POSTOPERATIVE OUTCOMES ASSOCIATED WITH PROCEDURAL SEDATION CONDUCTED BY PHYSICIAN AND NON-PHYSICIAN ANAESTHESIA PROVIDERS: FINDINGS FROM THE PROSPECTIVE, OBSERVATIONAL AFRICAN SURGICAL OUTCOMES STUDY (ASOS)

by

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DECLARATION

I, *Dr Freliza van der Merwe*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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List of Abbreviations

AANA: American Association of Nurse Anesthetists

ASA: American Society of Anesthesiologists

ASOS: African Surgical Outcomes Study

ATE: Average treatment effect

CAD: Coronary artery disease

CHF: Congestive heart failure

CKD: Chronic kidney disease

COPD: Chronic obstructive pulmonary disease

CRNA: Certified registered nurse anaesthetist

C/S: Caesarean section

CTV: Cardiothoracic and vascular

CVA: Cerebrovascular accident/disease

DAG: Directed acyclic graph

DM: Diabetes mellitus

ESM-Ketamine: Every Second Matters for Emergency and Essential Surgery-Ketamine

GBM: Generalized Boosted Model

GIT: Gastrointestinal tract

HICs: High-income countries

HIV/AIDS: Human immunodeficiency virus/Acquired immune deficiency syndrome

HPB: Hepatobiliary

IPTW: Inverse probability of treatment weighting

ISOS: International Surgical outcomes Study

LMICs: Low- and middle-income countries

NCD: Non-communicable disease

Chapter 1: Review of the Literature

Introduction

The complex nature of multiple surgical techniques and procedures, including endoscopic and minimally invasive procedures, has required the sophistication of sedation and anaesthesia techniques, requiring a wide range of practitioner skills. The field of sedation has advanced from the administration of combinations of small doses of benzodiazepines, opiates and intravenous anaesthesia agents, to the administration of target control infusions using complex computer algorithms. The debate continues as to the qualifications required of the practitioner for the safe performance of sedation techniques. In limited resource environments, non-physician practitioners, i.e. persons not qualified as medical doctors, are often entrusted with this task, and there are limited data on outcomes when compared with physicians and specialist anaesthesiologists, especially in low- and middle-income countries (LMICs).

Literature search

We conducted this narrative review with the aim to peruse the available literature on surgical outcomes, specifically focusing on the impact of procedural sedation, the non-anaesthetist and non-physician sedation provider, and ultimately outcomes from the African continent.

All publications relevant to the subject were obtained online, from the University of Cape Town Health Sciences Library search facility. For the purposes of this narrative review, a search was performed in April 2020, using the Pubmed and EBSCOhost databases, using the terms “sedation” AND “non-physician”, “sedation” AND “non-physician” AND “Africa”, “sedation” AND “Africa”, “non-physician AND “Africa”, and “sedation” AND “outcomes”. The search was restricted to adult patients ≥ 18 years of age. Literature not published in the English language was excluded.

Global and African outcomes after Surgery

Until recently, studies on postoperative outcomes were primarily conducted in high-income countries (HICs). Only 28% of the hospitals in which data were collected for the International Surgical Outcomes Study (ISOS) were in LMICs.[1] Despite advances in perioperative care, patients in LMICs still have a two to three times higher perioperative mortality risk compared to HICs. Anaesthesia-related risk factors have been identified as modifiable and preventable as regards mortality rate.[2] In 2017, Biccard et al conducted the African Surgical Outcomes Study (ASOS), a continental investigation including 25 countries in Africa. Over a 7-day period, a total of 11 422 patients were included. The overall postoperative complication rate was lower, but the mortality rate twice that reported by ISOS, which suggests a "failure to rescue" in the event of postoperative complications.[1,3]

Sedation to facilitate surgery

The use of sedation has gained popularity over the past two decades, being thought of as a safer, less invasive intervention than general anaesthesia, and a pleasant supplement for regional anaesthesia for many medical and surgical procedures. It is one of the fastest growing areas in the field of anaesthesia. This not only follows the advancement of diagnostic procedures and therapeutic interventions in medicine and surgery, but is also a consequence of improved patient education, which has led to the insistence on adequate anaesthesia or sedation for painful or stressful procedures and surgery.[4,5] The benefit of sedation over general anaesthesia varies between different procedures, but potentially may lead to a shortened hospital stay, decreased morbidity and mortality, and the avoidance of complications associated with general anaesthesia.[6]

Depending upon the health of the patient, the nature of the surgery, and the experience of the person administering the sedation, a procedure can be performed under sedation and analgesia appropriate to the procedure, without rendering the patient completely unconscious. Depth of sedation ranges from the awake state to that approximating to general anaesthesia. The American Society of

Anesthesiologists describes the continuum of depth of sedation as extending from minimal sedation (anxiolysis), to moderate sedation/analgesia (conscious sedation), then deep sedation/analgesia and finally general anaesthesia. Distinguishing features are described according to motor or verbal responses to external stimuli, capacity to maintain the airway, maintenance of spontaneous ventilation, and haemodynamic stability.[7]

Twenty-five years ago, Quine et al performed a prospective audit of upper gastrointestinal endoscopy across two regions in England. Thirty-six hospitals across East Anglia and the North West were included as sites for data collection. Overall, 14149 cases were recorded, of which 13036 were diagnostic, and 1113 therapeutic endoscopic procedures. Intravenous sedation, with or without local anaesthesia, was employed in 11998 of the cases. The authors investigated intra-procedural and post-operative complications, up to a period of 30 days following the procedure, paying special attention to those related to procedural sedation. Most of these patients received benzodiazepine-based intravenous sedation, with the most common drugs used being midazolam (mean dose 5.7 mg) in the North West, and diazepam (mean dose 13.5 mg) in East Anglia, with wide variation between age groups. A morbidity rate of 1:200 and mortality rate of 1:2000 was found for diagnostic endoscopy (where mortality was directly related to the procedure or sedation). Causes for all complications and deaths included aspiration pneumonia, cerebrovascular accident, myocardial infarction, cardiopulmonary arrest (suspected to be related to local anaesthetic overdose) and oesophageal perforation. Two thirds of these adverse events occurred within 7 days of the procedure. The most common type of complication was of a cardiorespiratory nature. Substandard monitoring practices and inconsistency with regards to availability of intravenous access, in combination with high doses of benzodiazepines were shown to contribute to sedation-related morbidity and mortality.[8] Since then, the development of sedation guidelines and structured training programmes have improved the safety of procedural sedation.[4,9] With the advancement of sedation techniques and training of sedation providers in the HICs, absolute contraindications to the provision of procedural sedation in these settings no longer exist.[5]

Sedation is often performed in the out-of-hospital environment,[10] and commonly done by non-anaesthetists. Data regarding the details of practice are scarce, and current guidelines for the administration of sedation, as well as minimum requirements for qualifications of practitioners practicing sedation are continuously being compiled and revised.[4,9] Since sedation is commonly performed in the out-of-theatre setting, it is difficult to audit. This applies both to identifying factors that put patients at risk for adverse outcomes related to sedation practice, and to the evaluation of the impact of attempts at improving practice. Databases have been implemented in HICs[10] and are encouraged in South Africa,[4] but no such analyses have been published. There is unfortunately limited data available on the conduct of sedation in Africa or LMICs overall. The increased need for essential surgical services worldwide has caused an expansion of the use of off-site procedural sedation in HICs, but even in these environments only a few studies exist examining outcomes. Notably, these studies often involve extensively trained non-anaesthesiologist sedation providers when considering outcomes.[11]

A place for non-physician anaesthesia providers

Of great concern is the global need for surgical intervention, which far exceeds the availability of this scarce resource.[2,10] This imbalance between demand and supply is more pronounced in LMICs, which applies to most African states.[12] A lack of essential anaesthesia services has been identified as a contributing human factor, with communities in rural Africa having access to one specialist anaesthetist per 2 000 000 population,[13] compared to one per 5 000 in the United Kingdom.[14] As a result, the responsibility of providing anaesthesia services in the rural areas is often delegated to nurse practitioners, in order to offer patients elective and emergency surgery. Half a century ago the discussion was already in progress as to whether a place exists for the non-physician medical practitioner in LMICs.[15,16] It is now clear that the need for the provision of essential surgery in LMICs necessitates the utilisation of non-physician anaesthesia providers.[17] Unfortunately it has been shown on a global scale that inadequate anaesthesia training and/or supervision of junior and trainee anaesthetists is a contributing factor to anaesthesia-related mortality.[18]

In contrast, registered nurse anaesthetists in the United States have been providing anaesthesia care since before the establishment of anaesthesiology as a medical speciality. The certified registered nurse anaesthetist (CRNA) continues to play a vital role in the provision of anaesthesia services (with or without anaesthesiologist supervision) across the USA. The American Association of Nurse Anesthetists (AANA) was established in 1931 and represents the majority of CRNA's in the US. This organisation has developed minimum required qualifications to practice as a CRNA and continues to ensure a high standard of training and service provision. This includes a degree of Bachelor of Science in Nursing, the certification of registered nurse and working experience of at least 1 year as a registered nurse in the intensive care unit, before being allowed to enrol in a CRNA training programme. The latter includes a further 2 to 3 years in a nurse anaesthesia educational programme, consisting of theoretical as well as clinical training in anaesthesia, completed with a certification examination. Even then, most of the approved work of a CRNA is under supervision of a qualified anaesthesiologist.[19]

In the last decade attempts have been made to compare patient outcomes after anaesthesia administered by physicians versus non-physicians. The studies available, mostly from HICs, failed to show high quality evidence in favour of one or the other.[20] In LMICs, no significant difference in outcomes after caesarean section has been shown for physician and non-physician anaesthesia providers.[21] When conducting the ASOS study, Biccard et al failed to show any significant difference in outcome when regional or general anaesthesia was provided by a physician compared to a non-physician provider.[3] Unlike the CRNAs (and equivalents) in HICs, non-physician anaesthesia practitioners in LMICs generally do not have access to adequate or standardised training, educational resources and clinical support and supervision.[10,22] Regardless, it has still not been significantly shown that they have worse outcomes than their physician counterparts where general and regional anaesthesia is pertained.

Ketamine in Africa – the role of the non-anaesthetist

After a study period extending from 2013 to 2017, involving 1216 procedures, Burke et al introduced the Every Second Matters for Emergency and Essential Surgery-Ketamine (ESM-Ketamine) package. Approximately 15% of patients received the ketamine package during a period of supervised training of the anaesthesia provider, and the 85% were unsupervised, i.e. “non-training cases”. Of these > 50% could be categorised as deep procedural sedation. Non-anaesthetist physicians and non-physicians with no anaesthesia training would undergo a 5 day training course on ketamine administration, and were supplied with a basic protocol to manage common side effects of the drug.[23] The aim of the intervention was to enable rural hospitals in Kenya to provide essential surgical services to their population, despite a lack of available anaesthesia services. They concluded that using this package to facilitate surgery by using either a general anaesthetic or procedural sedation, administered by briefly trained personnel, was safe. The limitation of the study was the lack of a control group, and the conclusion that ketamine is a safe alternative despite no data being presented on outcomes beyond the immediate postoperative period. Also, although the ketamine-related severe adverse outcomes were documented to be scarce (0.6%), the short follow-up time did not allow for conclusions as to whether the limited training of the anaesthesia providers affected outcomes in the long run.

Unfortunately, due to the limited number of other studies addressing adverse outcomes after general anaesthesia and sedation by non-physicians in Africa, and a subsequent lack of standardisation and universal protocols, the validity of the results of the ketamine study is difficult to ascertain.

Outcomes after non-physician sedation

As is the case with general anaesthesia, procedural sedation is often provided by non-physicians. The non-physician can either be the primary sedation provider, or can function as an observer, or assistant, while the operator takes responsibility for the procedure as well as the sedation. Because such an operator is primarily

focused on performing the procedure, a non-physician is responsible for monitoring the patient under sedation, and may even be expected to administer sedation and top-ups under the guidance of the practitioner.[4] Endoscopic procedures are commonly performed in this way.

In HICs there are a limited number of studies on outcomes after sedation administered by physicians- versus non-physicians. One such study demonstrated that with proper training of registered nurses and cardiologists, and the anaesthesia team on standby, a variety of cardiac procedures can be safely facilitated with the provision of procedural sedation by non-anaesthesia personnel.[24] Furthermore, in HICs the practice of nurse-administered propofol sedation has been accepted as a safe alternative to provision by a physician. This is on condition that the sedation is provided at a tertiary or high-volume surgery centre, with the provision of adequate training, appropriate protocols in place, the supervision of a surgeon, and if possible, available anaesthesia back-up.[25] Unfortunately, no similar studies on sedation by non-physicians have been conducted in LMICs, including the African continent.

Sedation in low-and middle-income countries

The data published on procedural sedation in LMICs are limited, and rare in Africa. Included in the ASOS cohort were 334 cases of procedural sedation. These cases and their outcomes were not specifically analysed or discussed in the original manuscript.[3] The aim of the present secondary analysis of the available ASOS data on sedation, was to compare outcomes following sedation by physician versus non-physician practitioners, and to establish whether procedural sedation by non-physicians is an acceptable alternative in the setting of limited availability of physicians. The ultimate goal was to make recommendations for improved patient safety related to the conduct of sedation. The primary objective of this sub-study was therefore to establish the incidence of perioperative complications (minor, moderate and severe complications, including death) following procedural sedation by physician versus non-physician practitioners. We hypothesised that the level of training of the sedation practitioner (physician vs non-physician) would affect the incidence of severe postoperative complications and death.

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Chapter 2: Manuscript

Title Page

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Bruce M Biccard: This author made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or revising it critically for important intellectual content; AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abstract

Background

There is an unmet need for essential surgical services in Africa. Limited anaesthesia services are a contributing factor. Non-physician anaesthesia providers are utilized to assist with providing anaesthesia and procedural sedation in order to make essential surgeries available. There is a paucity of data on outcomes following procedural sedation for surgery in Africa. We investigated the postoperative outcomes following procedural sedation by non-physicians and physicians in Africa. We hypothesized that the level of training of the sedation provider may be associated with the incidence of severe postoperative complications and death.

Methods

A secondary analysis of a prospective cohort of in-hospital adult surgical patients, representing 25 African countries was performed. An inverse probability of treatment weighting model was developed to assess the association between receiving procedural sedation conducted by a non-physician (vs physician) and in-hospital outcomes. All patients who only received procedural sedation for surgery were included. The primary outcome was the incidence of the composite of severe complications and death.

Results

336 patients met the inclusion criteria, of which 98 (29.2%) received sedation from a non-physician provider. The incidence of severe postoperative complications and death was 10/98 (10.2%) in the non-physician group, and 5/238 (2.1%) in the

physician group. The association between procedural sedation conducted by a non-physician provider and in-hospital outcomes showed an eight-fold increase in the odds of severe complications and death (odds ratio 7.7; 95% CI 2.5 to 23.7).

Conclusions

The modest number of observations in this secondary data analysis, suggests that shifting the task of procedural sedation from physicians to non-physicians in order to increase access to care may be associated with severe postoperative complications and death in Africa. Research focusing on identifying factors contributing to adverse outcomes associated with procedural sedation is necessary to make this practice safer.

Journal-ready manuscript

Introduction

The global need for safe surgery exceeds the human resources available to provide the necessary anaesthesia.[1,2] This unmet need is exaggerated in low- and middle-income countries (LMICs).[2] In Africa it is estimated that 95% of the population do not have access to safe and affordable surgery.[1] The number of physician anaesthesia providers is as low as one per 2 000 000 population in parts of Africa,[2,3] with a recommended minimum requirement of four anaesthesia providers per 100 000 population.[4] Non-physicians are therefore important anaesthesia providers in low resource environments. However, performance and safety may be negatively impacted by unstandardized training programmes and unreliable access to educational resources and clinical support.[5]

Sedation is frequently utilized in LMICs to facilitate essential surgeries when no formal anaesthesia services are available. Ketamine is commonly used due to its low cost, ease of storage, perceived safer risk profile and near-universal availability.[6-8] Formal protocols have been proposed to standardize the administration of ketamine.[6] The Every Second Matters for Emergency and Essential Surgery-Ketamine (ESM-Ketamine) package is an example of such a protocol to aid inexperienced physicians and non-physicians in the administration of ketamine. This protocol has been reported as a safe alternative when no anaesthetist is available.[6] The ESM-Ketamine protocol proposal is controversial, and not universally accepted.[9] It has however been included in recommendations for doctors and midwifes managing complications in pregnancy and childbirth.[10]

There remains limited data on outcomes associated with procedural sedation for surgery in the African context. Reported outcomes after procedural sedation from high-income countries are not generalisable to LMICs.[11] The main finding of the African Surgical Outcomes (ASOS) study[12] was that surgery overall is not safe in Africa, with mortality following surgery being twice the global average, despite a lower complication rate.[12] Analysis of the maternal and neonatal outcomes after surgical delivery show an even higher complication rate and 'failure to rescue'. [13] It is possible that a lack of physician anaesthesia providers in LMICs may compound perioperative and anaesthesia morbidity and mortality.[14] What we do not know is whether the level of training of sedation practitioners affects outcomes after procedural sedation in the African setting.

The objective of this study was to describe the surgical outcomes associated with procedural sedation for surgery by non-physician and physician anaesthesia providers in Africa. We hypothesised that the level of training of the sedation provider is associated with the incidence of severe postoperative complications and death.

Methods

Study design, setting and participants

This was a secondary analysis of the ASOS study – an international, prospective observational cohort study.[1] The ASOS study was registered on ClinicalTrials.gov (NTC03044899). The primary ethics approval was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal in South Africa (BE306/15). A waiver of consent was approved by all sites except the University of Witwatersrand. For hospitals under the University of Witwatersrand Ethics Board, written informed consent was obtained from all patients prior to surgery, with the exception of patients who were unable to give consent prior to surgery, where a deferred consent process was in place. The inclusion criteria for ASOS were all adult elective and emergency surgical in-patient cases performed during a 7-day period at the participating hospitals. The week of data collection was decided upon by each participating country between February and May 2016. Twenty-five countries in Africa participated, and a total of 11 422 patients were recruited.

This secondary data analysis included patients who received only procedural sedation to facilitate surgery, and was reported according to the STROBE guidelines.[2] In ASOS, procedural sedation was defined as a pharmacologically-induced reduced level of consciousness during which verbal contact is maintained. Ethics approval was granted by the Human Research Ethics Committee of the University of Cape Town, Faculty of Health Sciences (HREC072/2019).

Variables and data

The primary outcome was the incidence of the composite of severe complications and death following surgical procedural sedation. These complications were acute kidney injury, acute respiratory distress syndrome, anastomotic breakdown, arrhythmia, (cardiogenic) pulmonary oedema, gastro-intestinal bleed, bloodstream infection, myocardial infarction, pneumonia, postoperative haemorrhage, pulmonary embolism, stroke, surgical site infection (superficial), surgical site infection (deep), surgical site infection (organ/space) and urinary tract infection. These perioperative complications were reported according to pre-defined definitions and severity grading during study data collection, which are summarized in the Supplementary document (Supplementary Material 1).[1,3] The exposure of interest was the level of training of the sedation provider classified as non-physician or physician. Non-physicians included any sedation provider who is not a medical doctor. Physicians included all medical doctors, regardless of their level of anaesthesia training.

A directed acyclic graph (DAG) was specified prior to data analysis for the purpose of identifying variables that may confound the observed association between exposure to a non-physician sedation provider (compared to a physician) and the composite outcome of severe complications and death (Figure 1).

Bias

Characteristics of the case, the patient and the resource context may confound the association of interest. A causal inferential method was used to arrive at a least biased estimate of the average treatment effect (ATE) of exposure to a non-physician sedation provider. We used multiple imputation with sensitivity analyses to assess and minimise the risk of bias due to attrition.

Study size

All eligible patients from the ASOS cohort were included in this study.

Quantitative variables

Variables with greater than 15% missing observations were removed from the dataset defined according to the DAG (Figure 1). Thereafter multiple imputation by predictive mean matching was used to create five iterations of the dataset. All reported statistics and estimates in the main manuscript represent the pooled values derived from the five imputed datasets, unless indicated otherwise (Figure 2).

Based on the DAG (Figure 1), the following variables were considered in development of the statistical model: age (years), sex (male or female), smoking status (smoker or non-smoker), American Society of Anesthesiologists (ASA) physiological status (1 – 4), presence or absence of nine comorbidities [coronary artery disease (CAD), congestive heart failure (CHF), hypertension, cerebrovascular disease (CVA), diabetes mellitus (DM), chronic kidney disease (CKD), metastatic cancer, chronic obstructive airway disease (COPD), and human immunodeficiency virus (HIV/AIDS) infection], baseline haemoglobin (g/dl), type of procedure [orthopaedic, obstetric, gynaecologic, plastic, breast, gastrointestinal tract (GIT), hepatobiliary (HPB), urologic, head-and-neck, cardiothoracic and vascular (CTV), neuro and other surgery], urgency of surgery (elective, urgent and emergent), surgical severity (minor, intermediate or major), indication of surgery (infective, non-communicable disease (NCD), caesarean section (C/S), or trauma), use of a surgical safety checklist, estimated blood loss (ml), surgical duration (minutes), level of training of most senior surgeon in case (specialist, non-specialist physician, or non-physician), hospital level (primary, secondary, or tertiary)[4] whether or not the facility

is a university hospital, hospital funding (public, private or both), number of hospital beds and operating theatres at the facility, number of specialist obstetrician, surgeons and anaesthetists at the facility, and travel time to next nearest hospital (minutes; as a measure of ruralness) (Table 1). We merged levels in the “type of procedure” and “urgency of surgery” variables to improve covariate balance during model development.

Statistical analysis

We developed an inverse probability of treatment weighting (IPTW) model to estimate the least biased ATE. For each observed case we estimated the probability of exposure to a non-physician sedation provider using a Generalized Boosted Model (GBM).[5] The estimator aimed to reduce the mean standardized effect size of each variable on sedation provider status. We visually assessed model convergence, overlap of resulting counterfactual populations (the positivity assumption), and covariate balance between those exposed to a non-physician compared to a physician sedation provider. In the final exposure probability model, we included those variables that had any crude association with the outcome of interest. We excluded variables that were non-informative of the outcome or exposure because some levels in the binary variable had a zero sum. Where a multilevel categorical variable had multiple levels with a zero sum, like ‘type of procedure’, we merged levels to improve covariate balance. Our prior knowledge of the determinants of perioperative complications informed our decision to merge levels in multilevel variables.[6] We excluded variables that were considered mediators or occurred after assignment of exposure (for example, use of the surgical safety checklist). We considered absolute standardized differences larger than 0.1 to be

excessive. We used doubly robust estimation of the ATE to address excessive differences in covariates after IPTW.

To assess the risk of attrition bias, we conducted three sensitivity analyses in which we set the imputed values of the outcome variable to different values; i) missing values in the outcome variable carried over to the imputed datasets, ii) worst-case scenario – missing outcomes all set as experiencing the outcome, and iii) best-case scenario – missing outcomes all set as not experiencing the outcome.

Figure 2 describes the data flow and steps in the analysis.

Statistical analyses were performed in RStudio version 1.1.419 (RStudio Inc., Boston, MA, USA) running R version 4.0.1 (Taking Off Again). Multiple imputation was conducted with the 'mice' package[7] and IPTW with the 'twang'[8] package.

Results

336 of 11 422 patients included in ASOS received procedural sedation for surgery (Figure 2). The composite outcome of severe complication and death was missing in five (1.5%) cases. The median amount of missing data was zero, ranging from zero to 45 (13.4%). Missing observations are summarized in the Supplementary document (Supplementary Table S1). Non-physicians provided 98/336 (29.2%) of all the procedural sedations for surgery. The countries represented by the 336 patients are described in the Supplementary document (Supplementary Table S2).

The crude association with severe complication and death for all variables considered during model development are reported in the Supplementary document (Supplementary Table S3). The covariate balance for variables included in this analysis are reported in Table 2 and Supplementary document (Supplementary Figure S1: Love plots of mean effect sizes). In the observed unweighted population, patients managed by non-physician sedation providers were slightly younger (median age 34; [interquartile range 24 to 52]) compared to those managed by physicians (38; [27 to 58]). These patients had lower ASA physiologic status scores (91.8% had an ASA score of 1 to 2), compared to those managed by physicians (78.2% had an ASA score of 1 to 2). They were less likely to have minor surgery (38.8%, compared to 55.5%), more likely to have intermediate severity surgery (51.0%, compared to 30.7%), less likely to undergo surgery for non-communicable disease (41.8%, compared to 52.9%), less likely to undergo orthopaedic and gynaecologic surgery (37.8%, compared to 52.9%) and more likely to undergo plastic and breast surgery (24.5%, compared to 14.3%). Non-physician sedation providers were less likely to be the sedation provider in secondary level hospitals (18.8% of cases, compared to 32.6% of cases conducted by a physician), they were

more likely to be the sedation provider in university hospitals (58.7% of cases, compared to 36.2% of cases conducted by a physician), and they were more likely to be the sedation provider in private hospitals (20.8% of cases, compare to 6.4% of cases conducted by a physician). Sedation provided by non-physicians took place in hospitals with fewer specialist anaesthesiologists on staff (median 0; [interquartile range 0 to 2], compared to cases conducted by physicians (3; [1 to 8]).

Model convergence, positivity and covariate balance are summarised in the Supplementary document (Supplementary Figures S1-S4). The upper end of propensity scores in the weighted physician population and lower half of propensity scores in the weighted non-physician population do not overlap with any observations in their counterfactual populations. Covariate balance improved significantly with IPTW, so that the weighted population approached random exposure to non-physician compared to physician providers. After weighting, the number of specialist anaesthesiologists at the hospital remained unbalanced between the comparison groups. This variable was included both in the exposure probability model and the model estimating the ATE, providing a doubly robust estimate.

The incidence of the primary outcome is reported in table 3. Severe complications and death occurred in 15/336 (4.5%) patients. It was more common with non-physician providers (10/98; [10.2%]) than physician providers (5/236; [2.1%]).

The doubly robust estimated ATE of sedation provided by a non-physician, compared to a physician, is an odds ratio (OR) of 7.7 (95% confidence interval [CI] 2.5 to 23.7). This is similar in magnitude compared to the unweighted effect; OR 5.2 (95% CI 1.8 to 17.0), and the ATE by IPTW without doubly robust estimation, OR 6.2

(95% CI 2.0 to 19.3). Sensitivity analyses for the ATE are reported along with the main analysis in table 4.

A description of the patients who suffered the primary outcome is included in the Supplementary document (Supplementary Table S4).

Discussion

Principal findings

Based on our findings, severe complications are relatively common following procedural sedation in Africa. Nearly a third of procedural sedations were conducted by non-physician providers. Based on the ASOS cohort,[1] our analyses suggest an eight-fold increase in the odds of severe complications and death when procedural sedation is provided by a non-physician compared to a physician.

Strengths, weaknesses and important differences

The strengths of our study are that it provides data from a large prospective observational study of surgeries across Africa, and possibly provides the best estimate of risk associated with procedural sedation for surgery across the continent. Also, considering that >95% of complications occur in the postoperative period,[1] our study includes all in-hospital complications.

One of the limitations of our study is the small number of observed events. However, the prospective method of data collection, inherent masking of outcome assessors to the study hypothesis, and predefined outcome definitions may limit information bias in this small data set. Furthermore, we used multiple imputation to minimise and analyse the impact of attrition on the reported effect. In the unlikely event that all cases with missing outcome data experienced a severe complication or death, the average treatment effect would still be a fourfold increase in odds. We used a causal inference method to estimate the least biased effect given the available data. The magnitude of the estimated effect makes it unlikely that the true effect is null.

The extremes of the distributions of propensity scores for the physician and non-physician groups do not overlap. This is not unexpected but demonstrates that there are systematic differences in the group treated by non-physicians compared to physicians, so that the estimated ATE to some degree reflects a difference in health systems.

Some residual confounding is likely. Due to the secondary nature of the data we do not have information regarding the level of training and experience of the sedation provider, the amount of supervision and support (physical or telephonic) available, the type of sedation administered, or what monitoring was used. It is likely that in some environments where procedural sedation was administered, there was inadequate equipment and consumable resources for the administration of safe anaesthesia.[9] We also have no record of specific sedation-related complications and how these could have contributed to the severe postoperative complications or death. Furthermore, our study involved in-patient surgery only, and it is likely that a large proportion of procedural sedation for ambulatory surgery across Africa was excluded.

Implications of these findings

We propose a causal model for the relationship between sedation provider status and perioperative complications and death. In this model, details of the surgical case complexity and the internal- and external resource context in which the sedation provider practices are key determinants of the observed association. As with other methods of statistical adjustment, this approach to obtain a least biased estimate depends on whether all variables related to the outcome have been included and accurately measured. There will always be inherent uncertainly in the estimate of

effect, because determinants such as case complexity and resource context are difficult to define and measure.

Another consideration is whether sedation conducted by non-physicians to make essential surgery possible, is superior to not having access to surgery at all. Comparing non-physician outcomes to the alternative of not performing possibly lifesaving surgery due to lack of an available physician anaesthetist is ethically challenging. The concern is whether the risk of poor outcomes associated with non-physician sedation providers is a preventable harm, especially in the case of non-lifesaving surgery.

Although we do not know which anaesthesia drugs were used for sedation in our study, we would expect that the majority of procedural sedation administered by non-physicians in Africa would have been with ketamine.[10] The current published data does not support a safer risk profile for ketamine sedation compared to other agents, as it is associated with a similar complication rate with the exception of a significantly higher incidence of vomiting when compared to other anaesthetic agents used for sedation.[11] It is unlikely therefore that the association with severe complications and death we observed with non-physicians, compared to Burke's findings for example, can be ascribed to a variation in anaesthetic agents used for sedation.

It is possible that the postoperative morbidity and mortality described in our study may be a result of a working environment that is inadequately resourced to manage the complications of procedural sedation. The fact that non-physicians are required to provide sedation, may be a marker of a poorly resourced facility where 'failure to rescue' when complications arise in the perioperative period contributes to the high number of severe complications and death. We do not have data on medications,

working equipment, and supplies of oxygen, which may all be important contributors to outcome in this environment. It is important that we develop a better understanding of the circumstances in which procedural sedation is being practiced in Africa, in order to determine factors which may compromise patient safety.

Unanswered questions and future research

A large prospective, observational study on the conduct of procedural sedation in Africa is needed which documents the experience of the provider, the type of sedation, the case complexity, the hospital resource context (including the available monitoring, referral and support system, postoperative care available) and the incidence of intra- and/or postoperative complications in order to make procedural sedation safer. The relationship between procedural sedation-related complications and outcome should be specifically interrogated. Day-case surgery should be included in such a study.

Conclusion

In Africa, the practice of procedural sedation by non-physicians compared to physicians, may be associated with an increased risk of severe complications and death. The working environment in which non-physicians have to provide procedural sedation may also be a negative contributory factor to patient safety. It is important that we develop a better understanding of the circumstances in which procedural sedation is being practiced in Africa, in order to identify factors which may compromise patient safety and determine how to increase access to surgery without compromising safety.

Key Points

Question: Is there a difference in patient safety when procedural sedation is conducted by non-physicians or physicians in Africa?

Findings: This secondary analysis of the African Surgical Outcomes (ASOS) Study suggests an association with severe post-operative complications and death when procedural sedation is provided by a non-physician in Africa.

Meaning: The healthcare environment in which procedural sedation is provided by non-physicians in Africa may be associated with an increased risk for major morbidity and mortality and further research is needed to ensure appropriate and safe procedural sedation practice in low resource environments.

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Tables for publication

Table 1. Domains and definitions in the causal model of perioperative severe complications and death

Domain	Definition	Variable(s)
Postoperative outcome	Adverse postoperative patient outcomes recorded in-hospital	Composite of severe complications and death
Sedation provider proficiency	Level of training, experience and skill of the sedation provider	Non-physician versus physician sedation provider
System	The external referral system in which the hospital operates	Travel time to next nearest hospital (min) Hospital level (DCP-3 levels: primary, secondary, tertiary) Hospital funding (private, public or combined) University hospital (yes or no)
Resources	The internal resource context of the hospital	Number of beds Number of operating theatres Number of specialist perioperative providers (obstetricians, surgeons, anaesthesiologists)
Processes	Established standard operating procedures and processes within the hospital	*[Not directly measured]*
Surgery	Composition and skill of the surgical team	Training level of most senior surgeon in the operating theatre
Care	Quality of care	Use of a surgical safety checklist
Intraoperative events	Adverse intraoperative events	Duration of surgery Estimated blood loss
Case complexity	Characteristics of the patient and pathology	Sex, Age, Smoking status, ASA status, Comorbidities (Coronary Artery Disease, Congestive Heart Failure, Cerebrovascular Disease, Hypertension, Diabetes Mellitus, Chronic Kidney Disease, Chronic Obstructive Airway Disease, HIV infection), baseline Haemoglobin concentration, type of surgical procedure (surgical discipline), urgency of surgery, surgical severity (minor, intermediate or major), indication of surgery (infective, non-communicable, or trauma)

Table 2. Covariate balance table

	Unweighted Population			IPTW Population		
	Non-physician	Physician	ASD	Non-physician	Physician	ASD
n	98	238		204	296	
Age (years)	34 (24.3-52.0)	38 (27.0-57.8)	0.22	34.0 (25.0-55.9)	36.2 (27.0-57.0)	0.08
Hb (g/dl)	12 (10.0-13.2)	11.8 (10.1-13.1)	0.02	12 (10.0-13.0)	12.0 (10.1-13.2)	0.02
Specialist Anaesthetist	0.0 (0.0-2.0)	3.0 (1.0-8.0)	0.62	1.0 (0.0-3.9)	3.0 (1.0-7.0)	0.33
ASA						
1	69 (70.4)	108 (45.4)	0.25	122 (59.7)	144 (48.6)	0.11
2	21 (21.4)	78 (32.8)	0.11	55 (27.1)	93 (31.4)	0.04
3	8 (8.2)	44 (18.5)	0.10	27 (13.2)	50 (17.0)	0.04
4	0 (0.0)	8 (3.4)	0.03	0 (0.0)	9 (3.0)	0.03
Comorbidities						
CHF	0 (0.0)	9 (3.8)	0.04	0 (0.0)	11 (3.6)	0.04
DM	5 (5.1)	27 (11.3)	0.06	9 (4.6)	30 (10.2)	0.06
CKD	1 (1.0)	7 (2.9)	0.02	2 (0.8)	8 (2.7)	0.02
Urgency						
Nonelective	64 (65.3)	141 (59.2)	0.06	110 (54.0)	173 (58.5)	0.04
Severity						
Minor	38 (38.8)	132 (55.5)	0.17	100 (48.9)	159 (53.6)	0.05
Intermediate	50 (51.0)	73 (30.7)	0.20	82 (40.2)	95 (32.1)	0.08
Major	10 (10.2)	33 (13.9)	0.04	22 (10.9)	42 (14.3)	0.03
Indication						
NCD	41 (41.8)	126 (52.9)	0.11	109 (53.3)	157 (53.1)	0.00
Infective	28 (28.6)	49 (20.6)	0.08	40 (19.7)	60 (20.1)	0.00
Trauma	25 (25.5)	51 (21.4)	0.04	41 (20.3)	61 (20.6)	0.01
Caesarean section	4 (4.1)	12 (5.0)	0.01	14 (6.7)	18 (6.1)	0.01
Procedure						
***Other, and including orthopaedics, gynaecology**	37 (37.8)	126 (52.9)	0.15	93 (45.9)	152 (51.2)	0.05
Plastics and breast	24 (24.5)	34 (14.3)	0.10	34 (16.8)	40 (13.6)	0.03
Obstetrics	7 (7.1)	16 (6.7)	0.00	19 (9.5)	23 (7.9)	0.02
HPB, head and neck, GIT, CVT	18 (18.4)	44 (18.5)	0.00	37 (18.3)	57 (19.3)	0.01
Urology	9 (9.2)	14 (5.9)	0.03	15 (7.4)	19 (6.5)	0.01
Neurosurgery	3 (3.1)	4 (1.7)	0.01	4 (2.1)	5 (1.6)	0.00
Seniority of Surgeon						
Specialist	40 (41.2)	97 (40.8)	0.01	85 (41.9)	125 (42.1)	0.00

Physician, non-specialist	49 (50.5)	140 (58.8)	0.09	109 (53.3)	170 (57.4)	0.04
Non-physician	8 (8.2)	1 (0.4)	0.08	10 (4.72)	1 (0.5)	0.04
Hospital Level						
Primary	24 (25.0)	50 (21.2)	0.03	48 (23.7)	64 (21.7)	0.02
Secondary	18 (18.8)	77 (32.6)	0.13	44 (21.5)	90 (30.4)	0.09
Tertiary	54 (56.2)	109 (46.2)	0.09	112 (54.8)	142 (48.0)	0.07
University affiliation	54 (58.7)	85 (36.2)	0.20	95 (46.7)	116 (39.3)	0.07
Hospital Funding						
Government	74 (77.1)	207 (87.7)	0.10	170 (83.7)	251 (84.9)	0.01
Private	20 (20.8)	15 (6.4)	0.14	28 (13.6)	27 (9.3)	0.04
Government and private	2 (2.1)	14 (5.9)	0.04	6 (2.7)	17 (5.9)	0.03

Data are median (IQR) or n (%). Balance of covariates between groups exposed to non-physician versus physician sedation provider. The table compares the difference between groups before and after weighting (IPTW). A difference (ASD) of greater than 0.1 is considered excessive. *Other procedures include all types of procedures not specifically mentioned. IPTW=Inverse Probability of Treatment Weighting, ASD=Absolute Standardized Difference. Hb=haemoglobin. ASA=American Society of Anesthesiologists. CHF=Congestive heart failure. DM=Diabetes mellitus. CKD=Chronic kidney disease. HT=Hypertension. NCD=Non-communicable disease. HPB=Hepatobiliary. GIT=Gastrointestinal. CTV=Cardiothoracic and vascular.

Table 3. Incidence of severe complications and death in observed and weighted non-physician and physician provider populations

	Unweighted Population		IPTW Population	
	Non-physician	**Physician**	**Non-physician**	**Physician**
N	98	238	247	305
Severe complications and death	10 (10.2)	5 (2.1)	25.3 (10.2)	5.5 (1.8)

Data are n (%). IPTW=Inverse Probability of Treatment Weighting.

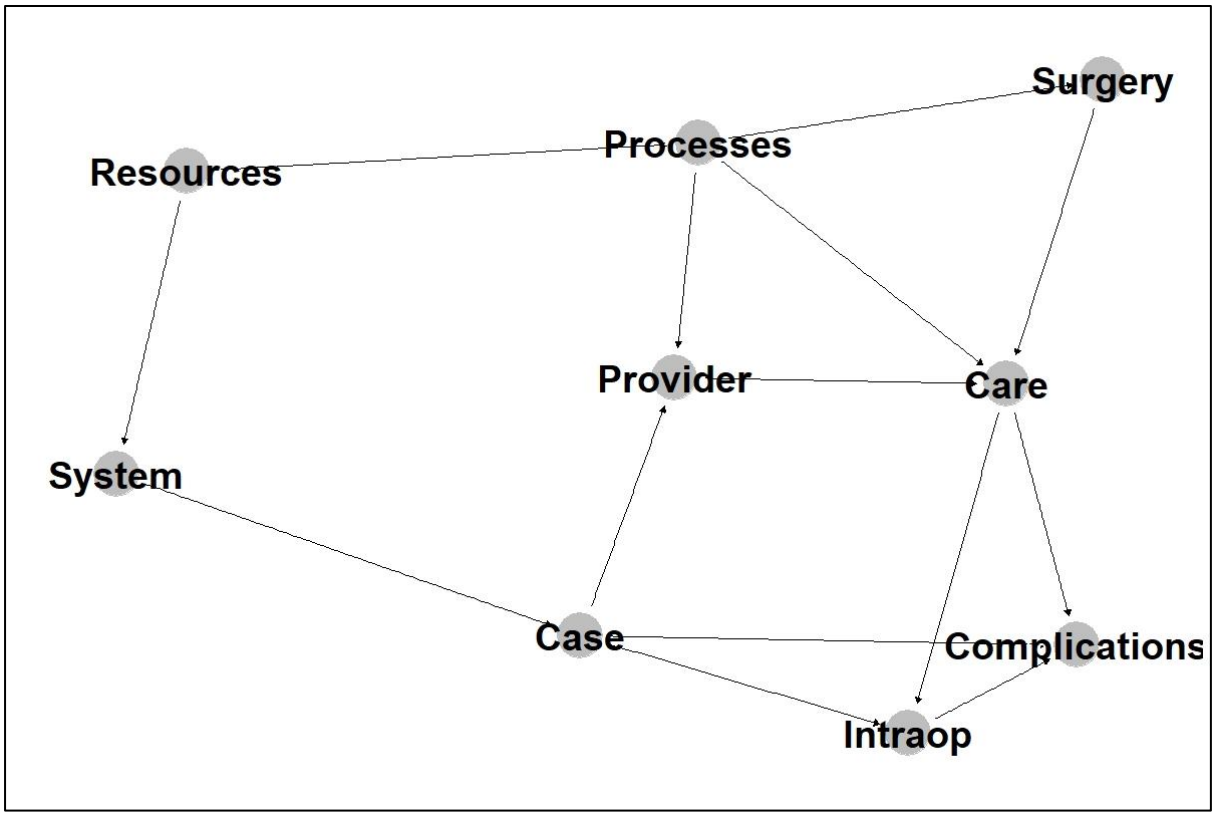
Table 4. Average Treatment Effect (ATE), Unweighted Association and Sensitivity Analyses between non-physician versus physician sedation provider status and outcome of severe complications and death

Parameter	Pooled odds ratio*	Lower 95%CI*	Upper 95%CI*
ATE	7.7	2.5	23.7
Unweighted association	5.2	1.8	17.0
Worst-case scenario ATE	4.0	1.5	10.6
Best-case scenario ATE	8.0	2.6	24.7
NAs retained ATE	7.8	2.5	24.2

* All estimates represent pooled values across the five imputed datasets. Reported ATE's represent doubly robust estimates. In 'worst-case scenario', analysis assumed that all unobserved outcomes experienced severe complication or death. In 'best-case' scenario, analysis assumed that no unobserved outcomes experienced severe complication or death. In 'NAs retained', imputed values for the outcome were replaced with 'NA' (empty cells), while keeping imputed values for the other covariates. 95%CI=95% confidence interval

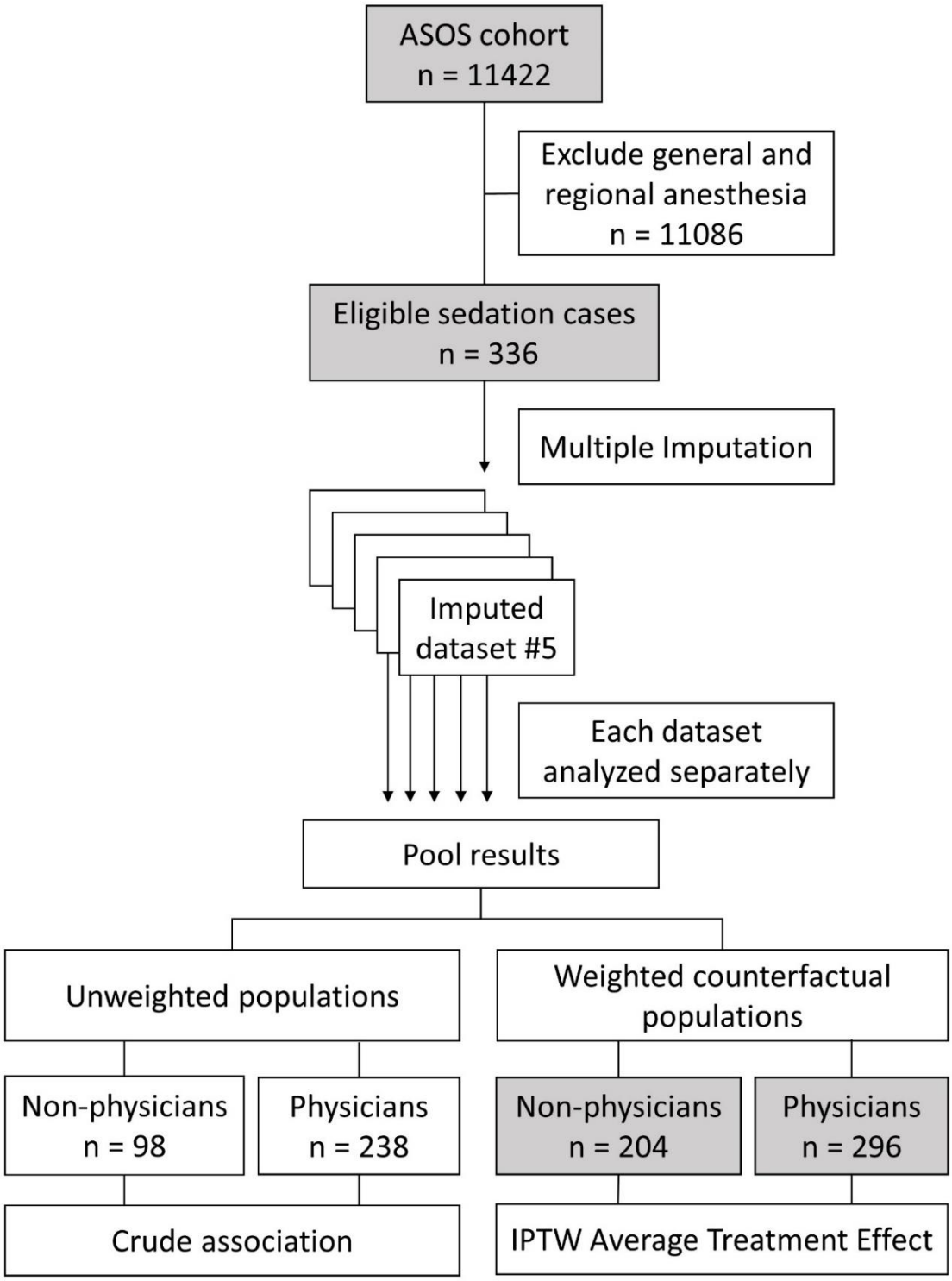
Figures for publication

Figure 1. Directed Acyclic Graph (DAG) of the factors leading to severe postoperative complications and death.



'Provider' is non-physician or physician sedation provider and represents the exposure of interest in the DAG. 'Complications' are severe postoperative complications or death and represent the outcome of interest in the DAG. 'System' refers to the referral system external to the hospital. 'Resources' refer to the hospital's internal resource context. 'Processes' refer to standard operating procedures and processes which dictate practice. 'Surgery' refers to the composition and skill of the surgical team. 'Care' refers to the quality of care provided in the perioperative period. 'Case' refers to the complexity of the case, including patient factors and pathology. 'Intraop' refers to intraoperative events.

Figure 2. Flow diagram of analysis procedure



IPTW=Inverse Probability of Treatment Weighting.

Chapter 3: Appendices

Appendix 1 – Additional tables not for publication

Supplementary Table S1: Summary of missing observations in raw dataset

Variable	Missing (n=336)	Percentage Missing
Hemoglobin	45	13.4
Travel time to nearest facility	33	9.8
University affiliation	9	2.7
Severe complications	5	1.5
Hospital level	4	1.2
Hospital funding	4	1.2
Number of hospital beds	4	1.2
Number of hospital theaters	4	1.2
Number of specialist obstetricians	4	1.2
Number of specialist surgeons	4	1.2
Number of specialist anaesthesiologists	4	1.2
Number of nurse anaesthetists	4	1.2
Number of nurse surgeons	4	1.2
Estimated blood loss	2	0.6
Most senior surgeon	1	0.3
Physician/non-physician status of sedation provider	0	0.0
Age of patient	0	0.0
Gender of patient	0	0.0
Smoking status	0	0.0
ASA classification	0	0.0
Comorbidities		
Coronary artery disease	0	0.0
Congestive heart failure	0	0.0
Diabetes Mellitus	0	0.0
Hypertension	0	0.0
Cerebrovascular accident	0	0.0
Chronic obstructive pulmonary disease	0	0.0
Human immunodeficiency virus	0	0.0
Chronic kidney disease	0	0.0
Procedure performed	0	0.0
Urgency of procedure	0	0.0
Severity of procedure	0	0.0
Indication for procedure	0	0.0
Safety checklist performed	0	0.0
Duration of surgery	0	0.0
Median	**0**	**0.0**
Lower range	**0**	**0.0**
Upper range	**45**	**13.4**

Supplementary Table S2: Representation of countries (Anonymized)

Country	Physician sedations		Non-physician sedations	
	Cases	Severe complications	Cases	Severe complications
A	7	1	-	-
B	-	-	1	0
C	-	-	1	1
D	-	-	18	1
E	25	0	6	2
F	-	-	18	1
G	3	0	2	1
H	3	0	8	1
I	8	0	2	0
J	10	0	-	-
K	1	0	2	0
L	9	0	5	1
M	7	0	-	-
N	17	0	-	-
O	1	0	1	0
P	6	0	4	0
Q	-	-	1	1
R	125	3	3	0
S	-	-	17	0
T	7	1	3	0
U	4	0	6	1
TOTAL	**233**	**5**	**98**	**10**

A - U: Anonymized countries.

Supplementary Table S3: Crude associations with composite outcome

	Odds ratio (95% confidence interval)
Physician/non-physician status of sedation provider*	5.101 (1.684-15.456)
Age*	1.010 (0.981-1.038)
Gender: female	1.113 (0.385-3.218)
Smoker	-
ASA classification*	
2	3.085 (0.718-13.263)
3	6.427 (1.467-28.152)
4	19.333 (2.689-139.008)
Comorbidities	
Coronary artery disease	-
Congestive heart failure*	2.755 (0.319-23.762)
Diabetes Mellitus*	3.737 (1.111-12.575)
Metastatic cancer	-
Hypertension	1.115 (0.303-4.099)
Cerebrovascular accident	-
Chronic obstructive pulmonary disease	-
Human immunodeficiency virus	-
Chronic kidney disease*	9.953 (1.452-43.548)
Hemoglobin*	0.941 (0.742-1.190)
Procedure performed	
Plastic surgery*	1.220 (0.302-4.891)
Obstetric surgery	1.010 (0.118-8.698)
Head and neck, GIT, CTV surgery*	1.200 (0.297-4.881)
Urological surgery	-
Neurosurgery*	3.710 (0.389-35.476)
Urgency	
Non-elective*	4.021 (0.877-18.436)
Severity	
Intermediate*	1.446 (0.491-4.260)
Major*	0.554 (0.066-4.667)
Indication	
Non-communicable disease*	1.590 (0.485-5.193)
Trauma	0.939 (0.235-3.755)
C/S	-
Estimated blood loss	0.998 (0.995-1.002)
Surgical duration	1.001 (0.990-1.012)
Safety checklist performed	1.684 (0.583-4.868)
Seniority of surgeon	
Physician non-specialist*	0.608 (0.214-1.730)
Non-physician surgeon	-
Hospital level	
Secondary*	4.867 (0.568-41.665)
Tertiaty*	3.789 (0.461-31.124)

University affiliation*	0.478 (0.148-1.541)
Hospital funding	
Private*	1.210 (0.261-5.649)
Private and government	-
Number of hospital beds	1.001 (0.999-1.002)
Number of hospital theaters	1.000 (0.916-1.093)
Number of specialist obstetricians	1.001 (0.924-1.084)
Number of specialist surgeons	0.994 (0.953-1.038)
Number of specialist anaesthesiologists*	1.020 (0.965-1.079)
Number of nurse surgeons	-
Travel time to nearest facility	0.998 (0.809-0.981)

Data is odds ratio (95% confidence interval). Univariable associations. *Variables associated with the outcome of interest; was therefore included in the IPTW model. GIT=gastrointestinal tract. CTV=cardiothoracic and vascular. C/S=caesarean section. IPTW=inverse probability of treatment weighting.

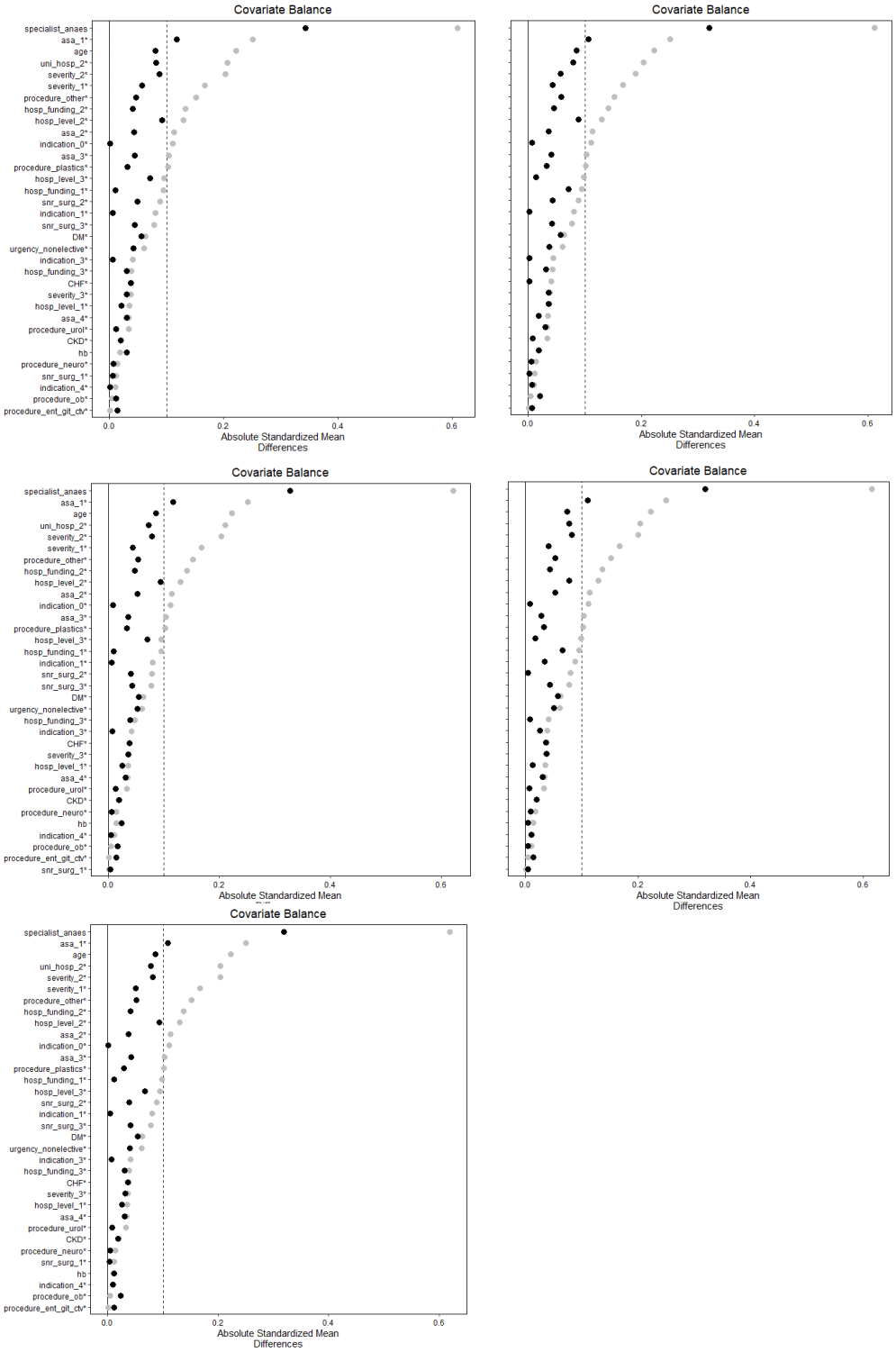
Supplementary Table S4: Description of patients who suffered the primary outcome.

Patient	Age	ASOS Surgical Risk calculator Score	Hospital category	Type of surgery	Type of complication	Status at discharge
			Physician-led Procedural sedation			
#1	43	12	Secondary	Other	Cardiovascular, other	Dead
#2	55	9	Tertiary	Other	Infectious, cardiovascular, other	Dead
#3	60	14	Tertiary	Other	-	Dead
#4	65	16	Secondary	Head and neck/GIT/HPB/CTV	Infectious	Dead
#5	76	17	Secondary	Head and neck/GIT/HPB/CTV	Infectious	Alive
			Non-physician-led Procedural sedation			
#6	19	9	Tertiary	Other	Infectious	Alive
#7	24	17	Tertiary	Neurosurgery	Infectious, other	Dead
#8	25	8	Tertiary	Plastics/Breast	Infectious, cardiovascular	Alive
#9	27	2	Tertiary	Obstetrics and Gynaecology	Infectious	Alive
#10	30	2	Tertiary	Plastics/Breast	Cardiovascular	Alive
#11	40	14	Secondary	Plastics/Breast	Infectious	Dead
#12	44	13	Secondary	Head and neck/GIT/HPB/CTV	Infectious	Dead
#13	45	9	Secondary	Other	Infectious	Alive
#14	55	4	Primary	Obstetrics and Gynaecology	Infectious	Alive
#15	57	5	Tertiary	Other	Infectious, cardiovascular, other	Dead

#1 - #15: Anonymized patients who suffered the primary composite outcome. GIT=Gastrointestinal. HPB=Hepatobiliary. CTV=Cardiothoracic and vascular.

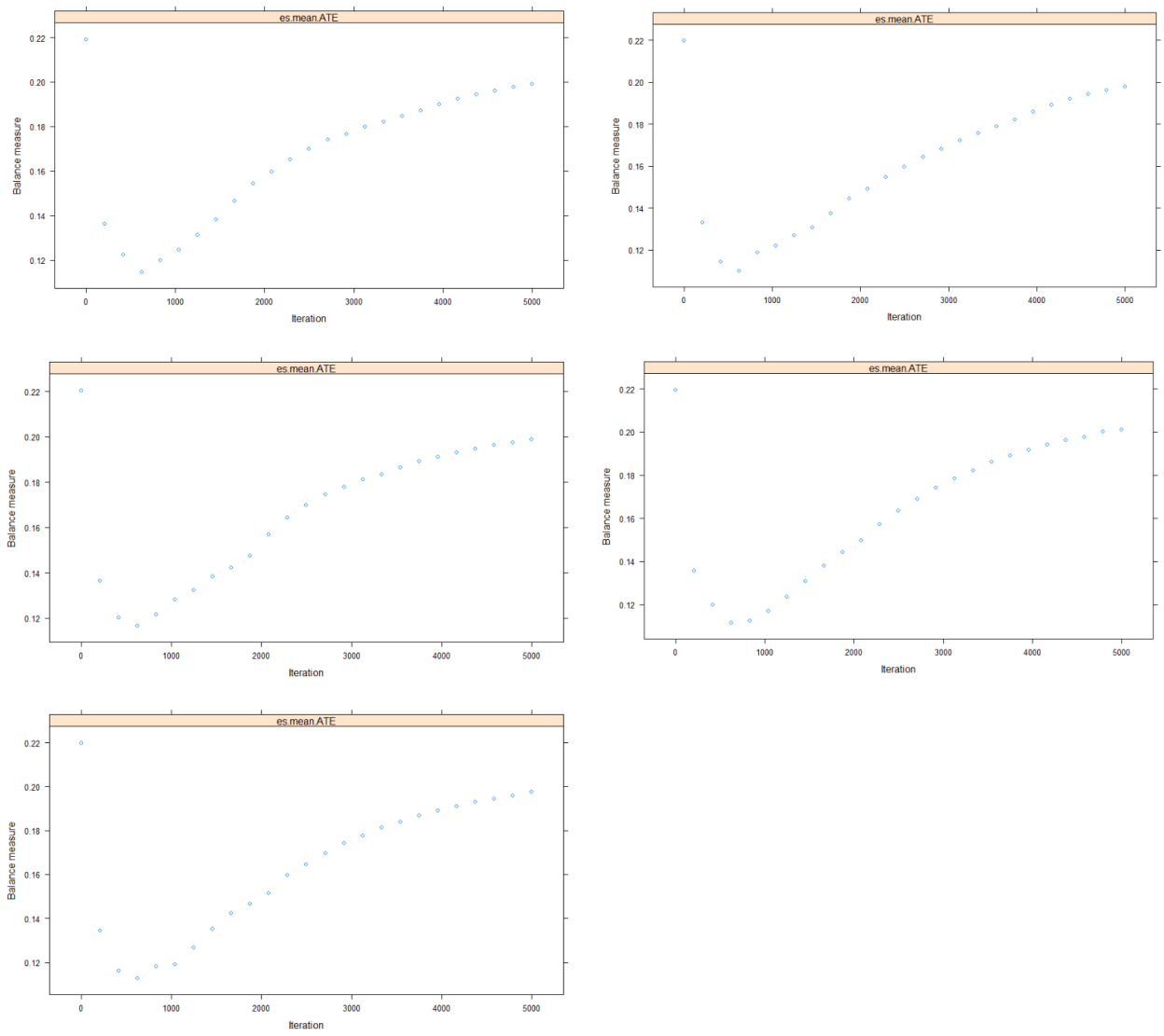
Appendix 2 – Additional figures not for publication

Supplementary Figure S1: Check balance of mean effect sizes in love plots (5 iterations); unweighted (grey) compared to weighted (black) effect sizes. Threshold for ASD = 0.1. (*indicates categorical variables)



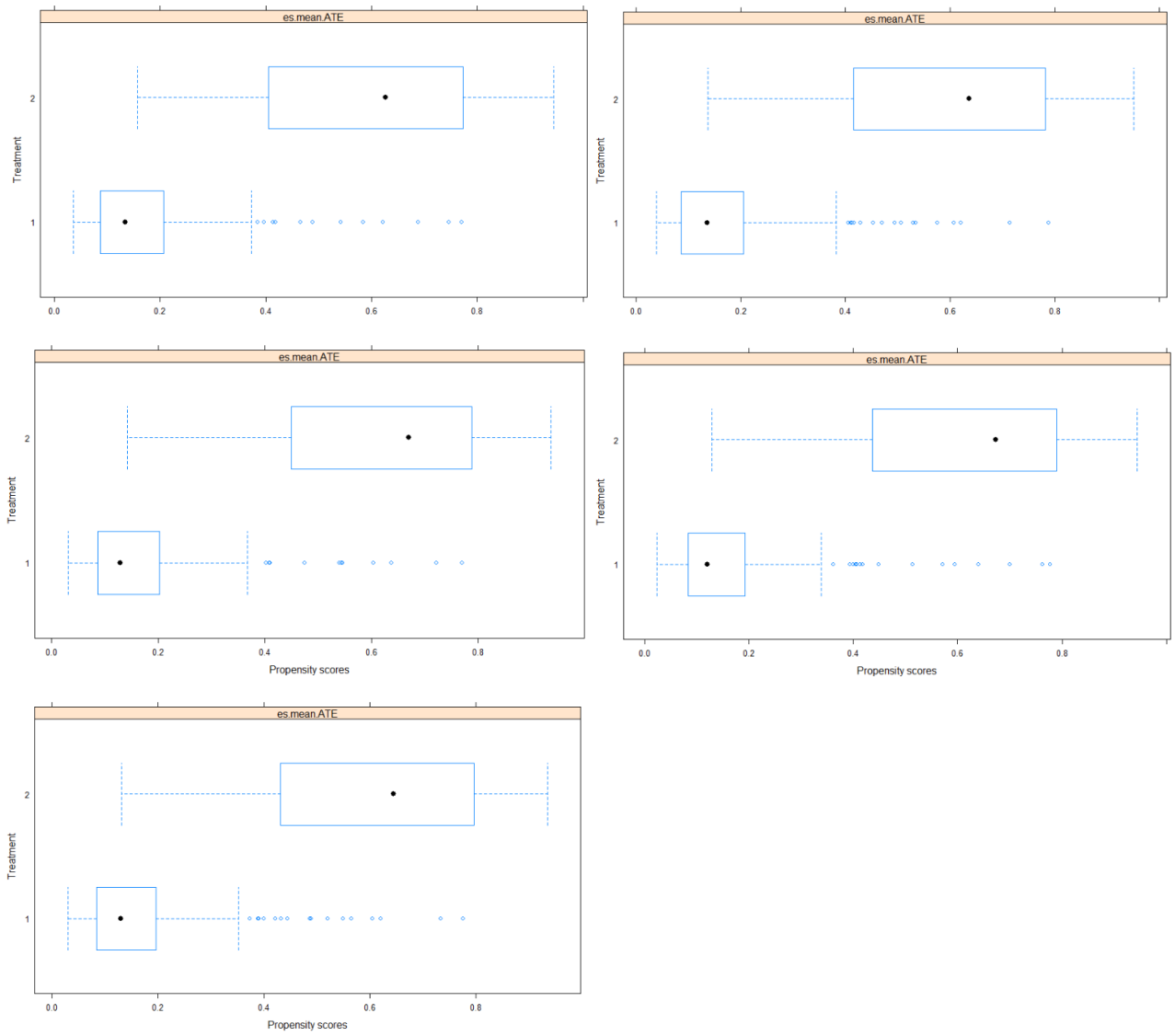
ASD=Absolute standardized difference.

Supplementary figure S2: Check convergence of GBM (5 iterations)



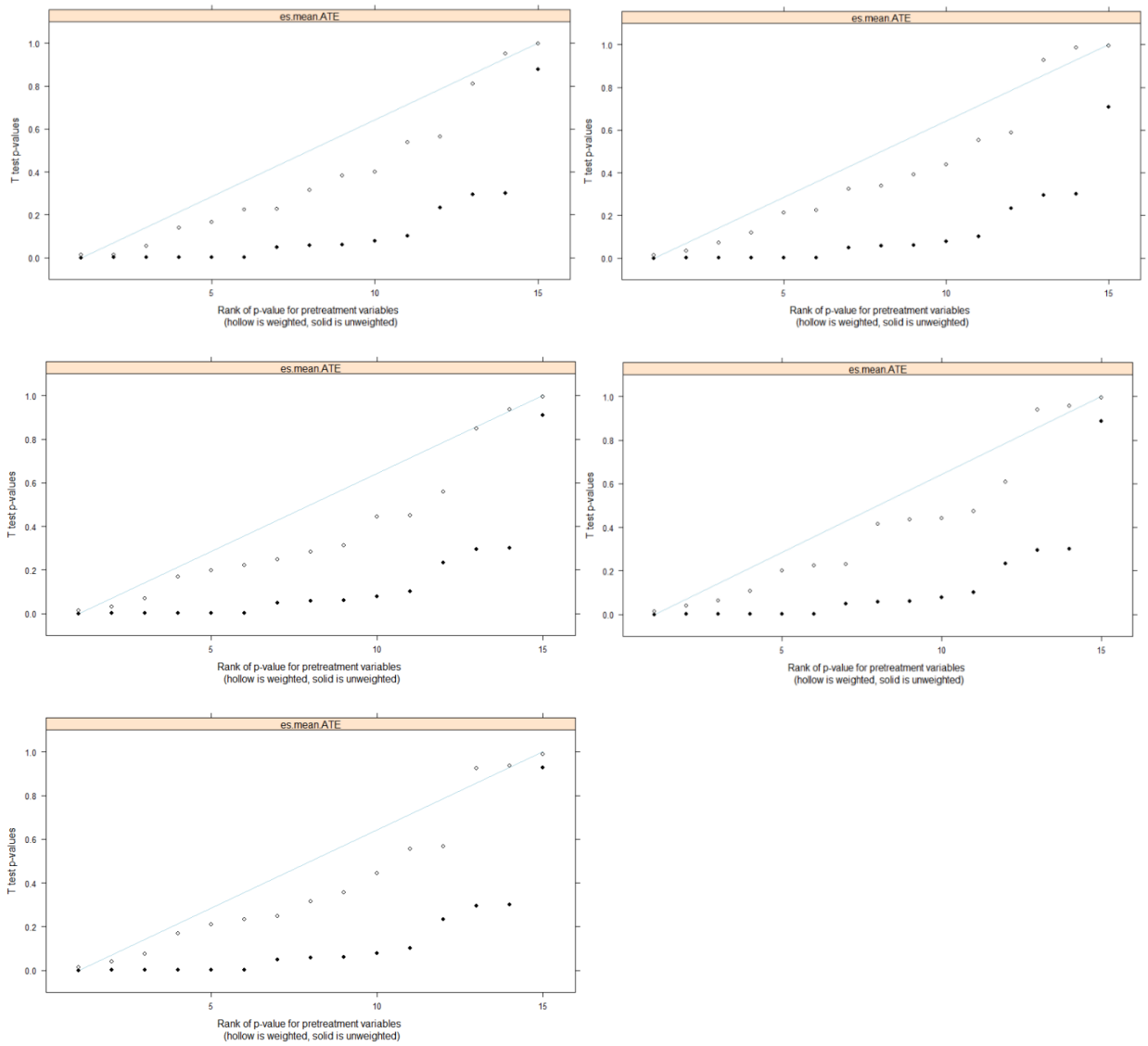
GBM=Generalized Boosted Model. ATE=Average Treatment Effect.

Supplementary Figure S3: Check overlap in weighted populations (5 iterations)



ATE=Average Treatment Effect

Supplementary Figure S4: Check distribution t-test of p-values for balance (5 iterations)



ATE=Average Treatment Effect

Appendix 3 – HREC Approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 February 2019

HREC REF: 072/2019

Prof B Biccard
Department of Anaesthesia and Perioperative Medicine
D-23
NGSH

Dear Prof Biccard

PROJECT TITLE: POSTOPERATIVE OUTCOMES ASSOCIATED WITH PROCEDURAL SEDATION CONDUCTED BY PHYSICIAN AND NON-PHYSICIAN ANAESTHESIA PROVIDERS: AN AFRICAN SURGICAL OUTCOMES STUDY (ASOS) SUBSTUDY (SUB-STUDY LINKED TO R004/2016) MMED CANDIDATE - DR F VAN DER MERWE

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

The HREC note that the PI from the registry Dr Cloete, is not on the protocol.

Approval is granted for one year until the 28 February 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Freliza van der Merwe will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval where necessary, before the research may occur.

Sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Appendix 4 – Strobe Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Comments
Title and abstract	1✓	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p. 29-30
Introduction			
Background/rationale	2✓	Explain the scientific background and rationale for the investigation being reported	p. 31-32
Objectives	3✓	State specific objectives, including any prespecified hypotheses	p.32
Methods			
Study design	4✓	Present key elements of study design early in the paper	p.33
Setting	5✓	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p.33
Participants	6✓	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p.33
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7✓	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.34
Data sources/ measurement	8✓	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group:	p.34
Bias	9✓	Describe any efforts to address potential sources of bias:	p.34
Study size	10✓	Explain how the study size was arrived at: *Prior studies were examined – this further discussed in the manuscript*	p.35
Quantitative variables	11✓	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	p.35-36
Statistical methods	12✓	(*a*) Describe all statistical methods, including those used to control for confounding	p.36-37
		(*b*) Describe any methods used to examine subgroups and interactions	p.36-37
		(*c*) Explain how missing data were addressed	p.36-37

		(*d*) If applicable, explain how loss to follow-up was addressed	p.36-37
		(*e*) Describe any sensitivity analyses	p.36-37
Results			
Participants	13✓	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p.38
		(b) Give reasons for non-participation at each stage	p.38
		(c) Consider use of a flow diagram	p.56
Descriptive data	14✓	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p.38, 50-51
		(b) Indicate number of participants with missing data for each variable of interest	p.38
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15✓	Report numbers of outcome events or summary measures over time	p.38-39, 50-51
Main results	16✓	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p.38-39, 50-53
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p.39-40, 51-53
Discussion			
Key results	18✓	Summarise key results with reference to study objectives	p.41
Limitations	19✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p.41

Interpretation	20✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p.42-43
Generalisability	21	Discuss the generalisability (external validity) of the study results	p.43-44
Other information			
Funding	22✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p.21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Appendix 5 – Instruction for authors, Anesthesia & Analgesia

Anesthesia & Analgesia has specific **Instructions for Authors** for submitting articles, which are found below. We strongly encourage all authors to read these instructions completely and carefully, and to prepare their manuscripts in accordance with these instructions.

Articles that are not submitted in accordance with our instructions may be returned for revision prior to peer-review or rejected outright.

Brevity is crucial for a well-written and effective scholarly article. Particular attention should thus be paid to the listed word count, reference count, and table/figure limits for each article type, both for an initial submission and any subsequent revisions.

The word count, reference count, and table/figure limits will be strictly enforced, resulting in a manuscript being returned to the author(s) for revision prior to any initial or a subsequent peer-review.

Occasionally, authors will be asked by the Journal Editorial Board to resubmit their work as a different article type. If so, this subsequent manuscript will be handled as an entirely new submission, with a corresponding new assigned manuscript number.

Any changes (additions or deletions) of authors will need to be justified and clearly communicated. See below, **Section 8.A. Role of Authors and Contributors**.

INSTRUCTIONS FOR AUTHORS

SECTION 1: *ANESTHESIA & ANALGESIA* ARTICLE TYPES: Each is described in detail below.

DESCRIPTIONS OF SPECIFIC ARTICLE TYPES

Anesthesia & Analgesia

Original Clinical, Health Services, or Educational Research Report

- An Original Clinical, Health Services, or Educational Research Report describes an investigation that focuses on the clinical practice of anesthesiology, perioperative medicine, critical care medicine, or pain medicine.
- Original Clinical, Health Services, or Educational Research Reports span the spectrum of patient-reported outcomes, clinical effectiveness, quality and performance improvement, patient safety, health services delivery, dissemination and implementation science, health policy, healthcare economics, population health, and education.
- An Original Clinical, Health Services, or Education Research Report includes a Title Page and structured Abstract of no more than **400 words**.
- A "Key Points" summary is also provided, which describes the Question, Findings, and Meaning, each composed of **one sentence**.
- These Reports are divided into four sections: Introduction, Methods, Results, and Discussion.
- The Introduction section should be focused and contain no more than **400 words**. The Introduction succinctly describes, in a series of short paragraphs, the significance of the topic, pertinent background, rationale for the study, *a priori* study aims or

objectives, and primary study hypothesis, and if appropriate, secondary study hypothesis.

- The Discussion section should also be focused and contain no more than **1,000 words**. The Discussion succinctly interprets the primary findings of the study and how they relate to previous published findings. The limitations of the present study are clearly stated. If applicable, future, related research opportunities are briefly proposed.
- An Original Clinical, Health Services, or Education Research Report ranges in total length from **1,500 to 4,000 words** (not counting the Abstract and references), with no more than **30-40 references** and **4-6 tables and/or figures**. Online supplemental material can be provided when appropriate.

SECTION 2: ARTICLE TYPES AT A GLANCE

Particular attention should be paid to the listed word count, reference count, and table/figure limits for each article type, both for an initial submission and any subsequent revisions.

These listed limits for word count, reference count, and tables/figures will be strictly enforced, resulting in a manuscript being returned to the author(s) for revision prior to any initial or a subsequent peer-review.

Anesthesia & Analgesia ARTICLE TYPES AT A GLANCE

Manuscript Type	Abstract:	Figures/Tables Limit	Reference Count Limit	Word Count Limit	Sections	Supplemental Material	Additional Information
Clinical, Health Services, or Education Report	Structured 400 word limit & Key Points Summary	4 to 6 tables and/or figures	30-40	1500-4000 (not including abstract and references)	Introduction, Methods, Results, and Discussion	When appropriate	EQUATOR checklist

SECTION 3: STANDARDIZED STUDY REPORTING REQUIREMENTS

A. Enhancing the Quality of and Transparency of Health Research (EQUATOR) Network

The Enhancing the Quality of and Transparency of Health Research (EQUATOR) Network was created to monitor and to propagate the proper use of guidelines to improve the quality of scientific publications by promoting transparent and accurate reporting of human subjects, health services, and animal research.

As advocated by the EQUATOR Network, *Anesthesia & Analgesia* strongly encourages adherence to the applicable statement/guidelines and checklist for all submitted research-related manuscripts (see Table below). Manuscripts adhering to the applicable statement/guidelines and checklist will typically receive a more favorable review by the Journal.

Adhering to the applicable statement/guidelines and checklist promotes consistent study design and manuscript content, which are major advantages for the Journal's authors, reviewers, editors, and readers.

Authors should consult the EQUATOR Network webpage and/or the webpage URL or citation listed in the Table below for the most current version of the specific, applicable **statement or guideline and its checklist**.

- **The applicable study checklist should be completed and uploaded under the EQUATOR Checklist File category at the time of initial manuscript submission via Editorial Manager.**

Acronym	Full Title of Guideline	Webpage URL or Citation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology	http://www.strobe-statement.org/

* The main CONSORT Statement is based on the "standard" two-group parallel design. However, there are several different types of randomized trials, some of which have different designs (e.g., cluster, non-inferiority and equivalence, or pragmatic trials), interventions (e.g., herbal medicinal, non-pharmacological, or acupuncture) and data (e.g., harms), for which specific CONSORT Extensions exist.

B. SPECIFIC STUDY TYPE AND ASSOCIATED PUBLISHED GUIDELINE

1. Randomized Controlled Trials. Authors reporting the results of a **randomized controlled trial** must follow the CONSORT statement and provide a completed CONSORT checklist. Authors must also provide a CONSORT flow diagram as Figure 1 of the submitted manuscript.

Please note that there are CONSORT Extensions for several different types of randomized trials, and the most applicable Extension should be followed by authors.

2. Non-Randomized Controlled Trials. Authors reporting the results of a **non-randomized controlled trial** must follow the TREND statement and provide a completed TREND checklist.

3. Observational Studies. Authors reporting the results of a **cohort, case-cohort, nested case-control, case-control, or cross-sectional study (or any other type of observational study of human subjects)**, or a retrospective data collection study must follow the STROBE statement and provide a completed STROBE checklist.

Authors submitting the results of such a quantitative observational study should clearly indicate (a) whether the primary outcome(s) were defined and established *a priori* at initiation of the study design or were created post hoc during data exploration ("data mining") and accompanying statistical analysis and (b) whether subgroup or sensitivity analyses were identified and established *a priori* or *post hoc*. For studies evaluating a treatment effect, indicate whether and how a clinically meaningful effect size was defined, once again either *a priori* or *post hoc*.

For further insights and directions, see Eisenach JC, Kheterpal S, Houle TT. Reporting of Observational Research in ANESTHESIOLOGY: The Importance of the Analysis Plan. Anesthesiology. 2016;124(5):998-1000.

4. Systematic Review or Meta-analysis. Authors reporting a **systematic review** or **meta-analysis of randomized trials or cohort studies** must follow the PRISMA (previously named QUOROM) Statement and provide a completed PRISMA checklist. Authors must also submit a PRISMA flow diagram as Figure 1 of the submitted manuscript.

5. Quality Improvement Research. Authors reporting the results of a **quality improvement study** must follow the SQUIRE 2.0 guidelines and provide a completed SQUIRE 2.0 checklist.

6. Qualitative Research. Authors reporting the results of a **qualitative study** (e.g., in-depth interviews and focus groups) must provide a completed SRQR checklist.

Alternatively, authors reporting the results of a **qualitative study** can provide a completed COREG checklist.

7. Mixed Methods Research. No definitive guidelines have been created for mixed (qualitative/quantitative) research. However, authors reporting the results of a mixed methods research study can reference the Good Reporting of A Mixed Methods Study (GRAMMS) framework.

See the following pertinent references:

Cameron RA, Trudy D, Scott R, Ezaz A, Aswini S. Lessons from the field: Applying the Good Reporting of A Mixed Methods Study (GRAMMS) framework'. Electronic Journal of Business Research Methods. 2013. https://works.bepress.com/roslyn_cameron/131/

O'Cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. J Health Serv Res Policy. 2008;13(2):92-98.

O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ. 2010 Sep 17;341:c4587.

8. Health Economic Evaluation Research. Authors reporting the results of a **health economic evaluation research study** must follow the CHEERS guidelines and provide a completed CHEERS checklist.

9. Diagnostic Accuracy. Authors reporting a **study of the accuracy of a diagnostic test** must follow the STARD statement and provide a completed STARD checklist. Authors must also provide a STARD flow diagram as Figure 1 of the submitted manuscript.

Alternatively, authors reporting studies of the accuracy of diagnostic tests can follow the TRIPOD Statement and provide a completed TRIPOD checklist.

10. Genetic Association Studies. Authors reporting a **genetic association study** must follow the STREGA guidelines and must submit a completed STREGA checklist.

11. Animal Studies. Authors reporting an **animal study** must follow the ARRIVE guidelines and must submit the ARRIVE checklist.

SECTION 4: STANDARDS FOR STATISTICAL METHODS AND STATISTICAL REPORTING

All authors who are presenting data and data analyses in their manuscripts submitted to the Journal are now required to attest via Editorial Manager that they have reviewed sections 4A and 4B below and have implemented all of the relevant items.

This should be done preferably before implementing their study data collection but certainly as they undertook their statistical analyses and prepared their manuscript for initial submission and any requested revision(s).

While *Anesthesia & Analgesia* has elected not to implement a required formal statistical checklist to be completed and submitted by authors, adhering to the guidelines below will avoid delays in the review process and generally improve the likelihood of publication.

A. Statistical Analyses and Methods as Promulgated by the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines

As advocated by the EQUATOR Network, *Anesthesia & Analgesia strongly* endorses adherence to the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines.

Please see Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: The "Statistical Analyses and Methods in the Published Literature" or "The SAMPL Guidelines." Handbook, European Association of Science Editors. 2013:23-6.

The SAMPL Guidelines can be accessed at http://www.equator-network.org/reporting-guidelines/sampl/.

B. For All Studies That Include Data Analysis and/or Estimation

BASIC STATISTICAL METHODS AND REPORTING THAT SHOULD BE INCLUDED IN ALL QUANTITATIVE MANUSCRIPTS.

The items outlined below are commonly missing or deficient in submitted manuscripts, leading to a lengthier and less favorable statistical review.

Authors are this strongly encouraged to proactively address all of these issues.

At the time of their initial online manuscript submission, the corresponding author will be asked to attest to reviewing and the online supplement that provides details for the following outline.

PLEASE NOTE: EACH MANUSCRIPT WILL BE EXPLICITLY EVALUATED ON EACH OF THESE ITEMS DURING ITS STATISTICAL REVIEW.

1. Abstract clearly and accurately states the study objectives/hypotheses and clearly describes data analysis and study findings
2. Study objectives and/or hypotheses clearly stated
3. Study design is appropriate for the stated aims
4. Primary and secondary outcomes clearly identified and defined
5. Statistical methods appropriate and clearly described
6. Baseline comparisons for randomized trial assessed with standardized difference, not P-values
7. Assumptions of the statistical analyses appropriately assessed
8. Type I error/multiple testing adequately addressed
9. Missing data appropriately described and handled
10. Sample size justified
11. Results section follows clearly from the study objectives and statistical methods
12. Treatment effect estimates and their variability are reported
13. Confounding is carefully addressed for observational studies
14. Tables and Figures clear and self-explanatory
15. Limitations of design and statistical methods clearly described
16. Conclusions and Interpretations justified by the design and results
    - Causation/association – use words connoting association for observational studies
    - Say "Non-significant" instead of "similar/equivalent"
    - Make inference on population not sample
    - Trend -- Do not say "trend" for non-significant findings
17. P-values appropriately reported
18. "Multivariable" instead of "multivariate" when multiple independent variables

SECTION 5: DIGITAL COPYRIGHT TRANSFER AGREEMENT

An Electronic Copyright Transfer and Disclosure Questionnaire is completed by the corresponding author during submission.

Upon submission, the co-authors are emailed a hyperlink to verify their co-authorship and complete the electronic Copyright Transfer and Disclosure Form within Editorial Manager.

Questions About the Copyright Transfer and Disclosure Form?

Please contact our editorial office at editor@anesthesia-analgesia.org

SECTION 6: OPEN ACCESS OPTION FOR PUBLICATION

Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. Please see the **Open Access page** for more details.

SECTION 7: *ANESTHESIA & ANALGESIA* MANUSCRIPT PREPARATION

Manuscript Organization

ALL articles should be arranged in the following order.

1. Manuscript, as a single file, consisting of Title Page, Abstract (not required for all article types – see Articles At A Glance), Body Text, References. Page numbers should be included, line numbers should not be included.
2. Tables (each Table should be a separate .doc file or placed at the end of the manuscript file)
3. Figure Legends (placed consecutively, in numerical order, all on the same page)
4. Figures (each Figure should be uploaded as a separate file)
5. Appendices (each Appendix should be a separate file)

Title Page

- Article Title
- First name, middle initial, and last name of each author, with their highest academic degree (M.D., Ph.D., *etc.*), and institutional affiliations.
- Name, mailing address, phone number, and e-mail address of the corresponding author.
- Disclosure of funding received for the work from National Institutes of Health (NIH), Wellcome Trust, Howard Hughes Medical Institute (HHMI), and all other financial support, including departmental or institutional funding. If no funding received, state Financial Disclosures: None
- Please list any conflicts of interest the authors have had within the 36 months of submission. If no conflicts, state Conflicts of interest: None
- Clinical trial number and registry URL, if applicable.
- **List the word count of the Abstract, Introduction, and Discussion. Also list the overall word count for the entire body of text (excluding Abstract and References).**
- Abbreviated Title (running head) that states the essence of the article (< 50 characters). This is not required for all article types (see above).
- List each author's individual contribution to the manuscript. For each author, please list the individual contribution using the following text: "Author Name: This author helped…"

Abstract

Manuscript Type	**Abstract Type**	**Number of words**
Original Clinical Research Report	**Structured**	**400**

- Structured abstracts should use the following sections: Background, Methods, Results and Conclusions.
- Please include the abstract in the main document file after the title page. You will also be prompted to include the abstract text during the submission process in Editorial Manager.

Key Points Summary

For Original Clinical/Laboratory Research Reports and Meta-Analyses, a "Key Points" summary should be included directly underneath the structured abstract. The key points summary should describe the Question, Findings, and Meaning, each composed of one sentence. Please format the summary as three bullet points:

- Question: [One Sentence Text]
- Findings: [One Sentence Text]
- Meaning: [One Sentence Text]

Glossary of Terms

A Glossary of Terms must be provided for ALL abbreviations/acronyms appearing in the manuscript, including trial names. Additionally, all abbreviations/acronyms must be spelled out upon first mention in both the Abstract and in the main Body of the paper, followed by the abbreviations/acronyms in parentheses; thereafter, the abbreviation/acronym should be used. Authors do not need to define standard abbreviations for standard units of measurements (e.g., kg, ml) in the Glossary of Terms. The Glossary of Terms should be included after the Abstract in the main manuscript file (or after the Title Page for articles without an Abstract) and before the Body of text.

Body

The body of the manuscript should typically be divided into four parts (does not apply to all article types – See Article Types At A Glance):

- Textual material (body text, tables, figure legends etc.) should be submitted as a .doc or .docx word processing file
- 12 point Arial or Times New Roman font
- Introduction (new page). This should rarely exceed one page in length.
    - Should ideally contain only 4 to 5 short paragraphs: (1) significance, (2) background, (2) rationale, and (3) the study's aims or objectives and if applicable, (5) primary study hypothesis, and if appropriate, the secondary study hypothesis.
    - Avoid the temptation and frequent tendency to provide an extensive literature review in the Introduction.
- Methods (new page)
    - A subsection entitled "Statistical Analysis" should appear at the end of the Methods section when appropriateA statement that the study was approved by the appropriate IRB/Research Ethics Committee and written informed patient consent was obtained, or that the requirement for written informed consent was waived. (See section C Protection of Human Subjects).
    - If applicable, authors should include their clinical trial registration number, registry, principle investigator and date of registration. (See section G Registration of Clinical Trials)
    - A statement indicating the author has followed the appropriate EQUATOR guidelines should be included in the Methods section.
        - Example: "This manuscript adheres to the applicable CONSORT guidelines."

        - A subsection entitled “Statistical Analysis” should appear at the end of the Methods section when appropriate
    - Results (new page)
    - Discussion (new page). Focuses on the findings in the current work

Acknowledgements

For acknowledgement of individuals or organizations, provide complete name, degrees, academic rank, department, institutional affiliation, city, state, and country. Add description of the contribution to the study.

References

Anesthesia & Analgesia follows the American Medical Associate (AMA) citation style; Consult the American Medical Association Manual of Style, 10th ed., New York, Oxford University Press, 2007, for style.

- Number references (as superscripts) in the sequence they appear in the text.
- In text, tables, and legends, identify references with superscript Arabic numerals.
- If there are 6 or fewer authors/editors, list all 6; if there are more than 6, list the first 3 followed by “et al.”
- Abbreviate names of journals according to the journals abbreviation list maintained by PubMed
- Manuscripts “In Press” – A “manuscript in press” is defined as an article that has been accepted for publication, but has not yet been published by the accepting journal, in print or online and is being cited as basis for the study being described in the submitted manuscript. Please submit an electronic copy (Word, PDF) of any "In Press" manuscript that is cited in the reference list, labeled as "In Press, Reference # ___."
- During revision, please double-check and confirm that your reference list and in-text reference citations are correct and updated to match the revised version of your manuscript. All references must appear in your reference list (even if the reference is not yet published), and a corresponding reference citation must also be cited in your manuscript for every reference listed in the reference list. In-text reference citations must appear in chronological order upon first mention in the manuscript.

Tables

- *Anesthesia & Analgesia* follows the American Medical Associate (AMA) table format.
- Tables should be uploaded as a separate Word file or presented in the main document word file, just after the references.
- Use a separate page for each table.
- Individual tables should not exceed two typed pages. If a table exceeds two typed pages, start a new table on the subsequent page.
- For any table that exceeds two typed pages and cannot be divided into a new table, the table should be submitted as a supplemental digital content file (see formatting requirements for Supplemental Digital Content files below).

- Double-space all table material.
- Do not submit tables as photographs or pasted images. Tables should be black and white only.
- Number the tables consecutively and cite them consecutively (on first instance) in the text.
- Do not create multi-part tables (e.g., Table 1A, Table 1B). Such tables should instead be cited as "Table 1," "Table 2," etc.
- Each table should have a brief title.
- Each column in a table should have a brief column header name.
- Use footnotes (not table titles or column headings) for explanatory matter and definitions of acronyms or abbreviations. Acronyms and abbreviations must be described with footnotes even if they are defined in the text or in other tables or figures.
- For footnotes within a table, use lower-case italicized letters in sequential alphabetical order.
- If you include a block of data, a table, or a figure from another source, whether published or unpublished, acknowledge the original source.

Appendices

- Uploaded as a separate file or in the main document file at the end of the body of text.
- Each appendix must be cited within the text, in consecutive order.
- Appendix content counts towards the table and/or figure limits. If the inclusion of an appendix exceeds the table and/or figure limit for the respective article type, submit the appendix as a supplemental digital content file.

Figure Legends

- Supply a legend for each figure.
- Group figure legends on a single page just after the references
- If a figure has multiple panels (e.g., left, right or A, B, C) please specify each panel in the legend.
- Repeat definitions of any acronyms or abbreviations used in the figure in its legend.

Figures

- Figures should be uploaded as separate .tiff, .jpeg, .pdf or .pptx files. Figures will have to be uploaded at a resolution of 300 dpi or higher at acceptance.
- Figures with multiple panels should be condensed into a single file for each figure (for example, Figure 1A through 1F should be in one file, Figures 2a through 2F should be in a second file, etc.). Each individual panel should be labeled with a capital letter.
- *Anesthesia & Analgesia* publishes in full color, and encourage authors to use color to increase the clarity of figures.
- Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray).
- Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink).

- Figure backgrounds and plot areas should be white, not grey.
- Axis lines and ticks should be black and thick enough to clearly frame the image.
- Axis labels should be large enough to be easily readable and printed in black.
- Number figures consecutively. Supply a brief title for each. Cite figures in the text in consecutive, numerical order on first instance.
- If a figure has already been published, acknowledge the original source. You must obtain and submit written permission from the copyright holder to reproduce the material when you submit the manuscript for review. Unpublished figures require permission of the author. Permission is required to reproduce any previously published material except for documents or figures in the public domain. See Permissions
- Define in a footnote all acronyms or abbreviations used in each figure.

Supplemental Material

- Authors may submit separate supplemental material to enhance their article's text and to be considered for online-only posting.
- Supplemental material may include the following types of content: text documents, graphs, tables, figures, audio, and video.
- Cite all supplemental digital content consecutively in the text (i.e., each supplemenalt file is numbered starting with 1)
- Citations should include the type of material submitted, should be clearly labeled, and should include a sequential number (Example “Supplemental Figure1”, “Supplemental Table 1”, “Supplemental Video 1”).
- Supplemental Legends should be submitted at the end of the manuscript file and should provide a brief description of the supplemental content. For example: “Supplemental Table 1: Lists all medications used in this study.”
- Each supplemental digital content file must be composed to standalone. For example, tables and figures must include titles, legends, and/or footnotes, following journal style, so the viewer can fully understand the supplemental content on its own. Production will not make any edits to the supplemental files; they will be presented as submitted.
- It is recommended to group multiple supplemental figures/tables into one supplemental digital content file when submitting. Each file will be given a permanent hyperlink when the Publisher prepares the supplemental digital content for posting. To avoid excessive hyperlinks in your publication, please group figures/tables.
- For audio and video files, enter the author name, videographer, participants, length (minutes), and size (MB) of file in Editorial Manager. Authors should mask patients’ eyes and remove patients’ names from supplemental digital content unless they obtain written consent from the patients and submit written consent with the manuscript. Copyright for video or audio supplemental digital content will be required upon acceptance.
- For a list of acceptable file types and size limits, please review LWW's requirements for submitting supplemental digital content: http://links.lww.com/A142

Additional Information

1. Units of Measurement

Use metric units. The units for pressures are mmHg or cmH2O. Diagonal slashes are acceptable for simple units, *e.g.*, mg/kg; when more than two items are present, negative exponents should be used, *i.e.*, $ml \cdot kg^{-1} \cdot min^{-1}$ instead of ml/kg/min.

2. Glossary of Terms and Abbreviations

A Glossary of Terms must be provided for ALL abbreviations/acronyms appearing in the manuscript, including trial names. Additionally, all abbreviations/acronyms must be spelled out upon first mention in both the abstract and in the main body of the paper, followed by the abbreviations/acronyms in parentheses; thereafter, the abbreviation/acronym should be used. Authors do not need to define standard abbreviations for standard units of measurements (e.g., kg, ml) in the Glossary of Terms. The Glossary of Terms should be included after the abstract in the main manuscript file (or after the title page for articles without abstracts).

3. Drug Names and Equipment

Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide manufacturer's name, city, state, and country. Be careful about the use of trademarked terms (*e.g.*, Thrombelastography™, TEG™, *etc.*).

4. Statistical Analysis

Detailed statistical methodology must be reported. Describe randomization procedures and the specific tests used to examine each part of the results; do not simply list a series of tests. Care should be taken with respect to a) parametric vs. nonparametric data, b) corrections for multiple comparisons, and c) rounding errors (summary statistics should not contain more significant digits than the original data). Median range (or percentiles) is preferred for nonparametric data.

5. Patient Identification

Do not use patients' names, initials, or hospital numbers. An individual (other than an author) must not be recognizable in photographs unless written consent of the subject has been obtained and is provided at the time of submission.

Permissions

Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyright form elsewhere, along with complete details about the source. Any permission fees that might be required by the copyright owner are the responsibility of the authors requesting use of the borrowed material, not the responsibility of

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Language Editing Services

Articles submitted to the Journal must be written with a solid basis of English language. Awkward or non-intelligible English grammar and syntax can adversely affect the review process and the likelihood of acceptance of a manuscript. **Authors whose native language is not English should thus strongly consider having their manuscript copy-edited by a native English language medical/technical writer prior to initial submission.**

If you need assistance in preparing a manuscript for submission, our publisher, Wolters Kluwer, in partnership with Editage, offers a range of editorial services for a fee, including:

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- Translation with Editing: Write your paper in your native language and Wolters Kluwer Author Services will translate it into English, as well as edit it to ensure that it meets international publication standards.
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- Artwork Preparation: Save precious time and effort by ensuring that your artwork is viewed favorably by the journal without you having to incur the additional cost of purchasing special graphics software.

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Section 8: EDITORIAL, ETHICAL AND LEGAL REQUIREMENTS

Anesthesia & Analgesia follows the International Committee of Medical Journal Editors (ICMJE) "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals"**.**

All authors submitting a manuscript to *Anesthesia & Analgesia* are required to understand and to adhere to the material below.

A. Role of Authors and Contributors

Anesthesia & Analgesia adheres to the ICMJE recommendations for defining the role of authors and non-author contributors

Anesthesia & Analgesia therefore defines manuscript **Authors** as meeting all of the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those individuals who do not meet all four criteria for authorship can be referred to as Collaborators as defined by the NLM and MEDLINE/PubMed: https://www.nlm.nih.gov/pubs/techbull/ma08/ma08_collaborators.html. These Collaborators are individually but separately listed as such on the Title Page of the submission. These Collaborators will be listed in a separate section at the end of the paper when it is published by Anesthesia & Analgesia. This section entitled "Collaborators" will be placed immediately after the Body of the text, to be followed by Acknowledgements, then Disclosures, and lastly, References.

If the manuscript has been authored by a subset of members of and/or on behalf of a larger group, that larger group can be listed by its formal name, which is preferably placed after the list of formally named authors.

Each manuscript must have a Corresponding Author. The corresponding author serves as the primary contact during the submission and review process on behalf of all co-authors. Upon submission, the corresponding author is required to attest to the validity and legitimacy of the data and interpretation. The corresponding author is responsible for ensuring that all authors have reviewed the manuscript and have completed the conflict of interest disclosures. If the manuscript is accepted, the corresponding author is responsible for reviewing the proof.

If during the manuscript review process or with a complete resubmission, an initial author is deleted or another author is added, this change must be justified in the revision cover letter. The deleted or added author must be formally notified in writing, with a copy of this co-author correspondence sent to the Journal Editorial Office.

Upon acceptance, the Editorial Office will also require a completed Authorship Change Verification form, finalizing the agreed upon authorship order for the accepted submission from each author listed, as well as, those who were added or removed. Authors may include all electronic signatures on one pdf form to finalize the agreement that the authorship order is correct.

B. Author Conflict of Interest

Anesthesia & Analgesia endorses the ICMJE recommendations for defining the role of authors' conflict of interest.

- *Anesthesia & Analgesia* holds that a conflict of interest exists when professional judgment concerning the primary interest, including patients' welfare or the validity of research, may be influenced by a secondary interest like financial gain. Perceptions of conflict of interest are as important as actual conflicts of interest.
- Authors therefore must define all funding sources supporting their work. This includes departmental, hospital, or institutional funds. The authors must disclose commercial associations that might pose a conflict of interest in connection with the work submitted. Financial relationships such as employment, consultancies, stock ownership or options, honoraria, patents, and paid expert testimony must also be reported.

C. Protection of Human Subjects

Research is a systematic investigation for the creation of generalizable knowledge. Any investigation submitted for publication demonstrates intent to create generalizable knowledge, and thus constitutes research.

The name of the institutional research ethical review and oversight committee varies with country and local custom. In the United States, this committee is called the Institutional Review Board (IRB). Other countries may use other terms (e.g., "Research Ethics Committee") for their research ethical review committee. "Institutional Review Board" is used here generically to refer to the local board that reviews the ethical treatment of human subjects and grants institutional approval for the study.

- Regardless of the country of origin, all clinical investigators undertaking human subjects research must abide by the "Ethical Principles for Medical Research Involving Human Subjects" outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association.

Clinical studies not meeting the Declaration of Helsinki criteria will not be considered for publication. If published research is subsequently found to be noncompliant, it will be retracted.

- On the basis of the Declaration of Helsinki, *Anesthesia & Analgesia* requires that all manuscripts reporting clinical research state in the first paragraph of the Methods section that:

1. The study was approved by the appropriate Institutional Review Board (IRB), and

2. Written informed consent was obtained from all subjects, a legal surrogate, the parents or legal guardians for minor subjects, or that the requirement for written informed consent was waived by the Institutional Review Board (IRB).

The Editors of *Anesthesia & Analgesia* may question the authors about the details of the IRB review, informed consent forms, or the consent process. On occasion, the Editor-in-Chief may request a copy of the approved IRB application from the author. Lack of appropriate consent or its documentation will be grounds for rejection or subsequent retraction.

- Patients also have a right to privacy regarding their protected health information (PHI). Access to their protected health information (PHI) should not occur without their written authorization of use or disclosure of PHI for the explicit purposes of (a) research or (b) an expanded case series (with an N > 3). Under certain circumstances, the requirement for patient written authorization may be waived by the Institutional Review Board (IRB).

D. Investigational Drugs

The Editorial Board of *Anesthesia & Analgesia* may exercise judgment about the ethics of a clinical trial involving investigational drugs that differs from the view of the investigators' Institutional Review Board. This situation most frequently occurs in studies involving neuraxial or perineural drug administration; drug studies in children; and nonconformity in dose, route, or indication ("off-label" use).

- Studies using drugs injected into the neuraxial (caudal, intrathecal, or epidural) or perineural space must meet at least one of three criteria:

1. The drug is approved for neuraxial or perineural administration by the United States (US) Food and Drug Administration (FDA) or the equivalent regulatory agency for the country in which the study took place.

2. The drug is not approved for neuraxial or perineural use, but it is widely used and accepted for neuraxial (e.g., fentanyl) or perineural administration. The publication of dosing guidelines in multiple textbooks represents a reasonable demonstration that a drug is widely used and accepted for neuraxial or perineural administration.

3. The study is performed under an Investigational New Drug (IND) or Biologics License Application (BLA) application approved by the US FDA or the equivalent agency in the investigator's country.

- *Anesthesia & Analgesia* is committed to expanding knowledge of the clinical pharmacology of drugs in children. However, studying drugs in children when there is no pediatric indication poses ethical concerns. Therefore, studies of drugs in children must meet at least one of three criteria:

1. The drug is approved for pediatric administration by the US FDA or an equivalent regulatory agency.

2. The drug is not approved for use in children but is widely used and accepted for pediatric administration. A reasonable demonstration that the drug is clinically accepted for use in children is when the administration in the study is consistent with the route, dose, and indication reported in multiple textbooks.

3. The study is done under an IND application approved by the US FDA or the equivalent agency in the investigator's country. Investigators in the United States are directed to the FDA website for further information on obtaining an investigator IND.

Anesthesia & Analgesia will not publish a paper describing a retrospective assessment involving pediatric drug administration, if the treatment would be considered inappropriate or unethical in a prospective trial.

- Drugs are commonly used off-label in clinical trials, and the practice is generally acceptable. However, the Editorial Board of *Anesthesia & Analgesia* reserves the right not to review a manuscript describing off-label administration of a drug if the Editorial Board believes the study posed unacceptable risk to subjects. To preclude such a determination, investigators are encouraged to obtain an Investigator IND from the US FDA or an equivalent agency in their country before initiating studies involving off-label drug administration.

E. Registration of Clinical Trials

All clinical trials involving assignment of patients to treatment groups must be registered prior to the start of the trial and any patient enrollment is undertaken.

The registry, registration number, principal investigator's name, and date of registration must be stated in the first paragraph of the Methods section of the manuscript.

Authors must state in the Methods section of their manuscript that registration of their clinical trial occurred prior to the start of the trial and any patient enrollment undertaken.

A number of registries have been approved by the International Committee of Medical Journal Editors (http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/), including http://www.clinicaltrials.gov (the most commonly used registry in the United States), http://isrctn.org, http://www.umin.ac.jp/ctr/index/htm, http://www.anzctr.org.au, and http://www.trialregister.nl. Submissions that have registered with the European Clinical Trials Database, EudraCT (https://eudract.ema.europa.eu/) meet this requirement.

F. Protection of Animal Subjects

Manuscripts describing investigations performed in vertebrate animals must explicitly state that the study was approved by the authors' Institutional Review Board for animal research (e.g., Institutional Animal Care and Use Committee, IACUC). The Journal expects humane and ethical treatment of all experimental animals, and requires that the study has been conducted in a manner that does not inflict unnecessary pain or discomfort upon the animals, as outlined by the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals (1996), prepared by the National Academy of Sciences' Institute for Laboratory Animal Research. A

statement to this effect should appear at the beginning of the Methods section of the manuscript.

G. Plagiarism

Plagiarism is the use of previously published material without attribution. **The Editorial Office screens all submitted manuscripts for plagiarism, using a sophisticated software program, prior to peer review.** This software screening process identifies passages of text that have been previously published and generates a qualitative/quantitative report. This report is reviewed by the Journal Editorial Board and its support staff.

Text copied from previously published work is interpreted using the following taxonomy:

- *Intellectual theft* is misrepresentation by an author that words and ideas previously published by another author represent the plagiarist's own scholarship. It is the most serious form of plagiarism. Intellectual theft identified during screening results in immediate rejection of the manuscript and a request for an explanation from the author.
- *Intellectual sloth* is the use of the words of another author to avoid the effort of writing new text. It commonly occurs when descriptions of research methodology are taken from prior publications. It is less serious than intellectual theft, because the text is generic and of no particular value. Submissions containing intellectual sloth are typically returned to the authors with a request that the copied text either correctly cite the original author or be rewritten in the authors' own words.
- *Plagiarism for scientific English* occurs when authors uncomfortable using scientific English compose their manuscripts as a patchwork of previously published sentences and paragraphs. Papers constructed in such a manner are rejected outright, primarily because patchwork plagiarism suggests that the authors may not understand the text they have submitted for publication.
- *Technical plagiarism* is the use of verbatim text not identified as taken verbatim, but simply referenced to the original source. The offense is a technical one, and authors are simply asked to correct it prior to peer review.
- "*Self-plagiarism"* occurs when an author uses his or her verbatim words from a previous manuscript in a new submission. Provided the authors are not engaged in duplicate publication, the Journal does not view "self-plagiarism" as misconduct. Authors are permitted to reuse their own words, and are encouraged to do so when describing identical research methods in multiple papers.

H. Duplicate Submission or Duplicate Publication

- *Duplicate submission* is concurrent submission of a nearly identical manuscript to two journals. It is improper for authors to submit a manuscript describing essentially the same research simultaneously to more than one peer-reviewed research journal. Authors should not submit the same manuscript, in the same or different languages, simultaneously to more than one journal. Duplicate submissions identified during peer review will be immediately

rejected. Duplicate submissions that are discovered after publication in the Journal will be retracted.

- *Duplicate publication* is prior publication of a manuscript with considerable content overlap, particularly in the research results, by the same author or co-authors. Prior publication may be in the same language or it may be a translation (usually from the author's native language to English). Submitted manuscripts must not have been published elsewhere, in whole or in part, on paper or electronically. This includes personal, departmental, educational, or other Internet sites. This does not apply to abstracts of scientific meetings or to lecture handouts (*e.g.*, IARS Annual Meeting, ASA Annual Meeting). *Anesthesia & Analgesia* requests that authors inform the Journal when results of a submitted manuscript have been previously presented or published in *any* venue. If a manuscript has been published previously, the submission to *Anesthesia & Analgesia* will be rejected unless it has already been published by the Journal, in which case it will be retracted.

I. Scientific Misconduct

When *Anesthesia & Analgesia* has concerns or receives allegations of scientific misconduct, *Anesthesia & Analgesia* reserves the right to proceed according to the procedures described below.

Anesthesia & Analgesia recognize its responsibility to appropriately address concerns allegations of misconduct. Examples of misconduct include: fraud, data fabrication, data falsification, plagiarism, improper designations of authorship, duplicate publication, misappropriation of others' research, failure to disclose conflict(s) of interest, and failure to comply with applicable legislative or regulatory requirements. Misconduct also includes failure to comply with any rules, policies, or procedures implemented by *Anesthesia & Analgesia*.

In general, *Anesthesia & Analgesia* follows the recommendations of the Committee on Publication Ethics (COPE) when working to address allegations of misconduct. When a concern or allegation is raised involved parties generally will be contacted to provide an explanation of the situation. As needed, *Anesthesia & Analgesia* may also contact the institution at which the study was conducted and any other involved journals. *Anesthesia & Analgesia* will attempt to determine whether there was misconduct and the Editor-in-Chief will respond with an appropriate action. Examples of action include:

- Sending a letter of explanation only to the person(s) involved or against whom the allegation is made.
- Sending a letter of reprimand to the same person(s), warning of the consequences of future, similar instances.
- Sending a letter to the relevant head of the educational institution and/or financial sponsor of the person(s) involved, expressing the concerns and information collected.
- Publishing in *Anesthesia & Analgesia* a notice of duplicate publication, "salami" publishing, plagiarism, or other misconduct, if clearly documented. In cases of ghostwritten manuscripts, the notice may include the names of the responsible companies as well as the submitting author(s).

- Providing specific names to the media and/or government organizations, if contacted regarding the misconduct.
- Formally withdrawing or retracting the article from *Anesthesia & Analgesia*, and informing readers and indexing authorities
- Banning an author or authors from publishing any manuscript in Anesthesiology for a specified time period, with notice to the author(s) institution.

Section 9: Common Reasons Why a Submission is Returned Without Review

- Incomplete Title Page - e.g., missing conflict of interest statement for each author or incomplete author information
- Abstract is missing in the Word file or not properly structured.
- Missing page numbers
- Entire manuscript is not double-spaced
- Methods section does not specifically state that the required Institutional Review Board (IRB) or Research Ethics Committee approval was obtained; and if applicable, a written informed consent and/or HIPAA Authorization form was completed for each enrolled patient.
- References do not adhere to AMA style.
- The above noted word count, reference count, and table/figure count limits are not followed for a specific article type.