The association between perioperative risk factors and the method of anaesthesia, and maternal and neonatal outcomes following caesarean delivery in Africa: a sub-study of a 7-day prospective observational cohort study.

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DECLARATION

I, Carmen Gerber, hereby declare that the work on which this dissertation/thesis 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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To George, my dad, thank you for all your support, for listening and believing, I dedicate my contribution to you.

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The association between perioperative risk factors and the method of anaesthesia, and maternal and neonatal outcomes following caesarean delivery in Africa: a sub-study of a 7-day prospective observational cohort study.

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Conflicts of interest

Professor Rupert Pearse has received research grants from Edwards Lifesciences, Nestle Health Sciences and Intersurgical, has given lectures and/or performed consultancy work for Nestle Health Sciences, Medtronic, Edwards Lifesciences, BBraun and GlaxoSmithKline, and is a member of the associate editorial board of the British Journal of Anaesthesia. The authors declare that they have no conflict of interest.

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Abstract

Background

Maternal and neonatal mortality is high in Africa. The African Surgical Outcomes Study found that maternal mortality following caesarean delivery in Africa is 50 times higher than in high-income countries, and independently associated with obstetric haemorrhage and anaesthesia complications.

Methods

A sub-study was conducted of a seven-day, international, prospective, observational cohort study of patients undergoing caesarean delivery in Africa. The aims were to determine the association between preoperative risk factors and the method of anaesthesia, and to examine the association between method of anaesthesia and i) pre- and post-delivery hypotension, ii) severe anaesthesia complications, iii) maternal mortality, and iv) neonatal mortality. In addition, the association was examined between pre-delivery intraoperative hypotension and neonatal outcomes. The primary outcomes were maternal and neonatal in-hospital mortality censored at 30 days. Secondary outcomes were a composite of four severe anaesthesia complications, the association between method of anaesthesia and intraoperative hypotension, and that between hypotension and neonatal outcomes.

Findings

3709 patients who received spinal (2968, 80%) or general anaesthesia (GA) (741, 20%) were recruited from 183 hospitals in 22 African countries from February to May 2016. Maternal mortality was higher with GA than spinal anaesthesia (11/729, 1.5%, versus 9/2881, 0.3%, $p = 0.001$), as was neonatal mortality (65/662, 9.8% versus 73/2669, 2.7%, $p < 0.001$). Independent predictors of GA as the method for caesarean delivery included gestational age, American Society of Anaesthesiologists (ASA) category, emergency surgery, eclampsia, placenta

praevia, placental abruption, and ruptured uterus. Spinal anaesthesia was administered to 48/94 (51.1%) patients with eclampsia, 12/28 (42.9%) with cardiac disease, 14/19 (73.7%) with preoperative sepsis, 48/76 (63.2%) with antepartum haemorrhage, 30/55 (54.5%) with placenta praevia, 33/78 (42.3%) with placental abruption and 12/29 (41.4%) with a ruptured uterus. There was no association between method of anaesthesia and intraoperative hypotension. There was no association between pre-delivery hypotension and neonatal mortality, cardiopulmonary resuscitation, or Apgar scores at 1 and 5 minutes.

Conclusion

Analysis of a large cohort of patients undergoing anaesthesia for caesarean delivery in Africa, showed that a larger proportion than in high-income countries received GA, and indicated which patients were more likely to require GA. GA was associated with maternal mortality, neonatal mortality, and severe anaesthesia complications. Spinal anaesthesia was often administered to patients with eclampsia or at high risk for obstetric haemorrhage. Focussed training in the principles of selection of method of anaesthesia, and specifically in the skills of safe GA, are recommended.

Key points summary

- **Question:** The association between maternal perioperative risk factors, method of anaesthesia and maternal and neonatal outcomes, following caesarean delivery in Africa, are unknown.
- **Findings:** One in 66 general anaesthetics were associated with a maternal death and one in 10 general anaesthetics were associated with a neonatal death, patients with eclampsia and those at high risk for obstetric haemorrhage often received a spinal anaesthetic.
- **Meaning:** Training in the principles of selection of mode of anaesthesia and in skills to provide a safe GA is essential for anaesthesia providers in Africa.

Glossary of Terms

ASA	American Society of Anaesthesiologists
ASOS	African Surgical Outcomes Study
CRF	Case report form
GA	General Anaesthesia
HICs	High-income countries
LMICs	Low- and middle-income countries
SASA	South African Society of Anaesthesiologists
SSSA	Safe Surgery South Africa

Introduction

Maternal and neonatal mortality is high in Africa. The African Surgical Outcomes Study (ASOS) found that maternal mortality in Africa following caesarean delivery is 50 times higher than in HICs (high income countries) and independently associated with obstetric haemorrhage and anaesthesia complications.[1]

Research by Sobhy et al. (2016), reported that 13.8% (95% CI 9.0-20.7) of caesarean-related maternal deaths in LMICs (low- and middle-income countries), were due to anaesthesia. Maternal mortality rates for general anaesthesia were 5.9 per 1000 operations and 1.2 per 1000 operations for neuraxial anaesthesia following caesarean sections in these countries, with the odds of deaths three times more likely among those receiving a general anaesthetic (OR 3.3, 95% CI 1.2-9.0), compared to neuraxial anaesthesia.[2]

Findings from the ASOS obstetric cohort in Africa indicated that anaesthesia-related complications following caesarean delivery were associated with an 11-fold (OR 11.47; 95% CI 1.20-109.20) increase in the odds for death.[1] The ASOS obstetric study reported higher rates, with an almost five-fold (OR 4.89 (95% CI 2.02-11.84; $p<0.001$) increase in the odds for death among maternal obstetric cases receiving a general anaesthetic.[1]

Sobhy et al. (2016) reported that the shortage in skilled providers, as well as perioperative maternal risk factors, increased maternal mortality in LMIC, with the maternal mortality rate for non-physicians (9.8 per 1000 anaesthetics (95% CI 5.2-15.7)) almost double the rate of physician anaesthetists (5.2 per 1000 (95% CI 0.9-12.6)).[2] In the ASOS obstetric sub-study a median of 0.7 specialists per 100 000 population (IQR 0.2-2.0) were available for perioperative care for caesarean delivery.[1]

The association between the method of anaesthesia for caesarean delivery in Africa, and maternal and neonatal outcomes, and the predictors of these outcomes, are unknown. To

address these shortcomings in current knowledge, we conducted a sub-study of the prospective observational study of adult patients undergoing caesarean delivery within ASOS.[3] This sub-study had three objectives. The first was to determine the association between preoperative risk factors and the method of anaesthesia. The second examined the association between method of anaesthesia and i) pre- and post-delivery hypotension, ii) severe anaesthesia complications, iii) maternal mortality, and iv) neonatal mortality. The third analysed the association between pre-delivery intraoperative hypotension and neonatal outcomes.

Methods

Study design

This was a sub-study of the obstetric cohort of the African Surgical Outcomes study (ASOS), a seven-day African national multicentre prospective observational cohort study of all patients ≥18 years of age, undergoing in-patient surgery.[1,3] The study was registered on the South African National Health Research Database (KZ_2015RP7_22), and on ClinicalTrials.gov (Identifier: NCT03044899). The primary ethics approval was from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa (BE306/15)[3].

Setting and participants

The study design has been previously described.[3] In brief, we sought to recruit as many centres as possible from each participating country, through convenience sampling. Each participating country selected a single recruitment week between February and May 2016. The obstetric cohort included all consecutive patients admitted to participating centres undergoing elective and non-elective caesarean delivery during the seven-day study cohort period. Preoperative recruitment and follow-up until discharge was performed by local investigators. The study was censored at 30 days postoperatively for patients who were still in hospital. All sites approved a waiver of consent, with the exception of the University of the Witwatersrand, South Africa, which required informed consent from all patients, with the option of deferred consent for patients unable to give consent before surgery.[3]

Variables

An obstetrics-specific case report form (CRF) was added to the ASOS dataset for the obstetric study (Supplementary Appendix 2), which included the following obstetric sub-study specific data; history of preeclampsia, eclampsia, cardiac disease, placenta praevia, placental abruption, ruptured uterus, sepsis, antepartum haemorrhage; gravidity and parity, gestational age, fetal distress, and the following neonatal outcomes; 1 and 5 minute Apgar scores, need for cardiopulmonary resuscitation following delivery, and neonatal in-hospital mortality censored at 30 days. A website provided educational support and a regularly updated 'frequently asked questions' webpage. The protocol and CRFs for the study were available in English and French on the study website (www.asos.org.za).[3]

Data were collected on paper CRFs and were pseudo-anonymised in that unique numeric codes were generated during transcription of data onto an internet-based electronic CRF. Soft limits were set for data entry, prompting investigators when data were entered outside these limits. This study is reported according to the STROBE statement.[4] The national leaders confirmed the face validity of the unadjusted outcome data for their countries.

Bias

To ensure a representative sample, we planned to include at least 90% of all patients presenting for surgery within the recruitment week. This objective was however difficult for the sites to achieve.[3]

Outcomes

The outcomes were maternal and neonatal in-hospital mortality censored at 30 days. Secondary outcomes were severe anaesthetic complications defined as a composite of failed intubation, pulmonary aspiration, cardiac arrest and severe hypoxia. Maternal intraoperative hypotension was defined as systolic blood pressure (SBP) < 80 mmHg. Neonatal outcomes were: i) mortality, ii) the need for cardiopulmonary resuscitation, and iii) Apgar scores at 1 and 5 minutes post-delivery.

Statistical analysis

Categorical variables were described as proportions and compared using the chi-square test and Fisher's exact test, as appropriate. Continuous variables were described as mean and standard deviation or median and interquartile range (IQR), and compared using the t-test or Mann-Whitney U-test as appropriate. Univariate analyses and binary logistic regression models were performed to evaluate the risk factors for maternal and neonatal mortality. The main model for predictors of the method of anaesthesia included all patients with complete dependent variable data (i.e., spinal or GA). A three-level generalised linear mixed model (GLMM) using a logit link was fitted to identify independent risk factors for the binary outcome of mortality, with patients being at the first level, hospital at the second and country at the third level, to account for the expected correlation in outcomes within hospitals and countries. Collinearity between potential risk predictors was evaluated by identification of a variance inflation factor; with risk predictors with a variance inflation factor >2 excluded. All risk factors were entered into the model, as there was no evidence of collinearity. An *a priori* decision was made to enter the following variables into the regression; gravidity, gestational age, American Society of Anesthesiologists (ASA) category, urgency of surgery, preeclampsia,

eclampsia, history of cardiac disease, preoperative sepsis, antepartum haemorrhage, placenta praevia, placental abruption, ruptured uterus, fetal distress, and whether the anaesthesia provider was a physician or non-physician. The model fulfilled the criteria for a minimum of 10 events per variable to construct a reliable logistic regression model for GA.[5] For all analyses, we performed a complete case analysis where patients with missing data were excluded. All variables had less than 5% missing data, with the exception of fetal distress (239/3709, 6.4%).[6]

Results are reported as adjusted odds ratios (OR) with 95% confidence intervals (CI). $p < 0{\cdot}05$ was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24 (SPSS Inc., Chicago, IL, USA).

Role of funding source

The study was funded by a self-initiated research grant of the Medical Research Council of South Africa awarded to BMB. The study website (www.asos.org.za) and data repository were maintained by Safe Surgery South Africa (SSSA) and the South African Society of Anaesthesiologists (SASA), who had no role in the study design, data acquisition, data analysis or writing of the paper.

Results

Participating countries

One hundred and eighty-three hospitals from 22 African countries participated in the ASOS Obstetric sub-study. These included 12 low-income countries (Benin (9 hospitals), Burundi (6 hospitals), Congo (1 hospital), Democratic Republic of the Congo (16 hospitals), Ethiopia (2 hospitals), Gambia (5 hospitals), Madagascar (6 hospitals), Mali (9 hospitals), Niger (1 hospital), Tanzania (3 hospitals), Uganda (8 hospitals), Zimbabwe (19 hospitals)) and 10 middle-income countries (Algeria (2 hospitals), Cameroon (5 hospitals), Ghana (2 hospitals), Kenya (5 hospitals), Libya (6 hospitals), Mauritius (6 hospitals), Namibia (15 hospitals), Nigeria (10 hospitals), South Africa (44 hospitals), Zambia (3 hospitals)).[3]

Participating hospitals

Hospital-specific data for the obstetric sub-study has previously been published.[1] In summary, data were submitted for 173/183 (94·5%) hospitals, of which 139/173 (80·3%) were government-funded hospitals, 22/173 (12·7%) privately funded, and 12/173 (6·9%) jointly funded hospitals. 77/169 (45·6%) were university-affiliated hospitals. 39/173 (22·5%) district hospitals, 58/173 (33·5%) regional hospitals, 34/173 (19·7%) central hospitals, and 42/173 (24·3%) specialised hospitals. These hospitals served a median population of 860 000 (IQR 265 317-2 000 000) people. Participating hospitals had a median of 339 (IQR 154-540) beds, 6 (IQR 2-7) operating rooms and 4 (IQR 1-7) critical care beds allowing invasive ventilation. The median ratio of critical care beds allowing invasive ventilation to hospital beds was 2·3% (IQR 0·2-4·6). The hospitals were staffed by a median of 3 (IQR 1-9) specialist surgeons, 2 (IQR 0-5) specialist anaesthesiologists, and 3 (IQR 1-6) specialist obstetricians, with a median of 0·7 (IQR 0·2-2·0) specialists per 100 000 population.

Study participants and patient characteristics

The study participants are shown in Figure 1. 3792 patients underwent caesarean delivery, of whom 3709 received spinal (2968, 80%) or GA (741, 20%) (Figure 1). The baseline patient characteristics are shown in Table 1. The patients who received GA had a significantly higher ASA category, underwent more emergency surgery, with a higher prevalence of eclampsia, cardiac disease, antepartum haemorrhage, placenta praevia, placental abruption, ruptured uterus, and fetal distress. Non-physician anaesthesia providers provided significantly more general anaesthetics for caesarean delivery, than physician providers.

Study outcome data

Maternal mortality was higher with GA (11/729, 1.5%) than spinal anaesthesia (9/2881, 0.3%, p=0.001). Neonatal mortality was higher with GA (65/662, 9.8%) than spinal anaesthesia (73/2669, 2.7%, p<0.001). The composite outcome of "all anaesthesia complications" was significantly more frequent in GA delivery (Table 1). Spinal anaesthesia was administered in 286/356 (80.3%) preeclamptic patients, 48/94 (51.1%) eclamptic patients, 12/28 (42.9%) patients with cardiac disease, 14/19 (73.7%) patients with preoperative sepsis, 48/76 (63.2%) patients with antepartum haemorrhage, 30/55 (54.5%) patients with placenta praevia, 33/78 (42.3%) patients with placental abruption and 12/29 (41.4%) patients with a ruptured uterus.

Independent predictors of the provision of GA for caesarean delivery included increasing gestational age, ASA categories, emergency surgery, eclampsia, placenta praevia, placental abruption, and ruptured uterus. There was no association with fetal distress or a non-physician anaesthesia provider (Table 2).

There was no association between the method of anaesthesiaand intraoperative hypotension (Table 3). GA was associated with higher neonatal mortality (65/662, 9.8%) than spinal anaesthesia (73/2669, 2.7%, $p<0.001$). There was no association between pre-delivery hypotension and neonatal mortality, cardiopulmonary resuscitation, or Apgar scores at 1 and 5 minutes (Table 4).

Discussion

The principal findings of this prospective observational study of patients undergoing caesarean delivery in Africa, were that: i) patients with increasing gestational age, higher ASA categories, emergency surgery, eclampsia, placenta praevia, placental abruption, and ruptured uterus where more likely to require GA, ii) GA was associated with maternal mortality, neonatal mortality, and severe anaesthesia complications, but not intraoperative hypotension, and iii) intraoperative hypotension was not associated with neonatal morbidity or mortality.[7]

A key finding was that GA was linked to higher maternal and neonatal risk, with one in 66 general anaesthetics associated with a maternal death and one in 10 general anaesthetics a neonatal death. While much of this risk may relate to the underlying condition, reducing the number of avoidable general anaesthetics may decrease the risks for anaesthesia-related and surgical complications.[8] Caesarean delivery rates in sub-Saharan Africa have been static at 3.5%, despite globally increasing trends.[9] GA was administered in 20% of patients in this cohort, which is higher than in high-income countries. In the United States, the use of GA has steadily declined since the 1980s, with current estimates suggesting that less than 6% of caesarean deliveries are performed under GA.[7] A larger proportion of emergency caesarean deliveries (14.6%) received GA. Our cohort was comprised largely of emergency surgery (77.9%), but even in the patients scheduled for elective surgery, GA was conducted in over 16% of cases. This high incidence may reflect either the comorbidities of the patients requiring caesarean delivery, or the differences in anaesthesia practice in Africa. Poor access to caesarean delivery may have resulted in delayed presentation and higher perioperative risk, which might partially explain the higher incidence of GA in our patients. Data relating to failed spinal anaesthesia was not captured, which may also have contributed.

Our findings suggest appropriate use of GA for high-risk caesarean deliveries, although this was associated with significantly more anaesthesia-related complications. A larger proportion of general anaesthetics for caesarean delivery in the cohort was administered by non-physician anaesthesia providers, however after adjusting for potential predictors of GA, no difference was found between category of anaesthesia provider and GA. Despite a higher overall incidence of GA, some subcategories of patients with comorbidities received a higher proportion of spinal anaesthesia than predicted in high-income countries. Two groups merit further discussion:

i. In patients with preeclampsia, GA is associated with increased maternal risk in low- and middle- income countries.[9] In our cohort, spinal anaesthesia was administered in 286/356 (80.3%) with preeclampsia, although there is little published data related to normal practice in preeclampsia. In patients with eclampsia, over half of patients received spinal anaesthesia. In a recent audit of practice by Jordaan et al in Cape Town, only 7/89 (7.9%) of eclamptic patients were deemed suitable for spinal anaesthesia.[11] The majority were excluded due to GCS < 14 (70.8%). We did not collect detailed data on these patients, but the difference in anaesthesia approach is concerning. It is likely that spinal anaesthesia was administered in this patient group despite low GCS, due either to lack of clinical expertise and/or inadequate postoperative facilities for ventilation. More research is required in this area.

ii. Spinal anaesthesia was administered in a high proportion of patients with active bleeding or a high risk of bleeding (antepartum haemorrhage, placenta praevia, placental abruption, and ruptured uterus). GA may be advisable in these patients due to current or anticipated haemodynamic instability. It is unusual to administer spinal anaesthesia in the setting of a ruptured uterus. This may reflect anaesthesia inexperience, or failure in antenatal diagnosis. In the South African setting, almost

two-thirds of deaths due to ectopic pregnancies occur without attempting administration of anaesthesia, and the lack of appropriately trained anaesthesia practitioners is frequently cited as an avoidable factor in these deaths.[11] The present study examined only patients who received surgery and may thus have underestimated deaths due to maternal haemorrhage in patients who did not receive anaesthesia due to haemodynamic instability. The inappropriate use of spinal anaesthesia in the setting of active bleeding may be a marker for reluctance to administer GA.

The nature of the original study precluded a detailed case report form, with certain information on spinal anaesthesia or GA, not available. This was a limitation and prevented a more detailed insight into the choice of method of anaesthesia. Furthermore, patients were predominantly recruited at state hospitals (80%) and in middle-income countries (66.3%). In approximately one in five cases, a specialist anaesthetist was involved in the management of patients, a situation which is unlikely to reflect the broader African context, limiting the generalisability of these findings. It is possible that reverse causality exists, in which more critically ill patients with worse outcomes are referred to tertiary institutions; however the South African Confidential Enquiry into Maternal Deaths suggests that mortality is higher in district hospitals.[13] It is therefore likely that our findings underestimate poor outcomes in low-resource environments.

Strengths of this research were that data were collected from a large, prospective study across Africa, with a high capture rate, with less than 5% missing data for all variables, except for fetal distress. This allowed assessment of associations between method of anaesthesia and clinical outcomes in a large cohort of patients undergoing caesarean delivery and provided valuable insights into anaesthesia practices in resource-limited settings. In particular, our study identified those patients at higher risk of complications of anaesthesia. This could enable

targeted, context-sensitive interventions that could be used to address risk in this population. The association of poor outcomes with GA may suggest that training methods could specifically target this area, and might include online support and mobile-based applications.

In conclusion, the study showed that a larger proportion of caesarean deliveries in Africa received GA, compared to high-income countries. GA was associated with maternal mortality, neonatal mortality, and severe anaesthesia complications. Spinal anaesthesia was often administered to patients with eclampsia or at high risk for obstetric haemorrhage. Focused training in the principles of selection of mode of anaesthesia, and specifically in the skills of safe GA, are recommended.

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Figure and Tables for publication

Figure 1. Flow diagram of the obstetric cohort and method of anaesthesia

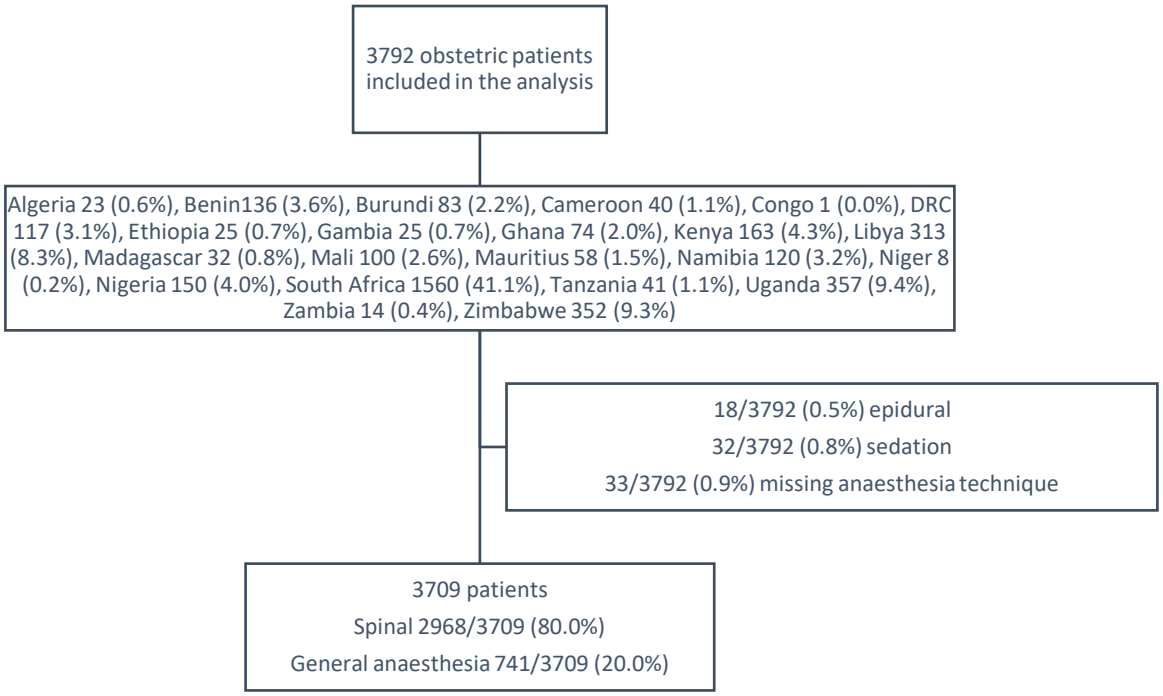

Table 1. Description of the African Surgical Outcomes Study (ASOS) obstetric anaesthesia sub-study patient cohort

	All patients (n=3709)	**Spinal anaesthesia (n=2968)**	**General anaesthesia (n=741)**	**P value**
Age (years)	28·6 (6·2)	28·6 (6.1)	28·6 (6·7)	1.00
Missing	3	0	3	
Parity	1 (0-2)	1 (0-2)	1 (0-3)	0·009
Missing	252	191	61	
Gravidity	2 (1-3)	2 (1-3)	2 (1-4)	0.002
Missing	252	191	61	
Gestational age	38 (37-39)	38 (37-40)	38 (36-39)	<0·001
Missing	270	201	69	
ASA category				
1	2004/3694 (54·3%)	1602/2960 (54·1%)	402/734 (54·8%)	<0.001
2	1503/3694 (40·7%)	1249/2960 (42·2%)	254/734 (34·6%)	
3	166/3694 (4·5%)	105/2960 (3·5%)	61/734 (8·3%)	
4	21/3694 (0·6%)	4/2960 (0·1%)	17/734 (2.3%)	
Urgency of surgery				
Elective	814/3690 (22·1%)	681/2954 (23·1%)	133/736 (18·1%)	0.003
Emergency	2876/3690 (77·9%)	2273/2954 (76·9%)	603/736 (81·9%)	
Maternal				
Preeclampsia	356/3709 (9·6%)	286/2968 (9·6%)	70/741 (9.4%)	0.944
Eclampsia	94/3709 (2.5%)	48/2968 (1·6%)	46/741 (6.2%)	<0.001
Cardiac disease	28/3709 (0·8%)	12/2968 (0.4%)	16/741 (2·2%)	<0.001
Preoperative sepsis	19/3709 (0·5%)	14/2968 (0.5%)	5/741 (0·7%)	0.562
Antepartum haemorrhage	76/3709 (2·0%)	48/2968 (1.6%)	28/741 (3.8%)	0.001
Placenta praevia	55/3709 (1.5%)	30/2968 (1·0%)	25/741 (3.4%)	<0.001
Placental abruption	78/3709 (2.1%)	33/2968 (1.1%)	45/741 (6.1%)	<0.001
Ruptured uterus	29/3709 (0·8%)	12/2968 (0.4%)	17/741 (2.3%)	<0.001

Fetal condition				
Fetal distress	1106/3470 (31·9%)	857/2787 (30.7%)	249/683 (36.5%)	0.005
Anaesthesia provider				
Physician	2785/3684 (75·6%)	2282/2948 (77·4%)	503/736 (68·3%)	<0.001
Non-physician	899/3684 (24.4%)	666/2948 (22.6%)	233/736 (31.7%)	
Anaesthesia complications				
Failed intubation	5/3709 (0.1%)	1/2968 (0.0%)	4/741 (0.5%)	0.007
Aspiration	1/3709 (0.0%)	1/2968 (0.0%)	1/741 (0.1%)	0.200
Cardiac arrest	4/3709 (0.1%)	2/2968 (0.1%)	2/741 (0.2%)	0.180
Severe hypoxia	2/3709 (0.1%)	0/2968 (0.0%)	2/741 (0.3%)	0.040
All anaesthesia complications*	12/3709 (0.3%)	3/2968 (0.1%)	9/741 (1.2%)	<0.001

Data are mean (SD) or n (proportion). Odds ratios were constructed for severe maternal outcomes with univariate binary logistic regression analysis. Denominators vary with the completeness of the data. * All anaesthesia complications is a composite of failed intubation, aspiration, cardiac arrest and severe hypoxia

ASA=American Society of Anesthesiologists.

Table 2. Multivariable association between preoperative factors and method of anaesthesia in the African Surgical Outcomes Study (ASOS) obstetric anaesthesia sub-study patient cohort

Risk factor	Odds ratio (95% CI)	P value
Gravidity	0.965 (0·90-1·03)	0.308
Gestational age	1.093 (1.052-1.135)	<0.001
ASA category		
1	Reference	
2	5.26 (1.29 – 21.46)	0.021
3	11.84 (2.93-46.31)	<0.001
4	11.48 (2.93 – 44.93)	<0·001
Urgency of surgery		
Emergency	1.40 (1.03 – 1.92)	0.033
Maternal comorbidity		
Preeclampsia	1.01 (0·69-1.47)	0·98
Eclampsia	3.92 (2.18-7.06)	<0.001
Cardiac disease	2.44 (0.86-6.87)	0.092
Preoperative sepsis	1.27 (0.26-6.27)	0.772
Antepartum haemorrhage	1.71 (0.90-3.26)	0.102
Placenta praevia	2.39 (1.19-4.78)	0.014
Placental abruption	6.23 (3.36-11.54)	<0.001
Ruptured uterus	3.61 (1.36-9.63)	0.010
Fetal condition		
Fetal distress	1.29 (1.00-1.66)	0.053
Anaesthesia provider		
Non-physician	0.89 (0·57-1.39)	0.595
Reference: physician		

Odds ratios were constructed for provision of general anaesthesia using a generalised linear mixed model controlling for country and hospital clusters

ASA=American Society of Anesthesiologists.

Table 3. The association between the method of anaesthesia and intraoperative hypotension

Hypotension	All patients (n=3702)	Spinal anaesthesia (n=2968)	General anaesthesia (n=741)	P value
Pre and post delivery				
SBP≥80 mmHg	3046/3479 (87.6%)	2436/2791 (87.3%)	610/688 (88.7%)	0.367
SBP<80 mmHg	433/3479 (12.4%)	355/2791 (12.7%)	78/688 (11.3%)	
Pre-delivery				
SBP≥80 mmHg	3208/3478 (92.2%)	2570/2791 (92.1%)	638/687 (92.9%)	0.525
SBP<80 mmHg	270/3478 (7.8%)	221/2791 (7.9%)	49/687 (7.1%)	
Post delivery				
SBP≥80 mmHg	3195/3479 (91.8%)	2565/2791 (91.9%)	630/688 (91.8%)	0.756
SBP<80 mmHg	284/3479 (8.2%)	226/2791 (8.1%)	58/688 (8.4%)	

SBP = systolic blood pressure

Table 4. The association between pre-delivery hypotension and neonatal outcomes

Outcome	SBP≥80 mmHg	SBP<80 mmHg	P value
Neonatal mortality (n=3702)	127/3066 (4.1%)	10/259 (3.9%)	1.000
Neonatal cardiopulmonary resuscitation (n=2968)	289/3193 (9.1%)	28/268 (10.4%)	0.440
Apgar at 1 minute	8 (7-9)	8 (7-9)	0.061
Apgar at 5 minutes	10 (9-10)	10 (9-10)	0.650
Apgar <5 at 5 minutes	117/3233 (3.6%)	15/271 (5.5%)	0.132

SBP = systolic blood pressure

Chapter 2. Appendices

Appendix 1. HREC Letter of approval from UCT Human Research Ethics Committee

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submisisons@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 March 2021

HREC REF: 150/2021

Prof B Biccard
Anaesthesia & Perioperative Medicine
D23 NGSH
Email: Bruce.Biccard@uct.ac.za
Student: drcgerber@yahoo.com

Dear Prof Biccard

PROJECT TITLE: AFRICAN SURGICAL OUTCOMES STUDY (ASOS) MMED-CANDIDATE-DR CARMEN GERBER-sub-study linked to R004/2016.

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.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 March 2022.

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)

The HREC acknowledge that the student: - Dr Carmen Gerber will also be involved in this study.

Please quote the HREC REF 150/2021 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.

HREC/REF 150/2021sa

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF 150/2021sa

Appendix 2. Case Report Form

African Surgical Outcomes Study (ASOS)

Age ☐☐☐ years Gender ☐ M ☐ F Current smoker ☐ Y ☐ N

ASA ☐ I ☐ II ☐ III ☐ IV ☐ V Black ethnicity (eGFR) ☐ Y ☐ N

Chronic co-morbid disease (tick all that apply):

☐ Coronary artery disease ☐ Congestive heart failure ☐ Diabetes mellitus
☐ Cirrhosis ☐ Metastatic cancer ☐ Hypertension
☐ Stroke or Transient ischaemic attack ☐ COPD / Asthma ☐ HIV / AIDS
☐ Chronic renal disease

Most recent blood results (no more than 28 days before surgery):

Haemoglobin ☐☐.☐ g/dL Leucocytes ☐☐.☐ x10^9/L Creatinine ☐☐☐.☐ µmol/L OR mg/dL
(circle appropriate unit)

Start of surgery time (24h) & date: h h : m m d d m m 2 0 1 6

Anaesthetic technique (✔) ☐ General ☐ Spinal ☐ Epidural ☐ Sedation ☐ Local ☐ Other regional

Surgical procedure category (select *single* most appropriate):

☐ Orthopaedic ☐ Breast ☐ Obstetrics
☐ Gynaecology ☐ Upper gastro-intestinal ☐ Lower gastro-intestinal
☐ Hepato-biliary ☐ Urology & Kidney ☐ Vascular
☐ Head and neck ☐ Plastics / Cutaneous ☐ Thoracic (lung & other)
☐ Thoracic (gut) ☐ Neurosurgery ☐ Cardiac surgery

Urgency of surgery: ☐ Elective ☐ Urgent ☐ Emergency

Severity of surgery: ☐ Minor ☐ Intermediate ☐ Major

Primary indication for surgery: ☐ Infective ☐ Non-communicable disease ☐ Traumatic injury ☐ Caesarean section

Surgical checklist used (e.g. WHO checklist) ☐ Y ☐ N

Blood loss during surgery: ☐☐☐☐☐ ml Duration of surgery: ☐☐☐☐ minutes

Critical care immediately after surgery ☐ Y ☐ N

Anaesthetic complications: ☐ Failed intubation ☐ Aspiration ☐ Cardiac arrest ☐ Severe hypoxia

Most senior anaesthetist present in operating room:

☐ Specialist ☐ Physician non specialist ☐ Non physician or nurse anaesthetist ☐ No anaesthetist

Most senior surgeon present in operating room:

☐ Specialist ☐ Physician non specialist ☐ Non physician or nurse surgeon

ASOS unique patient ID ☐☐☐☐☐☐☐☐☐

✂ –

Patient name: _____ DOB d d m m y y y y

Patient hospital number : _____

Caesarean Section

Maternal conditions (select all that apply)

Pre-eclampsia ☐ Eclampsia ☐ Cardiac disease ☐

Placenta praevia ☐ Placenta abruption ☐ Ruptured uterus ☐

Sepsis ☐ Antepartum haemorrhage ☐

Parity ☐☐ Gravidity ☐☐ Gestational age ☐☐

Foetal distress present ☐ Y ☐ N

During the operation

Systolic blood pressure <80 mmHg pre-delivery ☐ Y ☐ N

Systolic blood pressure <80 mmHg post-delivery ☐ Y ☐ N

Phenylephrine given ☐ Y ☐ N

Ephedrine given ☐ Y ☐ N

Other inotropes given (e.g. adrenaline) ☐ Y ☐ N

Hysterectomy done to control bleeding ☐ Y ☐ N

Neonatal outcomes

1 minute APGAR ☐☐ 5 minute APGAR ☐☐

Birth weight ☐☐☐☐ grams

Neonatal CPR following delivery ☐ Y ☐ N

Neonatal Status at discharge or at 30 days of age ☐ Alive ☐ Dead

ASOS unique patient ID ☐☐☐ ☐☐☐ ☐☐☐

✂- -

Patient name: ______________________________ DOB d d m m y y y y

Patient hospital number : ______________________

Postoperative Follow Up

Infection

Superficial surgical site	Mild ☐	Moderate ☐	Severe ☐	None ☐
Deep surgical site	Mild ☐	Moderate ☐	Severe ☐	None ☐
Body cavity	Mild ☐	Moderate ☐	Severe ☐	None ☐
Pneumonia	Mild ☐	Moderate ☐	Severe ☐	None ☐
Urinary tract	Mild ☐	Moderate ☐	Severe ☐	None ☐
Bloodstream	Mild ☐	Moderate ☐	Severe ☐	None ☐

Cardiovascular

Myocardial infarction	Mild ☐	Moderate ☐	Severe ☐	None ☐
Arrhythmia	Mild ☐	Moderate ☐	Severe ☐	None ☐
Pulmonary oedema	Mild ☐	Moderate ☐	Severe ☐	None ☐
Pulmonary embolism	Mild ☐	Moderate ☐	Severe ☐	None ☐
Stroke	Mild ☐	Moderate ☐	Severe ☐	None ☐
Cardiac arrest			Severe ☐	None ☐

Miscellaneous complications

Gastro-intestinal bleed	Mild ☐	Moderate ☐	Severe ☐	None ☐
Acute kidney injury	Mild ☐	Moderate ☐	Severe ☐	None ☐
Postoperative bleed		Moderate ☐	Severe ☐	None ☐
ARDS	Mild ☐	Moderate ☐	Severe ☐	None ☐
Anastomotic breakdown	Mild ☐	Moderate ☐	Severe ☐	None ☐
Other	Mild ☐	Moderate ☐	Severe ☐	None ☐

Critical care admission to treat postoperative complications ☐ No ☐ Yes

Days in critical care after surgery [d][d]

Days in hospital after surgery [d][d]

Status at hospital discharge or 30th postoperative in-hospital day ☐ Alive ☐ Dead

ASOS unique patient ID [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

✂- -

Patient name: ______________________________ DOB [d][d][m][m][y][y][y][y]

Patient hospital number : ______________________

Guidance for use of paper case record form (CRF)

Remove this page before use in data collection

1. **This CRF is provided in a format which can be edited. If required, national co-ordinators should edit the blood results units to fit with those used in your country (eg some hospitals measure creatinine in µmol/L whilst in others mg/dL is standard). In some countries there will be differences in the use of units between hospitals so local edits may also be required. The internet based CRF will allow you to choose the units for each hospital.**

2. **Baseline data will often be readily available to anaesthetists during surgery whilst follow-up data on complications may be most easily collected by surgeons.**

3. **Investigators should write the patient name and date of birth on the CRF. When you enter the data on the internet based CRF you will receive an ASOS patient ID. Please write this on the paper CRF as well in case we need to contact you to check your data.**

4. **Please take care to enter the date clearly and correctly. Mistakes are common data describing time and date.**

5. **We only ask about black ethnicity to calculate estimated glomerular filtration rate.**

ASOS unique patient ID | | | | | | | | | | |

✂----------

Patient name: _____ **DOB** d d m m y y y y

Patient hospital number : _____

Appendix 3. ASOS Supplementary Appendix Definitions

1. Mortality- in-hospital mortality
2. Serious adverse events are near miss, life-threatening complications related to pregnancy or child-birth- a composite of mortality, hysterectomy, and cardiac arrest.
3. Major bleeding risk- a composite of placenta praevia, placenta abruption, ruptured uterus, antepartum haemorrhage
4. Sepsis- reported in the preoperative maternal conditions
5. Severe infective complications- a composite of all severe infection complications
6. Severe cardiac complications- a composite all severe cardiovascular complications, including cardiac arrest which was not reported as an anaesthetic complication
7. Perioperative obstetric haemorrhage- a composite of antepartum haemorrhage, >1000ml intraoperative bleeding or severe postoperative bleeding
8. Anaesthetic complications- a composite of failed intubation, aspiration, cardiac arrest and hypoxia

Appendix 4. Author instructions for Anaesthesia and Analgesia

ANESTHESIA & ANALGESIA®

The Gold Standard in Anesthesiology

We greatly appreciate your interest in submitting your manuscript to *Anesthesia & Analgesia*. Our goal is to provide authors with a thorough yet timely review of their submissions. All **initial** decisions should be completed within 6 weeks, except for Review Articles and Special Articles, which may take up to 8 weeks. Authors will be updated as to the status of their manuscript via Editorial Manager.

Notice: The **Instructions for Authors** for *Anesthesia & Analgesia* have been further revised. New submissions should be prepared according to the Instructions that follow. Failure to do so may result in your submission being returned without review.

This now current Version 3.6 of these Instructions for Authors replaces the earlier Version 3.5.

As of July 1, 2019, *Anesthesia & Analgesia* is not receiving or considering new Brief Report manuscript submissions.

Brief Report manuscripts that have been submitted prior to July 1, 2019 will undergo a complete review and final decision by *Anesthesia & Analgesia*. Previously accepted Brief Report manuscripts will still be published by *Anesthesia & Analgesia*.

Authors seeking to submit to *A&A Practice* (formerly *A&A Case Reports*) can find its separate *A&A Practice* Instructions for Authors and submit their papers through the *A&A Practice* Editorial Manager Submission Site.

As of January 1, 2018, all Echo Rounds and Echo Didactics articles are published online only in *A&A Practice*. Please refer to these separate *A&A Practice* Instructions for Authors for Echo Rounds and Echo Didactics submissions.

***A&A Practice* remains fully editorially aligned and operationally integrated yet distinct from *Anesthesia & Analgesia*.**

Mission and Scope

Anesthesia & Analgesia exists for the benefit of patients under the care of health care professionals engaged in the disciplines broadly related to anesthesiology, perioperative medicine, critical care medicine, and pain medicine. The Journal furthers the care of these patients by

reporting the fundamental advances in the science of these clinical disciplines and by documenting the clinical, laboratory, and administrative advances that guide therapy. *Anesthesia & Analgesia* seeks a balance between definitive clinical and management investigations and outstanding basic scientific reports. The Journal welcomes original manuscripts containing rigorous design and analysis, even if unusual in their approach.

Authors are strongly encouraged to adhere to the fundamentals of English grammar, syntax, punctuation, and composition.

If a paper is poorly written and thus difficult to understand, it will likely **not** receive as favorable a review, despite presenting strong science and/or novel information. If indicated, please consider using a Language Editing Service (see below) to address this issue **before** your initial submission.

Anesthesia & Analgesia **Instructions for Authors**

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.

Please note that a **Glossary of Terms** is now required for all submissions to A&A Practice (except Letter to the Editor). See below, Section 6.

INSTRUCTIONS FOR AUTHORS

SECTION 1: *ANESTHESIA & ANALGESIA* ARTICLE TYPES

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.

- Study Reporting Requirement (EQUATOR)
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

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.

Please note, authors should mask patients' faces and remove patients' names from any figures, videos, or supplemental material containing images of patients unless they obtain written consent from the patients and submit written consent with the manuscript. Please note that it is not sufficient to mask patients' eyes.

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
CONSORT	Consolidated Standards of Reporting Trials (See footnote* below)	http://www.consort-statement.org/
TREND	Transparent Reporting of Evaluations with Nonrandomized Designs	http://www.cdc.gov/trendstatement/
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology	http://www.strobe-statement.org/
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses	http://www.prisma-statement.org/
SQUIRE	Standards for Quality Improvement Reporting Excellence	http://www.squire-statement.org/

SRQR or COREG	Standards for Reporting Qualitative Research Consolidated Criteria for Reporting Qualitative Research	PMID: 24979285 PMID: 17872937
CHEERS	Consolidated Health Economic Evaluation Reporting Standards	http://www.ispor.org/Health-Economic-EvaluationPublication-CHEERS-Guidelines.asp
STARD or TRIPOD	Standards for Accurate Reporting of Diagnostic Tests *Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis*	http://www.stard-statement.org/ http://www.tripod-statement.org/
STREGA	Strengthening the Reporting of Genetic Associations	http://www.equator-network.org/reportingguidelines/strobe-strega/
ARRIVE	Animal Research: Reporting of *In Vivo* Experiments	http://www.nc3rs.org.uk/arrive-guidelines

* 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, nonpharmacological, 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.

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
Original Laboratory Research Report	Structured	400
Narrative Review	Unstructured	400
Systematic Review	Unstructured	400
Meta-Analysis	Structured	400
Editorial	NA	NA
The Open Mind	NA	NA
Special Article	Unstructured	400
Letter to the Editor	NA	NA
Book and Multimedia Review	NA	NA
Meeting Report	NA	NA

- 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 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 Association (AMA) citation style; Consult the AMA Manual of Style, 11th ed., Oxford University Press, 2020 • Anesthesia & Analgesia follows the American Medical Association (AMA) citation style; Consult the AMA Manual of Style, 11th ed., Oxford University Press, 2020 (https://www.amamanualofstyle.com), 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 # ___."
- Do not include in the references non-peer reviewed papers that have been uploaded to a preprint server.
- 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
- Authors should mask patients' faces and remove patients' names from figures unless they obtain written consent from the patients and submit written consent with the manuscript. Please note that it is not sufficient to mask patients' eyes.
- Define in a footnote all acronyms or abbreviations used in each figure.

Video preparation

The video clip(s) accompanying A&A submissions should conform to the following:

- Formatted in MPEG, QuickTime (MOV), Windows Media Video (WMV) or MP4.
- Play on *both* Windows and Macintosh platforms. The review process will be delayed if the Editorial Office cannot play your video clip.
- Individual size should not exceed 15 MB. Use video-compression software to reduce video size if necessary.
- Optimal video frame dimensions of 480 x 360 pixels and 640 x 480 pixels. Videos of 320 x 240 pixels have inadequate resolution for teaching.
- Duration of individual video clip should be less than 15-25 seconds.
- Combinations of clips: If you combine several video clips, for example several TEE echocardiographic loops, please provide adequate time for each segment, and leave a suitable gap between the videos. Use appropriate labeling to ensure that the viewer can understand the timing of the pathology and events. Labeling can be added with video editing programs such as Adobe Premiere or iMovie.
- Authors should mask patients' faces and remove patients' names from videos unless they obtain written consent from the patients and submit written consent with the manuscript. Please note that it is not sufficient to mask patients' eyes.
- Authors should complete a video checklist form for each video when submitting a revised manuscript. The video checklist form provides the information necessary to upload the video on the journal website's video gallery.

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 supplemental 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.
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- 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 · kg^{-1} · 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.

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At the time of their initial manuscript submission, authors must provide 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

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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.**

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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.

When appropriate, a manuscript may have two formal first authors. These two formal first authors will have contributed relatively equally to the study and/or writing the manuscript. The two designated first authors are to be designated on the Title Page at the time of initial manuscript submission.

When appropriate, a manuscript may have two formal last authors. These two formal last authors will have contributed relatively equally to the study and/or writing the manuscript. The two designated last authors are to be designated on the Title Page at the time of initial manuscript submission.

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/clinicaltrials-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

1) Incomplete Title Page – e.g., missing conflict of interest statement for each author or incomplete author information 2) Abstract is missing in the Word file or not properly structured.

3) Missing page numbers
4) Entire manuscript is not double-spaced
5) 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. 7) References do not adhere to AMA style (see above).

8) The above noted word count, reference count, and table/figure count limits are not followed for a specific article type.

Appendix 5. STROBE checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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