoid issues with statistical analysis, only the first surgical procedure for each patient will be included in the study. For each procedure, patients will be stratified based on their surgical service and the hospital. For each stratum, patients will be alternately assigned to the intervention or control groups (i.e., 1st intervention, 2nd control, etc.). The control group will receive usual care (no prompts) and the intervention group will receive an alert to the anesthesiologist that the patient is at increased risk for POD with CDS prompts for clinical best practices. Postoperatively, for patients in both groups the medical providers caring for the patients will receive a notification to screen the patient for POD, and if the screen is positive a notification to screen the patient on each subsequent day until the delirium resolves.

Intervention Development: The intervention will be developed in line with the IMPACT Collaboratory steps for creating effective value propositions. Consistent with previous CDS deployments done by our team, the proposed interventions will be shared with departmental leadership for input and feedback on notification design and content. Specific feedback about frequency and thresholds of alerts will be solicited to gain buy-in and attempt to mitigate alert fatigue. Non-disruptive alerts that avoid hard stops will be used. Prior to intervention go live, education will be provided to the anesthesiologists via email communications as well as presentations at forums such as grand rounds, faculty meetings, residency meetings, etc. The education will specify that these alerts are part of a prospective randomized controlled trial. Selection of intraoperative best practices: The 12 intraoperative best practices across five domains that will be encouraged with CDS is contained in Table 1.

Table 1: Perioperative Best Practices		
Intervention Domain	**CDS Prompts**	
Avoid Potential Inappropriate Medication	Avoid Diphenhydramine	
	Avoid Scopolamine	
	Avoid Midazolam	
Perioperative Glycemic Control	Check preop glucose	
	Check Glucose q 2 hours	
	Maintain glucose<200	
	Check PACU Glucose	
Avoid Hypotension	MAP > 65 mmHg	
Maintain Normothermia	Use temperature probe	
	Maintain temperature >36	
Titrate Anesthetic Depth	Age adjusted MAC<1	
	Monitor anesthesia depth	
Preoperative	Intraoperative	Postoperative

Interventions were selected from the American College of Surgeons, the AGS, and ASA list of best practices, if they were relevant to the perioperative period, suggested as a specific objective action, and are documented in the EHR during usual care. All interventions are performed by the anesthesiologist and measured in the EHR.

CDS Notifications of the POD risk and best practice recommendations: All CDS notifications will be designed to be non-disruptive and will be displayed on a banner and sidebars and will not contain hard stops. Thus, the notifications will be informative of the patient risk and recommended best practices but will not interrupt clinical workflows. The preoperative notification display in the banner on the top of the EHR will contain notifications of the presence of CI, risk for POD, and preoperative recommendations. Similar alerts are already in use at MSHS. In the control arm, there will be no notification on the EHR screen. Intraoperative recommendations will be non-disruptive notifications on the side of the intraoperative record; postoperative notifications will be incorporated into the CDS alerts already in place for medication orders in the postoperative anesthesia care unit. All of the interventions will be designed without any hard stops and in a way that avoids disruptions in the clinical workflow (i.e., no new pop-up alerts will be used) as our previous work has shown non-disruptive interventions have been highly effective at changing provider behavior. Similar notifications for other purposes are already in place at the MSHS and can be created within several weeks. Our team has extensive experience creating such notifications in the EHR.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Inclusion Criteria: We will include patients with CI undergoing surgery, approximately 12,000 patients. For each patient only the first surgical procedure during the study period will be included. Patients will be identified as having CI if the established NLP

model yields a positive prediction (see preliminary data) or if the patient has structured data in the EHR indicative of cognitive impairment (i.e. Mini-Mental score exam <24, ICD codes for CI, etc.). The use of multiple criteria is crucial because our previous work has shown that using multiple techniques to identify clinical phenotypes is superior to any single technique independently. These models and techniques already exist at MSHS and there is no barrier to using the EHR data to identify patients with CI.

Historical controls will be identified from the existing EHR data warehouse (included) if they would have met criteria for inclusion in the one year prior to study launch.

For providers, all anesthesia providers (anesthesiologist, resident and nurse anesthetist) and medical providers completing the 4AT screens, including PAs on the surgical services, in all of the hospitals will be included in the study

4.2 Exclusion Criteria

Patients will be excluded if this not their first surgery since study start, if they do not have cognitive impairment based on EHR data, or if the surgery is for organ donation.

There will be no exclusion criteria for providers or historical controls.

4.3 Study Enrollment Procedures

All participants who meet the inclusion/exclusion criteria will be enrolled to the study and we will be obtaining a waiver of informed consent from the IRB based on the following criteria:

	Justification		
Waiver Criteria	Prospective Patients	Prospective Provider who is receiving the CDS prompts	Historical Controls
the research involves no more than minimal risk to the subjects	• recommendations strictly provide best practice guidance and do not mandate adherence to the recommendations • All recommendations are in current best practice guidelines	• CDS alerts are non-disruptive to clinical care (i.e. no hard stops) and similar to multiple alerts already in use	• Data will be deidentified and the only risk is in data loss
the research could not practicably be carried out without the requested waiver or alteration	• The trial is estimated to enroll about 12,000 patients over one year with some procedures taking	• Anesthesia providers are assigned to cases often at the last minute and change	• Contact information for historical patients may have changed or would

	place emergently at off hours	throughout the day. It would be impossible to enroll and remove patients dynamically with these frequent changes	no longer be available.
if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format	• The implementation of the trial in the EHR will not use any identifiable information and all data extracted will have PHI removed. In order to remove the PHI an honest broker not on the study team will perform the data extract and remove the PHI. Patient identifiers will be hashed, dates truncated to the year and all dates turned into relative dates.	• No identifiers on individual providers will be collected and there will be no analysis at the provider level	• No PHI on historical subjects will be collected
the waiver or alteration will not adversely affect the rights and welfare of the subjects;	• The CDS prompts will only be recommending codified best practices. • The final decision for all treatment rests in the hands of the anesthesia provider	• The CDS prompts are similar to those already in use and providers are free to ignore them if they wish	• There will be no identifiers of the patients collected as part of the historical review
whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation	• Given that the trial is only providing decision support recommendations to providers (which is a standard part of clinical care) there will be no direct notification to	Study results will be published in peer reviewed literature and those publications will be made available to the providers	• In line with standard practices for retrospective studies there will be no notification of patients after enrollment as this would require patient

	patients after participation		identification and introduce additional risk.

Randomization: Patients will be randomized within each hospital site at the level of the surgical case. To adjust for different POD risk amongst cases, we will use an established risk stratification model to classify each case into low, medium, and high baseline risk and randomize patients equally across the groups.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Intervention: The intervention is a CDS alert to promote 12 evidence based best practices in five domains: high-risk medication avoidance, glycemic control, hemodynamic management, normothermia, and anesthetic depth management, spanning the preoperative, intraoperative, and immediate postoperative periods. The CDS alerts will be designed to avoid disruptions in provider workflow.

Interventions were selected from the American College of Surgeons, the AGS, and ASA list of best practices, if they were relevant to the perioperative period, suggested as a specific objective action, and are documented in the EHR during usual care.

The intervention will be developed in line with the IMPACT Collaboratory steps for creating effective value propositions. Consistent with previous CDS deployments done by our team, the proposed interventions will be shared with departmental leadership for input and feedback on notification design and content. Specific feedback about frequency and thresholds of alerts will be solicited to gain buy-in and attempt to mitigate alert fatigue. Non-disruptive alerts that avoid hard stops will be used. Prior to intervention go live, education will be provided to the anesthesiologists via email communications as well as presentations at forums such as grand rounds, faculty meetings, residency meetings, etc. All interventions are performed by the anesthesiologist and measured in the EHR.

5.2 Handling of Study Interventions

The intervention will be developed in line with the IMPACT Collaboratory steps for creating effective value propositions. Consistent with previous CDS deployments done by our team, the proposed interventions will be shared with departmental leadership for input and feedback on notification design and content. Specific feedback about frequency and thresholds of alerts will be solicited to gain buy-in and attempt to mitigate alert fatigue. Non-disruptive alerts that avoid hard stops will be used. Prior to intervention go live, education will be provided to the anesthesiologists via email communications as well as presentations at forums such as grand rounds, faculty meetings, residency meetings, etc. All interventions are performed by the anesthesiologist and measured in the EHR. These anesthesiologists will not be part of the study team and will be performing the interventions as part of routine clinical care.

5.3 Concomitant Interventions

Any and all additional interventions to prevent POD or treat any other elements of anesthesia care will be allowed and at the complete discretion of the attending anesthesiologist. Further, in the event that the attending anesthesiologist feels that any of the interventions in the study protocol are unwarranted they retain sole discretion to ignore the CDS recommendations and prescribe care as they see fit.

5.4 Adherence Assessment

We will conduct an analysis to assess best practice adherence in the intervention vs control groups. For each of the 12 practices adherence will be measured as a binary variable; overall protocol adherence will be defined as the proportion of the 12 practices performed by the anesthesia team. The average adherence rate by study arm will be compared between the two study arms using the mixed model (or hierarchical generalized linear model for binary outcomes), treating hospital sites and providers as random effects. To examine learning effects in the control group and the time trend alone, we will create three segments one segment for the intervention group, one segment for the control group, and the third the historical control period. We will compare the three segments on the outcomes of interest using a segmented time series regression analysis.

For the post-operative delirium screen (4AT) notifications we will examine postoperative length of stay as a time series before and after the intervention and for enrolled patients as opposed to patients who are unenrolled because they have had a prior surgical procedure during the study period.

6 STUDY PROCEDURES

See next page

6.1 Schedule of Evaluations

Assessment	*Day of Surgery*	*Postoperative Days*
Informed Consent Form		
Demographics	***X***	
Structured data evidence of CI	***X***	
Medical History	***X***	
Current Medications	**X**	
Previous mini mental exam scores	***X***	
NLP Algorithm on clinical notes	***X***	
Performance of the 12 best practice interventions	***X***	
Vital Signs	***X***	
Inclusion/Exclusion Criteria	***X***	
Enrollment/Randomization	***X***	
Postoperative 4AT Scores		***X***
Adverse Events		***X***

6.2 Description of Evaluations

6.2.1 Screening Evaluation

A waiver of informed consent is being requested for study patients, providers, and the historical controls. Patients scheduled for surgery will be automatically identified in the EHR as having CI based on one of

- An existing natural language processing algorithm (NLP) currently under peer review
- Structured data from the EHR (i.e. mini-mental score<25, prescription of Donepezil, etc.

All providers who care for patients enrolled will be automatically enrolled. Prior to study go-live providers will be educated as to the protocol and informed that any CDS prompts can be followed or ignored at their discretion. No data on provider level CDS adherence will be collected by the study team.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Patients will be automatically enrolled based upon the presence of the above criteria in the EMR.

Randomization

Patients will automatically be randomized prior to surgery based on their underlying POD risk and hospital by an algorithm in the EHR. The randomization status of each patient will then be stored in the EHR in a way that can be extracted on the back end but is invisible to the provider.

6.2.3 Follow-up Visits

Patients will have routine postoperative care with the addition of at least one 4AT assessment by a medical provider on the care team. If post-operative delirium is present in the screen, providers will be encouraged to re-screen the following day, but only one assessment is needed for the present study's primary end point.

7 SAFETY ASSESSMENTS

Data on postoperative outcomes will be automatically extracted from the EHR.

7.1 Specification of Safety Parameters

All interventions are consistent with perioperative best practice and introduce no additional risk to the patients. Thus, no additional testing is necessary.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

As per above, the study interventions introduce no additional risk to the patient and thus additional monitoring is not needed.

7.3 Adverse Events and Serious Adverse Events

There are no adverse events (AEs) or serious adverse events (SAEs) directly associated with the study protocol. Any and all AEs and SAEs (hypo/hyperglycemia, acute kidney

injury, respiratory dysfunction, and death) are consistent with the risk of undergoing surgery and are not related to the study protocol.

7.3.1 Reporting Procedures

Severity of Event

There are no adverse events that will be attributable to the study intervention of decision support prompts. All of the AEs and SAEs can be automatically identified from the EHR feed and a list of relevant patients generated.

Relationship To Study Intervention

As noted above, there are no AEs or SAEs expected to result from study intervention

7.3.2 Follow-up for Adverse Events

N/A

7.4 Safety Monitoring

PI will present data safety monitoring reports to the DSMB as follows:

1. Prior to start of participant enrollment and data collection, submit DSMP for approval (1/31/22)
2. Six months after participant enrollment initiation
3. At end of study
4. Or at the discretion of the DSMB/NIA

Content of DSM report: (in addition to org., title, PI, IRB study #)

1. Study status (Participants screened, enrolled, completed, discontinued, risk vs. benefit, site performance
2. Safety information (AEs, SAEs, actions taken or planned to address issues)
3. Study quality (data quality, timeliness of data collection, fidelity of intervention based on measures of completeness of intervention components)

8 INTERVENTION DISCONTINUATION

N/A

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Primary hypothesis: CDS alerts that provide anesthesiologists caring for patients with CI real-time prompts regarding best practices, will increase adherence to these practices and reduce POD.

Analysis: We will evaluate the difference in POD incidence, using the 4 A's Test (4AT) in patients where providers received the CDS prompts vs controls.

Secondary hypothesis: The CDS prompts will improve the individual practice adherence and the influence of each practice adherence on POD prevention will be heterogeneous within and between study arms and groups.

Secondary analysis: We will perform a secondary analysis of the data to evaluate a) The ability of CDS prompts to increase best practice adherence, b) The impact of individual and overall practice adherence on POD prevention, and c) The efficacy of this tool in various sociodemographic subgroups to ensure that it is equitable.

Analysis: We will evaluate practice adherence within each study arm and identify individual practices that have significant improvement resulting from the implementation of the CDS prompt. We will also study the influence of each practice on POD prevention and test whether individual and overall practice effects on reducing POD differ between the study arms. Lastly, we will examine pathway adherence and effectiveness to reduce POD in key subgroups of gender, social determinants of health (SDOH), and race/ethnicity.

9.2 Sample Size and Randomization

9.2.1 Treatment Assignment Procedures

Treatment Assignment: In the perioperative period an anesthesia attending supervises multiple junior providers in pairings that change daily. Thus, randomization at the level of the provider is impossible and patients will be randomized at the level of the surgical procedure. In order to avoid issues with statistical analysis, only the first surgical procedure for each patient will be included in the study.

For each procedure, where the patient has been identified as having CI, the nomogram will be used to estimate the patient's risk of POD and assign the patient to one of three groups: high risk (>330 points, 30% risk of POD), medium risk (285-330 points, 15-30% risk of POD), and low risk (<284 points, <15% risk of POD). Patients will be stratified based on their risk grouping and the hospital. For each stratum, patients will be alternately assigned to the intervention or control groups (i.e., 1st intervention, 2nd control, etc.). The control group will receive usual care (no prompts) and the intervention group will receive an alert to the anesthesiologist that the patient is at increased risk for POD with CDS prompts for clinical best practices.

Patients will be automatically randomized by the EHR and the status of the randomization will only be visible in the back-end database. Providers caring for patients in the control group will not know the patient is included in the study. Given the short time frame of the CDS prompts and overall provider discretion there will be no need to unmask any participants.

Primary Endpoint Power: Power was calculated for the primary endpoint. Assuming 100,000 surgical procedures, with 40% over age 65 and 30% of those having CI, we will have roughly 12,000 patients to enroll - 5000 subjects in each study arm, Poisson regression achieves 80% power at a 0.05 significance level to detect a response rate ratio of at least 0.942 between the intervention group and the control group, assuming that the POD incident rate for the control is 0.30 and the mean hospital length of stay is 3 days. The detectable rate becomes 0.930 if we adjusted for an over-dispersion parameter of 1.5 (PASS 12. NCSS).

Secondary Outcomes Power:

a) Analysis of provider adherence: The table below shows the minimal detectable difference in the improvement of adherence due to use of CDS prompts assuming adherence for each individual item without intervention is no lower than 50%. The calculation was performed using the 2-sample z-test, using a conservative significance level (0.004) to account for multiple comparisons and the targeted power is at the 90% level.

MDI for the study arm	4.2%	4.0%	3.7%	3.2%	2.4%
Adherence % for the control arm	50%	60%	70%	80%	90%

Assume N=5000 per group and 90% power, using the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.005. (PASS 12. NCSS)

b) Effect of individual and overall practice adherence on POD: The AUC of the ROC curve for the base model that considers factors in nomogram is 0.8 (the null). The proposed study is powered at 90% to detect an increase of 0.016 when the study arm is added to the base model, using a two-sided z-test at a significance level of 0.05 (PASS 12. NCSS).

c) Analysis of Health Equity: It is currently unknown the if there are differences in POD rates or best practice adherence for each of these groups, thus impossible to accurately calculate power. For each of these analyses post-hoc power will be calculated and reported in the results. There are 12 practice items, we will use 0.004 alpha level for statistical significance in all individual practice adherence analyses. The usual 0.05 alpha level will be applied for all other analyses including the overall protocol adherence analysis. All tests will be 2-sided

9.3 Interim analyses and Stopping Rules

No interim analysis is planned.

9.4 Outcomes

9.4.1 Primary outcome

Primary Outcome: The Primary outcome will be postoperative delirium as measured by the 4 A's Test (4AT). The 4AT is a commonly used tool that identifies the presence/absence of POD. It consists of 4 sections; alertness, AMT4: Abbreviated Mental Test -4, attention, and acute change of fluctuating course. The 4AT is scored from 0-12, a score of 4 or more suggests delirium. We will estimate the incidence rate per person-day during postoperative days 0-7 for each treatment group. Patients free of POD within 7 days will be censored on day 7. Otherwise, follow-up time will be defined as time to POD or at the time of discharge, we will assume that patient do not have POD after discharge.

9.4.2 Secondary outcomes

The ability of CDS prompts to increase best practice adherence will be measured by documentation of the best practices in the EHR as part of the usual patient care. For example, the measure "Maintain Glucose <200" will be measured by documentation of a glucose value >200 in the EHR.

The impact of individual and overall practice adherence on POD prevention will be measured using the combination of the POD measurements and practice adherence measurement.

The efficacy of the tool in various sociodemographic subgroups will be measured using the socioeconomic and demographic information of the patient in the EHR.

The impact of delirium screening prompts on the medical providers will be measured by a time series analysis looking at all enrolled patients and patients that would have been enrolled in the one year prior to go-live.

9.5 Data Analyses

Primary Endpoint: We will perform marginal structural model for Poisson regression using the generalized estimating equation method. Marginal structural models estimate parameters through the use of inverse-probability weighting and allow for adjustment of time-dependent confounders (e.g., daily medical treatment) and informative drop outs, while accounting for clustering effects within time series data and providers.

Secondary Endpoints:

a) Protocol adherence: For each of the 12 practices adherence will be measured as a binary variable; overall protocol adherence will be defined as the proportion of the 12 practices performed by the anesthesia team. The average adherence rate by study arm will be compared between the two study arms using the mixed model (or hierarchical generalized linear model for binary outcomes), treating hospital sites and providers as random effects. To examine learning effects in the control group and the time trend alone, we will create three segments one segment for the intervention group, one segment for the control group, and the third the historical control period. We will

compare the three segments on the outcomes of interest using a segmented time series regression analysis. The daily average of the protocol adherence rate will be calculated, excluding days with fewer than 10 cases. Daily averages will also be calculated for patient and case-level covariates (e.g., hospital site, and factors considered in the nomogram). We will assess the degree of autocorrelation in the data (using the Durbin-Watson statistics) with an auto-regressive linear model of lag 2 using the Yule-Walker method, fitting a separate line for each of the four periods, with each period having its own slope (indicating the trend over time for that period) and intercept. To test for trends in adherence over time, we will test if the slopes for all workflow segments are equal to zero; if rejected, we will test whether the slope for the intervention group differs from that of the control group and if the slope fo the control group differs from the slope from a year before.

b) Effect of Individual and overall practice adherence on POD: We will examine the effect of each of the 12 best practices on POD using a hierarchical generalized linear mixed model for Poisson regression with log link for POD outcome that examines the effect of practice adherence (one practice item at a time and the overall protocol adherence), and its interaction with the study arm. The models will adjust for factors in the nomogram and treat hospital sites and providers as random effects. To understand if individual practice adherence and/or overall protocol adherence will improve the predictability of POD, we will perform a series of nested analyses that contrast the areas under the ROC curve between the base model that includes all factors in the nomogram and the testing model. For examples, the testing models could be 1) base model + study arm, and then 2) base model + study arm overall adherence rate.

c) Analysis of health equity on CDS efficacy in preventing POD: We will conduct a series of analyses to examine if the efficacy of the CDS pathway and/or the individual and overall practice adherence are homogeneous across different patient subgroups, such as biological sex, social determinants of health (SDOH), and race. We will report the POD incidence rates and the practice adherence rates across the subgroups and check if randomization was achieved within each of the subgroups. For each demographic factor, we will repeat the SA1 and SA2 analyses, and add an interaction term between the factor of interest and the intervention group (SA1) or practice adherence (SA2) to test if the CDS pathway efficacy or practice adherence varies depending on the demographic factor, adjusting for covariates that show significant disparities among subgroups.

d) Analysis of delirium screening prompt on medical provider post-operative care practices. At present not all patients with CI are screened for POD by their providers. Part of our intervention will be ensuring that all these patients are screened for POD by a medical provider on their care team. Because the patients are not currently being screened for POD we cannot do a direct time series analysis looking at POD rates as there is no pre-intervention control group. Thus we will do a segmented multivariate time series analysis looking at other clinical outcomes, in particular length of stay (LOS), which is associated with POD.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Automated Collection of Data from the EHR

All data for the study will be automatically extracted from the EHR database. The EPIC Clarity Database is a SQL relational database that is refreshed daily. Our group has already implemented a peer-reviewed perioperative data warehouse that extracts the necessary data from the Clarity database on a regular basis and cleans and organizes it to facilitate use.

All data necessary for the study, including presence of CI, underlying risk factors for POD from the nomogram, practice adherence by the anesthesiologist, and POD are readily contained and extracted from the data warehouse.

Any data extracts delivered to the study team for analysis will be deidentified and have dates binned at the level of the month to ensure patient anonymity. Data extracts required for reporting of AE/SAEs will have only the minimum necessary identifying information.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any third party except as needed for reporting of AE/SAEs.

All research activities will be conducted in as private a setting as possible.
The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.
The study participant's contact information will be securely stored at each clinical site for internal use during the study but will not be available to the study team. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which for purposes of statistical analysis and scientific reporting, will be transmitted to Mount Sinai for linkage, where data are analyzed and stored on a HIPAA compliant environment. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected.

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

N/A - we request a waiver of informed consent for all study participants. See section 4.3 for waiver justifications.

We also request a HIPAA waiver of authorization for the use of HIPAA-protected EHR data for this study.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept digitally on encrypted drives. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the sponsor or persons working on behalf of the sponsor (i.e. IMPACT research study staff, the DSMB and/or Safety Officer), the FDA, the NIA, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB or DSMB as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

The protocol of the study consists only of decision support prompts to the provider. The anesthesiologist has complete discretion to follow or ignore any or all recommendations based on their clinical judgement. Thus, failure to follow a recommendation will not be considered a protocol deviation.

13 COMMITTEES

The primary committee will consist of the PIs and Co-Is for this project (listed above) who will meet monthly to review study progress and address any issues.

In addition, an implementation committee will be formed consisting of clinical anesthesiologists (who will ultimately be subjected to the alerts) from the participating hospitals who will provide feedback on any decision support alerts and address any concerns as they relate to provider workflow.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures

developed by the Steering Committee as well as by the IMPACT Collaboratory. Any presentation, abstract, or manuscript will be made available for review by the IMPACT Collaboratory prior to submission.

15 REFERENCES

1. Culley, D.J.*, et al.* Poor Performance on a Preoperative Cognitive Screening Test Predicts Postoperative Complications in Older Orthopedic Surgical Patients. *Anesthesiology* **127**, 765-774 (2017).
2. Culley, D.J.*, et al.* Preoperative Cognitive Stratification of Older Elective Surgical Patients: A Cross-Sectional Study. *Anesth Analg* **123**, 186-192 (2016).
3. Dyer, C.B., Ashton, C.M. & Teasdale, T.A. Postoperative delirium. A review of 80 primary data-collection studies. *Arch Intern Med* **155**, 461-465 (1995).
4. Ansaloni, L.*, et al.* Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br J Surg* **97**, 273-280 (2010).
5. Association, A.P. *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: DSM-5*, (American Psychiatric Association, Arlington, VA, United States of America, 2013).
6. Evered, L.*, et al.* Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *British journal of anaesthesia* **121**, 1005-1012 (2018).
7. Vacas, S., Cole, D.J. & Cannesson, M. Cognitive Decline Associated With Anesthesia and Surgery in Older Patients. *Jama* (2021).
8. Monk, T.G., Saini, V., Weldon, B.C. & Sigl, J.C. Anesthetic management and one-year mortality after noncardiac surgery. *Anesthesia and analgesia* **100**, 4-10 (2005).
9. Rudolph, J.L.*, et al.* Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia* **63**, 941-947 (2008).
10. Silbert, B.*, et al.* Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. *Anesthesiology* **122**, 1224-1234 (2015).
11. Davis, D.H.*, et al.* Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain : a journal of neurology* **135**, 2809-2816 (2012).
12. Brown, C.H.t.*, et al.* Cognitive Decline after Delirium in Patients Undergoing Cardiac Surgery. *Anesthesiology* **129**, 406-416 (2018).
13. Fong, T.G., Tulebaev, S.R. & Inouye, S.K. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol* **5**, 210-220 (2009).
14. Moller, J.T.*, et al.* Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* **351**, 857-861 (1998).
15. Clegg, A. & Young, J.B. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing* **40**, 23-29 (2011).
16. Wang, N.Y., Hirao, A. & Sieber, F. Association between intraoperative blood pressure and postoperative delirium in elderly hip fracture patients. *PloS one* **10**, e0123892 (2015).
17. Siepe, M.*, et al.* Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* **40**, 200-207 (2011).
18. Sessler, D.I.*, et al.* Hospital stay and mortality are increased in patients having a `Triple Low' of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. *Anesthesiology* **116**(2012).

19. MacKenzie, K.K., Britt-Spells, A.M., Sands, L.P. & Leung, J.M. Processed Electroencephalogram Monitoring and Postoperative Delirium: A Systematic Review and Meta-analysis. *Anesthesiology* **129**, 417-427 (2018).
20. Saager, L.*, et al.* Intraoperative tight glucose control using hyperinsulinemic normoglycemia increases delirium after cardiac surgery. *Anesthesiology* **122**, 1214-1223 (2015).
21. Franco, K., Litaker, D., Locala, J. & Bronson, D. The cost of delirium in the surgical patient. *Psychosomatics* **42**, 68-73 (2001).
22. Hirsch, J., DePalma, G., Tsai, T.T., Sands, L.P. & Leung, J.M. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. *Br J Anaesth* **115**, 418-426 (2015).
23. Evered, L.A.*, et al.* Anaesthetic depth and delirium after major surgery: a randomised clinical trial. *British journal of anaesthesia* **127**, 704-712 (2021).
24. Ehrenfeld, J.M., Wanderer, J.P., Terekhov, M., Rothman, B.S. & Sandberg, W.S. A Perioperative Systems Design to Improve Intraoperative Glucose Monitoring Is Associated with a Reduction in Surgical Site Infections in a Diabetic Patient Population. *Anesthesiology* **126**, 431-440 (2017).
25. Nair, B.G.*, et al.* Intraoperative blood glucose management: impact of a real-time decision support system on adherence to institutional protocol. *Journal of clinical monitoring and computing* **30**, 301-312 (2016).
26. Nair, B.G., Horibe, M., Neradilek, M.B., Newman, S.F. & Peterson, G.N. The Effect of Intraoperative Blood Glucose Management on Postoperative Blood Glucose Levels in Noncardiac Surgery Patients. *Anesth Analg* **122**, 893-902 (2016).
27. Sathishkumar, S.*, et al.* Behavioral Modification of Intraoperative Hyperglycemia Management with a Novel Real-time Audiovisual Monitor. *Anesthesiology* **123**, 29-37 (2015).
28. McCormick, P.J., Levin, M.A., Lin, H.M., Sessler, D.I. & Reich, D.L. Effectiveness of an Electronic Alert for Hypotension and Low Bispectral Index on 90-day Postoperative Mortality: A Prospective, Randomized Trial. *Anesthesiology* **125**, 1113-1120 (2016).
29. Nair, B.G.*, et al.* Anesthesia information management system-based near real-time decision support to manage intraoperative hypotension and hypertension. *Anesth Analg* **118**, 206-214 (2014).
30. Nair, B.G., Horibe, M., Newman, S.F., Wu, W.Y. & Schwid, H.A. Near real-time notification of gaps in cuff blood pressure recordings for improved patient monitoring. *J Clin Monit Comput* **27**, 265-271 (2013).
31. Nair, B.G.*, et al.* Reducing Wastage of Inhalation Anesthetics Using Real-time Decision Support to Notify of Excessive Fresh Gas Flow. *Anesthesiology* **118**, 874-884 (2013).
32. Josephs, S.A., Lemmink, G.A., Strong, J.A., Barry, C.L. & Hurford, W.E. Improving Adherence to Intraoperative Lung-Protective Ventilation Strategies at a University Medical Center. *Anesth Analg* **126**, 150-160 (2018).