Clinical Trial Protocol

Title	Impact of intraoperative oxygenation practices on patient outcomes
Short title/Acronym	Intraop Ox
Version	Version 1.0
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Trial Summary

Title	Impact of intraoperative oxygenation practices on patient outcomes (Intraop Ox)
Background	More than 30 million patients receive mechanical ventilation during surgery each year in the U.S. Despite improvements in care that have decreased durations of hospitalization, 30-day mortality following moderate inpatient surgery is 3%, and 15% of patients suffer from perioperative organ injury. Lung injury, kidney injury (AKI), myocardial injury, and brain injury represent a large portion of perioperative morbidity. Oxygen administration during surgery may affect these complications, yet the optimal fraction of inspired oxygen (FiO2) during surgery remains unknown. There is biologic rationale for administration of lower, intermediate, or higher FiO2 during surgery. For example, a higher FiO2 increases oxygen content in tissues, may decrease regional hypoxia, and might limit poor clinical outcomes associated with perioperative ischemia. Conversely, a lower FiO2 may decrease reactive oxygen species production, attenuate reperfusion injury, and has been associated with lower rates of organ injury. An intermediate FiO2 could maximize the theoretical benefits or risks of a higher and lower FiO2. In current clinical practice, the approach to intraoperative oxygen administration varies considerably across providers and centers. In our recent 350,000-patient multicenter observational study, intraoperative FiO2 ranged from air (0.21) to pure oxygen (1.00). Patient and procedure factors accounted for less than 10% of the variability of FiO2 administration during surgery, whereas the anesthesiologist/anesthesia provider caring for the patient accounted for 15%, the medical center where the patient received surgery accounted for 25%, and over 50% of variability of FiO2 administration was not accounted for by any measured factor. These data suggest FiO2 administration is based on factors unrelated to knowledge of what oxygen administration strategy would result in the best outcomes for patients. Prior research has provided mixed evidence as to what intraoperative FiO2 leads to the best postoperative outcomes. A better understanding of the comparative effectiveness of common, standard-of-care approaches to intraoperative oxygen administration could improve the care clinicians deliver and patient outcomes. Thus, a large, multicenter trial to understand the optimal approach to oxygen administration during surgery is urgently needed.
Study Design	Multi-center, single-blinded, cluster-randomized, cluster crossover, clinical trial
Trial Groups	1. Lower FiO2 (FiO2 0.21-0.40) 2. Intermediate FiO2 (FiO2 0.40-0.80) 3. Higher FiO2 (FiO2 0.80-1.00)
Inclusion Criteria	1. Patient is located in a participating operating room 2. Patient's planned surgical case includes tracheal intubation

Exclusion Criteria	1. Patient is known to be less than 18 years old 2. Patient is known to be pregnant 3. Patient is known to be a prisoner. 4. Patient is American Society of Anesthesiologists (ASA) classification 6 (i.e., organ donor) 5. Patients's planned surgical case includes open heart surgery, defined as surgery on the heart or ascending aorta requiring sternotomy or thoracotomy. 6. Patient's planned surgical case requires prolonged apnea, bronchoscopy, airway surgery, or one-lung ventilation. 7. Patient's planned surgical case includes extracorporeal membrane oxygenation (ECMO). 8. Patient is known to have a history of bleomycin treatment. 9. Patient was enrolled in the trial in the prior 30 days.
Risks	Participation in this study involves minimal incremental risk because: • The three approaches to intraoperative oxygen administration are commonly used in routine clinical care; • The approaches are interventions to which patients would be exposed even if not participating in the research; • No established differences in risk and benefit are known to exist among the three approaches based on the currently available data; and • If a specific approach to oxygen administration is determined to be required for the optimal treatment of an individual patient at any point during the research, trial protocol specifies that treating clinicians will use the approach to oxygen administration that treating clinicians determine to be optimal, regardless of trial group assignment.
Benefits	The benefits are largely the indirect benefits to future patients that will result by a better understanding of which approach to oxygen administration during surgery optimizes patient outcomes.
Consent	The trial will be conducted with waiver of informed consent because: • Participation in the study involves minimal incremental risk • Obtaining informed consent is impracticable • The waiver does not adversely affect the rights and welfare of the subjects.
Randomization	Each hospital will be randomized to one of the three oxygen administration groups (cluster-level randomization) and will then crossover every month between the three oxygen administration groups (cluster-level crossover) in a randomly generated sequence using permuted blocks of three. All eligible patients undergoing surgery at a participating hospital will receive the oxygen administration strategy assigned for the 1-month period.

Primary Outcome	The primary outcome will be perioperative organ injury or inhospital death within 30 days of surgery. Specific organ injuries for this dichotomous outcome are AKI, myocardial injury, lung injury, and stroke, each of which is defined herein.
Secondary Outcome	30-day inhospital mortality
Exploratory Outcomes	Clinical: ∉ AKI ∉ Myocardial injury ∉ Lung injury ∉ Stroke ∉ Surgical site infection as defined by NSQIP ∉ Hospital length of stay Safety: ∉ Hypoxemia, defined as SpO2 < 80% (incidence and duration)
Process Measures	∉ FiO2 received ∉ SpO2 ∉ Treatment adherence ∉ Number of FiO2 titrations (defined as change in FiO2 ≥ 0.10)
Analysis	The primary analysis will compare the primary outcome between patients assigned to the lower, intermediate, and higher FiO2 groups with the use of a logistic regression model with independent covariates of group assignment, time, and site. In addition to assessing for an overall group effect within the model, we will report the differences between each pair of FiO2 groups by extracting estimates and 95% confidence intervals from the model.
Sample Size	54,000 patients
Expected Duration	36 months

1. Background

Perioperative mortality and organ injury remain major contributors to population health and morbidity. For example, acute kidney injury (AKI), myocardial injury, pulmonary complications, and neurologic complications including stroke affect up to 15% of patients following moderate-risk inpatient surgery. These acute organ injuries prolong critical illness and increase long-term morbidity such as chronic kidney disease, cognitive decline, and heart failure.[1–3] Perioperative organ injury increases odds of death at 30-days by 500%.[4–6] This translates into a significant source of population morbidity considering there are more than 200 million surgeries performed each year worldwide. Ischemia, reperfusion, oxidative damage, vascular dysfunction, and inflammation are major contributors to perioperative organ injury and poor outcomes. Oxygen is the key regulator of these processes and the health and function of aerobic processes, yet we do not know the best fraction of inspired oxygen (FiO_2) to administer during surgery, both for a population or for subgroups based on disease states or surgical procedures.

There is biologic rationale for administration of lower, intermediate, and higher FiO2 during surgery. For example, a higher FiO2 increases oxygen content in tissues,[7] may decrease regional hypoxia,[8] and might limit poor clinical outcomes associated with perioperative ischemia.[9] Conversely, a lower FiO2 may decrease reactive oxygen species production,[10,11] attenuate reperfusion injury,[12,13] and has been associated with lower rates of organ injury.[14] An intermediate FiO2 could maximize the theoretical benefits or risks of a higher and lower FiO2.

Before the routine use of continue pulse oximetry, anesthesiologists historically administered supplemental oxygen to avoid hypoxia, even for patients who were not expected to require supplemental oxygen. Now, continuous pulse oximetry provides the ability to detect and avoid hypoxemia while using lower, intermediate, or higher FiO2 level, but the approach to intraoperative oxygen administration varies considerably across providers and centers. In our recent 350,000-patient multicenter observational study, intraoperative FiO2 ranged from air (0.21) to pure oxygen (1.00). Patient and procedure factors accounted for less than 10% of the variability of FiO2 administration during surgery, whereas the anesthesiologist/anesthesia provider caring for the patient accounted for 15%, the medical center where the patient received surgery accounted for 25%, and over 50% of variability of FiO2 administration was not accounted for by any measured factor. These data suggest FiO2 administration is based on factors unrelated to knowledge of what oxygen administration strategy would result in the best outcomes for patients. Prior research has provided mixed evidence as to what intraoperative FiO2 leads to the best postoperative outcomes. Studies of intraoperative oxygen administration have focused primarily on narrow patient populations (e.g., patients undergoing colorectal or cardiac surgery) and reported conflicting data on the relationship between oxygen administration strategy and outcomes like surgical site infection (SSI), AKI, and mortality.[15–20] A better understanding of the comparative effectiveness of common, standard-of-care approaches to intraoperative oxygen administration could improve the care clinicians deliver and patient outcomes. Robust determination of clinically important effects of varied intraoperative FiO_2 requires thousands of patients but is critically important to the health of the millions of patients who undergo surgery each year. Thus, a large, multicenter trial to understand the optimal approach to oxygen administration during surgery is urgently needed.

2. Study Description

We propose a multi-center, single-blinded, cluster-randomized, cluster-crossover clinical trial comparing the effect of three commonly used intraoperative oxygen administration strategies on organ injury or death in adult patients having surgery. During the trial, each hospital will be considered a cluster. Each month will be considered a period. All eligible patients receiving surgery in a participating hospital (cluster) during a participating month (period) will receive the oxygen administration strategy assigned to the hospital for that one month period. After each period, the hospital (cluster) will cross over to another of the oxygen administration strategies. All other decisions regarding mechanical ventilation and patient management will be at the discretion of the treating clinicians.

3. Inclusion and Exclusion Criteria

3.1. Inclusion Criteria

1. Patient located in a participating operating room.
2. Patient's planned surgery includes tracheal intubation.

3.2. Exclusion Criteria

1. Patient is known to be less than 18 years old.
2. Patient is known to be pregnant.
3. Patient is known to be a prisoner.
4. Patient is American Society of Anesthesiologists (ASA) classification-6 (i.e., organ donor)
5. Patient's planned surgical case includes open heart surgery, defined as surgery on the heart or ascending aorta requiring sternotomy or thoracotomy.
6. Patient's planned procedure requires prolonged apnea, bronchoscopy, airway surgery or one-lung ventilation.
7. Patient's planned surgical case includes use of extracorporeal membrane oxygenation (ECMO).
8. Patient is known to have a history of bleomycin treatment.
9. Patient was enrolled in the trial in the prior 30 days.

3.2.1. Rationale for Exclusion Criteria

We will exclude patients who have conditions or history known to have increased risk with one of the treatment arms, patients receiving a procedure where administration of one of the treatment arms is impossible or highly difficult, and patients who are members of a vulnerable population. Patients with age less than 18 years will be excluded because this is a study of adults, and the study will occur at adult hospitals. Patients known to be pregnant will be excluded because the effects of different oxygen administration strategies on the fetus are unknown and will not be measured. Patients known to be prisoners will be excluded because prisoners may not have the autonomy to make decisions about their care. Patients with planned procedures to the heart or ascending aorta requiring sternotomy or thoracotomy will be excluded because these procedures typically require cardiopulmonary bypass, during which oxygen administration is controlled by a perfusionist using an oxygenator in the

cardiopulmonary bypass circuit, and mechanical ventilation is discontinued. In addition, the non-pulsatile flow of cardiopulmonary bypass impairs the ability of the pulse oximeter to measure arterial hemoglobin oxygen saturation, thereby impairing the ability to maintain SpO2 $\geq$ 94% while titrating FiO2. For the same reasons we will exclude cases that use ECMO. Patients with planned procedure requiring prolonged apnea or one-lung ventilation will be excluded because temporary cessation of ventilation and one-lung ventilation markedly reduce oxygen absorption and increase shunt. To counter these effects and limit hypoxemia, it is usual care to administer high FiO2 prior to apnea and during one-lung ventilation. Patients with planned airway surgery will be excluded because these surgeries require lower FiO2 to reduce risk of airway fire. Patients known to have a history of bleomycin treatment will be excluded because higher FiO2 can cause pulmonary toxicity in patients who have received bleomycin.[21] Cases occurring within 30-days of a prior included case will be excluded to ensure that each participant's outcomes are only associated with one case during each 30-day outcome observation window.

3.2.2. Documentation of Exclusion Criteria

The presence or absence of each of the eligibility criteria is routinely documented in a structure form in the electronic health record during the preoperative assessment of patients. Specifically, bleomycin exposure, planned tracheal intubation, and planned one-lung ventilation are documented in the preoperative anesthesia evaluation, pregnancy status is documented by the preprocedural nursing and noted within the OB section, prisoner status is denoted by an administrative flag, and planned surgery, patient age, and operating room location are denoted within the surgical case schedule. These data from the electronic health record will be used to assess eligibility at the time of trial enrollment, as described below.

4. Consent

This trial will only enroll patients who are already receiving oxygen administration during invasive mechanical ventilation for a surgical procedure. The trial will compare three standard-of-care approaches to oxygen administration during surgery. Each of the three approaches compared is commonly used in current clinical care, and no differences in risk or benefit between the three approaches are known. Because no rigorous data inform whether one approach results in better outcomes, the approach that an individual patient receives in clinical care varies based on arbitrary factors like the hospital and the clinician.[22] Participation in this study is limited to treatments patients would have received as a part of their clinical care outside of the research. We request a waiver of informed consent because the study involves minimal incremental risk, obtaining informed consent would be impracticable, and the waiver does not adversely affect the rights and welfare of the subjects.

Participation in this study involves minimal incremental risk because:

- The three approaches to intraoperative oxygen administration are commonly used in routine clinical care;
- The approaches are interventions to which patients would be exposed even if not participating in the research;
- No established differences in risk and benefit are known to exist among the three approaches based on the currently available data; and

- If a specific approach to oxygen administration is determined to be required for the optimal treatment of an individual patient at any point during the research, trial protocol specifies that treating clinicians will use the approach to oxygen administration that treating clinicians determine to be optimal, regardless of trial group assignment.

Obtaining informed consent would be impracticable because of:

- The cluster-level design. Oxygen is administered during surgery by teams of clinicians. As with other recent trials of oxygen administration during acute illness,[23] this trial is designed as a cluster-level trial so that all of the anesthesiology teams in the study environments will be working together to apply the intervention assigned to that period for all of the patients in their care as a group. The care environment as a whole will be altered to ensure adherence to the assigned intervention. For informed consent to be meaningful, dissent must be possible. If written consent were offered and a patient declined, the patient would still receive care by the anesthesiology teams working together to deliver the assigned intervention to all patients in their care. In order to receive care that was not influenced by the trial group assignment, the patient would have to undergo surgery at another health system. Thus, in this cluster-level trial at the health system scale, the lack of the capacity for meaningful dissent makes informed consent impracticable.
- The scale of the study. The scale of the trial population (54,000 adults undergoing surgery at four centers in the United States) means that research personnel could not practicably obtain written informed consent from every patient undergoing surgery every day at each participating center for the study period. Written informed consent is thus logistically impracticable.
- Informed consent would introduce bias and remove patients who may be most likely to benefit from the research. Excluding patients who are unable to provide written informed consent would preferentially exclude severely ill patients and those undergoing emergency surgery (those who lack decisional capacity or lack time in which to execute a robust informed consent process). Severely ill patients and those undergoing emergency surgery are patients for whom the risks of death and organ injury are highest and may be the group for whom the approach to intraoperative oxygen therapy matters most. Selectively excluding these patients because they are unable to provide written informed consent risks compromising the scientific integrity of the trial and obtaining a falsely "negative" trial result because patients most likely to benefit were systematically excluded.

The waiver does not adversely affect the rights and welfare of the subjects because:

- The study involves collection of only routine data generated as part of clinical care and documented by clinicians in the electronic health record.
- The study will occur in usual clinical-care settings in which patients are not offered choices about their level of oxygen therapy during surgery as a part of routine clinical care.

Because the study involves minimal incremental risk, obtaining informed consent would be impracticable, and the study would not adversely affect the welfare or privacy rights of the participants, we will request a waiver of informed consent. Previous randomized trials comparing standards of care for intraoperative oxygenation have also been completed under a waiver of informed consent including a 40,000-patient trial of intraoperative oxygen targets in critical illness that enrolled patients after elective surgery,[24] an 8000-patient cluster-crossover trial of video vs. direct laryngoscopy for tracheal intubation

in the operating room,[25] and a 6000-patient crossover trial of intraoperative oxygenation strategies in elective surgery patients.[26]

It was determined to be infeasible to notify patients of study participation because 1) there are no direct interactions between research personnel and patients, 2) the clinicians who deliver the study intervention (anesthesiologists and anesthetists in the operating room) have limited interaction with patients outside of the operating room (during which the patient has decisional capacity), and 3) patients may present directly to the operating room from a large variety of locations (e.g., emergency department, intensive care unit, hospital ward, pre-operative area), making it infeasible to use general notification approaches like posters or informational flyers.

5. Study Sites, Enrollment, Run-in Period, and Randomization

5.1. Study Sites and Enrollment Locations

Each participating hospital is a site, and enrollment locations are participating operating rooms.

5.2. Enrollment

All patients receiving surgery in a participating operating room will be screened for eligibility using the eligibility criteria in Section 3. Patients who do not meet inclusion criteria will be considered 'ineligible.' Patients who meet inclusion criteria but also meet at least one exclusion criterion will be considered 'excluded.' Enrollment in the trial ("time zero") will be considered to occur at the time of tracheal intubation for surgery in a patient who meets all inclusion criteria and no exclusion criteria.

5.2.1. Monitoring and Reporting of Eligibility of Enrolled Patients

If a patient is identified as having been enrolled without having met trial eligibility criteria at the time of enrollment, this will be considered a protocol deviation or a protocol violation. Site investigators will report such a protocol deviation or protocol violation to the trial primary investigators and coordinating center in accordance with the guidance on protocol deviations and protocol violations in Section 12.6.

5.2.2. Handling of Patients Found to Be Prisoners after Enrollment

If a patient who presents to surgery is not documented as a prisoner at the time of enrollment and following enrollment is discovered to be a prisoner, all study procedures will stop immediately, the patient will be withdrawn from the study, and the patient's study record will be expunged of all study data except the anonymous study ID, treatment assignment, and the reason for study exclusion (prisoner). Because the three study interventions are one-time, standard-of-care interventions which the patient was likely to receive in clinical care even if not participating in research, no further follow-up will occur.

5.3. Run-in Vanguard Phase

To assess and practice trial procedures, a run-in phase will be used. The run-in phase will include three one-month study periods, during which the trial will randomly assign each of the three oxygenation

strategies. Perioperative data and study outcomes will be collected from MPOG data reports, and we will assess protocol adherence and data management procedures. The run-in phase will be used to assess and improve delivery of the study intervention, collection of process measures and trial outcomes, methods and timeliness of data sharing between sites and the data and clinical coordinating centers, and feasibility for the trial. Procedures to improve these measures, such as alteration in adherence means (Section 6.5) or alteration in the processes for data transfer and review and site feedback, may be implemented during the run-in phase. Patients enrolled during the run-in phase will be included in the trial sample.

5.4. Randomization

Each hospital will be randomized to one of the three oxygen administration groups (cluster-level randomization) and will then crossover every month between the three oxygen administration groups (cluster-level crossover) in a randomly generated sequence using permuted blocks of three. Sites will be randomized in permuted blocks of 3 to maintain balance across treatments during each period (**Table 1**). All eligible patients undergoing surgery during the study period at a participating hospital will receive the oxygen administration strategy assigned for the 1-month period. This provides the best opportunity to balance treatment and any temporal effects across each hospital and across the study.

Table 1. Example treatment assignments (A: lower FiO2; B: intermediate FiO2; C: higher FiO2) showing sequence for 24 1-month periods and staggered start. Treatment assignment is randomized at each site in permuted blocks of 3, and treatment assignment is randomized in permuted blocks of 3 across sites during each period, ensuring balance of treatment assignments within and across sites throughout the study.

Site	Period																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	A	B	C	B	A	C	A	B	C	C	B	A	B	C	A	B	A	C	C	B	A	A	C	B
2				C	B	A	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B
3				A	C	B	B	C	A	A	B	C	A	B	C	B	C	A	A	B	C	B	A	C
4							C	A	B	B	C	A	C	B	A	A	B	C	B	C	A	C	B	A

6. Study Procedures

For enrolled patients, the study will control only the approach to oxygen administration during surgery, defined as the period from tracheal intubation until the first of emergence from anesthesia, extubation, or transfer out of the operating room.

For all patients in the study, regardless of the group to which they are assigned, continuous SpO2 monitoring will be used to maintain SpO2 values of 94% or greater at all times. This provides ample safety margin as SpO2 90-100% is considered normal and SpO2 <80% considered to represent intraoperative hypoxemia.

At any point during the study, if a treating clinician determines that a specific approach to oxygen administration is required for the optimal care of a patient, the treating clinician will be instructed to use that approach, regardless of the group to which they are assigned.

6.1. Lower FiO2 Group

For patients assigned to the lower FiO2 group, clinicians will be instructed to administer an FiO2 of <0.40 or the lowest FiO2 required to target an SpO2 ≥ 94%.

6.2. Intermediate FiO2 Group

For patients assigned to the intermediate FiO2 group, clinicians will be instructed to administer an FiO2 of 0.40-0.80 or the lowest FiO2 required to target an SpO2 ≥ 94%.

6.3. Higher FiO2 Group

For patients assigned to the higher FiO2 group, clinicians will be instructed to administer an FiO2 of >0.80 and target an SpO2 ≥ 94%.

6.4 Co-interventions

Other co-interventions such as tidal volume, respiratory rate, and positive end-expiratory pressure will be at the discretion of treating clinicians. Treating clinicians may opt to use a different approach to oxygenation administration if it is felt to be required for the safe care of the patient. The occurrence of such "crossover" event will be recorded along with the indication in the following manner. A Best Practice Advisory (BPA) pop-up will appear in the anesthetic record when the patient's FiO2 is above range and SpO2 is > 97% or if the patient's FiO2 is below range (see Electronic means in Section 6.5 Adherence). This prompt will encourage providers to adjust FiO2 accordingly but also provide opportunity to document the indication for not following target FiO2. All other aspects of intraoperative patient management in all study groups will be at the discretion of the clinicians. For all patients in the trial, best practices in intraoperative patient management will be encouraged according to departmental Center for Evidence-Based Anesthesia (CEBA) clinical pathways and Enhanced Recovery After Surgery (ERAS) protocols.

6.5 Adherence

The study will use human means (research personnel) and electronic means (information and alerts imbedded in the electronic health record) to promote adherence.

- Human means – Site research coordinators and Site investigators
    - Site personnel will promote study adherence within clinician groups at division and group meetings prior to and throughout the study.
    - Site personnel will circulate throughout operating rooms daily and be available throughout the study promoting study adherence and addressing questions and comments.
    - Site personnel will have access to a tablet dashboard with real time FiO2 and SpO2 in all participating ORs so that coordinators and investigators can target support in real-time for different procedures, patients, and providers.
- Electronic means – Anesthetic care record embedded banners, data, and prompts
    - Study banner. Electronic queries screen the surgical schedule and preoperative component of anesthetic record to identify eligible patients based on inclusion/exclusion criteria. A pre-procedure banner will alert anesthesia providers (anesthesiologist, resident,

fellow, certified registered nurse anesthetists, etc.) that the patient is included or excluded from the study, remind the provider of the treatment assignment based on the study period, and provide brief instructions on administering the treatment.

- Intra-procedure sidebar. A persistent sidebar will display the Study banner and minute-to-minute FiO2 and SpO2 data, color coded for in-range/on target, in-range/out of target, and out of range based on treatment assignment, FiO2, and SpO2.
- Intra-procedure best practice advisory (BPA). If the FiO2 and SpO2 are out of range (either the FiO2 is higher than treatment assignment and the SpO2 is >97% or the FiO2 is lower than the treatment assignment), a BPA pop-up will appear in the anesthetic care record alerting the provider that the FiO2 is out of range. The provider may alter FiO2 to get in-range and also will have opportunity to document any reason, for example the patient is now receiving a procedure that would have excluded the patient from study or the SpO2 monitor is unreliable. EHR embedded BPAs are commonly and effectively used by anesthesia providers during surgery to improve adherence to different quality measures and management plans, for example to promote glucose monitoring or antibiotic administration.

7. Data Collection and Outcome Measures

7.1. Data Collection

Data collected for the purposes of this study will be collected from data submitted to the Multicenter Perioperative Outcomes Group (MPOG) at University of Michigan as part of an existing Data Use Agreement and IRB 090658. The electronic health record data collected locally that are sent to MPOG are documented in the electronic health record as part of clinical care and electronically collected under the existing IRB 090658 study and data use agreement (independent from the present study). These data are defined by existing and validated MPOG phenotypes.[27] All clinical data will be collected from these existing MPOG data reports. The data elements that will be collected from these reports are:

Operating room ID
Admission Type
Age (Years)
AHRQ Complication - Pulmonary - All
Airway Type
Airway Type Notes
Airway: Arrived Intubated
Anesthesia CPT (Measures)
Anesthesia CPT (Primary)
Anesthesia Duration
Anesthesia End
Anesthesia Start
Anesthesia Technique: General
Anesthesia Technique: Neuraxial
Anesthesia Technique: Sedation
ASA Class

Baseline Blood Pressure - Mean
Blood Product Total - Cryoprecipitate
Blood Product Total - FFP
Blood Product Total - Platelets
Blood Product Total - PRBCs
BMI
Duration of Anesthesiology Attending Sign-in
Duration of Anesthesiology Resident Sign-in
Duration of CRNA and Anesthesia Assistant Sign-in
Elixhauser Comorbidity - AIDS \ HIV
Elixhauser Comorbidity - Alcohol Abuse
Elixhauser Comorbidity - Blood Loss Anemia
Elixhauser Comorbidity - Cardiac Arrhythmias
Elixhauser Comorbidity - Chronic Pulmonary Disease
Elixhauser Comorbidity - Coagulopathy
Elixhauser Comorbidity - Congestive Heart Failure
Elixhauser Comorbidity - Deficiency Anemia
Elixhauser Comorbidity - Depression
Elixhauser Comorbidity - Diabetes (Complicated)
Elixhauser Comorbidity - Diabetes (Uncomplicated)
Elixhauser Comorbidity - Drug Abuse
Elixhauser Comorbidity - Fluid/Electrolyte Disorders
Elixhauser Comorbidity - Hypertension (Complicated)
Elixhauser Comorbidity - Hypertension (Uncomplicated)
Elixhauser Comorbidity - Hypothyroidism
Elixhauser Comorbidity - Liver Disease
Elixhauser Comorbidity - Lymphoma
Elixhauser Comorbidity - Metastatic Cancer
Elixhauser Comorbidity - Obesity
Elixhauser Comorbidity - Other Neurological Disorders
Elixhauser Comorbidity - Paralysis
Elixhauser Comorbidity - Peptic Ulcer Disease, Excluding Bleeding
Elixhauser Comorbidity - Peripheral Vascular Disorders
Elixhauser Comorbidity - Psychoses
Elixhauser Comorbidity - Pulmonary Circulation Disorders
Elixhauser Comorbidity - Renal Failure
Elixhauser Comorbidity - Rheumatoid Arthritis Collagen Vascular Diseases
Elixhauser Comorbidity - Solid Tumor Without Metastasis
Elixhauser Comorbidity - Valvular Disease
Elixhauser Comorbidity - Weight Loss
Emergency Status (ASA Class) Yes/No
Endotracheal Tube
Extubation Times
First In Room Blood Pressure
Height (cm)
Intraoperative MAP (Minutes Under 65) - THRIVE

Intubation Time
Is Valid Case
Last Known Alive
Length of Stay After Procedure (Days)
Maintenance End
Measure: AKI-01
Measure: CARD-02
Measure: CARD-03
Measure: MORT-01
Measure: PUL-01
Measure: PUL-02
Measure: PUL-03
Measure: SMOK-01
Measure: SUS-07
Median Intraoperative Temperature
Mortality (In Hospital 30-day)
MPOG Complication - Acute Kidney Injury (AKI)
MPOG Complication - Acute Kidney Injury (AKI) - THRIVE
MPOG Complication - Renal Recovery
MPOG Patient ID
Nitrous Oxide Used
Patient In Room Date/Time
Patient Out Of Room Date/Time
PEEP Actual Median
PEEP Set Median
Postop Troponin I (Highest)
Postoperative Destination
Postoperative Destination Notes
Preop Blood Pressure - Mean
Preop BUN
Preop Calcium Ionized
Preop Creatinine (Most Recent within 60 days)
Preop EGFR (Lowest within 60 Days)
Preop EGFR (Most Recent)
Preop Glucose
Preop Hematocrit
Preop Hemoglobin
Preop HgbA1c
Preop INR
Preop Lactate
Preop Platelet Count
Preop PTT
Preop Sodium
Preop Total Bilirubin
Preop Troponin I (Highest)
Preop Troponin I (Most Recent)

Preop WBC
Primary Provider
Procedure Type: Bronchoscopy
Procedure Type: Cardiac
Race
Sex
Smoking Tobacco Classification (new)
Starting Provider
Surgery Duration
Surgery End
Surgery Start Date/Time
Surgical CPT (Primary)
Surgical CPTs (All)
Surgical Service
Tidal Volume Actual
Tidal Volume Actual (Median)
Tidal Volume Set
Tidal Volume Set (Median)
Tobacco Smoking Classification
Total Colloid Administered
Total Crystalloid Administered
Total Estimated Blood Loss (EBL)
Total Urine Output
Units Transfused
Ventilation During Intraop
Ventilator Start Time
Weight (kg)
Induction End
Induction Start
Measure: BP-01
Measure: BP-02
Measure: BP-03
Measure: BP-05
Measure: BP-06
PACU Duration
PACU End Time
PACU Start Time
Patient History - Sleep Apnea
Preop Albumin
Preop Alk Phosphatase
Preop ALT
Preop Arterial pH
Preop AST
Preop Bicarbonate
Preop Calcium Total
Preop Carbon Dioxide (pCO2), arterial

Preop Carbon Dioxide (pCO2), mixed venous
Preop Carbon Dioxide (pCO2), venous
Preop Chloride
Preop Potassium
Preop Protein
Preop PT
SpO2 %
Ventilator FiO2 % Measured
Ventilator FiO2 % Set
Oxygen Insp %
Oxygen Exp %
Nitrous Insp %
Nitrous Exp %
Fresh Gas Flow Total (L/min)
Flows Oxygen (L/Min)
Flows Air (L/min)
Flows Nitrous Oxide (L/min)
Ventilator Mode
Airway- Supplemental Oxygen
Peak inspiratory pressure
Tidal Volume actual
Ventilator Respiratory Rate Actual
Ventilator Respiratory Rate Set
Respiratory Rate Actual from EtCO2 tracing
Respiratory Rate - Unspecified source
Minute ventilation
Positive End Expiratory Pressure - Measured
Positive End Expiratory Pressure - Set
End Tidal CO2 (mmHg)
End Tidal CO2 %
rSO2 Index - Right Cerebral
rSO2 Index - Left Cerebral
rSO2 Index Cerebral
Regional Oxygen Saturation Baseline
Regional Oxygen Saturation
SvO2 %
Cardiac Rhythm
EKG Pulse Rate
BP Sys Non-invasive
BP Dias Non-invasive
BP Mean Non-invasive
Temp 1 - Unspecified Site
Temperature - Esophageal
BIS - Overall Trend (BIS Value)
Sedation Assessment (Richmond Agitation Sedation Scale-RASS)
Confusion Assessment Method (CAM) Score

Pain Score (Generic)
Pain Score (Visual Analog Scale)
CPT_nsqip
SSI_superficial
SSI_superficial_patos
SSI_superficial_days_from_surgery
SSI_deep
SSI_deep_patos
SSI_deep_days_from_surgery
SSI_organ_space
SSI_organ_space_patos
SSI_organ_space_days_from_surgery
SSI_dehis
SSI_dehis_days_from_surgery

In addition, the data collected for each patient during the course of the trial (described above), information on any adverse events, protocol deviations or violations, or unanticipated problems (as described below in Section 12) will be collected in a site-specific password-protected encrypted REDCap database only available to project team members with existing electronic health record system access rights.Sites may also collect and store locally data for the purposes of monitoring intervention delivery and validating data phenotypes developed by MPOG.

7.2 Study Outcomes

7.2.1 Primary Outcome

The primary outcome is organ injury or death within 30 days of surgery. This dichotomous composite outcome is considered to have occurred if either (a) the patient experienced organ injury (as defined below) or (b) the patient experienced in-hospital mortality (as defined below).

Organ Injury. For the primary outcome, organ injury will include AKI, myocardial injury, lung injury, and stroke. These organ injuries have been defined and validated by external consensus panels and patient registries,[28–32] incorporated into current MPOG phenotypes,[27] and reported in prior investigative studies.[14,33,34]

- AKI is defined according to creatinine based Kidney Disease Improving Global Outcomes criteria, specifically a 0.3 mg/dL or greater increase within 48 hours or a 50% or greater increase from baseline within seven days of surgery.[28] Patients with preoperative renal failure (end stage renal disease patients receiving maintenance dialysis or an estimated glomerular filtration rate <15 mL/ min/1.73 m^2) or no measured creatinine within 60 days preoperatively are excluded from analysis of AKI.
- Myocardial injury is defined as $\geq 99^{th}$ percentile of normal based on site-specific assay within 72 hours.[29,35,36] Patients with biochemical evidence of preoperative myocardial injury (plasma troponin greater than upper limit of normal within 42 days before surgery) or those undergoing cardiac procedures that could increase plasma troponin independent of myocardial injury are excluded from analysis of myocardial injury. Serum creatinine and troponin are measured based

on medical center and provider practices or according to clinical indication. These laboratory values are extracted from the electronic health record and computed to determine AKI and myocardial injury.

- Lung injury and stroke are defined using international classification of diseases, ninth revision or tenth revision (ICD-9 or ICD-10) hospital discharge diagnosis codes, as endorsed by international consensus guidelines, Agency for Healthcare Research and Quality Patient Safety Indicator reports for postoperative respiratory failure, and previously published clinical registry postoperative lung injury studies.[14,30–34]

Death. Death is defined as 30-day inhospital mortality defined as death during the same encounter as the procedure within 30 days.

7.2.2. Secondary Outcomes

The secondary outcome is 30-day inhospital mortality

7.2.3. Exploratory Outcomes

Clinical:

- ∉ AKI (as defined above)
- ∉ Myocardial injury (as defined above)
- ∉ Lung injury (as defined above)
- ∉ Stroke (as defined above)
- ∉ Surgical site infection as defined by National Surgical Quality Improvement Program (NSQIP) criteria. Similar to each of the other outcomes, surgical site infection is also currently captured using data in the Electronic Health Record for registry reporting.
- ∉ Hospital length of stay

Safety:

- ∉ Hypoxemia, defined as $SpO_2 < 80\%$ (incidence and duration)

7.2.4 Process Measures

- FiO2 received
- SpO2
- Treatment adherence. Minute-to-minute intraoperative FiO2 and SpO2 data will be collected for each case in order to measure treatment received and adherence to treatment. Adherence to treatment for each case will be measured by determining the percent of 10-minute epochs, starting 10 minutes after intubation and culminating 5 minutes prior to surgery end, during which the majority of time the FiO2 is within the specific range for the treatment and SpO2 > 93% or above range if SpO2 < 97% (i.e., necessary higher FiO2 to maintain SpO2).
- Number of FiO2 titrations during surgery (defined as change in FiO2 $\geq$ 0.10)

8. Risks and Benefits

8.1. Potential Risks of Surgery

Surgery with tracheal intubation, mechanical ventilation, and general anesthesia is associated with significant risk of intraoperative and postoperative morbidity and mortality. AKI, myocardial injury, pulmonary complications, and neurologic complications including stroke affect up to 15% of patients following moderate-risk inpatient surgery, and patients who experience a perioperative organ injury increase their odds of death at 30-days by 500%.[4–6]. Further, acute organ may increase long-term morbidity such as chronic kidney disease, cognitive decline, and heart failure.[1–3] Other complications of surgery with general anesthesia may include nausea, vomiting, aspiration, laryngeal injury, pneumothorax, delirium, cognitive dysfunction, seizures, peripheral neuropathies, hemorrhage, and mechanical damage to organs, vasculature, and other structures, urinary retention, coma, and paralysis.

These risks are present for anyone undergoing surgery and are present regardless of the FiO2 used during surgery. Learning whether the intraoperative FiO2 affects these risks is the purpose of this trial.

8.2. Potential Risks of Participation in the Intraop Ox Trial

Participation in this study involves minimal incremental risk because:

- Approaches to intraoperative oxygen administration being compared are commonly used in routine clinical care;
- The approaches to intraoperative oxygen administration being compared are interventions to which patients would be exposed even if not participating in the study (all patients undergoing surgery with tracheal intubation receive supplemental oxygen);
- No established differences in risk and benefit are known to exist between the approaches based on the currently available data; and
- If a specific approach to oxygen administration is determined to be required for the optimal treatment of an individual patient at any point during the research, trial protocol specifies that treating clinicians will use the approach to oxygen administration that treating clinicians determine to be optimal, regardless of trial group assignment.

Although no risks are currently known to differ among the patients provided a lower FiO2, intermediate FiO2, or a higher FiO2 during surgery (each of which is a standard-of-care approach in currently clinical care), it is possible that the results of the Intraop Ox trial will ultimately demonstrate a difference among the approaches to intraoperative oxygenation in the risk of mortality, organ injury, or another outcome.

8.3. Potential Benefits of Participation in the Intraop Ox Trial

The primary benefits of the Intraop Ox trial will be the indirect benefits to society that would result if one approach to intraoperative oxygenation is found to prevent complications of surgery with general anesthesia. Because millions of adults undergo surgery with general anesthesia each year, if one of the three approaches were found to prevent serious complications, the findings would immediately improve the care provided to millions of patients receiving surgery. Compared to the minimal risks of participation in the study, the pursuit of these benefits is reasonable.

8.4. Minimization of Risk

Federal regulations 45 CFR 46.111(a)(1) require that risks to patients are minimized by using procedures which are consistent with sound research design. This trial meets this human subjects protection requirement by incorporating numerous design elements to minimize risk to patients including the following.

First, all three treatment groups have been used during surgery in clinical practice for years with an established safety profile in the same populations included in the Intraop Ox trial. Second, the trial will exclude patients who have conditions or history known to have increased risk with one of the treatment arms and patients receiving a procedure where administration of one of the treatment arms is impossible or highly difficult. Third, if at any time a clinician believes that a specific approach to oxygen administration is required for the optimal treatment of an individual patient, they will use the approach to oxygen administration that they believe to be optimal, regardless of trial group assignment. Fourth, the trial protocol includes monitoring of adverse events, robust assessment of clinical outcomes, and an interim analysis by an independent DSMB, empowered to stop the trial or modify the trial protocol at any time.

Finally, to limit the risks associated with the collection of protected health information (PHI), the minimum amount of PHI necessary for study conduct will be collected. We will not collect any patient names, addresses, telephone numbers, email addresses, medical record numbers, or social security numbers. We will collect date of surgery and dates of certain outcomes such as death or organ injury. The data will be coded and stored in a secure online database only accessible by the investigators. To maximize participant privacy, only deidentified data will be available for analysis.

9. Statistical Considerations

9.1. General Considerations

We will present summary tabulations by treatment group. For categorical variables, the number and proportion of patients within each category (with a category for missing data as needed) of the variable will be presented. For continuous variables, the number of patients, mean or median as appropriate, and standard deviation or interquartile range as appropriate, will be presented.

We will analyze a single pre-specified primary outcome and a single pre-specified secondary outcome using a multiple degree-of-freedom test comparing the lower, intermediate, and higher FiO2 groups simultaneously, such that the null hypothesis will be rejected if there is strong evidence of any differences between the three groups. Consistent with recommendations of the Food and Drug Administration[26] and the European Medicines Agency,[27] the treatment effect on the primary outcome and the secondary outcome will each be assessed using a P value with a significance level of 0.05. Unless otherwise specified, all other analyses will emphasize estimates of effect size with 95% confidence intervals, as recommended by the *International Committee of Medical Journal Editors*.[28] Except for interim analyses, as specified below, there are no overarching statistical hypotheses addressed that used multiple tests and that would warrant familywise type-I error control (i.e., adjustment for multiple comparisons) across the independent hypotheses,[37,38] and no other corrections for multiple comparisons will be performed.

9.2. Sample Size Estimation

This sample size estimate for the trial was based on data from patients who would have met trial eligibility criteria who were cared for in the year 2024 at the four sites chosen for the trial Using these data, we estimated the distribution of the primary composite endpoint and its heterogeneity across the four sites(**Table 2**).

Table 2. Number of cases and incidence of organ injury or death in 2024 cases who would have been eligible to participate across the four sites anticipated to participate in the trial.

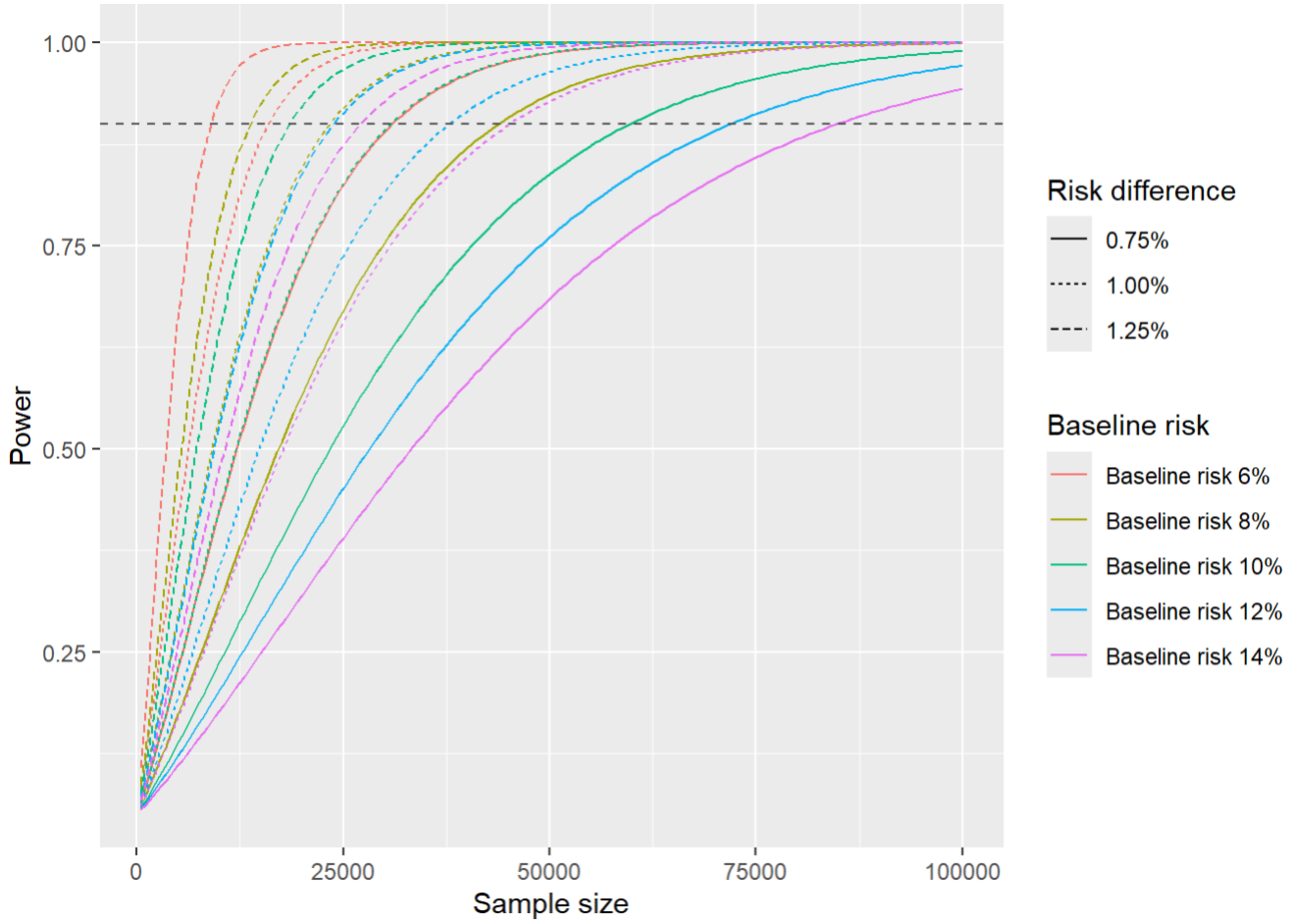
Site	Cases	No organ injury or death	Organ injury or death
A	14,242	12,566	1676
B	4059	3728	331
C	8606	7205	1401
D	15,689	14,344	1345
Overall	42,596	37,843 (88.8%)	4753 (11.2%)*

*In this preliminary analysis, however, we were unable to measure myocardial injury, one component of the organ injury composite, using serum troponin concentrations due to site-specific troponin assays and thresholds for injury. We therefore considered the measurement of serum troponin in the 72 hours after surgery as myocardial injury regardless of the value. We expect approximately 70% of the patients will not have a troponin concentration greater than the threshold for myocardial injury, based on our 2016-2019 prior study.[14] Thus, the baseline rate for the composite endpoint is likely approximately 2% less than 11.2% (**i.e., our best estimate is 9.3%**).

We used these data to develop a statistical simulation of the study design and primary endpoint accounting for crossover events, moderate heterogeneity across sites and over time (i.e., intracluster correlation), the effects of the study interventions (i.e., lower FiO2, intermediate FiO2, and higher FiO2), and the planned statistical analysis.

Based on the preliminary data available from the planned sites in 2024, we estimated that the baseline incidence of the primary outcome in the trial population will be 9.3% (i.e., **baseline risk = 9.3%**). During the design of the trial, we received feedback from stakeholders that, given the very large number of patients (millions) who receive surgery with tracheal intubation and general anesthesia each year, a difference of organ injury or death as small as 0.75% would be clinically significant (i.e., minimal clinically important difference **[MCID] = 0.75%**). We aimed to have at least 90% statistical power to detect such a difference at a two-sided alpha level of 0.05 (i.e., **power = 0.90**, **alpha = 0.05**). Our simulations (**Figure 1**) demonstrated that achieving 90% statistical power at an alpha level of 0.05 to detect a MICD of 0.75% with a baseline event rate of 9.3% (using the range of 8-12% to address uncertainty) would require enrolling approximately 54,000 patients (18,000 patients per group). This calculation uses the conservative assumption that the magnitude of the treatment effect for intermediate FiO2 vs. higher FiO2 or lower FiO2 vs. intermediate FiO2 is equal to that for lower FiO2 vs. higher FiO2 (i.e., no dose effect). This sample size provides appropriate robustness given uncertainty about the relative treatment effects between groups. For example, even when there is no effect of intermediate FiO2 vs. higher FiO2, there is still approximately 90% power to detect an absolute risk difference of 0.75% comparing lower FiO2 vs. higher FiO2 or lower FiO2 vs. intermediate FiO2. In addition, this sample size provides at least 80% power to detect a 0.75% risk difference even if the baseline incidence of the primary outcomes is as high as 12%. Thus, the proposed study design provides a robust opportunity to detect clinically important treatment effects. **Figure 1**. The sample size and power for a risk difference of 0.75%, 1.00%, and 1.25%, corresponding to a risk ratio of 1.0075, 1.0100, and 1.0125 respectively, are shown for a treatment effect of any two treatments (intermediate FiO2 vs. higher FiO2,

lower FiO2 vs. intermediate FiO2, or lower FiO2 vs. higher FiO2) across a range of possible baseline incidences of the primary endpoint.



As a cluster-randomized, cluster-crossover trial, this trial is designed to enroll in a fixed number of clusters for a fixed number of periods. We designed the trial with a sufficient number of clusters and periods to minimize intracluster correlation and to reach the target patient sample size based on the observational data from the MPOG registry in prior years. Because the trial will enroll at a fixed number of sites for a fixed number of periods, the total sample size of the trial will depend on the number of eligible patients who undergo surgery at participating sites during the study. At the interim analysis, the DSMB will evaluate the overall incidence of the primary outcome. If the rate of the primary outcome differs substantially from the original estimate of 9.3% in the initial sample size estimation, the DSMB may suggest that the investigators perform a sample size re-estimation and increase the sample size to maintain adequate statistical power to detect the planned risk difference in the outcome between groups.

9.3. Analysis Populations

The primary analysis will occur in an intent-to-treat (ITT) fashion among all patients randomized.

9.4. Statistical Analysis

Before enrollment is complete, a complete final statistical analysis plan will be made publicly available. Analyses conducted in accordance with the statistical analysis plan will be identified as *a priori*. Any additional analyses requested by the investigators or reviewers after completion of enrollment will be identified as *post hoc*. During data preparation and analysis, investigators, including the primary statistician, will remain blinded to treatment assignment.

9.4.1. Primary Analysis

We will measure the effect of the study treatments on the primary outcome (organ injury or inhospital death at day 30) using mixed-effects binomial regression with log link function adjusting for study period (1-24) and study site. At the final analysis, the scientific null hypothesis – intervention has no effect on primary outcome – will be examined by testing that the relative risk comparing the three study treatments are all equal to one using a two degree-of-freedom Wald test with a 5% type-I error rate. Relative risk and absolute risk difference estimates and 95% confidence intervals will be presented for each pair of treatments (lower vs. intermediate, lower vs. higher, and intermediate vs. higher), and used to interpret the directionality of any treatment effects.

9.4.2. Secondary Analyses

Secondary analyses include analysis of the secondary outcome, analyses of exploratory outcomes, sensitivity analyses of the primary, secondary, and exploratory outcomes, and sub-group (heterogeneity of treatment effect) analyses. All secondary analyses will be prespecified in a Statistical Analysis Plan published before conclusion of enrollment.

9.4.3. Heterogeneity of treatment effects

We approach examination of heterogeneity of treatment using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN).[39] As a result, we will measure heterogeneity in the effects of treatment on primary, secondary, and exploratory outcomes. To assess for effect modification with respect to the primary endpoint, we will perform a formal test of statistical interaction by extending the logistic regression model to estimate the effects of treatment group, the pre-specified proposed effect modifier, and the interaction between the study group and the pre-specified proposed effect modifier. We will report the estimated treatment effect and confidence interval in patients with and without these factors (for binary variables [for example, sex]) or above and below the median (for continuous variables [for example, BMI]) and the p-value for interaction. Forest plots will be used to graphically display the adjusted analyses, and locally weighted regression or partial effects plots will be used to portray the association between continuous covariates and the outcome. A list of prespecified subgroup analyses will be outlined in the detailed Statistical Analysis Plan and may include:

Sex
Age
BMI
Congestive heart failure
Peripheral vascular disease
Diabetes
Chronic kidney disease

Metastatic cancer
Baseline hemoglobin
Emergency surgery
Abdominal surgery

9.4.4. Handling of Missing Data

In the primary analysis, patients without postoperative measurement of serum creatinine or troponin will be assumed not to have suffered the outcome of interest (AKI or myocardial injury) based on the assumption that the laboratory data necessary for diagnosis were not obtained because there was no clinical indication for measurement. Patients without documentation of a stroke, lung injury, death are assumed not to have suffered those events. If data are missing for exploratory outcomes, we will perform complete-case analysis, excluding cases where the data for the analyzed outcome are missing. We do not expect any missing covariate data (study period and study site) in the primary analysis. In other adjusted analyses, missing data for covariates will be imputed using multiple imputation methods. Outcome data will not be imputed.

9.4.5. Interim Analysis

An interim analysis will be performed after 12 treatment periods to assess recruitment, rates of the primary outcome, and efficacy and safety of the intervention.

At the interim analysis, the DSMB may recommend modifying the sample size of the trial as required to maintain sufficient statistical power to detect the detectable difference specified in the initial sample size estimation.

At the interim analysis, the unblinded statistician will provide the DSMB with an analysis that compares the rate of the primary outcome in each treatment groupestimates of the odds ratios of each treatment compared to each of the other two treatments with 95% confidence intervals, and p-values corresponding to the null hypothesis that the odds ratio is equal to one, applying Haybittle–Peto method for controlling type-I error across the interim and final analysis. If there is strong evidence that one treatment assignment is superior to the other two treatment assignments (i.e., the p-values for the corresponding odds ratios are both less than 0.001), the trial will be terminated for efficacy. Likewise, if there is strong evidence that one treatment assignment is inferior to one or both of the other two treatments, then enrollment for the inferior treatment assignment will be halted for safety and subsequent randomizations will be 1:1 between the two remaining treatments. This conservative Haybittle–Peto approach ensures less than 0.001 chance of a type-I error at the interim analysis, which will allow the final analysis to be performed with no adjustment to the level of significance. In other words, the type-I error rate at the final analysis will remain at 0.05. The outcome of the interim analysis will have no effect on the implementation or interpretation of the final analysis. Safety will also be assessed qualitatively. The DSMB may make recommendations to terminate one treatment arm, or the study, as guided by the DSMB contract.

The DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

10. Privacy and Confidentiality

All patients will be assigned a unique study ID number for use in the coded study database. This study ID number will be associated with data collected from MPOG reports that use existing scripts that query the electronic health record to extract data. The electronic health record may be accessed again, as needed, between enrollment and study publication to respond to queries from the coordinating center focused on ensuring data completeness and quality, although we do not expect this to be frequent. The dataset for analysis will contain the unique study ID and no other patient identifiers aside from date of surgery and dates of outcomes. At no time during this study, its analysis, or its publication will patient identities be revealed in any manner. Patient names, addresses, telephone numbers, email addresses, or social security numbers will not be collected at any point.

11. Follow-up and Record Retention

Patients will be followed until hospital discharge. Data collected from the medical record will be stored in password- and firewall-protected MPOG data files, accessible only be research staff. All analyses occur within the firewall. There will be no hard copies of any participant data. Institutional policy requires research records be kept at least 7 years.

12. Safety Monitoring and Adverse Events

Assuring patient safety is an essential component of this protocol. Provision of a lower FiO2, an intermediate FiO2, and a higher FiO2 during surgery are all standard-of-care interventions that have been used in clinical practice for decades with an established safety profile. However, to mitigate any safety considerations, this protocol includes the:

1. Systematic collection of outcomes relevant to the safety of intraoperative oxygenation including measurements of hypoxemia, organ injury, and other morbidities.
2. Structured monitoring, assessment, recording, and reporting of adverse events.

12.1. Adverse Event Definitions

Adverse Event – An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any adverse event occurring during the research will be classified according to the following characteristics:

- **Seriousness** – An adverse event will be considered "serious" if it:
    - Results in death;
    - Is life-threatening (defined as placing the patient at immediate risk of death);
    - Results in inpatient hospitalization or prolongation of existing hospitalization;
    - Results in a persistent or significant disability or incapacity;
    - Results in a congenital anomaly or birth defect; or
    - Based upon appropriate medical judgment, may jeopardize the patient's health and may

require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- **Unexpectedness** – An adverse event will be considered "unexpected" if the nature, severity, or frequency is neither consistent with:
    - The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol; nor
    - The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

- **Relatedness** – The strength of the relationship of an adverse event to a study intervention or study procedure will be defined as follows:
    - Definitely related: The adverse event follows (1) a reasonable, temporal sequence from a study procedure AND (2) cannot be explained by the known characteristics of the patient's clinical state or other therapies AND (3) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
    - Probably or possibly related: The adverse event meets some but not all of the above criteria for "Definitely related".
    - Probably not related: The adverse event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
    - Definitely not related: The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
    - Uncertain relationship: The adverse event does not fit in any of the above categories.

12.2. Monitoring for Adverse Events

The time interval during which patients are eligible for the occurrence of adverse events begins at surgery and ends at hospital discharge. Adverse events occurring before randomization or after hospital discharge will not be collected. The lead investigator at each enrolling site will have primary responsibility for overseeing the monitoring, assessment, and reporting of adverse events. Site study personnel will evaluate for the occurrence of adverse events by communication with treating clinicians and reviewing reports from treating clinicians. If study personnel at a site identify a potential adverse event, the lead investigator at the site will be immediately notified. The lead investigator at the site will assess the seriousness, unexpectedness, and relatedness of the potential adverse event. With assistance as needed from the coordinating center and the trial primary investigator, the lead investigator at the site will determine whether the event qualifies for recording and reporting.

12.3. Recording and Reporting Adverse Events

The following types of adverse events will be recorded and reported:

- Adverse events that are Serious and Definitely Related, Probably or Possibly Related
- Adverse events that are Unexpected and Definitely Related, Probably or Possibly Related

Adverse events that do not meet the above criteria will not be recorded or reported. Adverse events that the lead investigator at a site assesses to meet the above criteria for recording and reporting will be entered into an adverse event electronic case report form in the trial REDCap database. The lead investigator at the site will record an assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness. For any adverse event that is **serious AND unexpected**, and definitely related, probably or possibly related, the lead investigator at the site will report the adverse event to the coordinating center and the trial primary investigators **within 24 hours** of becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the lead investigator at the site will report the adverse event to the coordinating center and the trial primary investigators **within 72 hours** of becoming aware of the adverse event. The coordinating center and the trial principal investigator will coordinate with the lead investigator at the site to obtain information about the adverse event regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness. The lead investigator at the site will be responsible for making final determinations regarding seriousness and unexpectedness. The coordinating center and trial principal investigator will be responsible for making final determinations regarding relatedness.

For adverse events that meet the above criteria for recording and reporting, the coordinating center will notify the DSMB, the IRB, and the sponsor in accordance with the following reporting plan:

Characteristics of the Adverse Event	**Reporting Period**
Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibility related.	Report to the DSMB, IRB, and sponsor within 7 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related.	Report to DSMB, IRB, and sponsor within 15 days of notification of the event.
All other adverse events meeting criteria for recording and reporting.	Report to DSMB in regularly scheduled DSMB safety reports.

The coordinating center will distribute the written summary of the DSMB's periodic review of reported adverse events to the IRB in accordance with NIH guidelines: (http://grants.nih.gov/grants/guide/notice-files/not99-107.html).

12.4. Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of patients receiving surgery and tracheal intubation, patients are at risk for death and other adverse outcomes due to their underlying illness and the risks of surgery and anesthesia. Clinical outcomes, including death and organ dysfunction/injury, will be systematically collected and analyzed for all patients. The primary, secondary, safety, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or site investigators believe the event is Definitely Related or Probably or Possibly Related to the study intervention or study procedures. This approach – considering death and organ dysfunction as clinical outcomes rather than adverse events and systemically collecting these clinical outcomes for analysis – is common in trials that

target postoperative morbidity and organ injury. This approach ensures comprehensive data on death and organ dysfunction for all patients, rather than relying on sporadic adverse event reporting to identify these important events. The following events are examples of study-specific clinical outcomes that would not be recorded and reported as adverse events unless treating clinicians or site investigators believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death (all deaths occurring prior to hospital discharge or 28 days will be recorded);
- Organ dysfunction
    - AKI
    - Myocardial injury
    - Lung injury
    - Stroke
- Surgical site infection
- Duration of hospitalization

12.5. Unanticipated Problems involving Risks to Subjects or Others

Investigators must also report Unanticipated Problems Involving Risks to Subjects or Others ("Unanticipated Problems"), regardless of severity, associated with study procedures **within 24 hours** of the site investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol; and (b) the characteristics of the subject population being studied; AND
- Definitely Related or Probably or Possibly Related to participation in the research (as defined above in the section on characteristics of adverse events); AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If any study personnel at a site become aware of an event that may represent an Unanticipated Problem, they will immediately contact the lead investigator for the site. The lead investigator at the site will assess whether the event represents an Unanticipated Problem by applying the criteria described above. If the lead investigator at the site determines that the event represents an Unanticipated Problem, the lead investigator at the site investigator will record the Unanticipated Problem in the Unanticipated Problem electronic case report form in the trial database. The lead investigator at the site will then communicate that an Unanticipated Problem has occurred to the coordinating center and the trial principal investigator **within 24 hours** of the lead investigator at the site becoming aware of the Unanticipated Problem. The coordinating center and principal investigator will coordinate with the lead investigator at the site to obtain information about the Unanticipated Problem. The coordinating center will report the Unanticipated Problem to the DSMB, IRB, and sponsor within 15 days of becoming aware of the Unanticipated Problem.

12.6 Protocol Deviations and Violations

Investigators will also monitor for Protocol Deviations and Protocol Violations. Protocol Deviations and Protocol Violations are defined as follows:

- Protocol Deviation: An incident involving noncompliance with the trial protocol that typically does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the resultant data. Deviations may result from the action of the participant, investigator, or staff.
- Protocol Violation: Accidental or unintentional changes to the IRB approved protocol procedures that affect the subject's rights, safety, welfare, and/or the integrity of the resultant data.

Protocol violations will be reported to the DSMB and IRB within 7 days of becoming aware of the event. Protocol deviations will be tracked and reported to the DSMB at the time of semi-annual meetings and to the IRB through continuing reviews.

13. Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to maximize the safety of patients in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the steering committee and sponsor with respect to:

- Participant safety and risk/benefit ratio of study procedures and interventions
- Initial approval of the protocol and subsequent amendments (with specific attention to study population, intervention, and study procedures)
- Adherence to the protocol requirements
- Completeness, quality, and planned analysis of data
- Ancillary study burden on participants and main study
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance

The DSMB will consist of members with expertise in bioethics, anesthesia, critical care medicine biostatistics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The coordinating center, principal investigators, and unblinded study biostatistician will be responsible for the preparation of all DSMB and adverse event reports. The DSMB will develop a charter and review the protocol and patient notification forms during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

14. References

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Tracking of Protocol Versions:

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