Section 1: Administrative Information

Title

The Effectiveness of an Anesthesiology Control Tower System in Improving Perioperative Quality Metrics and Clinical Outcomes: the TECTONICS randomized, pragmatic trial statistical analysis plan.

Trial registration

https://clinicaltrials.gov/ct2/show/NCT03923699

SAP and Protocol Versions

Protocol	SAP	Date
1.0	--	
1.0	1.0	2023 June 21
1.0	1.1	2023 Dec 13

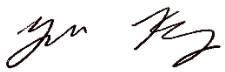
SAP Revisions.

1.0: first version
1.1: revisions based on review of available data
- Removed mean airway pressure outcome because it was not captured in the EHR. Replaced with peak airway pressure.
- Updated secondary outcomes to use the same method for multiplicity adjustment as the primary outcomes. There were not enough secondary outcomes for false-discover-rate type methods to be applicable.
- minor clarification in introduction
- operationalized detection of ACT not staffed (coordinator logs not available)
- added exclusion of subsequent cases during the outcome period of an index case to the population definition (previously in the analysis section)
- removed [Fritz 2019] method for baseline risk as not all patients had preoperative assessments for included covariates. Replaced with model using only procedure text.
- removed driving pressure requirement defining duration of ventilation due to use of negative pressure (spontaneous) ventilation.
- switched from HC3 to HC1 standard errors due to the small cluster size, large number of clusters, and high computational load when bootstrapping.

Roles and responsibilities:

Signatures

Author of SAP: Christopher Ryan King



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Section 2: Introduction

Background and rationale

Telemedicine is a highly scalable approach to potentially increasing quality of health care. So far, the usefulness of telemedicine for intraoperative anesthesia clinicians has not been prospectively evaluated. The TECTONICS trial randomized a large number of patients to standard of care or telemedicine support from the Anesthesia Control Tower (ACT) including a modern system of real-time alerts for intraoperative problems and machine-learning based identification of high-risk patients.

Objectives and hypotheses.

TECTONICS will rigorously assess the impact of a telemedicine intervention on patient-oriented outcomes: (1) death within 30 days (2) acute kidney injury (3) respiratory failure (4) postoperative delirium. We hypothesize that the incidence of each of these outcomes will be lower in the intervention group.

Secondary objectives include the effect of telemedicine support on quality of care metrics including (1) intraoperative normothermia (2) intraoperative normotension (3) lung-protective ventilation in the form of lower peak airway pressures (4) avoidance of postoperative hyperglycemia (5) avoidance of inadequate volatile anesthetic administration for age (6) appropriate antibiotic redosing (7) and avoidance of excessive volatile anesthetic consumption (high fresh gas flow).
We hypothesize that all the measures will have higher success rates in the intervention group.

Section 3: Study Methods

TECTONICS is a parallel-group unblinded two-arm randomized superiority trial. The unit of allocation is operating room (OR)-days, with patients nested within OR-days. Randomization is 1:1 without any stratification based on patient factors to telemedicine support (intervention) or usual care (control).

Randomization.

Pseudo-random number generation was performed centrally without stratification. Each day, a new row in a Microsoft SQL Server v17 database was created for each eligible OR included in the study. MS-SQL server's NEWID function was applied, and the rooms sorted by the resulting value, with the top

half (rounding down) of rooms allocated to control. Randomization therefore occurred with variable block size (due to occasional OR closures) centered on 58 or 59. Randomization occurred before any patient is eligible for intervention (before surgeries start). Randomization was periodically checked to be uncorrelated to room number. Randomization assignments were retrieved from the server automatically and displayed in the ACT.

Sample size.
The protocol document contains the assumptions used during trial design. Approximately 40,000 total patients were initially planned, acknowledging that changes at the study site suggested that accrual could proceed more quickly than prior data would suggest. Mid-way through the study, accrual was occurring at nearly double the estimated rate. The study PI and DSMB agreed to increase the target to 80,000 total patients to improve the likelihood of detecting small but clinically relevant differences in the primary outcome and to increase power in subgroups.

Framework
Superiority testing for all comparisons.

Statistical interim analyses and stopping guidance.
No interim efficacy analyses were planned. DSMB reports included group outcome rates, but no harm evaluation triggers were specified. No modifications to the analysis were planned.

Timing of final analysis.
The final analysis will be performed after a database lock with all patient data available.

Timing of outcome assessments.
Outcomes are assessed in a 30-day window after randomization.

Section 4: Statistical Principles

Confidence intervals and p-values.
Level of significance. p-values (and interval alpha values) less than .005 will be reported as convincing evidence. Values between .005 and .05 will be reported as suggestive evidence.

Multiplicity Adjustment
Primary outcomes will be reported with family-wise error rate control using the permutation-based methods of (Romano 2016). Secondary outcomes will be reported with adjustment to control the family-wise error rate using the same method and separate alpha budget.

Confidence intervals to be reported.
Wald-type 95% and 99.5% confidence intervals will be reported for the primary outcomes. We will report Bonferroni-adjusted and unadjusted confidence intervals.

Adherence and protocol deviations
Because the protocol allows telemedicine clinicians to contact intervention ORs at their discretion (many rooms have no indication for contact), and there are many more operating rooms than could feasibly be contacted, a useful per-protocol analysis is not possible. We will report the rate and type of contacts from the telemedicine clinicians to operating rooms by randomization status.

The protocol specifically allowed for contact between the ACT and control rooms where necessary to prevent imminent patient harm.

We will present the rate and rationale for cross-over from control to intervention.

Study Populations
Full Analysis Set: All adult patients with surgery in an eligible OR whose case is started during or within the 45 minutes before the ACT opens are included in the intention to treat population. The original protocol did not include the 45 minute grace period, which was added in discussion with the DSMB to include a larger number of cardiac cases which start earlier than general ORs at the study site. DSMB analysis initially included all patients whose surgery started *and* ended within the hours of the ACT. Patients with scheduled surgery who do not proceed to the OR are not included. Surgeries during days in which the ACT is not staffed are not included. Inclusion does not depend on outcome assessment; imputation of missing outcomes is discussed below. No other populations will be reported.

Section 5: Trial Population

Screening.
Surgeries are automatically checked against a list of approved operating rooms. Ages are automatically extracted from the electronic health record to verify adult status. Patients with unknown ages (for example, victims of violence with redacted personal information) are included.

Eligibility criteria:
All adults (18 years and older) undergoing surgical procedures with anesthesia services in these operating rooms are included. Labor and operative delivery is conducted in a separate administrative area and is also excluded unless it occurs in the main surgical ORs. There are no other exclusion criteria related to procedure type, comorbid illnesses, or planned disposition other than the requirement that some anesthesia clinician be requested (excluding e.g. organ procurement and minor procedures performed without anesthesiology services) and the requirement for the procedure to take place in an operating room (excluding sedation-based procedure suites such as the cardiac diagnostic laboratory).

Subsequent surgeries on an included patient are not eligible until the 30-day outcome window of the index case has been concluded.

ACT Staffing exclusion
Because study coordinators did not track days in which the ACT was closed due to a lack of medical staff, we infer it using the activity log in the AlertWatch interface. Days in which no activity is recorded after 10am are excluded.

Recruitment
Recruitment is automatic with a waiver of consent.

Withdrawal and follow up.
Because the trial accrues with a waiver of consent, withdrawal is not possible. Outcome imputation is discussed in the analysis section below.

Baseline characteristics
Baseline measured characteristics and their summaries will include:

Name	Type	Summary	Distance Measure
Age	Continuous	Mean, SD	SMD

Race	Categorical	Proportions	Phi
Ethnicity	Binary	Proportion	Cohen's d
ASA-PS	Categorical	Proportions	Phi
Atrial fibrillation	Binary	Proportion	Cohen's d
Anemia	Binary	Proportion	Cohen's d
Asthma	Binary	Proportion	Cohen's d
Coronary Artery Disease	Binary	Proportion	Cohen's d
Current Cancer	Binary	Proportion	Cohen's d
Chronic Kidney Disease	Binary	Proportion	Cohen's d
ESRD	Binary	Proportion	Cohen's d
COPD	Binary	Proportion	Cohen's d
Stroke or TIA	Binary	Proportion	Cohen's d
Dementia or MCI	Binary	Proportion	Cohen's d
Diabetes	Binary	Proportion	Cohen's d
DVT or PE	Binary	Proportion	Cohen's d
Obstructive Sleep Apnea	Binary	Proportion	Cohen's d
Hypertension	Binary	Proportion	Cohen's d
Anesthesia Type	Categorical	Proportions	Phi
Functional Capacity	Categorical	Proportions	Phi
Surgical service	Categorical	Proportions	Phi
Procedure-specific mortality	Continuous	Median, IQR	SMD

Section 6: Analysis

OUTCOME DEFINITIONS

Measurement	**Definition**
Thirty-day postoperative mortality	Death of any cause occurring in or out of the hospital, within 30 days of the index surgery. Captured by hospital vital statistics, which includes in-hospital events, routine clinical and billing follow-up. Note that for patients without planned follow up, vital statistics were not used to ascertain out of hospital death.
Postoperative delirium	Defined as an acute change in consciousness or cognition. It has a fluctuating course, and is characterized by inattention, disorganized thinking and altered level of consciousness. Nursing staff in the surgical intensive care and cardiac-thoracic intensive care units regularly assess all patients using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) instrument. It is administered every 12-24 hours depending on clinical context while in the ICU. CAM-ICU scores within 30 minutes of a documented deep level of sedation (Richmond Agitation Sedation Scale < -3) are excluded. All other delirium assessments within 7 days will be included, with any positive evaluations yielding a positive event.
Postoperative respiratory failure	Defined as mechanical ventilation occurring or continuing 24 hours after surgery, or re-intubation and mechanical ventilation within 30 days of surgery [Abbott 2018] Patients with tracheostomies and

	preoperative ventilation are excluded. Airway events within 24 hours after surgeries within 30 days of the index operation are excluded. That is, a 24 hour window of ventilation is allowed after all surgeries without triggering a positive event.
Postoperative acute kidney injury	Modified KDIGO stage-1 AKI using creatinine criteria: (i) an increase in serum creatinine by 50% compared with preoperative maximum within 7 days or (ii) a 0.3 mg / dL absolute increase within the first 48 hours. Patients with diagnosed renal failure, serum creatinine >4 mg/dl, and dialysis in the last week) are excluded.

Secondary outcome measures and definitions.

Measurement	**Definition**
Temperature management	Temperature ≥ 36°C at end of surgery (maximum temperature in the final 10 minutes of intraoperative record).
Antibiotic redosing	Antibiotic redosing compliant with guidelines developed by the institutional pharmacy and therapeutics committee. Patients without an indicated redosing event are excluded.
Mean arterial pressure management	Fraction of time during surgery with mean arterial pressure ≥ 60 mmHg
Peak inspiratory pressure with mechanical ventilation	Fraction of time during surgery with peak inspiratory pressure ≤ 30 cmH_2O. Only cases with mechanical ventilation are included. Mechanical ventilation is detected with sustained EtCO2 > 20 mmHg, tidal volume > 150 mL, PEEP > 2 cmH2O. The first and last 8 minutes are excluded to account for activities around intubation and extubation.
Hyperglycemia	Blood glucose > 200 mg/dL at end of surgery (first glucose measurement after anesthesia stop within 24 hours).

Antibiotic	Adult Dose	Redosing Interval[1,2]
Ampicillin/sulbactam	3 g	q2h
Aztreonam	2 g	q4h
Cefazolin	< 120 kg: 2 g ≥ 120 kg: 3 g	q4h
Cefepime	2 g	q4h
Cefoxitin	2 g	q2h
Ceftriaxone	2 g	q12h
Ciprofloxacin	400 mg	q8h
Clindamycin	900 mg	q6h
Ertapenem	1 g	q24h
Gentamicin (traditional)	1.5 mg/kg	q8h
Gentamicin (extended interval)	5 mg/kg	q24h
Linezolid	600 mg	q10h
Meropenem	1000 mg	q2h
Metronidazole	500 mg	q8h
Piperacillin/tazobactam	3.375 g	q2h
Vancomycin	< 80 kg: 1 g ≥ 80 kg: 1.5 g	q12h

Anesthetic delivery	Patients without ≥ 15 consecutive min of volatile anesthetic concentration ≤ 0.3 MAC during mechanical ventilation, defined as in "Peak inspiratory pressure" above. Patients with doses of sedatives at greater than the following dose-rates are excluded: propofol > 40 mcg/kg/min, ketamine > 0.3 mg/kg/hr.
Fresh gas flow rates	Proportion of patients with efficient fresh gas flow for ≥90% of the mechanical ventilation period defined above. "Efficient" fresh gas flow is defined as <= 2 L/minute for sevoflurane and <= 1 L/minute for isoflurane and desflurane. Only times with > 0.3 age adjusted MAC are included.

Analysis Methods

Only the first randomized case for each patient in a 30-day window will be included in the analysis. This is a modification of the protocol (analyzing patients based on the initial randomization in 30 day windows) based on discussion with the DSMB.

All primary outcomes are binary. Because the treatment is assigned in clusters (OR-days), generalized estimating equations using HC1 cluster-robust standard errors as implemented by (Zeileis 2006) and a Poisson link function will be used to estimate rate ratios and standard errors. These will be the primary treatment effects. Wald tests using these standard errors and clustered permutation tests (permute assignments within day) will be used to generate p-values.

Tables containing un-clustered data and un-clustered analysis will also be presented.

Because of the large sample size and randomized design, the primary analysis will not adjust for covariates.

The primary analysis (and permutation test) does not depend on parametric distributional assumptions and is robust to misspecification of covariance.

Sensitivity analyses

Analyses of alternative specifications of above outcomes include

- Quantitative differences in average temperature
- Quantitative differences in time-weighted hypotension using MAP under 65 mmHg.
- Quantitative differences in log-creatine changes
- Quantitative differences in average peak airway pressure
- Quantitative differences in time with efficient fresh gas flow
- Treating missing CAM-ICU as 'negative'. The rationale for this analysis is that low-risk patients with no symptoms are often skipped in this nursing assessment. The overwhelming majority of wards and outpatient participants without assessments are likely not delirious.
- Including subsequent surgeries independent of an index case.
- A composite sum of primary outcomes, treating missing as negative (0).

Planned hypothesis generating subgroup analyses:

- Excluding patients without diabetes from blood glucose analyses
- Including only cases with >50% overlap with the hours of operation of the ACT

- ASA >= 3
- Including only top quartile in baseline ML mortality risk using an XGBoost model of the procedure text derived from historical outcomes.
- Stratification by Surgical service
- Age >= 65

Missing data

Missingness in all the primary endpoints is informative, and therefore usual imputation methods for missing-at-random data are not applicable.

- Mortality: Patients discharged alive without subsequent medical system contact are assumed to be alive at 30 days.
- Respiratory failure: Patients without documented mechanical ventilation events are assumed to have no event. Patients discharged from hospital in less than the at-risk window are assumed to have no event.
- Delirium: Patients without CAM-ICU scores, or scores only around deep sedation, are not included in the analysis. No other imputation is used.
- Acute kidney injury: Patients without baseline creatinine measurements are assumed to have normal values (single imputation) for their age, sex, weight, race, and CKD variable using an XGBoost (Chen 2016) imputation model from all patients with measured baseline creatinine. Patients without postoperative creatinine measures are assumed to not have acute kidney injury. Because of the sensitivity of criteria (ii) [an increase of 0.3 mg/dL], it is not applied when preoperative creatinine is not measured.

Patients with missing secondary outcomes are not included in the analysis of those outcomes.

Because no covariates enter the primary analysis, imputation is not necessary.

Additional analyses

No additional treatment population analyses are planned

Harms

Harms will be analyzed using qualitative methods (thematic analysis) of case-report forms.

Statistical Software

The main analysis will be performed in R 4.3.0. A container and list of all included packages and libraries will be released with the primary analysis. The planned list of packages includes: 'magrittr', 'data.table', 'forcats','readxl', 'sandwich', 'lmtest', 'DescTools' , 'dplyr', 'lubridate', 'tidyr', 'stringr', 'ggplot2', 'xgboost', 'boot', 'matrixStats', 'effectsize', 'randtoolbox', 'gridExtra', 'readr', 'openssl', 'scales' ,'bit64'

References

Statistical methods

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Fritz BA, Maybrier HR, Avidan MS. Intraoperative electroencephalogram suppression at lower volatile anaesthetic concentrations predicts postoperative delirium occurring in the intensive care unit. Br J Anaesth. 2018 Jul;121(1):241-248. doi: 10.1016/j.bja.2017.10.024. Epub 2018 Jan 17. PMID: 29935578; PMCID: PMC6200110.

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Data Management Plan
Details of data management to be included with primary publication

Trial master file
None

Standard operating procedure document
The recommended procedures inside the ACT will be included with the primary publication.