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ABSTRACT

Introduction Millions of patients receive general anaesthesia for surgery annually. Crucial gaps in evidence exist regarding which technique, propofol total intravenous anaesthesia (TIVA) or inhaled volatile anaesthesia (INVA), yields superior patient experience, safety and outcomes. The aim of this pilot study is to assess the feasibility of conducting a large comparative effectiveness trial assessing patient experiences and outcomes after receiving propofol TIVA or INVA.

Methods and analysis This protocol was cocreated by a diverse team, including patient partners with personal experience of TIVA or INVA. The design is a 300-patient, two-centre, randomised, feasibility pilot trial. Patients 18 years of age or older, undergoing elective non-cardiac surgery requiring general anaesthesia with a tracheal tube or laryngeal mask airway will be eligible. Patients will be randomised 1:1 to propofol TIVA or INVA, stratified by centre and procedural complexity. The feasibility endpoints include: (1) proportion of patients approached who agree to participate; (2) proportion of patients who receive their assigned randomised treatment; (3) completeness of outcomes data collection and (4) feasibility of data management procedures. Proportions and 95% CIs will be calculated to assess whether prespecified thresholds are met for the feasibility parameters. If the lower bounds of the 95% CI are above the thresholds of 10% for the proportion of patients agreeing to participate among those approached and 80% for compliance with treatment allocation for each randomised treatment group, this will suggest that our planned pragmatic 12 500-patient comparative effectiveness trial can likely be conducted successfully. Other feasibility outcomes and adverse events will be described.

Ethics and dissemination This study is approved by the ethics board at Washington University (IRB# 202205053), serving as the single Institutional Review Board for both participating sites. Recruitment began in September 2022. Dissemination plans include presentations at scientific conferences, scientific publications, internet-based educational materials and mass media.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study has rigorous methods and clear milestones, which will inform the feasibility of conducting a large, pragmatic, multi-centre, comparative effectiveness trial.
⇒ Embedding of the trial within an active and ongoing electronic health record based clinical research and quality improvement collaborative allows the use of automated capture and processing for confirmation of study exposures and outcomes.
⇒ The outcome of intraoperative awareness is difficult to ascertain accurately, depending on the occurrence of unintended awareness during surgery, memory of the awareness episode and willingness to report the awareness experience.
⇒ The threshold proportion of >10% set for enrolment feasibility is low, but we anticipate that the actual enrolment percentage will be >50%.
⇒ This feasibility pilot study is being conducted at only two midwestern academic medical centres in the USA, which means that its findings regarding feasibility measures might not generalise to other US institutions.

Trial registration number NCT05346588.

INTRODUCTION

Every year, millions of people receive general anaesthesia for surgery.[1] These patients are placing their lives and safety in the hands of anaesthesia clinicians. This requires deep trust and places a heavy burden of responsibility on these clinicians. For surgical procedures that require general anaesthesia, the decision to use total intravenous anaesthesia (TIVA) versus inhaled volatile anaesthesia (INVA) is often made by the clinician administering the anaesthetic agent. Outside of

known, extremely rare contraindications such as malignant hyperthermia with inhaled volatile agents and allergies to propofol, there is not a clear time that one of these two methods of anaesthesia should or should not be chosen based on clinical outcomes and safety.

However, the anaesthesia care team's choice between TIVA or INVA may drive completely different patient experiences.[2] While there are some known advantages (eg, decreased postoperative nausea and vomiting) and disadvantages of propofol TIVA[2–5] or INVA,[6 7] crucial gaps in evidence exist including many features of recovery from general anaesthesia as well as adverse outcomes and safety-related aspects of general anaesthesia. If either TIVA or INVA was associated with a superior recovery experience from surgery, this would be a major factor in driving both patient and clinician decision-making regarding the choice of anaesthetic technique. Such a transformative finding would immediately impact care for millions of people worldwide.

Regarding the feasibility of conducting a large comparative effectiveness trial, there is information lacking regarding whether: (1) a sufficient proportion of approached patients would consent to the trial; (2) anaesthesia clinicians would comply with the random treatment allocations and (3) relevant clinical and patient-reported data could be collected and transferred successfully.

Study objectives and endpoints

We will conduct a 300-patient randomised feasibility pilot trial[8 9] in two health centres to provide key lessons and information for the planned 12 500-patient Trajectories of Recovery after Intravenous propofol versus inhaled VolatilE anesthesia (THRIVE) trial. Study objectives and endpoints are listed in table 1.

METHODS

Study design

This trial is designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines[10] to establish the feasibility of conducting a 12 500-patient, pragmatic, comparative effectiveness trial with clinical and patient-centred outcomes. It is a two-centre, randomised, feasibility pilot trial in 300 patients undergoing non-cardiac surgeries, in which one group will receive propofol TIVA and the other inhaled volatile general anaesthesia (see figure 1) between 1 September 2022 and 30 June 2023. Eligible, consented patients will be randomised 1:1 to each of the treatment groups, stratified by clinical site and procedural complexity (outpatient, major inpatient and minor inpatient) with approximately 150 patients per site. Patients enrolled in the trial will be blinded to treatment assignment. Both propofol TIVA

Table 1 Study objectives and endpoints

Objectives	Endpoints	Justification for endpoints
Primary		
Establish the proportion of patients who agree to participate, expressed as a fraction of those approached to enter the study	Proportion of patients who consent to participate in the study among those who are approached by the study team	In order to ensure adequate enrolment in a large comparative effectiveness trial, the proportion of patients who consent to participate must be analysed
Evaluate the proportion of patients who receive each random treatment allocation per protocol	Proportion of patients who receive their randomised treatment allocation for each intervention group	In order to assess relevant patient and clinical outcomes in a large comparative effectiveness trial, adherence to the study protocol for each treatment allocation must be determined
Secondary		
Evaluate pilot data capture instruments and data management tools	Proportion of data collection instruments and fields that are completed at each timepoint Proportion of patients with complete intraoperative electronic health record (EHR) data, proportion of patients with successful linking of the patient-reported outcomes, EHR and enrolment process databases (MyDataHelps, MPOG import manager, MQUARK) Proportion of enrolled patients with successful transfer of data into analytic case files Proportion of safety and adverse events with accurate and complete documentation	In order to analyse relevant clinical and patient outcomes in a large comparative effectiveness trial, successful data collection, data linkage and data transfer must be established

MPOG, Multicenter Perioperative Outcomes Group; MQUARK, MPOG Quality and Research Kit.

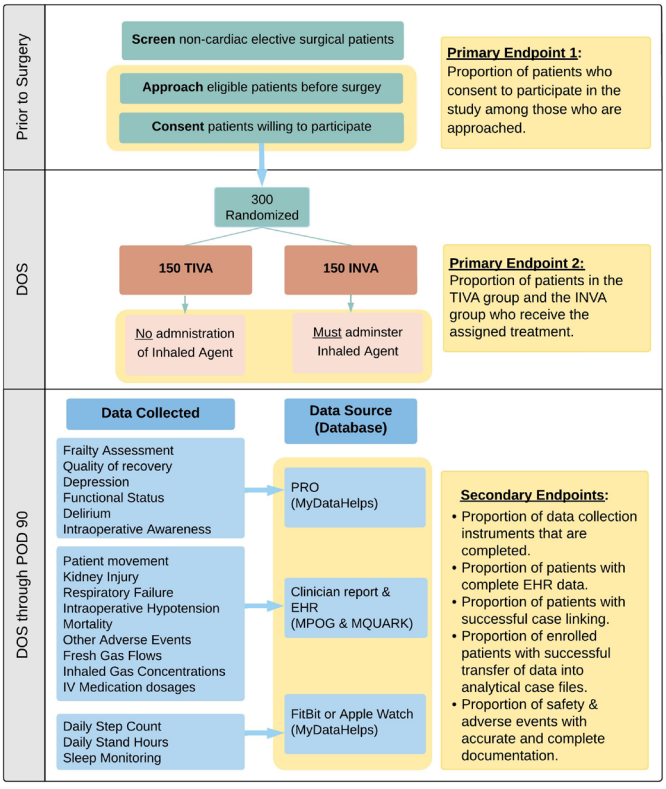

Figure 1 Diagrammatic representation of patient flow through study. DOS, day of surgery; EHR, electronic health record; IV, intravenous; MPOG, Multicenter Perioperative Outcomes Group; MQUARK, MPOG Quality and Research Kit; other adverse events, propofol-related infusion syndrome, malignant hyperthermia, unplanned admission after outpatient surgery; POD, postoperative day; PRO, patient-reported outcome completed by the patient or during research coordinator interview; TIVA, total intravenous anaesthesia.

and inhaled volatile can be used for patients undergoing general anaesthesia via endotracheal tube or laryngeal mask airway. Neither treatment allocation drives the use of a specific airway management technique (ie, endotracheal tube vs laryngeal mask).

Cocreation and patient and public involvement

This feasibility pilot trial[8 9] was conceptualised by a diverse group of stakeholders, with a range of relevant expertise and experiences (eg, clinical trialists, research coordinators, anaesthesiologists, certified registered nurse anaesthetists, surgeons, patient partners, statisticians, research methodologists, implementation scientists, data managers, hospital system leaders). Patient partners, who had themselves previously experienced either (or both) INVA and propofol TIVA, were able to contribute especially meaningfully based on their salient lived experiences of general anaesthesia and recovery from anaesthesia. Our stakeholders participated in planning discussions for the feasibility trial during 2021 and provided intellectual input to the development of this protocol. All stakeholders were provided access to this protocol during its evolution via a collaborative document, and were encouraged to comment and edit the text. This process of iterative protocol development occurred between May 2021 and April 2022. Additionally, a companion storyboard (online supplemental appendix 1: Feasibility trial storyboard) to this protocol was codesigned in partnership with THRIVE lead patient partners in January 2022 to provide a complementary graphic representation of the core features of this protocol. The storyboard served as a communication enhancement tool by visually breaking the trial's core features into easily comprehensible components, thereby facilitating stakeholder dialogue and understanding. A webinar was held on 22 February 2022 with patient partners and other stakeholders during which the storyboard was presented. The webinar format design and pre-event survey were cocreated with our THRIVE patient partners and the webinar itself was moderated by two lead THRIVE patient partners. THRIVE patient partners were placed in leadership positions during the webinar to facilitate feedback and suggestions via breakout sessions. When patients, compared with research or hospital staff, interview other patients, they often collect responses that are more verbose, elicit more practical and informational needs from patients, and the responses more closely resemble detailed patient experiences.[11] Throughout the webinar, stakeholders were given further opportunity to provide feedback and suggestions. Stakeholders attending the webinar completed a questionnaire cocreated with our THRIVE patient partners and successfully identified the key motivations for the THRIVE feasibility pilot trial, the questions the feasibility trial is designed to answer, and how patients will be partners in the research. Individual meetings were also held between THRIVE investigators and patient partners (and other stakeholders), where the protocol and the storyboard were discussed, and feedback was obtained to improve understanding, accessibility and relevance to patients and other stakeholders.

Study patients and setting

Patients include adults undergoing elective non-cardiac surgery expected to last ≥60 min requiring general anaesthesia with a tracheal tube or laryngeal mask airway (or similar supra-glottic device). This study and all data collection will take place at Barnes-Jewish Hospital Complex (St. Louis, Missouri) and Michigan Medicine (Ann Arbor, Michigan). Table 2 provides information about the expected enrolment numbers, inclusion and exclusion criteria of patients.

Study procedures and timeline

Recruitment and informed consent

This study will enrol 300 patients aged 18 years or older who are able to participate in informed consent and are undergoing elective non-cardiac surgery requiring general anaesthesia. We will blend multiple complementary enrolment strategies which can be tailored to the needs of enrolment centres in the larger trial. Electronic health record (EHR)-based identification of candidate

Table 2 Enrolment, inclusion and exclusion criteria

Expected patient enrolment	Inclusion criteria*	Exclusion criteria†
150 patients at Washington University School of Medicine 150 patients at University of Michigan	1. Aged 18 years or older 2. Undergoing elective non-cardiac surgery expected to last ≥60 min requiring general anaesthesia with a tracheal tube or laryngeal mask airway (or similar supra-glottic device)	1. Inability to provide informed consent in English 2. Pregnancy (based on patient report or positive test on the day of surgery) 3. Surgical procedure requiring general, regional, neuraxial anaesthesia administered by an anaesthesia clinician (anaesthesiologist, CRNA, anaesthesiology assistant) occurring within 30 days prior to or planned to occur within 30 days after surgery date 4. Contraindication to propofol TIVA or inhaled volatile (eg, documented allergy to propofol, history of severe postoperative nausea or vomiting, concern for or history of malignant hyperthermia) based on self-report 5. Surgical procedures requiring a specific general anaesthesia technique (eg, TIVA required for neuromonitoring) 6. Hospital approved, written protocol mandating a particular anaesthetic technique 7. History of intraoperative awareness during general anaesthesia based on patient self-report 8. Planned postoperative intubation

*Patients must meet all eligibility criteria to participate.
†Patients may meet any one or more of the exclusion criteria to become ineligible to participate.
TIVA, total intravenous anaesthesia.

participants and digital approach methods are the foundation of the THRIVE study. However, enrolment sites may use a variety of approaches to reach groups that are less comfortable with digital means. We anticipate the following methods: (1) individualised outreach to participants at home, (2) in-clinic enrolment during preoperative assessment and (3) surgical patient community engagement.

After reviewing upcoming clinic or operating room schedules research coordinators may reach out to patients via emails, phone calls and/or through patient portal messages to inform them of this study. Eligible patients or those who have expressed interest in participation will be approached for further discussion of the study, eligibility assessment and completion of enrolment procedures. Prior to the surgery, patients will complete written informed consent via one of two mechanisms: (1) study coordinator-mediated eConsent on a study tablet or computer; or (2) self-consent using modules on a personal smartphone, tablet or website. Patients will be asked a series of questions assessing their understanding of the consent document. Patients will be considered fully consented when they answer all four questions correctly.

Patients may opt to provide information from wearable devices either study-provided wearable device (Apple Watch or Fitbit) or their own device if they already have one. Participation in the wearable device signal aspect of the study is optional and will not affect eligibility in the overall study.

Blinding

Both treatments are initiated after the patient is unconscious and ceased prior to a patient regaining consciousness. In addition, the EHR available in the patient portal does not reveal these intraoperative anaesthesia details. As a result, the patient should be blinded to their treatment allocation. Avoiding such unblinding will be part of the education process at each enrolment centre. After completion of the patient-reported outcomes collection at postoperative day 90, patients will be intentionally unblinded and be informed of their treatment allocation and treatment received. Anaesthesia clinicians caring for patients in the operating rooms cannot practically or ethically be blinded, since they will be administering one of the two anaesthetic techniques which are being compared in this trial. Study personnel collecting and analysing outcome data, designated healthcare workers administering the post-Brice questionnaires, and the intraoperative awareness classification team, will all be blinded to intervention allocation.

Table 3 provides detailed information about data collection timepoints.

Data

Data systems

The study uses three distinct information systems to collect patient and procedure data. These data are integrated to provide a complete study record:

- Multicenter Perioperative Outcomes Group (MPOG) import manager[12] takes data from the EHR at each

Table 3 Data collection timepoints

Data	Baseline preoperative	Day 0 DOS	Day 1	Day 2	Day 7	Day 14	Day 21	Day 30	Day 90
Window (days)	–30 to 0	n/a	n/a	n/a	–1 to +2	–1 to +3	–1 to +3	–1 to +7	–1 to +14
Screening and eligibility criteria	x								
Informed consent	x								
Randomisation		x							
Anaesthetic and intraoperative medications administered		x							
Quality of Recovery-15 (QOR-15) instrument	x	x	x	x	x				
Patient Health Questionnaire (PHQ) 2/8¶	x				x				
Modified Brice Interview±follow up questionnaire for patients who report memories			x					x	
Risk Analysis Index surgical frailty assessment	x								
Ultra-Brief Confusion Assessment Method (UB-CAM)	x	x	x						
Change from preoperative baseline in WHO Disability Assessment Scale 2.0 (WHODAS 2.0)	x							x	x
Patient satisfaction questions									x
Safety and adverse events†		x			x			x	x
Exploratory wearable data‡	x				x	x	x	x	

Day denotes the days after surgery.
*At the time of informed consent, the following will be performed: QOR-15, UB-CAM, PHQ-2/PHQ-9, WHODAS 2.0.
†Safety and adverse events include intraoperative awareness, intraoperative undesired patient movement, acute kidney injury, respiratory failure, intraoperative hypotension (mean arterial pressure (MAP) <65 mm Hg for 20 min or greater and MAP<55 mm Hg for 20 min or greater), all-cause 30-day mortality, propofol related infusion syndrome, malignant hyperthermia, unplanned admission after outpatient surgery in an ambulatory setting.
‡FitBit or Apple Watch baseline data will be collected 7–14 days prior to surgery, after informed consent.
DOS, day of surgery.

participating institution, standardises it against a common data dictionary and transfers the data to the Data Coordinating Center (DCC) at the University of Michigan. Perioperative information will be collected via this system.

- MQUARK (MPOG Quality and Research Kit) will be used to manage patient screening, enrolment and randomisation. This existing research system has been customised to the needs of the THRIVE study and provides seamless integration with data collected from the other systems. Patient enrolment details, patient demographics, per protocol treatment delivered and clinician report of intraoperative patient movement will be entered into MQUARK.
- MyDataHelps (CareEvolution, Ann Arbor, MI) is a patient-facing application that allows the collection of

patient-reported outcome data via the administration of surveys. Surveys can be completed by dedicated smartphone application, email or web. Additionally, data will be obtained from wearable devices (Apple Watch or Google FitBit) using the MyDataHelps application.

Data collection

Box 1 Summarises the data that will be collected. In addition, using the pre-existing MPOG structured EHR data for all patients receiving care at each enrolment site, we will be able to broadly assess the demographics of eligible patients and compare to patients actually approached, consented and randomised.

Definitions

Elective surgery

Elective surgery is defined as any operation that can be performed with advanced planning and is subject to patient or clinician choice.

Per-protocol treatment

Propofol TIVA treatment will be met if the patient receives intravenous propofol and does not receive any inhaled anaesthetics (sevoflurane, isoflurane, desflurane, nitrous oxide). Extremely brief episodes (<5 min) of inhaled volatile end tidal concentration detected by the automated MPOG data interface shall be considered as compliant with the TIVA protocol. This can occur during the administration of inhaled medications that are not anaesthetics but erroneously measured as such (eg, albuterol) or due to inadvertent activation of the volatile vaporizer which is immediately detected and corrected.

INVA treatment will be met if the patient receives an inhaled volatile anaesthetic agent (sevoflurane, isoflurane, desflurane). The choice of inhaled agent(s) to administer will be at the discretion of the clinician administering anaesthesia.

Patients in both groups may receive additional intravenous adjuncts as deemed appropriate by the clinical team. All other clinical interventions (eg, general anaesthesia airway type (laryngeal mask airway vs endotracheal tube), depth of anaesthesia, peripheral nerve blockade analgesia, neuraxial analgesia) will be at the discretion of the treating anaesthesia clinicians and recorded in the EHR. Each site will be expected to determine the method of ensuring EEG monitoring is consistent (the same) in both treatment arms (ie, if patients receiving TIVA at a site have processed EEG monitoring, then patients at that site receiving INVA should also have processed EEG monitoring).

Safety and adverse events

The US Office for Human Research Protections and the US Food and Drug Administration, the following broad definition is provided: a safety or adverse event is any untoward or unfavourable medical occurrence in a human subject, including any abnormal sign, symptom or disease, temporally associated with the subject's

Box 1 Data collection

Patient enrolment details

⇒ Patient demographics (age, race, ethnicity, gender identity (self-reported if available, from EHR if research team is unable to contact the patient)).
⇒ Patient screened.
⇒ Patient attempted approach (contacted via phone or email).
⇒ Patient approached.
⇒ Patient eligibility or ineligibility after approached.
  ⇒ Reason for ineligibility.
⇒ Patient consent or decline to participate.
  ⇒ Reason for declining to participate.
  ⇒ Role of optional wearable device in decision to participate.
⇒ Patient withdrawn after consent obtained.
  ⇒ Reason for withdrawal.
⇒ Patient randomised.
  ⇒ If patient is not randomised, reasons why will be collected.

Per protocol treatment delivered

⇒ If randomised treatment is not delivered, reasons for protocol deviation will be collected.

Patient-reported outcome (PRO) completed by the patient or during a research coordinator interview (see online supplemental appendix 2)

⇒ Risk Analysis Index surgical frailty assessment.[20]
⇒ Quality of Recovery-15 Instrument.[21]
⇒ Patient Health Questionnaire-2 and Patient Health Questionnaire-8.[22–24]
⇒ Modified Brice Interview.[25–28]
⇒ Ultra-Brief Confusion Assessment Method.[29 30]
⇒ WHO Disability Assessment Scale 2.0.[31 32]
⇒ Patient satisfaction with the study.

Clinician and healthcare worker completed

⇒ Intraoperative undesired patient movement questionnaire.
⇒ Processed electroencephalogram use.
⇒ Surgeon attending question regarding the acceptability of the operating conditions during the case.
⇒ Michigan Awareness Classification Instrument[33] and a structured follow-up questionnaire for participants who report memories during the Modified Brice Interview (see online supplemental appendix 3 for Awareness assessment procedures).

Electronic health record (EHR) data via automated MPOG interface

⇒ Serum creatinine (preoperative and postoperative).
⇒ Intraoperative mean arterial pressure.
⇒ All-cause mortality at postoperative days 30 and 90.
⇒ Surgical duration.
⇒ Anaesthesia duration.
⇒ Fresh gas flows.
⇒ Inhaled volatile or nitrous oxide inspired and expired concentration.
⇒ Total dose (including boluses and infusions) and infusion time (in minutes) of intravenous medications administered between anaesthesia start and stop. Medications of interest include propofol, dexmedetomidine, remifentanil, fentanyl, sufentanil and ketamine.
⇒ Naloxone administration.
⇒ Processed electroencephalogram use.

Electronic health record review by research coordinator

⇒ Continued mechanical ventilation or reintubation.

Continued

Box 1 Continued

⇒ Occurrence of malignant hyperthermia.
⇒ Occurrence of propofol related infusion syndrome.

Wearable device data (FitBit or Apple Watch)

⇒ Daily step count.
⇒ Daily stand hours.
⇒ Total sleep time, sleep onset latency, wake after sleep onset, sleep efficiency, midpoint of sleep.

Feasibility of the data management procedures

⇒ Proportion of patients with complete intraoperative EHR data to establish protocol compliance.
⇒ Proportion of patients with successful linking of the PRO, EHR and enrolment process databases (MyDataHelps, MPOG import manager, MQUARK).
⇒ Proportion of enrolled patients with successful transfer of data into analytic case files.
⇒ Proportion of safety and adverse events with accurate and complete documentation.

EHR, electronic health record; MPOG, Multicenter Perioperative Outcomes Group; MQUARK, MPOG Quality and Research Kit.

participation in the research, whether or not considered related to the subject's participation in the research.[13 14] One of our patient partners was asked to provide their perspective on what they would view as a safety or adverse event, and they provided the following definition: 'I consider a safety or adverse event to be something that occurs in relation to the trial that threatens my life or has the potential for long-term negative impact on me'.

Consistent with these definitions, and of relevance to the anaesthetic techniques we will be testing in our trial (table 4). Summarises the adverse events that will be collected.

Feasibility metrics

Feasibility metrics for the planned future pragmatic clinical trial will be assessed throughout this trial and after completion of this trial using the approach outlined by Chan *et al*,[8] taking into account the core features of pragmatic trials:

- **Intervention development**. We will assess the acceptability, appropriateness and feasibility of the study protocol as perceived by key stakeholders (anaesthesia clinicians) using the Acceptability of Intervention Measure, Intervention Appropriateness Measure and Feasibility of Intervention Measure. Each has 4-item in a Likert scale from 'completely disagree' to 'completely agree'.[15]
- **Research ethics**. We will assess whether it is feasible to obtain consent prior to surgery. We will also ascertain the minimum time frame prior to surgery that obtaining consent would be acceptable to key stakeholders (eg, patients, family members, surgeons, anaesthesia clinicians).
- **Patient identification and eligibility**. We will be identifying eligible patients using automated searches of the EHR and the surgical schedule. We will assess how reliable and comprehensive this approach is in identifying eligible patients, seeking to improve its performance over the course of the pilot study.
- **Recruitment of individuals**. We will plan to enrol patients having a diversity of surgical procedures, as well as patients historically under-represented in research.
- **Setting**. It will be important to demonstrate in this feasibility pilot that we can enrol patients having inpatient major and minor surgeries, as well as patients scheduled for outpatient surgical procedures.

Table 4 Serious adverse events and adverse events

Severe adverse events	Adverse events
► Intraoperative awareness (see online supplemental appendices 2 and 3) ► Respiratory failure, defined as unplanned postoperative intubation or reintubation or continued mechanical ventilation >6 hours postoperatively, assessed on postoperative day 0 ► All-cause mortality at postoperative days 30 and 90 ► Propofol related infusion syndrome, defined as acute refractory bradycardia in the presence of metabolic acidosis, and at least one of the following: rhabdomyolysis, acute kidney injury occurring after the start of propofol or hypertriglyceridaemia,[34 35] occurring during intraoperative administration and confirmed by the clinical team ► Malignant hyperthermia, defined as unexplained muscle rigidity, tachycardia, hypercapnia, and rapidly increasing temperature leading to metabolic acidosis, rhabdomyolysis, disseminated intravascular coagulation and ventricular arrhythmias,[36 37] occurring intraoperatively, confirmed by the clinical team	► Hospital admission no later than 24 hours after surgery performed at an ambulatory care centre ► Acute kidney injury, defined as a serum creatinine increase of 50% of 0.3 mg/dL from preoperative baseline within 7 days of surgery[38] ► Cumulative duration of mean arterial pressure <55 mm Hg for 20 min or greater[39 40] ► Cumulative duration of mean arterial pressure <65 mm Hg for 20 min or greater[39 40] ► Moderate or severe intraoperative undesired patient movement based on clinician report (see online supplemental appendix 2)

- **Organisation**. In the pilot, we will need to show that the interventions (TIVA and INVA) can be delivered without the provision of additional resources (eg, personnel, equipment) in usual clinical settings.
- **Flexibility of delivery**. Although we will be educating clinicians about TIVA and INVA, we will be able to assess the delivery of these interventions both within the context of the feasibility pilot and within the context of usual care.
- **Flexibility of adherence**. It will be important to establish that in both treatment groups, the anaesthetics are administered such that there is sufficient difference between the groups. Specifically, for patients receiving INVA, it will be important to show that they receive a sufficient concentration of inhaled anaesthetic agents for a sufficient duration of the general anaesthesia.
- **Follow-up**. We plan to interview patients and their care partners to ensure that participation in the feasibility pilot is not onerous. The purpose of these interviews will be to understand the patients' experiences of and engagement with the study process and to establish whether the study procedures are acceptable. These interviews will also investigate recommendations for optimisation of study procedures. Our goal is that patients should find that participation in the study enhances their overall perioperative experience, regardless of treatment allocation.
- **Primary outcome**. We have proposed to use certain validated patient-centred outcomes in the feasibility pilot. We will interview patients and care partners to ascertain that the outcome measures chosen are informative and important to patients.

Sample size

To assess the primary feasibility objectives of the study, we calculate the sample size that provides at least 80% power to test whether feasibility criteria meet prespecified thresholds, using one-sample binomial tests. The hypotheses for the two primary feasibility objectives are:

- Enrolment. We hypothesise that the proportion of patients who consent to participate in the study among those who are approached by the study team (π) is greater than 10%. This can be expressed in the hypothesis testing framework as:
  H_0: $\pi \leq 0.10$
  H_1: $\pi > 0.10$
- Compliance with randomised assigned treatment (propofol TIVA treatment allocation and inhaled volatile general anaesthesia). We hypothesise that the proportion of patients in the propofol TIVA group who receive the assigned treatment (ie, they receive no inhaled agents as part of their anaesthetic) (π_{TIVA}) is greater than 80% and proportion of patients in the INVA group who receive the assigned treatment (ie, they do receive inhaled agents as part of their anaesthetic) (π_{INH}) is greater than 80%. This can be expressed in the hypothesis testing framework as:
  $H_{0.TIVA}$: $\pi_{TIVA} \leq 0.80$
  $H_{1.TIVA}$: $\pi_{TIVA} > 0.80$
  and
  $H_{0.INH}$: $\pi_{INH} \leq 0.80$
  $H_{1.INH}$: $\pi_{INH} > 0.80$

With 300 patients consented and randomised (150 per treatment group) from among no more than 3000 patients approached to participate in the feasibility study, we have at least 80% power to detect the prespecified thresholds with a one-sided type I error of 2.5% (equivalent to a two-sided type I error of 5% in the context of a two-sided 95% CI and assuming a 1.3% dropout for the intervention compliance feasibility outcome (ie, two patients per treatment group).

A simulation approach was used to examine the percentage of times in 1000 simulations it could be claimed that the feasibility proportion is greater than the prespecified threshold if the true proportion is a specific value under the alternative hypothesis, with various sample sizes. Specifically, power is calculated as the number of times in 1000 simulated trials that the 95% lower confidence bound of the simulated proportion is greater than the prespecified threshold for various hypothesised 'true' proportions. In each simulated trial, n observations are generated from a Bernoulli distribution under a hypothesised 'true' proportion. 95% CIs for these binomial proportions are generated (using the Wald method to estimate the SD) and evidence for the (alternative) hypothesis if based on whether the 95% lower confidence bound is ≥ the prespecified threshold.

For the enrolment feasibility criterion, with 3000 patients approached and 300 consented, if the true proportion of patients who consent is 11.6% or greater, there is at least 80% power to detect a 10% or greater proportion. If the proportion of patients who consent is 11.9% or greater, there is at least 90% power to detect a 10% or greater proportion.

For the compliance with randomised assigned treatment feasibility criterion, with 150 randomised patients in a treatment group and assuming 1.3% dropout (ie, 148 patients analysed), if the true proportion of compliance with assigned treatment is 80.3% or greater, there is at least 80% power to detect an 87.6% or greater proportion. If the proportion of compliance with assigned treatment is 88.8% or higher, there is at least 90% power to detect an 80% or greater proportion. Note that evidence that both treatment groups achieve this criterion is needed, we do not need to adjust the type I error (ie, CI level) for multiplicity.

Statistical methods

Descriptive statistics (mean, SD, median, IQR and minimum and maximum for continuous variables and frequency and proportions for categorical variables) will be provided overall and by treatment group to describe the study population. Proportions and 95% CIs will be calculated to assess whether prespecified thresholds are met for critical feasibility parameters: enrolment and

compliance with TIVA and inhaled volatile general anaesthesia allocation. If 95% lower confidence bounds are greater than the thresholds of 10% (enrolment) and 80% (treatment compliance for both treatment groups), there will be greater confidence that a pragmatic full-scale trial can be conducted successfully. Other feasibility outcomes (eg, completion of data collection) will be described similarly.

Descriptions of clinical and patient-reported outcome measures (table 1) will also be provided, but no inferential statistical analyses will be performed, since the purpose of this feasibility study is to estimate the magnitude of clinical and patient-reported outcomes for each treatment group.

The analysis set will be the modified intention-to-treat population, defined as all randomised participants who receive a TIVA or INVA during their procedure.

Monitoring

Adverse event reporting and safety monitoring

The short-term side effects of propofol TIVA and INVA are well recognised and can be attributed as low-risk in a controlled intraoperative setting. The safety and adverse events for this study are described above.

As part of the informed consent process for this study, patients will be informed of the rare safety and adverse events. The research team at each participating site will monitor the study for all safety and adverse events or any unanticipated problems involving risk to the patients or others. Serious adverse events will be reported to the Institutional Review Board (IRB), the PI at each site and an independent safety officer.

A data and safety monitoring plan will be implemented and include a Data Safety and Monitoring Board (DSMB). There is a charter to guide the functions of the DSMB, and the DSMB will produce reports in accordance with the Patient-Centered Outcomes Research Institute (PCORI) guidelines. The DSMB will provide independent safety oversight of this trial, as well as the general conduct of the trial.[16] The DSMB will comprise independent, multidisciplinary experts from multiple institutions. The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments in which the patients have consented to participate and to assure the regulatory bodies and the public (and possibly funding agencies) that conflicts of interest do not compromise either patient safety or trial integrity.[17] These members will not have financial, proprietary or professional conflicts of interest, which may affect the impartial, independent decision-making responsibilities of the DSMB.[16 18] Each member will sign a Conflict-of-Interest Certification to confirm that no conflict exists. In order to optimise performance, there will be between three and five people on this advisory board.[19]

Premature discontinuation

Patients will be withdrawn if the investigator decides that discontinuation is in the best interest of the patient, or the patient requests withdrawal from the study at any point. There will be no prespecified interim analysis. Early stoppage will be based on safety concerns only, which are not anticipated given that both anaesthetic techniques are in regular, routine clinical practice.

We will discontinue collection of any new data after the request has been processed; however, data collected prior to the date of withdrawal can be used for research initiated after the date of withdrawal.

Potential risks

The risks to patients in this feasibility study are anticipated to be no greater than the risks associated with the planned surgery and general anaesthesia. There is a small risk of breach of confidentiality. As this feasibility study is evaluating a trial comparing the two most common techniques used for general anaesthesia in the USA, we do not anticipate any additional risk to participating patients.

Patients will not incur any study-related expenses. Regardless of their participation in THRIVE, each patient may receive either a propofol TIVA or INVA. Both treatment allocations are in routine use and have similar technical charges associated with them. The anaesthesiologist and/or nurse anaesthetist professional charges are identical with each treatment option. In routine care, there is no discussion of cost differential between the two options given this similarity.

If a patient is provided a study wearable device, there is a small chance that they may experience local reactions to materials in the wearable device (Apple Watch, Fitbit, etc) due to allergies, environmental factors, extended exposure to irritants like soap or sweat, and other causes. Patients will be advised to remove their wearable device and consult their physician if they experience redness, swelling, itchiness or any other irritation. In the event that the study team becomes aware of unexpected medical events reported from wearable devices the patient will be advised to seek appropriate medical care for diagnosis and treatment.

Procedures to minimise potential risks

Data privacy protections will be consistently applied to study data to minimise risk of privacy loss. Patients will not be identified by name in any analyses, reports or publications. Some patients may wonder about the confidentiality of the information collected from the surveys and other data. The PIs, coinvestigators and study personnel have been trained in the protection of patient confidentiality and will be able to reassure the small number of anticipated patients who might raise concerns. Patients who have a negative experience of general anaesthesia or recovery from general anaesthesia (or any aspect of their participation in the feasibility pilot trial) will have the opportunity to speak about their experiences to a member of the THRIVE team. Participation in the study will be voluntary and the study procedures will be described in the consent process. All study staff have or will receive

training in the responsible conduct of research prior to the onset of the study.

ETHICS AND DISSEMINATION

This study is approved by the ethics board at Washington University (IRB# 202205053), serving as the single IRB for both participating sites.

Protocol amendments

All protocol modifications made during the course of this feasibility study will be communicated to the IRB, DSMB and PCORI. Protocol modifications include, but are not limited to, changes to eligibility criteria, per protocol treatment definitions, outcomes collected and data analysis.

Protection of patients

This is a study to evaluate the feasibility of conducting a pragmatic randomised comparative effectiveness trial that will evaluate whether general anaesthesia performed with propofol TIVA or INVA is associated with an improvement in postoperative quality of recovery and/or a difference in the incidence of intraoperative awareness under general anaesthesia. For this feasibility trial, patients will provide informed consent. Patients will undergo the standard preoperative anaesthesia assessment and will be enrolled for the study prior to surgery. Both interventions in this study are established, routine standards of care. Thus, participation in this trial is not considered to have the potential for increased risk.

Sources of materials

Research material from patients will be obtained from the EHR at each participating institution (including the MPOG database) in addition to survey data collected by blinded research assistants, and data from wearable devices (Apple Watch or Google FitBit) using the MyDataHelps application.

List of protected health information collected for study

In order to facilitate follow-up, compensation for participation and linkage to vital records data, we will collect individual identifiers including name, birth date, social security number, medical record number, addresses and telephone numbers. Access to protected health information (PHI) will be restricted to study personnel in roles directly requiring it for trial operations or required in the analysis and interpretation of study data.

Data management

The potential risk of disclosure of confidential information is guarded against by maintaining data on a secure server with access limited to the key research personnel. The primary database server and all information system servers will be housed at the DCC (University of Michigan) and compliant with enterprise information assurance requirements (firewall, VPN, intrusion detection). All data stored electronically will be encrypted at rest. In addition, datum level audit trails, role-based access, two-factor authentication and minimal necessary use of identifiers will be implemented. While no paper records or case report forms are expected, software downtime procedures may include the temporary use of paper records. Any physical research materials containing PHI will be stored in a locked cabinet inside a locked research office in case of a software downtime paper process. We will customise and deploy the existing MQUARK application to support this trial. This web-based application, hosted at the University of Michigan, will be the primary interface for the study sites. Sites will use this to document patient screening, approach, consenting and enrolment electronic case report forms (eCRFs). MQUARK includes customisable, data-driven eCRFs to capture data gathered by research coordinators at each site. MQUARK has been used to document clinical quality projects and prospective observational research for more than 10 000 patients across MPOG sites, and has met strict medicolegal, audit trail, electronic signature and disaster recovery requirements across federal and state regulations. Only deidentified data will be sent out to research team members and data analysts for further data analysis. All persons involved in recruitment and data collection will undergo training in Human Subjects Research and Health Insurance Portability and Accountability Act. Only restricted members of the research team will be able to access this data. Deidentified data will be shared with the wider members of the research team.

Dissemination policy

The THRIVE team will disseminate the protocol and its contents through various channels, including peer-reviewed publication, media, blogs and plain language summaries on our website. We will present the protocol at relevant international scientific meetings. Patient partners will participate fully in these efforts to disseminate the contents of the protocol. Our team will communicate progress in the feasibility trial to relevant stakeholders (eg, clinicians, hospital leaders, funding partners) and relevant updates will be appropriately communicated on social media platforms such as, LinkedIn, Twitter, Instagram. The final results of the feasibility pilot trial will be presented at scientific meetings, published in a peer-reviewed publication, included on clinicaltrials.gov, shared with patients who participated in the trial, and disseminated on relevant media and social media platforms.

DISCUSSION

This feasibility study will inform the design and conduct of a 12 500-patient multicentre, patient-centred trial, comparing intravenous propofol anaesthesia with INVA. Contingent on the success of the feasibility phase, the overarching specific aims of the planned 12 500 patient THRIVE trial will be: (1) compare the early patient quality of recovery after anaesthesia and surgery following two

commonly used and established anaesthetic techniques: (a) TIVA with propofol and (b) INVA; (2) compare the medium term trajectories of patient recovery after anaesthesia and surgery following two commonly used and established anaesthetic techniques; (3) determine whether the rare and devastating complication of intraoperative awareness is similarly uncommon with propofol TIVA and INVA.

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Contributors SKheterpal and MSA are the senior authors of the THRIVE feasibility protocol. Their contributions include conceptualising the study design, drafting and editing the protocol, organising conduct across all contributing sites and patient partner community members. BRTP and DAC are the primary authors of the THRIVE feasibility protocol. Their contributions include conceptualising the study design, drafting and editing the protocol, organising feedback from all contributing sites and patient partner community members, and coauthoring the manual of operations for study conduct. CS, ST-P and ZW contributed to the THRIVE feasibility protocol by editing the protocol and conceptualising the study design, including the statistical modelling of the study. MDN, MP, AJ, SKumar and SHG critically revised the THRIVE feasibility protocol and approved the final version. The THRIVE research group reviewed and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the THRIVE feasibility protocol.

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Disclaimer All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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1/23/2023

Feasibility pilot trial for the Trajectories of Recovery after Intravenous propofol versus inhaled VolatilE anesthesia (THRIVE) Trial

Feasibility Trial Storyboard

THRIVE

Storyboard Contents

1) **What is general anesthesia**
2) Different **recovery pathways** after general anesthesia
3) Two main **types of general anesthesia**
4) **Patient experiences with these types** of anesthesia
5) **Design** of the THRIVE trial
6) **Need for a feasibility pilot trial** first
7) **Objective** of the THRIVE feasibility pilot trial
8) **Timeline** for the trials
9) **Participation** in the feasibility pilot trial
10) **Success** in the feasibility pilot trial
11) **Patients as partners** in the research

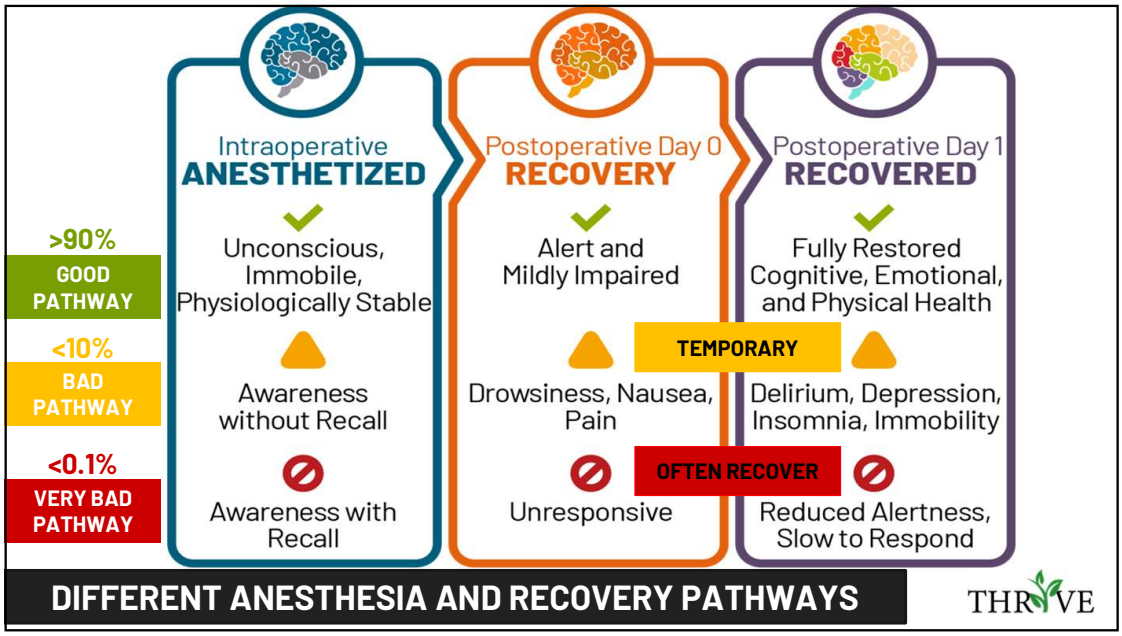
THRIVE

1/23/2023

What is general anesthesia?

It is the administration of anesthetic medicines to produce a **temporary and completely reversible state of unconsciousness (not awake), amnesia (not forming memories), and immobility (not moving)** during which surgical procedures can be safely performed.

THRIVE



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Today there are two main types of general anesthetic medicines

INHALED

INTRAVENOUS

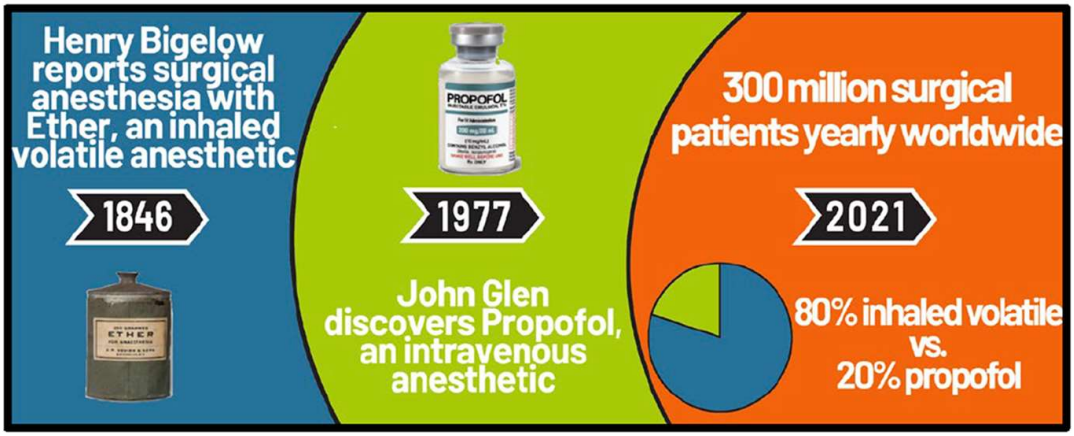
Inhaled anesthetics are breathed into the lungs. From there they are carried in the blood to the brain.

Intravenous anesthetics are given into the veins. They are carried in the blood to the brain.

Temporary Unconsciousness

THRIVE

Both main types of general anesthetic medicines have been around for over 50 years.



There are 50 million surgeries yearly in the USA.

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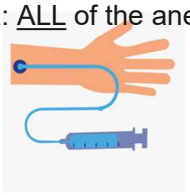
The **common terms** to describe anesthetic choices in this study are:

1) **TIVA** or **T**otal **I**ntra**v**enous **A**nesthesia: ALL of the anesthetic medicines are given into a vein



IV anesthetics

1) **INVA** or **In**haled **v**olatile anesthesia: at least SOME of the anesthetic medicines are given by breathing into the lungs

Inhaled anesthetics

THRIVE

But we still do not know which type of general anesthesia results in a better patient experience.

THRIVE

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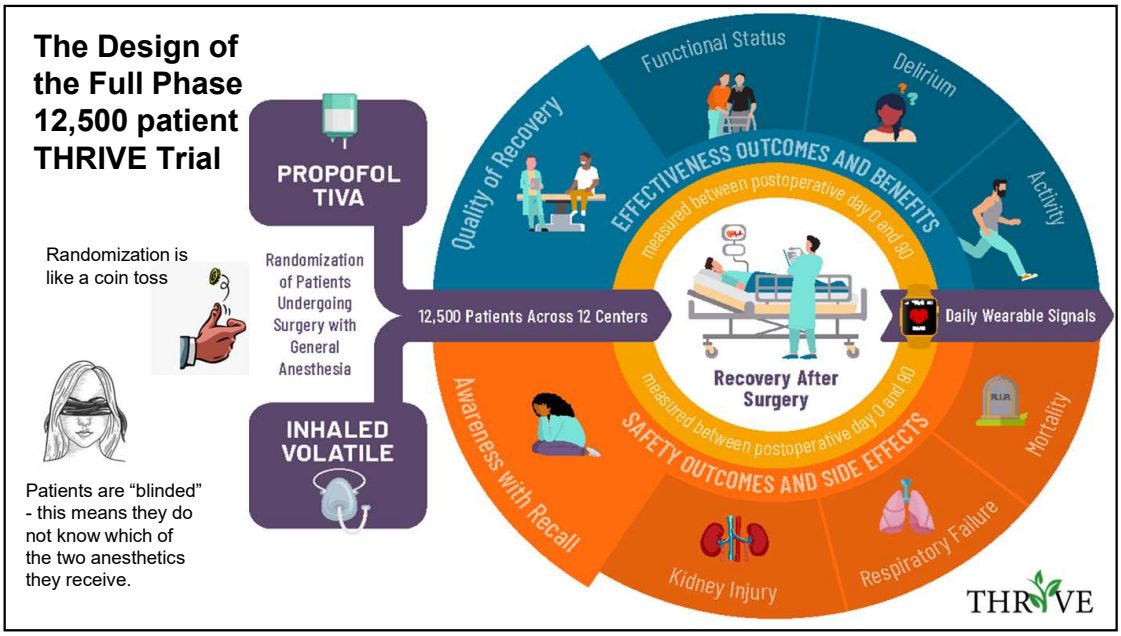
The THRIVE trial will be conducted in at least 12 sites across the USA. These sites will be selected from the centers shown on the map.

The Design of the Full Phase 12,500 patient THRIVE Trial



1/23/2023

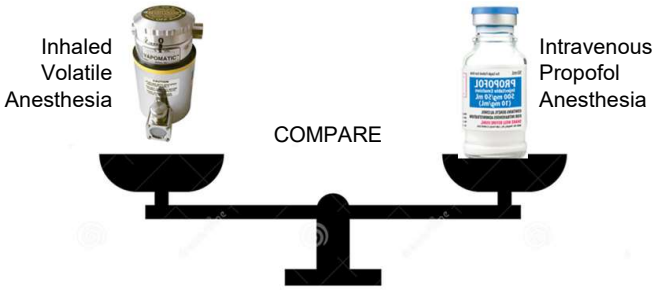
FEASIBILITY PILOT TRIAL

- But before we can do the full-scale 12,500 patient THRIVE trial at 12 hospital complexes across the USA, we have to show that it is possible to conduct this trial.
- So we need to conduct a 300 patient feasibility pilot trial at two US hospital complexes first.

THRIVE

Objective of the THRIVE Feasibility Pilot Trial

To evaluate the feasibility [can it be done] of a pragmatic [practical], comparative effectiveness [comparing two common practices], randomized [like a coin flip] trial [experiment] of patient experiences of recovery from intravenous propofol [one common type of anesthesia] versus inhaled volatile anesthesia [another common type of anesthesia].



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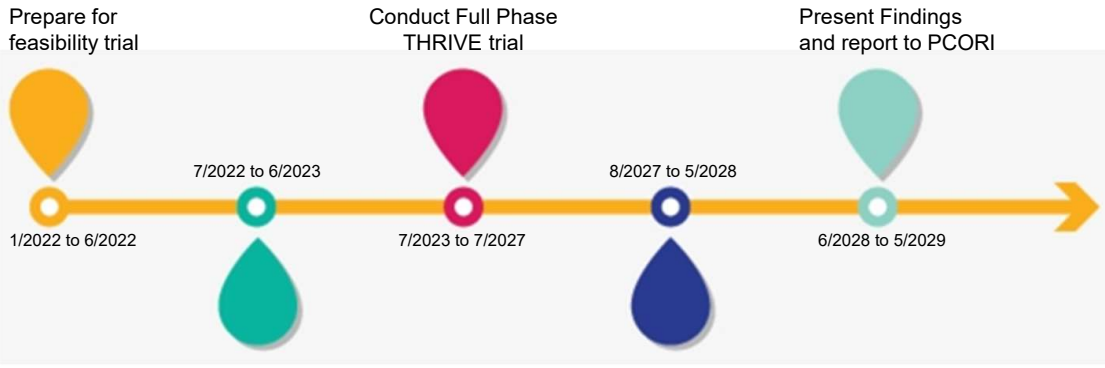
Projected Timeline



THRIVE

Who may take part in the THRIVE Feasibility Pilot Trial?

- 18 years of age or older
- Able to provide informed consent (agreement to take part)
- Having a surgery that does not involve the heart
- Having general anesthesia with unconsciousness
- Having breathing tube to help with breathing during surgery

THRIVE

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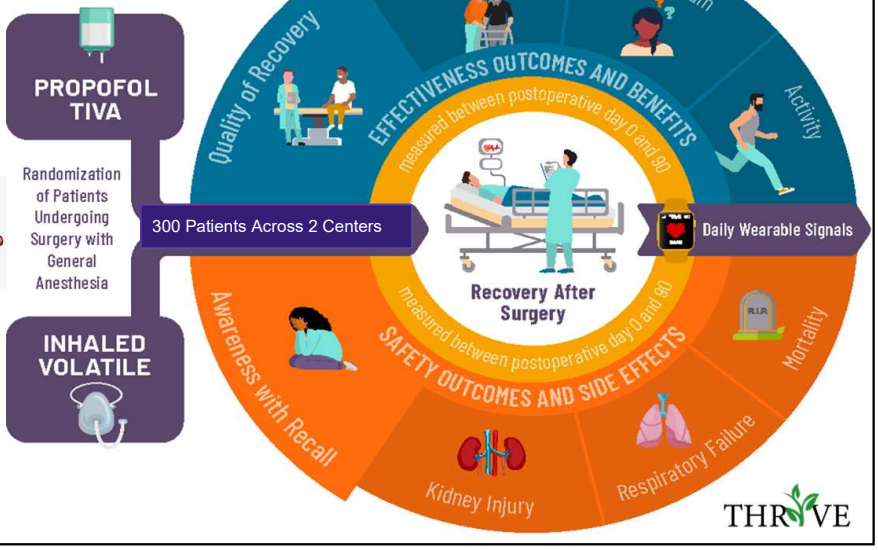
Who may not take part in the THRIVE Feasibility Pilot Trial?

- Unable to agree to take part
- If you are pregnant
- Will receive general anesthesia prior to or after the planned surgery
- Medical condition or allergy that would make anesthesia unsafe
- Requiring a specific type of general anesthesia based on their surgery
- Having surgery at a hospital with specific general anesthesia protocols
- History of waking up during surgery
- Will still have a breathing tube after surgery

THRIVE

The Design of the Feasibility Phase 300 patient Trial

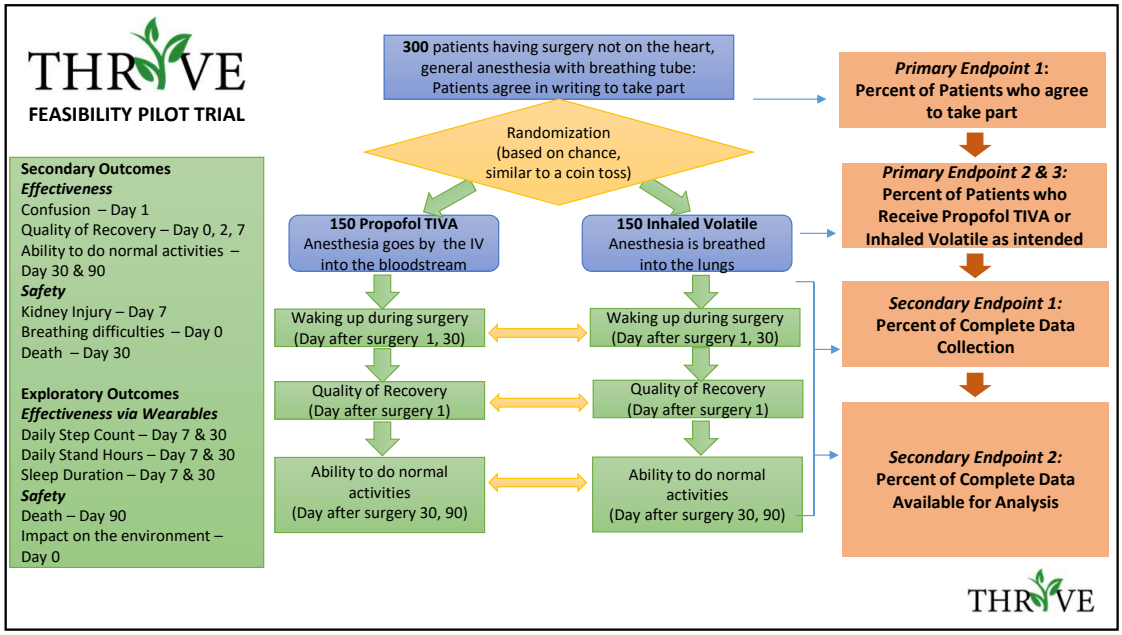


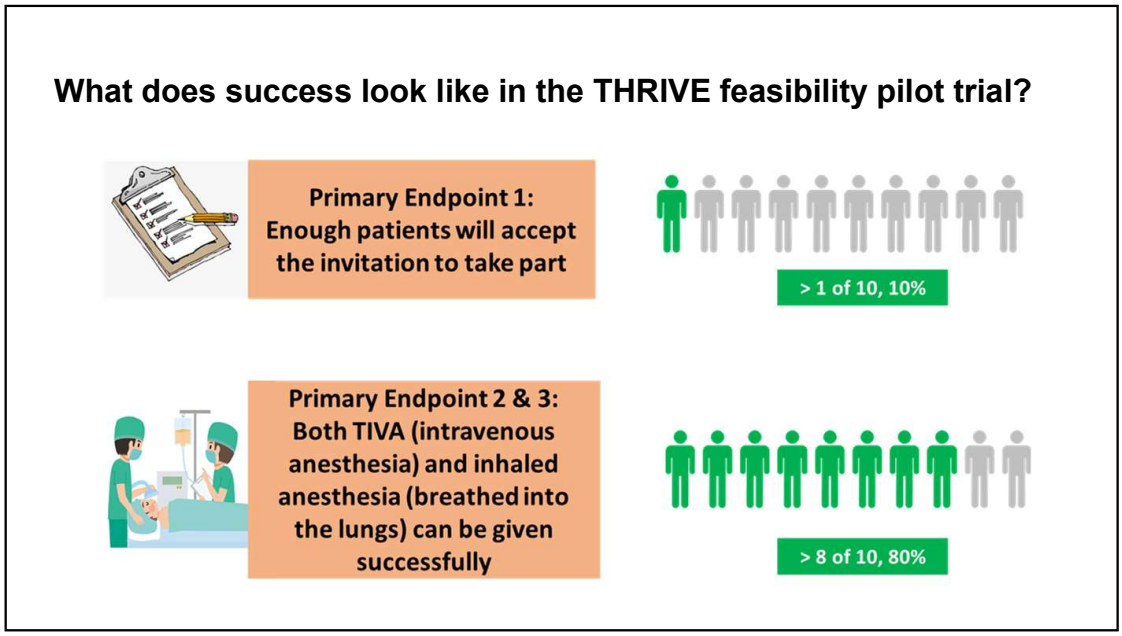
Randomization is like a coin toss

Patients are "blinded" - this means they do not know which of the two anesthetics they receive.

THRIVE

1/23/2023


THRIVE
FEASIBILITY PILOT TRIAL
300 patients having surgery not on the heart, general anesthesia with breathing tube: Patients agree in writing to take part
Randomization (based on chance, similar to a coin toss)
150 Propofol TIVA Anesthesia goes by the IV into the bloodstream
150 Inhaled Volatile Anesthesia is breathed into the lungs
Waking up during surgery (Day after surgery 1, 30)
Quality of Recovery (Day after surgery 1)
Ability to do normal activities (Day after surgery 30, 90)
Waking up during surgery (Day after surgery 1, 30)
Quality of Recovery (Day after surgery 1)
Ability to do normal activities (Day after surgery 30, 90)
Primary Endpoint 1: Percent of Patients who agree to take part
Primary Endpoint 2 & 3: Percent of Patients who Receive Propofol TIVA or Inhaled Volatile as intended
Secondary Endpoint 1: Percent of Complete Data Collection
Secondary Endpoint 2: Percent of Complete Data Available for Analysis
Secondary Outcomes
Effectiveness
Confusion – Day 1
Quality of Recovery – Day 0, 2, 7
Ability to do normal activities – Day 30 & 90
Safety
Kidney Injury – Day 7
Breathing difficulties – Day 0
Death – Day 30
Exploratory Outcomes
Effectiveness via Wearables
Daily Step Count – Day 7 & 30
Daily Stand Hours – Day 7 & 30
Sleep Duration – Day 7 & 30
Safety
Death – Day 90
Impact on the environment – Day 0
THRIVE


What does success look like in the THRIVE feasibility pilot trial?
Primary Endpoint 1: Enough patients will accept the invitation to take part
> 1 of 10, 10%
Primary Endpoint 2 & 3: Both TIVA (intravenous anesthesia) and inhaled anesthesia (breathed into the lungs) can be given successfully
> 8 of 10, 80%

1/23/2023

What does success look like in the THRIVE feasibility pilot trial?

Complete data collection from questionnaires (study surveys) and information from the electronic medical record.
The goal is to have at least 90% of the data complete at each time point and with each survey or medical record log.

>90% complete data from the electronic medical record and from the questionnaires, which ask questions about outcomes that matter to patients.

Patients and clinicians will be interviewed to find out:

1) What can we do so that more patients will participate in THRIVE when asked?
1) What might make some patients not want to participate in THRIVE?
1) What can we do so that anesthesia doctors and nurses will be successful in delivering both types of anesthesia (TIVA and inhaled) in THRIVE?
1) What are some of the difficulties faced by anesthesia doctors and nurses in delivering both types of anesthesia (TIVA and inhaled)?

THRIVE

10

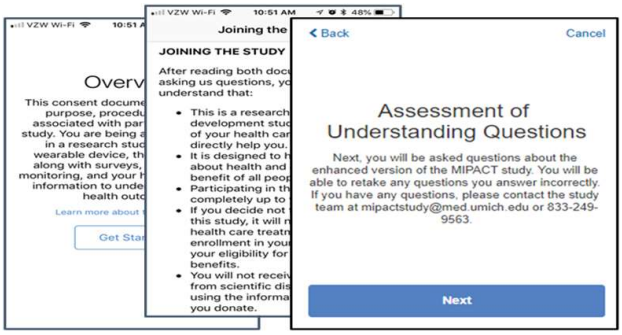
1/23/2023

THRIVE Use of Innovative Technology

THRIVE

Consent Form & Education Material

- Consent forms will be electronic and can be viewed on a tablet or device
- A participant educational video will be available and can be viewed on a tablet, device or the THRIVE website



THRIVE

1/23/2023

We are inviting **participating patients to partner in the research** by answering questionnaires about their experience of anesthesia and recovery and by wearing a smart-watch (Apple or FitBit) that collects information on behavior (e.g. sleep patterns, step counts)

THRIVE

Wearable Data

- Patients will be asked to wear Fitbit or Apple Watches for 30 days after surgery.
- We will evaluate daily step count, daily stand hours and sleep time on days 7, 14, 21, 30 after surgery
- We will compare the information from the Fitbit or Apple watch with the information provided in the questionnaires.
- **Encouraging patients to wear the device will be important**

THRIVE

1/23/2023

Before Surgery, Patients will be asked Questions About:

1. General information about themselves (e.g., education level, household income, gender identify, marital status, socioeconomic status)
2. Women's Health
3. Smoking, drug and alcohol use
4. Mood
5. Ability to do normal activities
6. Confusion
7. Sleep quality

THRIVE

After Surgery, Patients will be asked Questions About:

1. Quality of recovery
2. Waking up during surgery
3. Confusion
4. Mood
5. Ability to do normal activities

THRIVE

1/23/2023

We are grateful for **participating patients who partner in this research** and acknowledge their time and efforts are valuable.

Patients will be compensated.

THRIVE

We Will Keep Patients Safe & Protected

THRIVE

1/23/2023

Positive Experiences

We aim to foster a positive patient experience by establishing supportive relationships with participants, built upon open communication, easy accessibility to THRIVE team members study resources and setting clear expectations.

Patients who have a positive experience of general anesthesia or recovery from general anesthesia (or any aspect of their participation in the feasibility pilot trial) will have the opportunity to speak about their experiences to a member of the THRIVE team.

THRIVE

Negative Experiences

Patients who have a negative experience of general anesthesia or recovery from general anesthesia (or any aspect of their participation in the feasibility pilot trial) will have the opportunity to speak about their experiences to a member of the THRIVE team.

THRIVE

15

1/23/2023

Patient Protection

- Data privacy protections will be consistently applied to study data
- Patients will not be identified by name in any analyses, reports, or publications
- All investigators and study personnel will be trained in the protection of patient confidentiality
- No patient will be asked to provide information against his/her will

THRIVE

Glossary of Terms

Analgesia: Refers to the lessening of pain or pain relief

Amnesia: Refers to the loss of memories

Delirium: A serious disturbance in mental abilities including symptoms such as tiredness, agitation, difficulty focusing, hallucinations, uncooperative behaviors, and disorganized thinking after the surgery

Distressing Awareness: Waking up for some time during surgery and remembering this afterwards, and being distressed or in pain during this episode

Full Recovery: Complete recovery on the day after surgery such that you are able to function at the same level as you could before surgery, including self-care, mental activities (e.g. newspaper and book reading), and common daily activities (driving, cooking, housework)

Functional Status: Ability to perform normal daily activities

THRIVE

1/23/2023

Glossary of Terms

Induction: In anesthesia, this refers to the transition from being awake to temporarily losing sensation or awareness

Intraoperative awareness: Waking up for some time during surgery and remembering this afterwards, but not being distressed or in pain during this episode

Pilot study: Small-scale study conducted in preparation for a larger investigation

Perioperative: Refers to the period around the time of surgery (including before surgery, during surgery and after surgery)

Quality of Recovery: How people feel and function after surgery (e.g. feeling rested, having pain, able to return to work)

Sedation: A state of being relaxed or sleepy because of a drug

THRIVE

Appendix 2. Patient and Clinician Instruments

Quality of Recovery-15 Patient Survey

Part A

How have you been feeling in the last 24 hours?

(0-10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily
2. Been able to enjoy food
3. Feeling rested
4. Have had a good sleep
5. Able to look after personal toilet and hygiene unaided
6. Able to communicate with family or friends
7. Getting support from hospital doctors and nurses
8. Able to return to work or usual home activities
9. Feeling comfortable and in control
10. Having a feeling of general well-being

Part B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain
12. Severe pain
13. Nausea or vomiting
14. Feeling worried or anxious
15. Feeling sad or depressed

Reference**:** Stark, Peter A., Paul S. Myles, and Justin A. Burke. 2013. “Development and Psychometric Evaluation of a Postoperative Quality of Recovery Score: The QoR-15.” *Anesthesiology* 118 (6): 1332–40.

Patient Health Questionnaire-2 (PHQ-2)

Over the last *2 weeks*, how often have you been bothered by any of the following

problems?

Not at all (0), Several days (1), More than half the days (2), Nearly every day (3)

1. Little interest or pleasure in doing things

2. Feeling down, depressed, or hopeless

The PHQ-2 consists of the first 2 questions of the PHQ-8. Scores range from 0 to 6. The recommended cut point is a score of 3 or greater. Recommended actions for persons scoring 3 or higher are one of the following: Administer the full PHQ-8.

Patient Health Questionnaire-8 (PHQ-8)

Over the last *2 weeks*, how often have you been bothered by any of the following problems?

Not at all (0), Several days (1), More than half the days (2), Nearly every day (3)

1. Little interest or pleasure in doing things

2. Feeling down, depressed, or hopeless

3. Trouble falling or staying asleep, or sleeping too much

4. Feeling tired or having little energy

5. Poor appetite or overeating

6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down

7. Trouble concentrating on things, such as reading the newspaper or watching television

8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving .around a lot more than usual

Scoring: If two consecutive numbers are circled, score the higher (more distress) number. If the numbers are not consecutive, do not score the item. Score is the sum of the 8 items. If more than 1 item missing, set the value of the scale to missing. A score of 10 or greater is considered major depression, 20 or more is severe major depression.

References:

Kroenke K, Spitzer RL, Williams JBW. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care* 2003;41:1284–92.
Kroenke K, Strine TW, Spitzer RL, *et al.* The PHQ-8 as a measure of current depression in the general population. *Journal of Affective Disorders.* 2009;114:163–73. doi:10.1016/j.jad.2008.06.026

Modified BRICE

1. What is the LAST thing you remember before going to sleep? Pick one
   - Being in the pre-op area
   - Seeing the operating room
   - Being with family
   - Hearing voices
   - Feeling a mask on face
   - Smell of gas
   - Burning or stinging in the IV line
   - Other
2. What is the FIRST thing you remember after waking up? Pick one
   - Hearing voices
   - Feeling breathing tube
   - Feeling mask on face
   - Feeling pain
   - Seeing the operating room
   - Being in the recovery room
   - Being with family
   - Being in ICU
   - Nothing
   - Other
3. Do you remember anything between going to sleep and waking up?
   - No
   - Yes

   If patient answers Yes, check all that apply
   - Hearing things
   - Feeling things (eg sensation of the breathing tube)
   - Feeling surgery without pain
   - Experiencing pain
   - Being unable to move or breathe
   - Other
4. If you answered yes to the previous question, was this distressing to you? Yes or No

Reference: Brice DD, Hetherington RR, Utting JE. A Simple Study of Awareness and Dreaming During Anesthesia. *British Journal of Anaesthesia*. 1970;**42**:535–42. doi:10.1093/bja/42.6.535

Structured follow-up questionnaire for patients who report memories of the period between "going to sleep" and "waking up" at either routine postoperative interview

1. Do you still have memories of events that occurred during your surgery? Yes/No/Unknown
2. What do you remember during your surgery?
    a. Did you hear anything? If yes, what?
    b. Did you experience any emotions? If yes, what? Fear, helplessness, anger, frustration, other
    c. Did you experience any sensations? If yes, what?
    d. Did you try to move? If yes, could you?
    e. What was your breathing like?
    f. Did you see anything? If yes, what did you see?
    g. Did you try to open your eyes? If yes, could you?
    i. Did the experience distress you?
3. Do these memories trouble you now? If yes, how do they trouble you?
4. Have you experienced stress at any point because of these memories?
    a. Have you felt any negative emotions because of your memories? If yes, what emotions? (1) Fear, (2) Helplessness, (3) Anger, (4) Frustration, (5) Other
    b. Do you avoid any situation now as a result of your experiences? If yes, what?
    c. Do you currently experience flashbacks?
    d. Do you currently have bad dreams?
    e. Has your social life been affected?
5. Did you go to the ICU after your surgery? If yes, did you still have your breathing tube in?
6. Did your awareness experience take place before the start of surgery, during surgery, or when you were waking up after the surgery?
7. Do you think your awareness experience took place in the operating room, in the ICU, or both? Why do you think this?
8. Have you spoken to a health counselor about this experience? Who have you spoken to in the hospital about this experience?
9. Do you suffer from insomnia currently?
10. Are you easily awakened from regular sleep?
11. Would you like to speak to a professional about your experiences?
12. May we contact you again to talk more about your experiences?

Reference: Avidan MS, Jacobsohn E, Glick D, *et al.* Prevention of intraoperative awareness in a high risk surgical population. *N Engl J Med* 2011;**365**:591–600.

Michigan Awareness Classification Instrument

Note: to be completed if positive screen for Brice

Class 0: No awareness

Class 1: Isolated auditory perceptions

Class 2: Tactile perceptions (e.g., surgical manipulation or endotracheal tube)

Class 3: Pain

Class 4: Paralysis (e.g., feeling one cannot move, speak, or breathe)

Class 5: Paralysis and pain

*An additional designation of “D” for distress was also included for patient reports of fear, anxiety, suffocation, sense of doom, sense of impending death, etc.

Reference: Mashour GA, Tremper KK, Avidan MS. Protocol for the “Michigan Awareness Control Study”: a prospective, randomized, controlled trial comparing electronic alerts based on bispectral index monitoring or minimum alveolar concentration for the prevention of intraoperative awareness. *BMC Anesthesiol* 2009;9:7.

Clinician Questions

[If randomized to TIVA]: Q1: Did you administer TIVA according to the protocol definition (e.g, you did NOT administer an inhaled volatile agent or nitrous oxide as part of your anesthetic regimen)

- Yes
- No

If not, why not? [Open-ended response]

[If randomized to volatile]: Q1: Did you administer Inhaled Volatile-based Anesthesia according to the protocol definition? (e.g., you administered an inhaled volatile agent as part of your anesthetic regimen)?

- Yes
- No

If not, why not? [Open-ended response]

Q2: Was there any clinical concern for propofol-related infusion syndrome during the case?

- Yes
- No

Q3: Was there any clinical concern for malignant hyperthermia during the case?

- Yes
- No

Q4: Was EEG monitoring used throughout the case?

- Yes
- No

Q5: Did the patient have any undesired intraoperative movement or breathing during the surgery?

□ No

□ Yes

□ Mild: Undesired spontaneous breathing or non-purposeful movement with no impact on the surgery or patient outcome. _____ times

□ Moderate: Movement that impacted the surgery (e.g., required a pause in the surgery for coughing or straining). _____ times

□ Severe: Movement with a marked negative impact on the surgery (e.g., a patient injury, loss of sterility of the surgical field, other surgical complication) _____ times

World Health Organization Disability Assessment Schedule 2.0 (12 item version)

This questionnaire asks about difficulties due to health conditions. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.

Think back over the past 30 days and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please circle only one response.

In the past 30 days, how much difficulty did you have in:
Options: None, Mild, Moderate, Severe, Extreme or cannot do
1. Standing for long periods such as 30 minutes?
2. Taking care of your household responsibilities?
3. Learning a new task, for example, learning how to get to a new place?
4. How much of a problem did you have joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?
5. How much have you been emotionally affected by your health problems?

In the past 30 days, how much difficulty did you have in:
6. Concentrating on doing something for ten minutes?
7. Walking a long distance such as a kilometer [or equivalent]?
8. Washing your whole body?
9. Getting dressed?
10. Dealing with people you do not know?
11. Maintaining a friendship?
12. Your day-to-day work?

H1: Overall, in the past 30 days, how many days were there difficulties present?
Record number of days____
H2: In the past 30 days, for how many days were you totally unable to carry out your usual activities or work because of any health condition?
Record number of days____
H3: In the past 30 days, not counting the days that you were totally unable, for how many days did you cut back or reduce your usual activities or work because of any health condition?
Record number of days____

Reference: Ustün TB, Chatterji S, Kostanjsek N, *et al.* Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organ* 2010;**88**:815–23.

Risk Analysis Index for measuring frailty in surgical populations

Medical Comorbidities

Have you had unintentional weight loss in the past 3 months (<10 lbs)?	No or Yes
Renal failure?	No or Yes
Chronic/congestive heart failure?	No or Yes
Poor appetite?	No or Yes
Shortness of breath (at rest)?	No or Yes

Cognition, Residence & Daily Living

Do you reside in a setting other than independent living?	No or Yes
Check answer: Skilled nursing, Assisted living, Nursing home	
Were you admitted within the past 3 months?	No or Yes

Activities of Daily Living & Cognitive Decline

Mobility/Locomotion: Choose one:

Independent,
Supervised,
Limited assistance,
Extensive assistance,
Total dependence

Eating: Choose one:

Independent,
Supervised,
Limited assistance,
Extensive assistance,
Total dependence

Toilet Use: Choose one:

Independent,
Supervised,
Limited assistance,
Extensive assistance,
Total dependence

Personal Hygiene: Choose one:

Independent,
Supervised,
Limited assistance,
Extensive assistance,
Total dependence

Have your cognitive skills or status deteriorated over the past 3 months? No or Yes

Adapted from: Hall DE, Arya S, Schmid KK, *et al.* Development and Initial Validation of the Risk Analysis Index for Measuring Frailty in Surgical Populations. *JAMA Surg* 2017;**152**:175–82.

Ultra-brief CAM

Please see**:** Ultra-Brief Confusion Assessment Method (UB-CAM). NIDUS. 2020.https://deliriumnetwork.org/measurement/ub-cam/ (accessed 20 Jan 2023).

References:

Fick DM, Inouye SK, Guess J, *et al.* Preliminary development of an ultrabrief two-item bedside test for delirium. *J Hosp Med* 2015;**10**:645–50.

Motyl CM, Ngo L, Zhou W, *et al.* Comparative Accuracy and Efficiency of Four Delirium Screening Protocols. *J Am Geriatr Soc* 2020;**68**:2572–8.

Appendix 3: Intraoperative Awareness Assessment Procedures

Modified Brice Administration & Timing

The Modified Brice questions will be released to the patient for self-administration on the morning of POD1. A blinded research coordinator may administer and help facilitate if the patient is still in the hospital on POD1. In patients who are CAM negative on POD1 and in patients who do not experience prolonged intubation, the Brice questions will be sent to the patient for self-administration on POD30 if awareness is not reported on POD1. If awareness is reported on POD1, the Brice questions will not be sent to the patient on POD30. Patients who are CAM positive or who experience prolonged intubation on POD1 will receive the modified Brice questions on POD30 regardless of the responses on POD1. When a Brice screen is positive, the appropriate healthcare worker will be notified within 24 hours of the positive screen to perform the follow up questionnaire.

Follow up questionnaire for patients who report memories between "going to sleep" and "waking up"

This interview will be administered by a trained healthcare worker, blinded to the intervention the patient received, from either Washington University School of Medicine or the University of Michigan. Study team members of the CCC and DCC, including the trained healthcare worker, will be notified of a positive Brice screen automatically via an email from MyDataHelps. The healthcare worker will call the patient and perform the follow up questionnaire within 1 to 2 business days of notification and within 7 business days of the positive Brice screen. This healthcare worker will offer to contact, or provide contact information for, a licensed psychologist or psychiatrist, should the patient wish to talk to one. This will be in accordance with the local process established for referring patients who experience intraoperative awareness for counseling at each participating institution.

The healthcare worker will record the interview with the patient’s consent and save it for the awareness adjudication team to review.

Final Assessment of Awareness Events; Michigan Awareness Classification

The awareness adjudication team will be blinded to the intervention the patient received. The team, which is independent of the Brice screening team and post-Brice interview healthcare worker, will adjudicate whether the awareness report was a definite awareness event, possible awareness event, or related to something else (e.g., PACU, ICU). After determining the final status of the awareness event, the team will then apply the Michigan Awareness Classification.