

Peri-operative Outcomes of Neonatal Surgeries at an Academic Institution

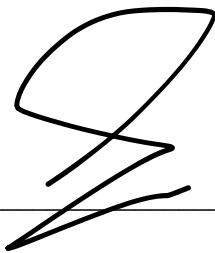
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A research report submitted to the Faculty of Health Sciences,
University of the Witwatersrand, Johannesburg,
in the partial fulfilment of the requirements for the degree of
Master of Medicine in the branch of Anaesthesiology

Johannesburg, 2023

Declaration

I, Laika Essa, herewith declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Signed

On this 08 day of November 2023

Dedication

To all the neonates who were dealt life's most difficult cards, you fought bravely.

Acknowledgements

To my supervisor Dr Zainub Jooma, thank you for having an endless supply of patience and contagious enthusiasm for this research topic. I am so grateful for your unwavering guidance.

To my other supervisors, Dr Theshni Govender and Dr Tanusha Ramdin, thank you for your advice, assistance, and involvement in this research project.

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List of Abbreviations

ASA	American Society of Anaesthesiology
CI	Confidence Interval
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
FiO ₂	Fraction of inspired oxygen
HICs	High income countries
ICU	Intensive care unit
IQR	Interquartile range
LMICs	Low- and middle-income countries
NEC	Necrotising Enterocolitis
OR	Odds ratio
PMA	Post-menstrual age
rSO ₂	Regional cerebral oxygen saturation
SA	South Africa
SAPSOS	South African Paediatric Surgical Outcomes Study

Draft Article

The article is prepared according to the Author Guidelines for British Journal of Anaesthesia (BJA) and may differ from the rest of the document (Appendix 8).

Peri-operative Outcomes of Neonatal Surgeries at an Academic Institution

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Abstract

Background

Neonates undergoing anaesthesia have a high incidence of peri-operative critical events. In South Africa, there is a higher rate of peri-operative morbidity and mortality compared to high income countries. The rate of intra-operative critical events is unknown. Our aim was to investigate the incidence of peri-operative critical events and to identify factors associated with poor outcomes.

Methods

A retrospective, cross-sectional study was carried out at a quaternary academic hospital in Johannesburg, South Africa. A sample of 100 neonates was used where an anaesthetic was performed for an emergency or elective surgery. The neonates' demographics were described and risk factors for peri-operative critical events were identified. Associations between risk factors and the prevalence of peri-operative critical events, morbidity and mortality were assessed.

Results

Intra-operative critical events occurred in 78% of neonates. Intra-operative critical events included cardiovascular (50%), body temperature correction (47%), glucose or electrolyte correction (41%), airway (25%), and oxygenation (13%) events. Prematurity (<37 weeks) and low birth weight (<2500g) were associated with a higher incidence of critical events; OR (95% CI) 8.84 (2.92 – 33.2) $p < 0.001$ and OR (95% CI) 9.10 (2.81, 41.1) $p < 0.001$ respectively. Post-operative morbidity was found in 78% of neonates and mortality in 31%. Post-operative infection occurred in 66% of neonates and contributed to 46% of deaths.

Conclusion

There is a higher incidence of critical events in our neonatal surgical population compared to high income countries. Prematurity and LBW are significant pre-operative risk factors for critical events. Post-operative infection contributed significantly to morbidity and mortality.

Keywords:

Mortality, morbidity, neonatal anaesthesia, neonatal surgery, outcomes, peri-operative

TOTAL WORDS: 248 (MAX 250)

Introduction

Providing safe anaesthesia to neonates is a well-recognised challenge throughout the world ¹. Despite an increase in neonates with complex co-morbidities presenting for high-risk surgical procedures, there is a large gap in research performed for this population ². There remains a lack of standardised guidelines and outcome measures that are available to anaesthetists caring for these high-risk patients ^{3,4}. It is known that adverse events in the developing neonate lead to an increase in morbidity and mortality. Two recent studies in high income countries (HICs) have investigated intra-operative anaesthetic events: Anaesthesia PRactice In Children Observational Trial (APRICOT) ⁵ and NEonate-Children sTudy of Anaesthesia pRactice IN Europe (NECTARINE) ². There is no South African research published on intra-operative events in neonates. Our aim was to describe the incidence of the peri-operative anaesthetic critical events and outcomes in neonates undergoing anaesthesia and to identify factors associated with poor outcomes.

Methods

We conducted a retrospective cross-sectional study examining records between 2018-2019 at Charlotte Maxeke Johannesburg Academic Hospital, a quaternary hospital, where neonatal surgeries are performed. The most recent period before the COVID-19 pandemic was chosen as the usual pathways for referral, time to presentation and standard of care were disrupted due to the pandemic. Approval to conduct this study was obtained from the Human Research Ethics Committee (Approval: M210853 granted on the 13th of October 2021 from the University of Witwatersrand - HREC) and other relevant authorities.

The sample size for the study was calculated using the Raosoft ® sample size calculator. A sample size of 96 was calculated using population size of 130 (based on the annual case rate) and event rate of 35.3% from the NECTARINE study ², using a power of 80% and margin of error of 5%. A sample of 100 was sought and records were examined during the study period until this was achieved.

All neonates from birth until 28 days of life where a general anaesthetic, regional/ neuraxial anaesthetic or both were performed for elective or emergency general surgery, were eligible. Records were considered complete if peri-operative critical events and a 30-day outcome could be ascertained and only complete records were included. Neonates who underwent a

diagnostic procedure were excluded. Surgeries performed after the index surgery were excluded as a separate record but were included as a morbidity.

The primary researcher (LE) reviewed theatre records (emergency and elective, during core hours and after hours) for eligible cases. All databases available to the researcher were searched for the relevant information. A data collection sheet was used to capture information.

Data Collection and Variables

A data collection sheet was designed with input from the researchers in anaesthesia, paediatric surgery and paediatrics. The variables and outcomes (Supplementary Table 1) were adapted from three similar studies ^{2,5,6}. Variables were categorised according to pre-operative risk factors, details of surgery and anaesthetic performed, intra-operative and post-operative critical events. An intra-operative critical event was defined as any adverse event which required an intervention in the categories of airway, respiratory, cardiovascular, neurological, temperature correction, electrolyte/ glucose correction and drug errors. These events are further described in Supplementary Table 1. Post-operative critical events were adverse events resulting in morbidity such as relook surgeries, bleeding requiring surgical intervention, infection, unplanned intensive care unit (ICU) admissions and other events such organ dysfunction and iatrogenic injuries. Outcomes were defined as a 30-day mortality. Figure 1 shows the exclusion process of study participants in an analysis of neonates undergoing surgical procedures at Charlotte Maxeke Johannesburg Academic Hospital between 1 January 2018- 31 December 2019.

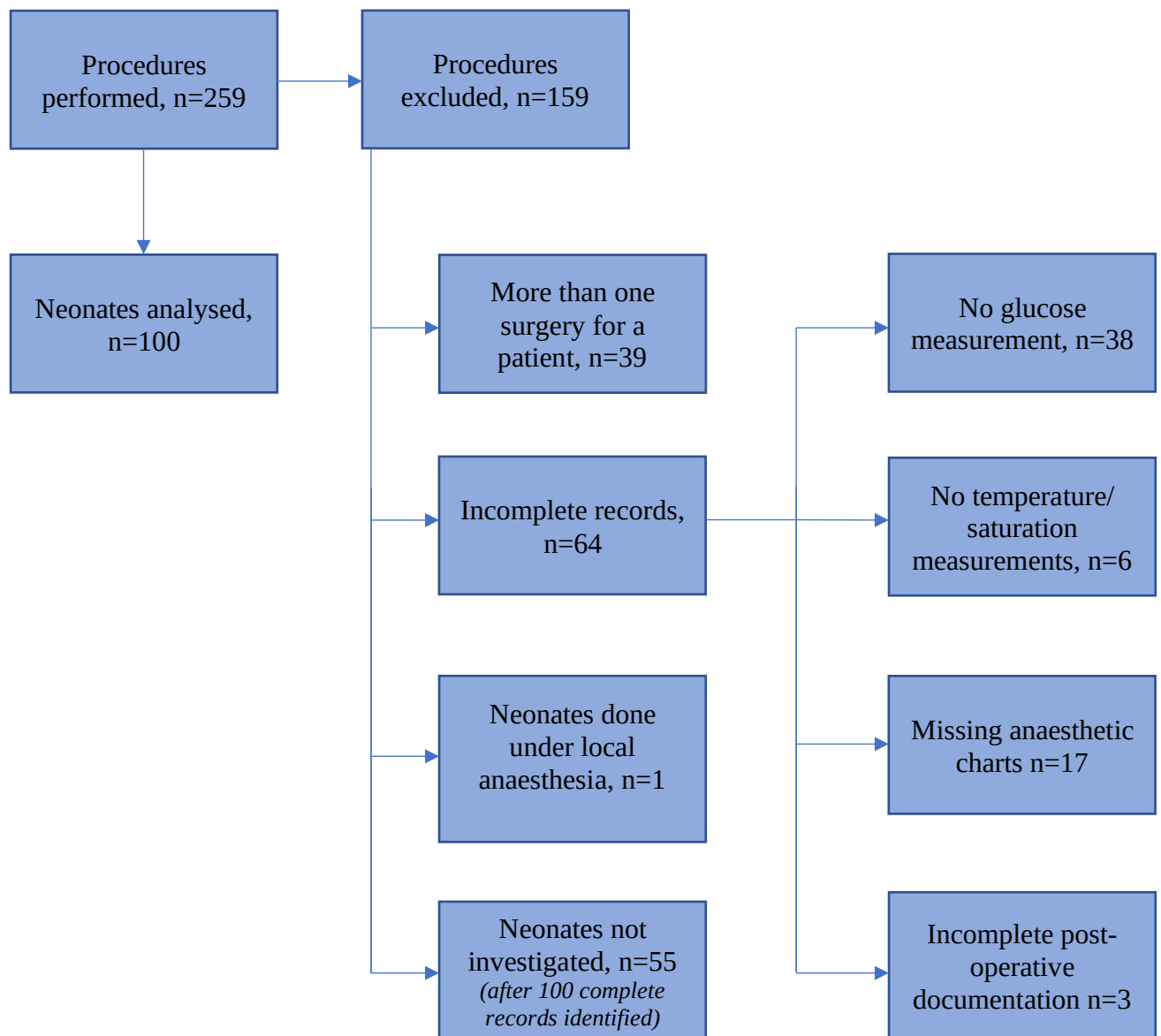


Figure 1: Consort flow diagram of included patients

Statistics

Statistical analyses were conducted in the R Statistical Environment (v4.0.4). Data were summarised using medians and interquartile ranges or mean and standard deviation depending on the distribution of the data. When looking for associations between critical events and various demographic and clinical variables, the critical event outcome variable was dichotomised into ‘yes’ if there was at least one critical event (of any type), or ‘no’ there were no critical events (of any type), and logistic regression was then used to test for associations. Similarly, logistic regression was used when looking for associations between

post-operative critical events and morbidity and mortality. A p-value <0.05 was considered statistically significant.

Results

Demographics and types of anaesthesia and surgeries performed are described in Table 1.

Table 1: Characteristics of neonates

Characteristic n=100	n (%)
Sex	
Female	51 (51%)
Male	49 (49%)
Birth weight (g) (median (IQR))	2328 (1765, 2905)
>2500g	42 (43%)
Low birth weight (LBW): 1600-2400	39 (40%)
Very low birth weight (VLBW): 1000-1500	11 (11%)
Extremely low birth weight (ELBW): <1000	6 (6%)
Missing	2
Weight at surgery (g) (median (IQR))	2300 (1730, 2825)
>2500	47 (47%)
LBW: 1600-2400	34 (34%)
VLBW: 1000-1500	13 (13%)
ELBW: <1000	6 (6.0%)
Gestational age at birth (weeks) (median (IQR))	37.0 (33.0 – 38.2)
>37	51 (51%)
34-36	15 (23%)
28-34	0 (0%)
Missing	34
Gestational age at surgery (weeks) (median (IQR))	37.6 (34.3 - 39.5)
>37	53 (53%)
34-37	19 (20%)
28-34	23 (24%)
Missing	5
ASA (median (IQR))	3.00 (2.00, 3.00)

I	3 (3%)
II	35 (35%)
III	53 (53%)
IV	8 (8%)
V	1 (1%)
Critical events per neonate (median (IQR))	2 (1, 3)
1	17 (17%)
2	31 (31%)
3	23 (23%)
>4	7 (7%)
Congenital abnormality	14 (14%)
Cardiac abnormality	24 (24%)
Pre-operative respiratory support	58 (58%)
Nasal prongs	22 (22%)
High flow nasal cannula oxygen	1 (1%)
Nasal continuous positive airway pressure	2 (2%)
High frequency oscillatory ventilation	0 (%)
Conventional ventilation	34 (34%)
Pre-operative cardiovascular support	12 (12%)
Other pre-operative organ dysfunction	35 (35%)
Renal	23 (23%)
Liver	14 (14%)
Coagulopathy	9 (9%)
History of critical events	49 (49%)
Airway critical event	5 (5%)
Oxygenation critical event	38 (38%)
Cardiovascular critical event	14 (14%)
Neurological critical event	6 (6%)
Other critical event	12 (12%)
Previous ICU admission	38 (38%)
Duration of anaesthesia (minutes) (median (IQR))	174 (135, 220)
Type of anaesthesia	
General anaesthesia only	90 (90%)

Combined general and regional/ neuraxial anaesthesia	10 (10%)
Regional/ neuraxial anaesthesia only	0 (0%)
Category of surgery	
Emergency	78 (78%)
Elective	22 (22%)
Laparotomy	81 (81%)
NEC	16 (16%)
Gastroschisis closure	10 (10%)
Jejunal atresia repair	12 (12%)
Duodenal atresia repair	10 (10%)
Bowel perforation	21 (21%)
Bowel obstruction	5 (5%)
Other	25 (25%)
Thoracotomy	9 (9%)
Oesophageal Atresia	9 (9%)
Tracheoesophageal Fistula	5 (5%)
Inguinal Hernia Repair	3 (3%)
Other (including urogenital, renal and debridements)	10 (10%)

Critical events occurred in 78% of neonates (Table 2). One or more critical event per category neonate may have occurred per neonate.

Table 2: Incidence of critical events per category

Critical event per category	
Airway n=25 (%)	
Intubation >2 attempts	11 (11%)
Saturation <90%	15 (15%)
Bradycardia	5 (5%)
CPR (respiratory cause)	0 (0%)
Difficult face mask ventilation	0 (0%)
Bronchial Aspiration	3 (3%)
Oxygenation n=13 (%)	
Need for FiO ₂ > 0.7	6 (6%)
Recruitment Manoeuvre	3 (3%)
Change/ Reposition/ Dislodge/ Obstructed tube	8 (8%)
Pneumothorax	2 (2%)
Laryngospasm	0 (0%)
Bronchospasm	0 (0%)
Post-operative Stridor	0 (0%)
Unanticipated Stridor	0 (0%)
Unanticipated Post-operative Respiratory Support	0 (0%)
Glucose/ Electrolyte Correction n=41 (%)	
Correction of Electrolytes	14 (14%)
Correction of Hypoglycaemia	33 (33%)
Correction of Hyperglycaemia	1 (1%)
Cardiovascular Critical Event n=50 (%)	
Administration of Blood Products	47 (47%)
Administration of vasopressors/ inotropes	22 (22%)
Arrhythmia	0 (0%)
CPR (cardiovascular cause)	1 (1%)
Body Temperature Correction n=47 (%)	
Cooling Measures	4 (4%)
New warming measures (equipment used to warm patient after establishing relative hypothermia)	43 (43%)

Table 3 shows the relationship between patient risk factors and occurrence of critical events. Gestational age at surgery and birth weight were identified as statistically significant risk factors. Each of these variables were dichotomised: above or below 2500g (low birth weight-LBW) and older or younger than 37 weeks (premature). These variables were then tested for an association with each category of critical events.

Table 3: Occurrence of a critical event in relation to patient risk factors

Demographic	No critical event (n=22) n (%)	Critical event occurred (n=78) n (%)	OR (95%CI)	p-value
Weight (g)				
>2500	17 (17%)	25 (25%)	8.84 (2.92 – 33.2)	<0.001
<2500	4 (4%)	52 (52%)		
Unknown	1	1		
Gestational age (weeks)				
>37	19 (86%)	32 (41%)	9.10 (2.81, 41.1)	<0.001
<37	3 (14%)	46 (59%)		
Pre-operative ICU admission	7 (32%)	31 (40%)	1.41 (0.53 - 4.07)	0.5
History of pre- operative respiratory support	10 (45%)	48 (62%)	1.92 (0.74 - 5.09)	0.2
History of cardiovascular support	2 (9.1%)	10 (13%)	1.47 (0.35 - 10.1)	>0.9
Previous critical event as described above	8 (36%)	41 (53%)	1.94 (0.74 - 5,35)	0.2
Number of Surgeries			1.16 (0.63 - 2.57)	0.7
1	16 (73%)	58 (74%)		
2	5 (23%)	13 (17%)		
3	1 (4.5%)	4 (5.1%)		
4	0 (0%)	2 (2.6%)		
5	0 (0%)	1 (1.3%)		

There was no statistically significant association between gestational age at surgery and birth weight with occurrence of airway and oxygenation critical events. The incidence of cardiovascular critical events was higher in neonates with a LBW and prematurity OR (95% CI): 4.34 (1.88 – 10.5), $p < 0.001$, and 6.00 (2.59– 14.7), $p < 0.001$, respectively. Body temperature correction was also statistically significant in LBW and premature neonates: OR (95% CI): 2.40 (1.06 – 5.57), $p = 0.037$ and 2.25 (1.02 – 5.07), $p = 0.048$, respectively. Glucose or electrolyte correction was statistically significant in premature neonates: OR (95% CI): 2.71 (1.21 – 6.29), $p = 0.017$. There was no significant association between LBW and glucose or electrolyte corrections intra-operatively.

There was no significant association between American Society of Anaesthesiologists (ASA) physical score and occurrence of any intra-operative critical event. Longer duration of anaesthesia was associated with the following intra-operative critical events (OR (95% CI)): airway 1.009 (1.003 – 1.016), $p = 0.010$, oxygenation 1.009 (1.002 – 1.017), $p = 0.012$ and body temperature correction 1.010 (1.004 – 1.019), $p = 0.006$. Emergency surgery did not influence the rate of intra-operative critical events.

Morbidity was found in 78% of neonates, where one or more post-operative critical event occurred per neonate: post-operative infection in 66 neonates (66%), 22 required relook surgeries (22%), 6 (6.0%) had unplanned ICU admissions and 57 (57%) had other complications. These included multi-organ dysfunction (anaemia, coagulopathy, neonatal jaundice, cardiac failure) and iatrogenic injury (pneumothorax post central venous line insertion and drip site ulcers). Morbidity was higher in LBW (62%) and premature (56%) neonates. There were no statistically significant associations between pre-operative risk factors such as LBW and prematurity and post-operative morbidity (specifically rate of post-operative infection and relook surgeries required). Neonates who had a cardiovascular critical event intra-operatively were found to have higher rates of morbidity OR (95% CI): 3.451 (1.272 – 10.49), $p = 0.20$. Airway, oxygenation, glucose or electrolyte correction and body temperature correction were not significantly associated with morbidity.

There were 31 neonates who died from various causes at 30 days (Figure 2). Other causes of death included tension pneumothorax, congestive cardiac failure and disseminated intravascular coagulopathy. Of the non-survivors, 71% (22) had a LBW and 65% (20) were premature. There was an increased odds of death in premature neonates compared to neonates

born at term OR (95% CI): 2.51 (1.06-6.19), $p=0.040$. Oxygenation and cardiovascular critical events were associated with increased mortality OR (95% CI): 4.52 (1.350 – 16.07), $p=0.016$ and 7.333 (2.796 – 21.97), $p<0.001$ respectively. Table 4 shows post-operative risk factors for death. LBW, airway critical events, body temperature correction and glucose or electrolyte corrections did not have an association with mortality.

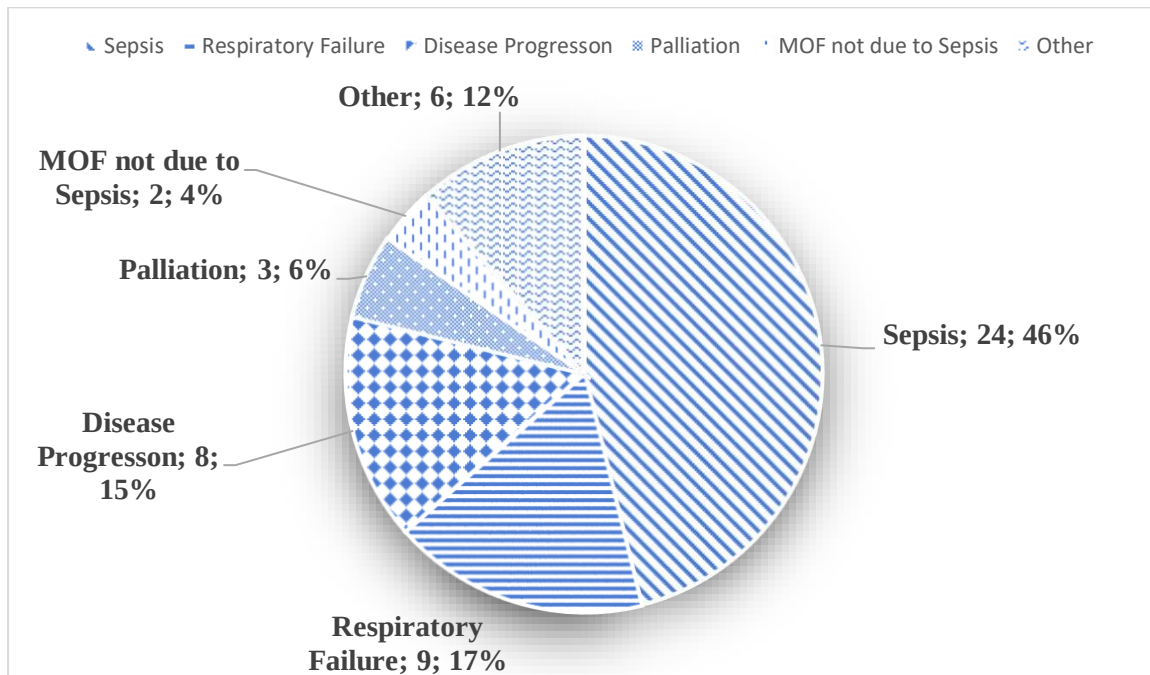


Figure 2: Causes of death

Table 4: Post-operative risk factors for death

Characteristic	Non-survivor, n=31 n (%)	Survival to discharge, n=69 n (%)	OR (95% CI)	P-value
Unplanned ICU admission	3 (9.7%)	3 (4.3%)	2.357 (0.414 - 13.42)	0.3
Bleeding that required surgical intervention	0 (0%)	0 (0%)	n/a	n/a
Infection	26 (84%)	40 (58%)	3.770 (1.381 - 12.190)	0.015
Relook surgeries	10 (32%)	12 (17%)	2.262 (0.841 - 6.042)	0.10
Other	26 (84%)	31 (45%)	6.374 (2.344 - 20.61)	<0.001

Discussion

Our study revealed a high incidence of intra-operative critical events (78%) compared to HICs (35.1%)². There is limited data on intra-operative critical events in other LMICs. A study in Niger found an incidence of 11.7% but limitations in trained paediatric anaesthetists and resources makes comparisons to our study difficult⁷. Prematurity, LBW and a longer duration of anaesthesia were significantly associated with intra-operative critical events which was similar to other studies^{2,5}. The anatomical and physiological immaturity found in premature and LBW neonates predispose them to adverse events when undergoing anaesthesia and surgery.

All procedures were performed under general anaesthesia with few combined general and neuraxial/ regional anaesthesia (10%) as compared to HICs (29.6%)². Other LMIC studies report a rate of 3.9 – 10%^{7,8}. The hesitance to perform neuraxial anaesthesia most likely stems from patient-related factors in our setting. As discussed, many neonates presenting for surgery have organ dysfunction such as coagulopathies and renal dysfunction. Abdominal pathology such as exposed visceral contents and perforations with compromised haemodynamics would preclude the positioning that neuraxial anaesthesia entails. Some surgeries were performed in ICU when neonates were too unstable to be transported and this clinical condition, would discourage the performance of regional/ neuraxial anaesthesia.

Intra-operative events

The most common critical events encountered were cardiovascular and correction of hypothermia and hypoglycaemia. LBW and premature neonates were more likely to have a cardiovascular (CV) event. The high prevalence of CV events was consistent with HICs². Although unlike HICs, blood transfusions accounted for most of the interventions in our study. There appeared to be preference for transfusions over inotropes or crystalloid boluses, presumably, to optimise oxygen delivery in the presence of foetal haemoglobin. In our setting, the decision to transfuse is usually determined clinically, based on pre-operative haemoglobin concentration, intra-operative blood loss and haemodynamics. An accurate transfusion trigger could not be elucidated due to the retrospective nature of our study. Studies have shown that liberal transfusion thresholds in ELBW neonates did not confer long term benefits and rapid administration of high volumes of fluid may, in fact, be harmful⁹⁻¹¹. In critically ill neonates where septic shock is suspected, early inotropic support is recommended after fluid boluses¹⁰.

Gestational age is used to guide normal mean arterial pressures, leading to variations in acceptable blood pressures and this may have contributed to the high number of CV events in our study. A major finding in the NECTARINE study was the significant effect of a composite event comprising of anaemia, hypotension and hypoxia on morbidity and mortality¹². Promoting tissue oxygenation is paramount to avoiding poor long-term outcomes, yet the ways in which to best achieve this remains unknown in neonates. The use of blood pressure as an accurate surrogate of organ perfusion in neonates has been criticised¹³. Studies have explored the use of other modalities such as near-infrared spectroscopy (NIRS) which is used to monitor cerebral oxygenation and thus, cerebral perfusion^{14,15}. The NECTARINE study reported that its use did not confer any major benefit and, in our setting, NIRS is a resource that is not freely available^{2,12}.

Hypothermia requiring active warming measures was common (43%) compared to HICs (4.5%)². We found that there was a statistically significant relationship between hypothermia and LBW and premature neonates. It is possible that in our setting, the first insult occurs during transportation of critically ill neonates from a relatively distant ICU to the theatre complex. With an increased body surface area to weight ratio and an inability to thermoregulate, neonates readily lose body heat and succumb to environmental factors¹⁶. In our theatres, ambient theatre temperature cannot be easily changed for neonatal surgery.

Hypothermia is prevented using conductive and convective warming systems as well as polyethylene wrappings on exposed limbs ^{17,18}. Despite this, our study demonstrated that a longer duration of anaesthesia resulted in an increased risk of hypothermia. This can be explained by the prolonged exposure and evaporative heat losses which occur during open surgery as well as the long theatre times. Preventative heat loss strategies should be explored further.

Our incidence of *hypoglycaemia* (33%) was higher than HICs (2,8%) . The NECTARINE study reported glucose measurements in only 50% of their cohort ². In our study, charts without documented glucose measurements were considered incomplete, resulting in the exclusion of 38 neonates. This reveals either poor documentation or a universal failure in what should be routine practice. Glucose monitoring is crucial as poor physiological compensation during any fasting period should be anticipated in the neonate. Failing to monitor glucose may be detrimental due to the prolonged starvation times which are common in our setting ¹⁹. This is evidenced by the high number of glucose replacement among premature neonates. Another factor to be considered is that neonates with sepsis are likely to have episodes of hypoglycaemia and need to be monitored vigilantly ²⁰.

Respiratory critical events (airway and oxygenation) were less common as compared to HICs where hypoxaemia triggered 36% of interventions in a prospective study ². In our setting there is always an experienced anaesthetist overseeing a trainee which allows for better management of airway and oxygenation difficulties.

No *drug errors or neurological critical events (NCE)* were reported in our study. There are no formalised reporting structures for drug errors in our setting and the onus is on the anaesthetist involved to document these errors. Thus, this may not be a true reflection of practice. Reports in HICs show that NCE such as seizures occurred at a low rate of 0.49 to 1.6 per 10 000 anaesthetics but was associated with significant morbidity ^{5,21}. LMICs lacked studies to compare NCE. Anaphylaxis and paediatric drug errors were uncommon in HICs , ranging from 0.002 - 0.003% for anaphylaxis and 0.0001- 2.6% for drug errors ^{5,22-24}. Though there is limited data, LMIC countries report a low incidence of drug errors (0.002% - 0.003%) ^{25,26}. Despite a relatively low incidence of drug errors, the majority are devastating and yet, easily preventable when simple strategies are implemented ^{22,24,27}.

Morbidity

Post-operative critical events occurred in 78% of neonates which is higher than the South African Surgical Outcomes Study, which included both paediatrics and neonates (9.7%), and a more recent neonatal-specific surgical study (57.58%)^{6,28}. In contrast, HICs report a post-operative complication rate of 16.3%². In our study, the most common post-operative complications were sepsis and relook surgeries, in keeping with another South African study⁶. In HICs, the majority of post-operative complications were respiratory-related followed by surgical complications².

The types of surgeries performed in HICs and LMICs are different. HICs mostly performed inguinal hernia repairs, whereas in our study laparotomies for necrotising enterocolitis (NEC), gastroschisis and intestinal atresia predominated². These conditions result in disruption of physiological processes leading to fluid and heat losses, electrolyte disturbances, respiratory compromise, and infection. This is reflected in our study as most of our neonates scored an ASA score of three or more due to pre-existing organ dysfunction. Antenatal care provides an opportunity for prenatal screening, genetic counselling and early diagnosis, so that delivery at appropriate hospitals where surgical services are offered may be planned²⁹. There is a lower percentage of antenatal care received in LMICs compared to HICs, which may explain the higher prevalence of congenital abnormalities found in LMICs^{30–32}. Prompt referrals and surgical interventions for these conditions is paramount which is not always possible in LMICs, where there are unreliable transport and referral systems, delayed recognition and inappropriate resuscitative measures^{29,32}. Neonates then present in extremis with severe dehydration or shock, electrolyte abnormalities and hypothermia³². Although this was not investigated in our study, another study based at our institution, revealed that referrals from regional or district hospitals formed the majority of surgical cases (65.6%) and deaths (57.9%)³³. Risk factors for increased morbidity in our study were intra-operative cardiovascular critical events and prematurity, which overlaps with HICs². It is plausible that neonates who have more severe disease requiring CV support would face more post-operative consequences. Prematurity, with its multitude of physiological aberrations, would render these neonates more vulnerable.

Mortality

Our mortality rate (31%) fell within range of other similar South African studies and LMICs (11–36.9%)^{6,33–35}. This was much higher than HICs which reported a mortality rate of 4.1%

at 30 days ², and lower compared to the highest mortality rate of 35.7% in a South African study ³³. The commonest cause of death in our setting was sepsis followed by respiratory failure, which is consistent with many studies from South Africa, other LMICs and HICs ^{2,6,32–36}. We reported no intra-operative deaths resulting from anaesthesia, contrasted to studies from other LMICs ³². Intra-operative oxygenation and cardiovascular critical events as well as post-operative infection and other post-operative critical events, were important risk factors for mortality in our study. We attribute this to demographics, disease burden, types of surgeries encountered and the post-operative implications thereof. In our study, of the neonates who died, many had a LBW and were premature. In our setting, there is also relative overcrowding in ICU, which increases the risk of sepsis with drug-resistant organisms ³³.

Strengths of the study

Our study was based at one of the two academic quaternary public sector hospitals, where neonatal surgeries are performed. We used other similar studies from HICs to guide variables and outcomes when designing the data collection sheet. A single researcher collected all the data using all available databases. Incomplete records were excluded to ensure completeness of data.

Limitations

This was a single centre study examining neonates with surgical pathology which limits generalisability. Due to the retrospective nature of our study, we relied on the integrity of records for data collection. For this reason, we could not investigate clinical thresholds for intervention as done in the NECTARINE study. Limited records were used which represents a fraction of the neonatal surgeries performed during this time frame. This may contribute to potential missing data bias. Certain factors that were not investigated, such as time to surgery from referral or diagnosis and use of the WHO surgical safety checklist, may have provided a meaningful context to interpret results. Although associations have been made between risk factors and outcomes, these results must be interpreted with caution as this is a retrospective, descriptive study rather than a randomised controlled trial.

Conclusion

In our setting, there is a high incidence of critical events in the surgical neonatal population. Prematurity and LBW are significant pre-operative risk factors for critical events. Post-operative infection was the largest contributing factor to morbidity and mortality. Although

the risk factors for critical events were similar, the incidence and mortality was substantially higher than that found in HICs.

This was a novel study as it was the first study which delved into the intra-operative events and outcomes in neonatal anaesthesia in South Africa. Further prospective research involving multiple sites will garner more information to direct meaningful change in practice.

Details of authors' contribution

LE: study design, data collection, data analysis, drafting and revising of the final manuscript.

TG and TR: study design and revising of the final manuscript.

ZJ study design, data analysis, drafting and revising of the final manuscript.

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Dr S Essa (University of Witswatersrand, Johannesburg): revising the manuscript.

Disclosures

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Declarations of interest

The authors declare that they have no conflict of interest.

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Appendices

Supplementary Table 1: Variables and outcomes

	Sub-categories	Variables
Pre-operative risk factors	Demographics	ASA Physical score
		Gestational age at surgery
		Weight at surgery
		Sex
		Cardiac/ Congenital abnormality
		Prior organ support
		Prior critical event
		Prior ICU admission
Details of surgery and anaesthetic performed	Anaesthesia and surgery	Duration
		Procedure
		Emergency/ Elective
		Type of anaesthetic
Intra-operative critical events	Airway critical events	More than two attempts at intubation
		Drop in saturation <90%
		Associated bradycardia
		Cardiopulmonary resuscitation (airway related)
		Difficult face mask ventilation
		Bronchial aspiration
	Oxygenation	Need for FiO ₂ higher than 0.7
		Change/ repositioning of dislodged/ obstructed tube
		Pneumothorax
		Laryngospasm
		Bronchospasm
		Post-operative stridor
		Unanticipated stridor

		Unanticipated post-operative respiratory support
	Electrolyte/ Glucose Critical Correction	Correction of electrolytes
		Correction of hypoglycaemia (what value)
		Correction of hyperglycaemia
	Cardiovascular critical event	Administration of blood products
		Administration of vasopressors/ inotropes
		Cardiopulmonary resuscitation (cardiovascular related)
	Neurological critical event	Seizures
	Drug adverse events	Drug errors
		Drug adverse side effects
	Body temperature correction	Cooling measures
		New warming measures
Post-operative critical events	Morbidity	Post-operative bleeding requiring surgery
		Unplanned ICU admission
		Post-operative infection
		Relook surgeries since index surgery
		Any other critical event (anaemia, thrombocytopenia, coagulopathies)
	30-day mortality and cause of death	Nosocomial sepsis
		Respiratory failure
		Disease progression
		Multi-organ failure not due to sepsis
		Palliation
		Other

References

1. Kuan CC, Shaw SJ. Anesthesia for Major Surgery in the Neonate. *Anesthesiol Clin*. 2020 Mar;38(1):1–18. DOI 10.1016/j.anclin.2019.10.001
2. Disma N, Veyckemans F, Virag K, Hansen TG, Becke K, Harlet P, et al. Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE). *Br J Anaesth*. 2021 Mar 31;2021 June(126 (6)):1157–72. DOI: 10.1016/j.bja.2021.02.016
3. Razavi C, Walker SM, Moonesinghe SR, Stricker PA. Pediatric perioperative outcomes: Protocol for a systematic literature review and identification of a core outcome set for infants, children, and young people requiring anesthesia and surgery. *Paediatr Anaesth*. 2020 Apr;30(4):392–400. DOI 10.1111/pan.13825
4. Gargon E. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative. *Matur J*. 2016 Sep;91:91–2. DOI 10.1016/j.maturitas.2016.06.007
5. Habre W, Disma N, Virag K, Becke K, Hansen TG, Jöhr M, et al. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *Lancet Respir Med*. 2017 May;5(5):412–25. DOI 10.1016/S2213-2600(17)30116-9
6. Withers A, Cronin K, Mabaso M, Brisighelli G, Gabler T, Harrison D, et al. Neonatal surgical outcomes: a prospective observational study at a Tertiary Academic Hospital in Johannesburg, South Africa. *Pediatr Surg Int*. 2021 Aug;37(8):1061–8. DOI: 10.1007/s00383-021-04881-7
7. M S Chaïbou H Abarchi. Prospective, observational study of perioperative critical incidents, anaesthesia and mortality in elective paediatric surgical patients at a national referral hospital in Niger. *South Afr J Anaesth Analg*. 2022 Mar 3;28(1):16–20. DOI <https://doi.org/10.36303/SAJAA.2022.28.1.2462>
8. Newton MW, Hurt SE, McEvoy MD, Shi Y, Shotwell MS, Kamau J, et al. Pediatric Perioperative Mortality in Kenya: A Prospective Cohort Study from 24 Hospitals. *Anesthesiology*. 2020 Mar;132(3):452–60. DOI 10.1097/ALN.0000000000003070
9. Harley A, George S, King M, Phillips N, Keijzers G, Long D, et al. Early Resuscitation in Paediatric Sepsis Using Inotropes - A Randomised Controlled Pilot Study in the Emergency Department (RESPOND ED): Study Protocol and Analysis Plan. *Front Pediatr*. 2021;9:663028. DOI 10.3389/fped.2021.663028
10. Spaggiari V, Passini E, Crestani S, Roversi MF, Bedetti L, Rossi K, et al. Neonatal septic shock, a focus on first line interventions. *Acta Bio-Medica Atenei Parm*. 2022 Jul 1;93(3):e2022141. DOI 10.23750/abm.v93i3.12577
11. Franz AR, Engel C, Bassler D, Rüdiger M, Thome UH, Maier RF, et al. Effects of Liberal vs Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants: The ETTNO Randomized Clinical Trial. *JAMA*. 2020 Aug 11;324(6):560–70. DOI 10.1001/jama.2020.10690

12. Bertolizio G, Disma N, Engelhardt T. After nectarine: how should we provide anesthesia for neonates? *Curr Opin Anaesthesiol.* 2022 Jun 1;35(3):337–42. DOI 10.1097/ACO.0000000000001126
13. Turner NM. Intraoperative hypotension in neonates: when and how should we intervene? *Curr Opin Anaesthesiol.* 2015 Jun;28(3):308–13. DOI 10.1097/ACO.0000000000000196
14. Dix LML, van Bel F, Lemmers PMA. Monitoring Cerebral Oxygenation in Neonates: An Update. *Front Pediatr.* 2017;5:46. DOI 10.3389/fped.2017.00046
15. da Costa CS, Greisen G, Austin T. Is near-infrared spectroscopy clinically useful in the preterm infant? *Arch Dis Child Fetal Neonatal Ed.* 2015 Nov;100(6):F558–561. DOI 10.1136/archdischild-2014-307919
16. Singer D. Pediatric Hypothermia: An Ambiguous Issue. *Int J Environ Res Public Health.* 2021 Oct 31;18(21):11484. DOI 10.3390/ijerph182111484
17. Kent AL, Williams J. Increasing ambient operating theatre temperature and wrapping in polyethylene improves admission temperature in premature infants. *J Paediatr Child Health.* 2008 Jun;44(6):325–31. DOI 10.1111/j.1440-1754.2007.01264.x
18. McCall EM, Alderdice F, Halliday HL, Vohra S, Johnston L. Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. *Cochrane Database Syst Rev.* 2018 Feb 12;2(2):CD004210. DOI 10.1002/14651858.CD004210.pub5
19. Kouvarellis AJ, Van der Spuy K, Biccard BM, Wilson G. A prospective study of paediatric preoperative fasting times at Red Cross War Memorial Children's Hospital, Cape Town, South Africa. *South Afr Med J Suid-Afr Tydskr Vir Geneeskde.* 2020 Sep 30;110(10):1026–31. DOI 10.7196/SAMJ.2020.v110i10.14814
20. Gupta BK, Shrivastava AK, Chetri P. Glycemic status and its effect in Neonatal Sepsis - A prospective study in a Tertiary Care Hospital in Nepal 2019. *J Adv Pediatr Child Health.* 2019 Sep 27;2:015–9. DOI 10.29328/journal.japch.1001006
21. Raghavan KC, Hache M, Bulsara P, Lu Z, Rossi MG. Perianesthetic neurological adverse events in children: A review of the Wake-Up Safe Database. *Paediatr Anaesth.* 2021 May;31(5):594–603. DOI 10.1111/pan.14165
22. Leahy IC, Lavoie M, Zurakowski D, Baier AW, Brustowicz RM. Medication errors in a pediatric anesthesia setting: Incidence, etiologies, and error reduction strategies. *J Clin Anesth.* 2018 Sep;49:107–11. DOI 10.1016/j.jclinane.2018.05.011
23. Gariel C, Cogniat B, Desgranges FP, Chassard D, Bouvet L. Incidence, characteristics, and predictive factors for medication errors in paediatric anaesthesia: a prospective incident monitoring study. *Br J Anaesth.* 2018 Mar;120(3):563–70. DOI 10.1016/j.bja.2017.12.014
24. Lobaugh LMY, Martin LD, Schleelein LE, Tyler DC, Litman RS. Medication Errors in Pediatric Anesthesia: A Report From the Wake Up Safe Quality Improvement Initiative. *Anesth Analg.* 2017 Sep;125(3):936–42. DOI 10.1213/ANE.0000000000002279

25. Amor M, Bensghir M, Belkhadir Z, Ghannam A, Azendour H, Drissi Kamili N, et al. Medication errors in anesthesia: a Moroccan university hospitals survey. *Ann Fr Anesth Reanim*. 2012 Nov;31(11):863–9. DOI 10.1016/j.annfar.2012.07.024
26. Llewellyn RL, Gordon PC, Wheatcroft D, Lines D, Reed A, Butt AD, et al. Drug administration errors: a prospective survey from three South African teaching hospitals. *Anaesth Intensive Care*. 2009 Jan;37(1):93–8. DOI 10.1177/0310057X0903700105
27. Martin LD, Grigg EB, Verma S, Latham GJ, Rampersad SE, Martin LD. Outcomes of a Failure Mode and Effects Analysis for medication errors in pediatric anesthesia. *Paediatr Anaesth*. 2017 Jun;27(6):571–80. DOI: 10.1111/pan.13136
28. Torborg A, Cronje L, Thomas J, Meyer H, Bhattay A, Diedericks J, et al. South African Paediatric Surgical Outcomes Study: a 14-day prospective, observational cohort study of paediatric surgical patients. *Br J Anaesth*. 2019 Feb;122(2):224–32. DOI 10.1016/j.bja.2018.11.015
29. Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. *Surgery*. 2015 Jul;158(1):3–6. DOI 10.1016/j.surg.2015.04.011
30. Chirdan LB, Ngiloi PJ, Elhalaby EA. Neonatal surgery in Africa. *Semin Pediatr Surg*. 2012 May;21(2):151–9. DOI 10.1053/j.sempedsurg.2012.01.007
31. Ullrich SJ, Kakembo N, Grabski DF, Cheung M, Kisa P, Nabukenya M, et al. Burden and Outcomes of Neonatal Surgery in Uganda: Results of a Five-Year Prospective Study. *J Surg Res*. 2020 Feb;246:93–9. DOI 10.1016/j.jss.2019.08.015
32. Ekenze SO, Ajuzieogu OV, Nwomeh BC. Challenges of management and outcome of neonatal surgery in Africa: a systematic review. *Pediatr Surg Int*. 2016 Mar;32(3):291–9. DOI 10.1007/s00383-016-3861-x
33. Saggars RT, Ballot DE, Grieve A. An analysis of neonates with surgical diagnoses admitted to the neonatal intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital, South Africa. *South Afr Med J Suid-Afr Tydskr Vir Geneeskde*. 2020 May 29;110(6):497–501. DOI 10.7196/SAMJ.2020.v110i6.14326
34. Siyotula T, Arnold M. An analysis of neonatal mortality following gastro-intestinal and/or abdominal surgery in a tertiary hospital in South Africa. *Pediatr Surg Int*. 2022 May;38(5):721–9. DOI 10.1007/s00383-022-05100-7
35. Ekenze SO, Modekwe VO, Ajuzieogu OV, Asinobi IO, Sanusi J. Neonatal surgery in a developing country: Outcome of co-ordinated interdisciplinary collaboration. *J Paediatr Child Health*. 2017 Oct;53(10):976–80. DOI 10.1111/jpc.13610
36. Ameh EA, Dogo PM, Nmadu PT. Emergency neonatal surgery in a developing country. *Pediatr Surg Int*. 2001 Jul;17(5–6):448–51. DOI 10.1007/s003830000551

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Appendices

Appendix 1: Proposal and Annexures

Peri-operative Outcomes in Neonatal Surgeries at an Academic Institution

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1. Introduction

Providing anaesthesia for neonates is oftentimes very challenging for the anaesthetist. It requires the consideration of several factors. The anatomy and physiology of neonates are considerably different to adults. The immaturity of organ systems renders this population extremely vulnerable to the significant insult of surgery and anaesthesia. Patients have poor physiological compensatory mechanisms for changes in glucose, body temperature, cardiovascular instability and oxygen delivery ¹. This is complicated by the lack of validated physiological parameters when this population undergoes anaesthesia ². This may be explained by the rapidly evolving nature of a neonate's anatomy and physiology ³. Currently there are no evidence-based protocols to treat deviations in physiology ⁴.

Blood pressure has been shown to change at different stages in a neonate making it extremely difficult to predict the appropriate parameters to target intra-operatively ³. There are studies to suggest that there may be less cerebral autoregulatory reserve ³. As the majority of anaesthetic agents used induce a degree of hypotension, the combination of lack of established blood pressure targets and poor cerebral autoregulation increases the risk of cerebral hypoperfusion ³.

Adverse respiratory events tend to occur more commonly in the neonate due to anatomical and physiological differences which leads to quicker desaturation and potentially a more difficult intubation ⁵. Post anaesthesia, post-extubation stridor and apnoeas can also occur ⁵.

Immature liver and renal tubular function results in unpredictable biotransformation and clearance of drugs ^{5,6}. Preterm infants are more susceptible to hypoglycaemia due to a deficiency of glycogen stores ⁵. However, during general anaesthesia, the surgical stress response results in a hyperglycaemia. Rapid changes in osmolarity can result in osmotic diuresis, intracerebral haemorrhage and worsening of an already present hypoxic ischaemic injury ⁶.

Neonates who present for surgery are often critically ill and may have multiorgan dysfunction in addition to a myriad of co-morbidities like extreme prematurity, extreme low birth weight and congenital abnormalities such as congenital heart disease or malformations ⁵. The surgeries that are performed on neonates can also be major, high-risk procedures like cardiac

surgeries or laparotomies for conditions such as necrotising enterocolitis (NEC). These factors also contribute to the increased morbidity and mortality.

The higher frequency of adverse events in the developing neonate can be extremely damaging and ultimately leads to an increase in morbidity and mortality. The lack of universal outcomes makes it difficult to report critical events that may impact on patients' morbidity and mortality.

Clinical outcomes are “measurable changes in health, function and quality of life” that are integral in evaluating efficacy of current interventions thereby assessing quality of care ⁴. In the 1970s, the World Health Organization published guidelines for the minimal requirements on how to describe outcomes in cancer trials ⁴. Since then, the need for outcome sets has become more apparent and investigated ³. Outcome sets establishes minimum outcomes that should be reported on which then facilitates consistency among different trials thereby allowing direct comparisons ⁷. Clinical outcomes need to be specific and relevant so that they may be used to improve evidence-based practice ^{4,7}. The value of having universal outcome sets would be that multiple trials within a certain domain may be compared reliably ⁷.

The limitations occur when clinical outcomes have no clear definition. Core Outcome Measures in Effectiveness Trials (COMET) are used to guide outcomes in an age group above 18 years of age ⁴. Paediatric outcomes cannot be extrapolated from adult data as the anatomy, physiology and metabolism differ so greatly between the two groups ⁴. Currently there are no outcome sets used for paediatrics ⁴. This may be attributed to the evolving anatomy, physiology and metabolism of patients resulting in an array of possible outcomes in paediatrics. One paediatric outcome set would not necessarily be appropriate for all age groups ⁴.

Neonates are already an established population suffering from a higher morbidity and mortality ⁴. Thus the need for developing clear and relevant outcome sets are becoming imperative for quality improvement in this subpopulation ⁴.

A Paediatric Peri-operative Outcomes Group has been developed to tackle the lack of outcomes sets in the different age groups of the paediatric population ⁴. The charter that was drawn up has been registered with COMET and is undergoing stepwise investigation and research so that appropriate outcome sets for paediatrics may be formulated ⁴. The principle

behind establishing peri-operative outcome sets would be to strengthen trial results so comparisons can be made between multiple studies ⁷. Once comparisons can be made, interventions that were found to be beneficial, harmful or not effective can be incorporated into formulating evidence-based protocols.

There have been a few notable studies that have been published on peri-operative outcomes (inclusive of anaesthetic adverse events) in the paediatric population thus far. Independent risk factors are varied but most of these studies confirm that younger age, such as infants and neonates bear the highest risk of peri-operative adverse events ⁸. In a European study, there was a higher incidence of cardiovascular instability in infants and particularly in neonates amongst the paediatric population (neonates made up 12,1% of all patients who developed cardiovascular instability) ⁸. A history of prematurity resulted in an increase relative risk of respiratory critical events by almost two ⁸. Other notable risk factors that contributed to the occurrence of adverse events were medical history such as comorbidities and American Society of Anaesthesiology (ASA) physical score as well as physical condition such as fever and airway hypersensitivity ⁸.

Following this study, another specific study focussing on neonatal outcomes established that the overall incidence of critical events which required interventions was 35,3%. Of these critical events, cardiovascular instability comprised of the majority (60,7%), followed by hypoxaemia with saturations below 85% (35%) and red blood cell transfusions (5,1%) where the transfusion trigger was a haemoglobin of less than 8,6 g.dl⁻¹ ⁹. Interventions for blood glucose and temperature were less common ⁹. The main predisposing risk factors were length of surgery and younger neonates as 70% of events occurred in neonates below the age of 32 weeks post-menstrual age (PMA) at the age of surgery ⁹. In this neonatal surgical population, the overall mortality was found to be 3,2% of which 2% occurred by day 30 ⁹. The commonest causes of mortality were cited to be sepsis and multiorgan failure ⁹. Notable risk factors contributing to this were early PMA at the time of surgery, pre-operative intensive organ support as well as comorbidities ⁹. An adverse event which composed of hypotension, hypoxaemia and anaemia was also linked to a significantly increased mortality and morbidity ⁹.

In the South African Paediatric Surgical Outcomes study (SAPSOS) which looked at post-operative outcomes, SA was shown to have a higher post-operative complication rate of 9,7% than high income countries (HICs) (1-6%) in the paediatric population ¹⁰. Post-operative

complications were predominantly infection-related as compared to HICs ¹⁰. Risk factors predisposing patients to post-operative complications were ASA physical status, infection as an indicator for surgery, surgical urgency and severity of surgery ¹⁰. In another South African-based study looking at peri-operative events particularly at anaesthetic adverse events, the overall paediatric mortality was low at 0,5% however of the children who died, 53% were below the age of one year with the highest overall rates belonging to the neonatal group ¹¹. Statistically, it was extrapolated that children below the age of one year, in particular neonates, were recognised as being an independent predictor of mortality ¹¹.

In the context of Africa, neonatal surgery unfortunately exposes the poor socio-economic status and many pitfalls of the continent. Neonatal surgical mortality in HICs have reduced from 50% in the 1950s to 5% in the past few years ¹². The improvement of mortality rates in HICs have been ascribed to the better comprehension of neonatal physiology, advancements in surgical and anaesthetic techniques, better diagnostic facilities with transport and the establishment of neonatal intensive units ¹³.

However, in Africa this figure has remained unacceptably high with reported mortality rates of between 16 - 40% ¹². The highest mortality rate was recorded in gastric perforations and oesophageal atresia ¹². The most significant risk factors contributing to mortality were sepsis, anaesthetic complications and malnutrition ¹³.

There are two studies to our knowledge that have been carried out in this population undergoing surgery within SA. The first study by Saggars et al ¹⁴ reported that in a neonatal intensive care unit at a tertiary institution, there was a high prevalence of surgical conditions (34,6%) ¹⁴. Abdominal surgery formed most of the surgical procedures performed (83,7%) and resulted in a mortality of 35,2% ¹⁴. Identified predictors of a poor outcome, defined as the mortality rate, was the presence of NEC, late onset sepsis with gram negative organisms, younger gestational age, lower birth weight and patients born outside of the tertiary institution ¹⁴.

In the second study by Withers et al ¹⁵ published in 2021, morbidity in the neonatal surgical population was shown to be 57,58% ¹⁵. Using the Clavien-Dindo classification, nosocomial sepsis was at the forefront of morbidity at 54,99% with gram negative and fungal sepsis most commonly implicated, followed by surgical complications at 18,51% ¹⁵. Overall mortality at 30 days was 21, 74% with sepsis cited as the most common cause of death at 87,5% followed

by respiratory failure (27,5%)¹⁵. It also confirmed the high prevalence of NEC in the younger age group of neonates (34,4%) and the associated high mortality of 40% of all deaths occurring by day 30¹⁵. The presence of NEC was an independent predictor of mortality and morbidity in the neonate¹⁵.

There are currently no standard outcome measures that have been validated for the neonatal population. There has been one European study⁹ which looked at peri-operative neonatal outcomes including mortality and morbidity. However in South Africa, which is a resource and skills limited country, there has only been two studies looking solely at mortality amongst the neonatal surgical population¹⁴. The studies published thus far in SA^{14,15} focus mainly on surgical morbidity and mortality without encompassing all peri-operative events like intra-operative anaesthetic and surgical incidents. Thus, there remains a large knowledge gap pertaining to the peri-operative course and outcome of the neonatal surgical population. Research would capture more information in this area and this is important as it would pave the way to quality improvement and evidence-based protocols with the intention of improving outcome and quality of patient care.

2. Aim

The aim of this study is to assess retrospective and prospective peri-operative outcomes of neonates undergoing surgery at an academic institution.

3. Objectives

The primary objectives of this study are to:

- Describe the demographics of the neonatal surgical population
- Estimate the incidence of peri-operative anaesthesia critical events
- Determine relevant peri-operative risk factors
- Compare relevant risk factors with incidence of peri-operative anaesthesia critical events

The secondary objectives are to:

- Estimate the peri-operative morbidity and mortality outcomes

- Compare outcomes with identified relevant peri-operative risk factors

4. Research assumptions

Neonate: A newborn specifically within the first 28 days of life. A preterm infant will be classified as a neonate according to their chronological age corrected for gestational age.

Gestational age (GA): Time duration from the first day of the last normal menstrual to delivery date ¹⁶

Chronological age (Post-natal age): Time duration from delivery date (birth date) ¹⁶

ASA Physical Status Classification ¹⁷:

ASA I: A normal healthy patient

ASA II: A patient with mild systemic disease

ASA III: A patient with severe systemic disease

ASA IV: A patient with severe systemic disease that is a constant threat to life

ASA V: A moribund patient who is not expected to survive without the operation

ASA VI: A declared brain-dead patient whose organs are being removed for donor purposes

Preterm: Gestational age <37 complete weeks ¹⁸

Low birth weight: Birth weight <2500 grams ¹⁸

Very low birth weight: Birth weight <1500 grams ¹⁸

Extremely low birthweight: Birth weight <1000 grams ¹⁸

Outcomes in this study will be divided into peri-operative anaesthesia critical events and post-operative outcomes.

To our knowledge, there are two international studies and one South African that have elucidated peri-operative outcomes and critical events from which our study has been adapted:

- The Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE) study ⁹
- Incidence of severe critical events in paediatric anaesthesia (APRICOT) study ⁸
- Neonatal Surgical Outcomes Study ¹⁵

These were all prospective studies and will be described as stated below. The occurrence of ANY of the events will be accepted as an adverse event:

Peri-operative Anaesthesia Critical Events:

1. Airway management
 - More than 2 attempts of intubation, which require alternative ways of achieving intubation and number of attempts OR
 - Drop in saturation below 90%; 85%; 80% OR
 - Bradycardia and/ or associated cardiopulmonary resuscitation OR
 - Difficult face mask ventilation OR
 - Bronchial Aspiration OR
2. Oxygenation:
 - Need for higher FiO₂ than routine practice that is higher than 0.7 OR
 - Recruitment manoeuvre used OR
 - Change or repositioning of a dislodged or obstructed tube OR
 - Pneumothorax OR
 - Laryngospasm OR
 - Bronchospasm OR
 - Post-operative stridor OR
 - Unanticipated post-operative respiratory support

3. Electrolyte or glucose correction:
 - Interventions to correct electrolytes
 - Interventions for hyper-/hypoglycaemia
4. Cardiovascular Interventions
 - Administration of blood products OR
 - Administration of vasopressors or inotropes OR
 - Arrhythmia OR
 - Cardiopulmonary resuscitation
5. Correcting body temperature:
 - Cooling measures implemented OR
 - New warming measures implemented
6. Neurological:
 - Seizures
7. Drug Critical Events:
 - Anaphylaxis
 - Drug Error
8. Other critical event not stated above.

Post-Operative Critical Events (based on the NECTARINE study ⁹):

1. Unplanned Intensive care admissions OR
2. Post-operative bleeding requiring surgical intervention OR
3. Post-operative infection, whether surgical site or other site OR
4. Relook operations since index surgery
5. Other critical event not stated above.

Post-Operative Outcomes:

1. 30-Day Mortality
2. Outcome: survival to discharge or death (non-survivor).

5. Demarcation of study field

The study will be conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) affiliated to the Faculty of Health Sciences at the University of the Witwatersrand. The hospital performs approximately 23 600 surgeries annually with approximately 1000 being general paediatric surgeries. Of these, 130 are in neonates. There is one paediatric intensive care unit with 15 beds. This unit is shared between neonatal and paediatric critical care admissions.

6. Ethical considerations

Permission will be requested from the Chief Executive Officer (CEO) of CMJAH to access patient records (Appendix A). Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical), the Graduate Studies Committee of the University of the Witwatersrand and from the Heads of Department of Anaesthesia, Paediatric Surgery and Paediatrics (Appendix B).

The study will look at records of patients that have been operated and thus no patient consent will be needed. Anonymity will be protected as the only clinical data from patient records will be used and patient and staff personal details will not be used in the data collection. Instead, each patient will be assigned a numeric data code and only the researcher will have access to the anonymised data.

This study will document the events in the peri-operative period at the discretion of the attending physicians and thus there will be no difference to usual care of the patients.

Data that is collected will be compiled from as well as stored and managed on RedCap ¹⁹. This is a secure online application which can hold and store databases. The data will only be viewed by the researchers once permissions are granted. The data collected will be accessed by the researcher and supervisors only to maintain confidentiality. This study will adhere to the principles set out by the Declaration of Helsinki ²⁰ and the Good Clinical Practice Guidelines ²¹.

7. Research Methodology

7.1 Research design

This study will be a retrospective, cross sectional and descriptive study design.

7.2 Study population

The study population will include all neonates from birth until 28 days of life where a general anaesthetic, regional anaesthetic or both are performed for elective or emergency surgical procedure within a two year period from 2018-2019 at CMJAH.

7.3 Study sample

7.3.a Sample size

The sample size will include a minimum of 100 neonates with complete records who underwent surgery within a two year period at CMJAH from 2018-2019. The approximate number of annual neonatal surgeries performed at CMJAH is 130. The critical event rate from previous studies such as the NECTARINE study ⁹ was 35, 3% hence we anticipate a similar if not a higher rate. Using the Raosoft ® sample size calculator with a population sample of 130 and event rate of 35.3%, a sample size of 96 was calculated; hence a minimum sample of 100 will be sought.

7.3.b Sampling method

Non-probability, convenience, consecutive sampling will be used as only patients that fulfil a specific inclusion criterion and are accessible to the researcher (as outlined above) will be included in the study (17).

i. Inclusion criteria

- All neonates from birth to until 28 days of life will be eligible.
- Neonates with complete records in 2018/ 2019. Complete records are where a 30-day outcome and major peri-operative critical events may be established.
- General anaesthesia, regional anaesthesia or both.

- Elective or emergency procedure.

ii. Exclusion criteria

- All diagnostic procedures including Cardiac Catheter procedures, MRI and CT scan.
- Any procedure following the index surgery will be not regarded as a separate record. It will be included as a post-operative event. Risk factors and intra-operative events will fall under the same patient/ record.
- Patients who have records missing where:
 - a 30-day outcome (as described) cannot be established.
 - peri-operative critical events cannot be ascertained (e.g missing anaesthetic charts).

7.4 Data collection

The primary researcher (LE) will need to identify potential candidates for the study by surveying the elective and emergency theatre books in E12 (designated paediatric general surgery theatre at CMJAH). In this book, there is a record of patient details including demographics and surgical procedures done. A list will be made of all potential neonates eligible for the study. With this information, all patient records available (from anaesthesia, paediatric surgery and paediatrics) on the candidate will be searched to identify completed neonatal records. Once a completed neonatal record is established, a data collection sheet will be used to document critical events. This data collection sheet (Appendix E) drawn up with input from all involved departments such as anaesthesia, paediatric surgery and paediatrics. The data will be gained from all data bases available to the researcher (RedCap ¹⁹, Healthspace, physical and electronic records).

7.5 Data analysis

The researcher will capture the raw data on REDCap ¹⁹ and it will be analysed in consultation with a biostatistician. Statistical analyses were conducted in the R Statistical Environment (v4.0.4). All continuous variables were summarised using median and interquartile range. Categorical data were summarised as number and percentage. When looking for associations between critical events and various demographic and clinical variables, the critical event outcome variable was dichotomised into ‘yes’ there was at least one critical event (of any type), or ‘no’ there were no critical events (of any type), and logistic regression was then used to test for associations. Similarly, logistic regression was used when looking for associations

between postoperative critical events and morbidity [post-operative infection (yes/no), and relook surgery (yes/no)] and mortality [survived (yes/no)]

A p-value <0.05 will be considered significant. Data will be reported using odds ratios with 95 % confidence intervals. Only valid cases will be analysed for each variable (i.e., cases with missing data will be excluded from the analysis).

8. Significance of the Study

Neonates have been established as a high-risk population that are more likely to suffer from peri-operative complications as compared to the rest of the paediatric population ⁸. Despite this knowledge, there remains limited literature for this group in the SA context. The reason for the lack of research may be mainly attributed to the absence of validated outcomes and this may be due to the lack of standardised parameters in this population.

This study will assist in highlighting the factors associated with poor outcomes allowing for improvement measures to be devised and implemented.

9. Validity and Reliability

The Validity and Reliability of the study will be maintained by:

- Use of an appropriate study design.
- Employing appropriate data collection methods.
- A clearly stated definition of peri-operative outcomes.
- A single researcher will collect data.
- Data will be analysed with assistance of a biostatistician.

10. Potential limitations

There is a possibility of missing or incomplete records or illegible data which will not be used. Due to the non-probability sampling methods that will be used, the study also risks yielding a sampling bias which may limit inferences and conclusions. All outcomes as defined may not be clearly stated as the design for collection will be retrospective.

The study has a limitation of being representative of the peri-operative outcomes at a single institution which may not be generalisable to outcomes in neonates in the South African context as a whole.

11. Project outline

11.1 Time frame

	Mar- May 2021	June 2021	Jul- Sept 2021	Oct-Dec 2021	Jan- Feb 2022	Mar- June 2022	July 2022
Proposal preparation							
Proposal Submission							
Ethics Approval							
Post graduate Approval							
Data Collection							
Data Analysis							
Draft Article							
Submission							

11.2 Financial plan

	Price per Page	Number of Pages	Copies	Total
Proposal	R1/ page	30	6	R 180
Postgraduate form	R1/ page	2	1	R 2
Final submission	R1/ page	100	2	R 200
Binding	R30		2	R 60
				R 442

References

1. Azhibekov T, Noori S, Soleymani S, Seri I. Transitional cardiovascular physiology and comprehensive hemodynamic monitoring in the neonate: relevance to research and clinical care. *Semin Fetal Neonatal Med.* 2014 Feb;19(1):45–53. DOI: 10.1016/j.siny.2013.09.009
2. Turner NM. Intraoperative hypotension in neonates: when and how should we intervene? *Curr Opin Anaesthesiol.* 2015 Jun;28(3):308–13. DOI 10.1097/ACO.0000000000000196
3. Houck CS, Vinson AE. Anaesthetic considerations for surgery in newborns. *Arch Dis Child Fetal Neonatal Ed.* 2017 Jul;102(4):F359–63. DOI 10.1136/archdischild-2016-311800
4. Razavi C, Walker SM, Moonesinghe SR, Stricker PA. Pediatric perioperative outcomes: Protocol for a systematic literature review and identification of a core outcome set for infants, children, and young people requiring anesthesia and surgery. *Paediatr Anaesth.* 2020 Apr;30(4):392–400. DOI 10.1111/pan.13825
5. Kuan CC, Shaw SJ. Anesthesia for Major Surgery in the Neonate *Anesthesiol Clin.* 2020 Mar;38(1):1–18. DOI 10.1016/j.anclin.2019.10.001
6. O'Brien F, Walker IA. Fluid homeostasis in the neonate. *Paediatr Anaesth.* 2014 Jan;24(1):49–59. DOI: 10.1111/pan.12326.
7. Gargon E. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative. *Matur J.* 2016 Sep;91:91–2. DOI 10.1016/j.maturitas.2016.06.007
8. Habre W, Disma N, Virag K, Becke K, Hansen TG, Jöhr M, et al. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *Lancet Respir Med.* 2017 May;5(5):412–25. DOI 10.1016/S2213-2600(17)30116-9

9. Disma N, Veyckemans F, Virag K, Hansen TG, Becke K, Harlet P, et al. Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE). *Br J Anaesth*. 2021 Mar 31;2021 June(126 (6)):1157–72. DOI: 10.1016/j.bja.2021.02.016
10. Torborg A, Cronje L, Thomas J, Meyer H, Bhattay A, Diedericks J, et al. South African Paediatric Surgical Outcomes Study: a 14-day prospective, observational cohort study of paediatric surgical patients. *Br J Anaesth*. 2019 Feb;122(2):224–32. DOI 10.1016/j.bja.2018.11.015
11. Meyer HM, Thomas J, Wilson GS, de Kock M. Anesthesia-related and perioperative mortality: An audit of 8493 cases at a tertiary pediatric teaching hospital in South Africa. *Paediatr Anaesth*. 2017 Oct;27(10):1021–7. DOI 10.1111/pan.13214
12. Chirdan LB, Ngiloi PJ, Elhalaby EA. Neonatal surgery in Africa. *Semin Pediatr Surg*. 2012 May;21(2):151–9. DOI 10.1053/j.sempedsurg.2012.01.007
13. Ekenze SO, Ajuzieogu OV, Nwomeh BC. Challenges of management and outcome of neonatal surgery in Africa: a systematic review. *Pediatr Surg Int*. 2016 Mar;32(3):291–9. DOI 10.1007/s00383-016-3861-x
14. Saggars RT, Ballot DE, Grieve A. An analysis of neonates with surgical diagnoses admitted to the neonatal intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital, South Africa. *South Afr Med J Suid-Afr Tydskr Vir Geneeskde*. 2020 May 29;110(6):497–501. DOI 10.7196/SAMJ.2020.v110i6.14326
15. Withers A, Cronin K, Mabaso M, Brisighelli G, Gabler T, Harrison D, et al. Neonatal surgical outcomes: a prospective observational study at a Tertiary Academic Hospital in Johannesburg, South Africa. *Pediatr Surg Int*. 2021 Aug;37(8):1061–8. DOI: 10.1007/s00383-021-04881-7
16. Couto, Jim. Age Terminology During the Perinatal Period. *American Academy of Pediatrics* [Internet]. 2004;114. Available from: <https://pediatrics.aappublications.org/content/pediatrics/114/5/1362.full.pdf>
17. Hurwitz EE, Simon M, Vinta SR, Zehm CF, Shabot SM, Minhajuddin A, et al. Adding Examples to the ASA-Physical Status Classification Improves Correct Assignment to Patients. *Anesthesiology*. 2017 Apr;126(4):614–22. DOI 10.1097/ALN.0000000000001541
18. Kliegman, Robert. *Nelson Essentials of Pediatrics*. 8th ed. Vol. 1. Elsevier; 2022. #227.
19. Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. (*J Biomed Inform*. 2009 Apr; 42(2):377-81).
20. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013 Nov 27;310(20):2191–4. DOI: 10.1001/jama.2013.281053

21. Makubalo L. South African Good Clinical Guidelines [Internet]. 2006. Available from: <https://www.dst.gov.za/rdtax/index.php/guiding-documents/south-african-good-clinical-practice-guidelines/file>

Annexure 1: Data Collection Sheet

Confidential

Perioperative Neonatal Outcomes
Page 1

Demographics

Patient Number	
Date of Birth	
Sex	☐ Male ☐ Female
Birthweight(g)	
Gestational age (weeks)	
Gestational age at time of surgery (weeks)	
Date of Surgery	
Age at Surgery	
Weight(g)	
Date of Admission	
Preoperative ICU Admission	☐ Yes ☐ No

Confidential

Perioperative Neonatal Outcomes
Page 1**Medical History**

Name

ASA Physical Score

Congenital Abnormality or Syndrome

☐ Yes
☐ No

Type of Congenital Abnormality/ Syndrome

Cardiac Abnormality

☐ Yes
☐ No

Type of Cardiac Abnormality

Respiratory Support prior to Surgery

☐ Yes
☐ No

Type of Respiratory Support prior to Surgery

☐ Nasal prongs
☐ Nasal Continuous Positive Airway Pressure
☐ High Flow Nasal Cannula O2
☐ High Frequency Oscillatory Ventilation
☐ Conventional Ventilation

Cardiovascular Support prior to Surgery

☐ Yes
☐ No

Other Organ Support prior to Surgery

☐ Yes
☐ No

Organ Support

☐ Renal
☐ Liver
☐ Coagulopathy
☐ Other

Type of Other Organ Support

History of previous critical event

☐ Yes
☐ No

Critical event

☐ Airway Critical Event
☐ Oxygenation Critical Event
☐ Cardiovascular Critical Event
☐ Neurological Critical Event
☐ Other

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Confidential

Page 2

Critical event

*Confidential**Perioperative Neonatal Outcomes
Page 1*

Anaesthesia and Surgery

Name

Date of Surgery

Category of Surgery

- ☐ Elective
☐ Emergency

Number of Surgeries

Procedure

Duration(minutes)

Anaesthetic Technique

- ☐ General
☐ Regional
☐ Sedation

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Perioperative Neonatal Outcomes
Page 1**Peri-operative Anaesthesia Critical Events**

Name _____

Peri-operative critical events

- ☐ Airway critical event
☐ Oxygenation critical event
☐ Electrolyte/ glucose critical correction
☐ Cardiovascular critical event
☐ Body temperature correction
☐ Neurological critical event (seizures)
☐ Drug critical event
☐ Other critical event

Airway Critical Event

- ☐ More than 2 attempts at intubation
☐ Drop in saturation < 90%
☐ Bradycardia
☐ Cardiopulmonary resuscitation
☐ Difficult face mask ventilation
☐ Bronchial aspiration

Number of intubation attempts _____

Saturation Drop

- ☐ 85-89%
☐ 80-84%
☐ < 80%

Types of Oxygenation adverse events

- ☐ Need for Fio2 higher than 0,7
☐ Recruitment manoeuvre
☐ Change/ Repositioning of a dislodged/ obstructed tube
☐ Pneumothorax
☐ Laryngospasm
☐ Bronchospasm
☐ Post-operative stridor
☐ Unanticipated post-operative respiratory support

Type of electrolyte intervention

- ☐ Correction of Electrolytes
☐ Correction of Hypoglycaemia
☐ Correction of Hyperglycaemia

Type of CVS intervention

- ☐ Administration of blood products
☐ Administration of vasopressors/ inotropes
☐ Arrhythmia
☐ Cardiopulmonary Resuscitation

CPR Duration(minutes) _____

Type of Body Temperature Intervention

- ☐ Cooling measures
☐ New warming measures

Type of Drug Critical Event

- ☐ Anaphylaxis
☐ Drug Error

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Page 2

Other critical event _____

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Perioperative Neonatal Outcomes
Page 1**Post-operative Critical Events**

Name _____

Post-operative critical events

- ☐ Unplanned Intensive care admissions
☐ Post-operative bleeding, requiring surgical revision
☐ Post-operative infection
☐ Relook surgeries since index surgery
☐ Other critical event

Post-operative Infection

- ☐ Surgical site
☐ Other source

Other source of infection

- ☐ Tracheal Aspirate
☐ Blood culture
☐ Urine
☐ Stool
☐ Line
☐ Other

Other Source _____

Procedure

- ☐ Anastamotic leak
☐ Relook post clip and drop
☐ Adhesive bowel obstruction
☐ Intra-abdominal collection
☐ New-onset NEC grade 3b
☐ Abdominal compartment syndrome
☐ Sheath dehiscence
☐ Colostomy or Ileostomy
☐ Serosal Injury at previous repair
☐ Relook and closure of Gastroschisis
☐ Other

Other _____

Other Critical Event _____

Confidential

Perioperative Neonatal Outcomes
Page 1

Post-operative Outcomes

Name	
Post-operative Outcomes	☐ Survival to discharge ☐ Non-survivor
Non-survivor	☐ Before 30 days last post-operation ☐ After 30 days last post-operation
Suspected cause of death	☐ Nosocomial Sepsis ☐ Respiratory Failure ☐ Pulmonary Haemorrhage ☐ Multi-organ Failure not due to Sepsis ☐ Disease Progression ☐ Palliation ☐ Other
Other suspected cause of death	

Appendix 2: Approval letter from the Department of Anaesthesia



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF ANAESTHESIA
Area 361
Charlotte Maxeke Johannesburg Academic Hospital
University of the Witwatersrand
Tel: 011 488 4344
Fax: 086 765 3477

16 August 2021

Dr Laika Essa
Registrar: Anaesthesia
University of the Witwatersrand

Dear Dr Essa

MMED RESEARCH PROJECT: DR LAIKA ESSA

Your proposed research project entitled: "Peri-operative outcomes in neonatal surgeries at an academic institution" will be beneficial in providing data to improve the perioperative management of neonatal patients at our hospital.

However, preconditions are that the study has no cost implications to the hospital and has to be approved by the relevant ethics authority, university and hospital research committees before data collection can start.

I fully support you in this research endeavor and look forward to the findings.

Yours sincerely,

Prof EE Oosthuizen
Clinical head: Department of Anaesthesia
CMJAH

Appendix 3: Approval letter from Department of Paediatric Surgery



University
of the Witwatersrand
Johannesburg



Department of Paediatric Surgery

Charlotte Maxeke Johannesburg Academic Hospital

Telephone +27 (0)11 488 4146 • Email: mapunda.ellenm@gmail.com or ellen.mapunda@wits.ac.za

05 August 2021

Dear Dr Laika Essa

RE: PERMISSION TO CONDUCT A STUDY / ACCESS PATIENTS' FILES

Permission is granted for you to access patients' files at Charlotte Maxeke Johannesburg Academic Hospital, Department of Paediatric Surgery for your research / study titled
"Peri-operative Outcomes in Neonatal Surgeries at an Academic institution."

Best wishes and warm regards

A handwritten signature in black ink, appearing to be "E.M. Mapunda".

Dr E.M. Mapunda
Head of Clinical Unit
Paediatric Surgery, CMJAH

Appendix 4: Approval letter from Department of Paediatrics



Department of Paediatrics and Child Health
Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

ENQUIRIES : Prof MC Mulaudzi
TEL : 011 488 4246/ 4637
EMAIL : Mphelekedzeni.Mulaudzi@wits.ac.za

Date: 10 August 2021

To: Human Research Ethics Committee (HREC)-WITS

Dear Madam/Sir

Permission to conduct a research study in Paediatrics and Child Health Department at CMJAH

The Department of Paediatrics and Child Health at Charlotte Maxeke Johannesburg Academic hospital give permission the researcher to conduct a study in the department as stated below:

Research Title: "Peri-operative Outcomes in Neonatal Surgeries at an Academic Institution".

Principal Investigator: Laika Essa

Supervisor: Zainub Jooma

Co-Supervisor/s: Theshni Govender / Tanusha Ramdin

This permission is given in support to your application to the WITS-HREC. The researcher/s cannot start collecting data without the clearance certificate from the HREC.

P.P Tanusha Ramdin Ram

Prof. Mphelekedzeni Mulaudzi
Head of Department
Paediatrics and Child Health, CMJAH

10 August 2021

Date

Appendix 5: Approval letter from CEO of CMJAH



GAUTENG PROVINCE

HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: Ms. TT Mahlangu

Email: Thandi.Mahlangu4@gauteng.gov.za

Tel: 011 488 3365

Ref: 1/7/2

Date: 24 October 2021

GP_202108_050

To: Dr Laika Essa

RE: FINAL APPROVAL OF STUDY

RE: PROVISIONAL APPROVAL OF STUDY TITLE: PERI-OPERATIVE OUTCOMES IN NEONATAL SURGERIES AT AN ACADEMIC INSTITUTION

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/Not Supported

Signed by: Jayshina Punwasi
Signed at: 2021-10-25 10:09:06 +02:00
Reason: Witnessing Jayshina Punwasi

Dr J. Punwasi
Clinical Director

Approved/Not Approved

Signed by: Gladys Magugudi Bogoshi
Signed at: 2021-10-25 10:25:58 +02:00
Reason: Witnessing Gladys Magugudi Bo



Ms. G Bogoshi
Chief Executive Officer: CMJAH

Appendix 6: Approval letter from Post Graduate Office



Private Bag 3 Wits, 2050
 Fax: 027117172119
 Tel: 02711 7172076

Reference: Mrs Sandra Benn
 E-mail: sandra.benn@wits.ac.za

18 August 2021
 Person No: 446033
 PAG

Dr L Essa
 404 Chartwell
 32 2nd Avenue
 Killarney
 2193
 South Africa

Dear Dr Laika Essa

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Peri-operative Outcomes in Neonatal Surgeries at an Academic Institution* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

A handwritten signature in black ink, appearing to read 'S. Benn'.

Mrs Sandra Benn
 Faculty Registrar
 Faculty of Health Sciences

Appendix 7: Human Research Ethics Committee Clearance Certificate



R49 Dr L Essa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M210853

NAME:
(Principal Investigator)

Dr L Essa

DEPARTMENT:

School of Clinical Medicine
Department of Anaesthesia
Medical School
University

PROJECT TITLE:

Peri-operative outcomes of neonatal surgeries at an academic institution

DATE CONSIDERED:

2021/08/27

DECISION:

Approved unconditionally

CONDITIONS:

NOTE:

If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR:

Drs Z Jooma, T Govender and T Ramdin

APPROVED BY:


Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL:

2021/10/13

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in August and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).


Signature of Principal Investigator

13/10/2021
Date

Appendix 8: Author's guidelines (British Journal of Anaesthesia)

Aims and Scope

The *British Journal of Anaesthesia (BJA)* publishes high-impact original work in all branches of anaesthesia, critical care medicine, pain medicine and perioperative medicine including fundamental, translational and clinical sciences, clinical practice, technology, education and training. In addition, the *Journal* publishes review articles, important case reports, correspondence and special articles of general interest.

Manuscripts

For guidance, the requested size for articles is:

Clinical investigations: up to 3000 words, 40 references, and 6 tables or figures.

Laboratory investigations: up to 3000 words, 40 references, and 6 tables or figures.

Review articles: up to 5000 words, 150 references and 6 tables or figures.

Editorials: up to 2500 words, 25 references and 2 tables or figures. Include a 3-4 sentence summary. The Editorial should include: a brief introduction to the paper, a brief background to the paper, a succinct overview of the paper, a balanced evaluation of the paper's strengths and weaknesses, a discussion of the importance of the work and its potential or real translational impact, and a discussion of future directions. Consider an illustration explaining the key concepts if it helps support the Editorial.

Special articles: Articles that do not fit one of the other article types (such as guidelines, and articles about history and education) must be approved by the Editorial Office (please contact editorialoffice@bjanaesthesia.org) prior to submission. Special articles have up to 4000 words, 150 references and 4 tables or figures, and include an unstructured Abstract up to 250 words.

Case reports: up to 1500 words, 15 references and 1 table or figure.

Correspondence: up to 1000 words, 10 references and 1 table or figure.

Book Reviews: 600-800 words approximately.

The word count refers to the main body of text, excluding the title page, abstract, references etc. Submissions that do not follow this guidance on word count or numbers of tables and figures may be returned without being reviewed. Authors wishing to submit manuscripts with tables and figures in excess of the recommended number should justify this in the cover letter.

For clinical and laboratory investigations, review articles and case reports it is possible to include supplementary material (such as expanded tables of results or additional figures for investigations or additional references for reviews) for on-line only publication. Authors should specify in their submission letter which files are to be considered for on-line only publication, and clearly refer to the on-line material in the main article text.

The *BJA* will also consider guidelines and position papers for publication. Authors interested in publishing such items should contact the Editor-in-Chief directly to discuss this possibility.

Please note that the *BJA* does not typically publish unsolicited obituaries.

Review Articles

The *BJA* welcomes review articles on clinical and scientific subjects. Authors are advised to contact the Editor-in-Chief before preparing or submitting a review to ascertain the appropriateness of the subject for the *Journal* and to prevent duplication of reviews that have been commissioned or published recently.

Narrative reviews should cover all aspects of a subject and avoid being opinion based. Narrative reviews should follow a logical structure, but the Introduction, Methods, Results, Discussion format is not required. The Abstract should not be structured but should give a clear indication of the objectives and findings of the review.

Systematic reviews should be presented in the "Introduction, Methods, Results, Discussion" format and must include a structured Abstract. These reviews must follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (<http://prisma-statement.org/>). Systematic reviews must be pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO) (<https://www.crd.york.ac.uk/prospero/>), and the registry number must be cited in the Methods and under the Abstract. Additionally, authors must state in the Methods section whether a protocol exists for review and, if so, indicate where this protocol can be accessed. The objective of systematic reviews must be to produce an evidence-based conclusion. Authors should note that if there are few randomised controlled trials available (e.g., only 4 studies with a total of 200 patients), the value of the review will be limited as the level of evidence is inadequate. Meta-analysis of inadequate evidence will have a low priority for publication (e.g. studies with a high-risk of bias, retrospective studies, small number of total subjects).

Forest plots - please include full details in the reference list for all studies mentioned the Forest plot. Any studies not already cited in the main text of the manuscript must be cited in the figure caption.

Case Reports

The *BJA* welcomes case reports that describe new clinical problems or new approaches to established clinical problems. Case reports must be novel, important and impactful, and provide a significant learning point for other anaesthetists. Just because a case is clinically challenging does not mean that it is appropriate to publish it as a case report. The acceptance rate for case reports is considerably lower than for clinical and laboratory investigations. Authors are referred to an editorial on this subject (*British Journal of Anaesthesia* 2008; 100: 744) for further background.

The *BJA* requires permission from the patient or patient's relatives for submission of the case report for potential publication. This must be obtained before submission of the manuscript and must be stated in the cover letter. If photographs of the patient (in any form) are used, a specific signed permission from the patient or patient's relatives must be obtained and a copy of this submitted with the manuscript. [Click here to download a Patient Consent Form.](#)

Failure to comply will result in rejection of the manuscript.

Book Reviews

Book reviews are by request only, which would be sent via the BJA Editorial Office. Once the book is received, the review is required to be completed within six weeks (please inform the Editorial Office should an extension be required). The book review is to be uploaded via Editorial Manager, selecting 'Book Review' as the manuscript type. Book reviews are usually about two sides of A4 (double-spaced), 600-800 words approximately. Please ensure that the book details are added to the main document. These details are included in the letter, which accompanies the book.

Submission Declaration and Verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see [Multiple, redundant or concurrent publication](#) for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted,

it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify originality, the article may be checked by the originality detection service [Crossref Similarity Check](#).

Preprints

Please note that [preprints](#) can be shared anywhere at any time, in line with Elsevier's [sharing policy](#). Sharing of preprints (e.g. on a preprint server) will not count as prior publication (see '[Multiple, redundant or concurrent publication](#)' for more information). The *BJA* requests that submitting authors update their preprint with a footnote to confirm that their paper is under review at *BJA* to inform readers as to the manuscript status. After acceptance in *BJA*, this footnote should be updated to include a link to the final published article.

Authorship

The *BJA* follows the ICMJE criteria for authorship (see [this link](#)). All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted, and 4) all authors must agree 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.

For large, multicentre studies, the group of investigators should identify individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship. If the author list includes a group name, then all members of the group must meet the full criteria for authorship as described above. If all members of a group do not meet all authorship criteria, a group must designate one or more individuals as authors or members of a writing group who meet full authorship criteria. Other group members who are not authors may be listed as collaborators (sometimes called non-author contributors). These will be listed on PubMed as collaborators rather than authors. In order to be indexed as collaborators, the names of the group members should be listed in an **Appendix** in the main text document, before the Reference list. The group should also be included in the main author list. There should be a note associated with the author list clearly stating that the full list of author and collaborator names appears elsewhere in the paper. Collaborator names are searchable on PubMed in the same way as authors. PubMed rules for this can be found [here](#).

For an example of a previously published paper in *BJA* which lists collaborators in the correct format, please see [this article](#).

Changes to authorship

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Please write your text in good English (the house style of *BJA* and *BJA Education* is UK English). Please see [here](#) for a guide to preferred spellings. Authors who think that their English language manuscript requires editing to eliminate spelling or grammatical errors and to conform to correct scientific English may wish to use the [English Language Editing service](#) available from Elsevier's WebShop.

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Preparing Your Manuscript

The standard layout of a manuscript is:

- Title page

- Abstract including Keywords (see further guidance on when to use a Structured Abstract)
- Introduction
- Methods
- Results
- Discussion
- Details of authors' contributions
- Acknowledgements
- Declaration of interests
- Funding
- Appendices (if applicable)
- References
- Tables (including a title and legend, with any essential abbreviations defined)
- Legends to figures

The pages should be numbered in the top right-hand corner, the title page being page one. Each section should start on a separate page. Different types of studies (e.g. randomised controlled trial, matched cohort study) will contain different elements. Guidance on each type of study can be found on the EQUATOR (Enhancing the QUALity and Transparency Of health Research) Network website (<http://www.equator-network.org/>), along with appropriate checklists. There are checklists available for each type of study on the EQUATOR Network. You are strongly encouraged include the appropriate checklist (e.g. STROBE, CHEERS, AGREE) with your submission to the *BJA*. A [CONSORT checklist](#) is required for clinical trials (see below). It is also advisable to include the ethics committee approved protocol with clinical trial submissions.

Title Page

Titles should provide a reasonable indication of the contents of the paper. Avoid enigmatic or vague titles such as 'An unusual cause of hypotension'. Titles in the form of a question, such as 'Is propofol epileptogenic?', or which draw conclusions about the research ('Propofol causes seizures') are discouraged. The Editors reserve the right to edit the title. The title page should include the name(s) and institutional affiliation(s) including city and country of all author(s). No postnominals. Note that it is the house style of the *BJA* for full author names to be spelled out (i.e. please do not use initials for your first name). Do not include street

address and city code for institutional affiliation, just institutions, city and country. It should be made clear which affiliation refers to which author by use of numerical superscripts following each author. Details of the authors' qualifications and post (e.g., consultant, senior lecturer) are not included. An author's present address, if it differs from the address at which the work was carried out, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers (^{1 2 3} etc.). The corresponding author and email should be indicated with an asterisk. A Twitter handle can also be included for the corresponding author.

A short running title containing not more than 50 characters (including spaces) should be included on the title page.

If a preliminary account of the results has been given in a published abstract, it is customary to refer to this on the title page.

Abstract

The Abstract will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background, Methods, Results and Conclusions) for Clinical Investigations, Laboratory Investigations and Systematic Reviews. Abstracts are not required for Editorial, Book Reviews and Correspondence. For Narrative Reviews and Special Articles, the Abstract (label as Summary) should not be structured. The Abstract should give a succinct account of the study or contents in up to 250 words, with rare exceptions granted by the Editor. The Results section should contain primary outcomes with relevant statistics. Effect sizes and confidence intervals should be included in addition to P values or confidence intervals. Exact P values should be included, unless the P value is <0.001. It is important that the results and conclusion given in the Abstract are the same as in the Article, as the Abstract may be used, as it stands, by abstracting journals. References are not included in this section. Avoid use of nonstandard abbreviations in the Abstract.

Keywords

Five to eight keywords should be included on the title page of all manuscripts under the heading Keywords. They should be in alphabetical order, and with UK English spelling. Please consider repeating any important terms from the title of the article in both the keywords and in the Abstract, to ensure maximum discoverability of your article online. Avoid keywords that are only one word or are too general (e.g. "anaesthesia"); keywords that are too short will render the search unspecific, whereas keywords that are too long may filter

articles to such a great extent that your paper could be excluded.

For advice on choosing keywords and improving the discoverability of your manuscript please visit <https://www.elsevier.com/connect/authors-update/top-tips-making-your-article-visible-with-seo>.

Introduction

The recommended structure for this section is;

- Background to the subject
- What is known / unknown about it
- Hypothesis
- Aim of your study

As a rule, the Introduction should be covered in a maximum of 1.5 pages double-spaced. The introduction should give a concise account of the background of the problem and the objectives of the investigation. It should state what is known about the problem to be studied at the time the study was started. Previous work with a direct bearing on the present problem should be quoted. The final paragraph should clearly state the primary and, if applicable, secondary aims of the study.

Methods

The Methods section should give a clear but concise description of how the study was conducted. Subjects covered in this should include:

- Ethics approval / licence (including date and administering institution)
- Registration (including date) (if applicable)
- Patient population
- Inclusion / exclusion criteria
- Conduct of the study
- Measurements and data handling
- Primary and secondary endpoints
- Sample size calculation
- Statistical analyses

Ethics approval/licence

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Regardless of the country of origin, all clinical investigators describing human research must abide by the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and amended by the World Medical Association (<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>). Investigators are encouraged to read and follow the Declaration of Helsinki. Clinical studies that do not meet the Declaration of Helsinki criteria will be denied peer review. If published research is subsequently found to be non-compliant it will be withdrawn or retracted.

On the basis of the Declaration of Helsinki, the *BJA* requires that manuscripts reporting clinical research state in the first paragraph of the Methods section that:

- The study was approved by the appropriate Ethics authority.
- Written informed consent was obtained from all subjects, a legal surrogate, or the parents or legal guardians for minor subjects, or that the requirement for written informed consent was waived by the ethics committee, or that the research was conducted under a national, regional or institutional process that obviated the need for approval.
- In countries where formal ethics committee approval is not mandatory for a non-interventional study, evidence should be provided that the study was submitted to the ethics committee and deemed exempt from review and/or consent from the patient or patient's relatives. The name of the committee and the study reference number should be cited in the Methods.

Human subjects must not be identifiable. Do not disclose patients' names, initials, hospital numbers, dates of birth, or other protected personal or healthcare information. Keep copies of ethics approval and signed consent forms. In unusual circumstances the Editors may request blinded copies of these documents to address questions about ethics approval and study conduct. For more information, please review [Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals](#). Unless you have written permission

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Drugs

When a drug is first mentioned, it should be given by the international non-proprietary name (INN), followed by the chemical formula in parentheses if the structure is not well known, and (if relevant) by the proprietary name (with an initial capital letter) and the manufacturer with location. A figure giving the molecular configuration of the drug is necessary only in the case of the earliest reports of a new drug. Drug dosages are normally given by the name of the drug followed by the dose (e.g. propofol 2.5 mg kg⁻¹). Use the SI system of units. Dose, route, and frequency of administration must be provided. Do not confuse drug dose with concentration.

Multiple Publications of Human or Animal Trials

In the interest of minimising the risk to human and animal subjects, as well as promoting efficient use of scarce research funds, investigators sometimes pose several questions and make multiple measurements in a single study with the intent of publishing multiple manuscripts. Division of data from a single research study into multiple manuscripts is acceptable, provided three requirements are met:

1. The cover letter for every paper derived from the study explains the need for dividing the study into multiple manuscripts. This applies even if only one of the submissions is to the *BJA*. It is essential that the cover letter states that other parts of the study are currently under consideration or in press with another journal. The *Journal* will consider the appropriateness of the division as part of the review process. Any manuscripts related to the same study should be submitted for consideration by the reviewers as a supplementary PDF file through ScholarOne Manuscripts.
2. In all manuscripts after the first, the investigator must disclose that the data have been previously reported, with appropriate citation to the first manuscript. This practice is essential for scientific continuity. For example, should a question arise about the conduct of the study in one manuscript, readers should be able to identify all manuscripts based on the same experimental data.
3. Measurements must not interfere with each other. Such interference may happen in ways that are not evident at the time of the study. For example, measurements of pain

thresholds may make it impossible to measure sedative effects. The potential for interfering measurements may not be evident if the pain thresholds and sedation effects are reported in separate manuscripts that are not appropriately cross-referenced.

Human Subjects

Data on the age (mean with range), weight (kg), sex, height (m), criteria for selection, etc. (patient *characteristics*, **not** *demographics*) should be presented. Authors of clinical investigations should report the 'sex' of participants and use the words 'sex', 'male' and 'female' in their manuscripts, unless the 'gender' of participants is relevant to their hypotheses. The numbers and percentages of both male and female patients (and other sexes/genders as appropriate) should be reported in the text and/or tables. If appropriate, the incidence of primary outcome should be reported in males and females (and other sexes/genders as appropriate), and sex/gender should be considered as covariates in multivariable models, or the reason for exclusion explained. These recommendations are consistent with existing advice for preclinical and clinical research.

The sex/gender, age, weight, height, and eligibility criteria should be presented, with an indication of the general state of health of participants (e.g., ASA physical status) and types of operations being undertaken. More complex information is best presented as a table. When patient or next-of-kin consent was required by the ethics committee, this should be indicated.

Clinical Trials

In accordance with the [Clinical Trial Registration Statement](#) from the International Committee of Medical Journal Editors, all clinical trials in *BJA* must be registered in a public trials registry available in English at or before the onset of participant enrolment. This requirement applies to all clinical trials that begin enrolment after 1 January 2009. Research is considered to be a clinical trial if it involves prospective assignment of human subjects to an intervention or comparison group to study the relationship between a health-related intervention and a health outcome. Further details of which clinical trials are covered by this policy are in the updated ICMJE guidelines (<http://www.icmje.org>). The registry must be accessible to the public at no charge, searchable, open to all prospective registrants, available in English, and managed by a not-for-profit organisation. The registry must include the following information: a unique identifying number, a statement of the intervention(s), study

hypothesis, definition of primary and secondary outcome measurements, eligibility criteria, target number of subjects, funding source, contact information for the principal investigator, and key dates (date of ethics approval, registration date, start date/date of first subject enrolled, and completion date). The following registries are recommended by ICMJE: [Clinical Trials](#), [ISRCTN Register](#), [UMIN Clinical Trials Registry](#), [Australia New Zealand Clinical Trials Registry](#), [Nederlands Trial Register](#).

In accordance with the ICMJE's recommendation, the *BJA* will also accept registration of clinical trials in any of the **primary** registries that participate in the World Health Organization's (WHO) International Clinical Trial Registry Platform (<http://www.who.int/ictrp/en/>). Primary registries are WHO selected registers managed by not-for-profit entities that will accept registrations for any interventional trials, delete duplicate entries from their own registry, and provide data directly to the WHO. Please note that registration in any WHO **partner** registry is insufficient. Authors are requested to provide the exact URL and unique identification number for the trial registration at the time of submission on the title page of their submission. This information will be published in the article.

Clinical trial reports should also comply with the Consolidated Standards of Reporting Trials (CONSORT) and include a standardised flow diagram presenting the enrolment, intervention allocation, follow-up, and data analysis with number of subjects for each (visit [here](#) for more information on CONSORT and [here](#) for the required template diagram). Please also refer specifically to the CONSORT Checklist of items to include when reporting a randomised clinical trial.

Results posted in the same clinical trials registry in which the primary registration resides will not be considered prior publication if they are presented in the form of a brief abstract (500 words or less) or a table.

Statistical analysis plan reporting and HARKing (Hypothesising After Results are Known)

Publication of a time-stamped statistical analysis plan prior to data analysis is strongly recommended for both interventional and observational studies. In the absence of a publicly available statistical plan, we strongly encourage authors to report that their statistical analysis plan was approved by the authors before analyses began or acknowledge that their

submission is based on testing a hypothesis after the main study results were known (for example: "Based on striking patterns in the dataset, we conducted the following post hoc analysis...The results of this analysis should be regarded as hypothesis-generating.").

Reporting checklists **must** be provided as supplementary data. An appropriate flow diagram should be included in the manuscript, as recommended by the following guidelines:

Randomised controlled trials (RCTs): [CONSORT checklist](#), [flow diagram](#), and CONSORT Checklist for Reporting of Harms in RCTs should be provided. [Customized CONSORT checklists](#) are available for trials with parallel group design, cluster-randomised trials, noninferiority and equivalence randomised trials, pragmatic trials and trials of nonpharmacological treatment.

Non-randomised studies: guidelines described in [Transparent Reporting of Evaluations with Nonrandomized Designs \(TREND\)](#) should be provided.

Observational studies: STROBE statement reporting checklists **must** be provided. Please check the **STROBE statement website** for up-to-date information concerning specific study types, including observational studies in epidemiology, genetic association studies, cohort studies, case-control studies, and cross-sectional studies.

Diagnostic accuracy studies: for studies where the performance of two or more diagnostic tests are compared, submissions **must** include the STARD checklist and [STARD Flowchart of Diagnostic Test Results](#).

Translational human studies: We are particularly keen to receive manuscripts that undertake innovative clinical and translational research in humans. In addition to adhering to, and providing, STROBE (or other appropriate) checklists, we refer authors to two articles (PMID:22029804, 21677197) that provide helpful guidance on justification of sample size calculations in this type of submission.

Research Using Animals

Institutional approval

All animal studies **must** have been conducted within the guidelines of the appropriate national body as well as be approved by institutional review board(s), and accompanied by a specific declaration of such approval and number in the Methods. Authors **must** submit a

supplementary file detailing compliance with [ARRIVE \(Animal Research: Reporting of In Vivo Experiments\) guidelines](#) for reporting on animal studies. For animal models, the genotype, strain, source, number of backcrosses, sex, and age of animals studied **must** be provided in the manuscript.

Studies that involve the use of animals must clearly indicate that Institutional approval was obtained and state the UK Home Office Licence number or equivalent code that the studies were performed under. European studies with animals should follow the EU directive 2010/63 and provide a national and/or institutional approval number. It is recognised that animal welfare legislation can vary between countries. The *BJA* uses the UK standards as a baseline and reserves the right to reject manuscripts judged not to meet these standards, even when local approval has been granted.

ARRIVE guidelines

The contribution of animal research in enabling better health for humans and animals is incontrovertible and the *BJA* is committed to the publication of research studies that use animal models. This demands the same rigorous attention to detail as in clinical trials. Failure to describe research methods and to report results appropriately has scientific and ethical implications for the entire research process and the reputation of those involved. Experiments involving animals should be appropriately designed, correctly analysed and transparently reported to increase validity of the results and maximise the scientific gain including use of blinding, randomisation, etc. A minimum amount of relevant information must be included to ensure that the methods and results of a study can be reviewed, analysed and repeated. It is strongly encouraged that animal studies are accompanied by the [ARRIVE guidelines](#).

Anaesthesia

The methods of anaesthesia and analgesia for research studies involving animals should be the best available to ensure the welfare of the animals involved. Submissions that ignore this guidance may be returned without being assessed. Reducing the potential for pain and distress is a significant refinement and provision of safe and effective anaesthesia that does not interfere with specific research objectives also reduces the numbers of animals used. Authors must also state how they assessed and monitored the adequacy of anaesthesia. Some anaesthetics have interactions that are important to certain areas of research. Whichever agents are used, an appropriate plane of anaesthesia for the intervention must be assessed and achieved. This is particularly important when neuromuscular blocking agents are used.

Information on potentially suitable anaesthetic regimens can be obtained from a variety of sources, including the veterinary advisor at your research institution, specialist laboratory animal anaesthesia and general veterinary anaesthesia textbooks.

Analgesia

Every effort should be made to minimise pain or distress in research studies that are conducted using animals. Not only is this important for ethical reasons, but also because pain is a source of stress that can cause undesirable effects on the outcome of research projects. Provision of effective pain relief can only be done by assessing the degree of pain experienced by the animal involved. Animal pain assessment is difficult and time-consuming to implement effectively, so that it is tempting to simply give all animals a "standard dose" of analgesic. Often, all that is possible is to use doses that have been established to be safe and effective in some of the tests used in rodents during early drug development. Provided these limitations are appreciated, some strategies for pain management that make best use of our existing knowledge include:

- If methods of pain assessment have been developed for the species used, these should be adapted to the requirements of the particular research procedure
- If methods of pain assessment are not available, consider devoting resources to developing some form of scoring system
- If pain scoring is not possible, determine the analgesic protocol based on experience with other surgical procedures in that species
- If possible, use doses that have been established using studies that have employed pain scoring systems
- Attempt to evaluate the efficacy of the analgesic regimen selected using clinical assessment (your veterinary advisor will be able to help you to recognise pain in laboratory animals)
- Prepare a rescue analgesia protocol and an immediate euthanasia protocol for animals which appear to be in severe pain

Use of animal models of pain to investigate analgesia techniques is a particular challenge for journals in the field of anaesthesia. Such studies must be conducted with extremely careful regard to animal welfare. Rarely will this journal publish studies where an analgesic agent has been compared to a placebo in an animal model of severe pain. The book '*Laboratory animal anaesthesia*' by P. Flecknell (4th Edition, 2015, Academic Press) provides a helpful

introduction for safe, effective and appropriate anaesthesia and analgesia in animals used in research studies.

Euthanasia

Animals used for research are usually euthanised at the end of a study for the purpose of sample collection or post-mortem examination. Animals may also be killed because they are experiencing severe pain or distress. The method of killing the animal after the experiment is completed should be chosen carefully and must be detailed in the Methods. The method used should be appropriate to the species and should not confound any objective of the research - veterinary advice should be sought. The conduct of euthanasia for those working with laboratory animals in the UK is quite straightforward. Either the Code of Practice for the Humane Killing of Animals under Schedule 1 to the Animals (Scientific Procedures) Act 1986 is followed or a project and personal licence authorisation is obtained to use a technique not covered by this Code. An updated code of practice for schedule 1 killing has been published by the Animal Procedures Committee and is available online at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/662364/Guidance_on_the_Operation_of_ASPA.pdf. The use of carbon dioxide for killing is a subject of much debate and is not suitable for rabbits. For rodents, use of carbon dioxide is permitted but other methods are preferable.

Laboratory Studies

Cell lines

Authors must describe the source of all cell lines utilized, including information on testing for mycoplasma contamination.

Antibodies

Detailed description of all antibodies used for flow cytometry, immunoblotting, immunoprecipitation and immunohistochemistry must be included in tabular form in Supplementary Methods, providing the source and catalogue/clone number for commercial antibodies or a description/reference to a description of the generation of custom antibodies. Evidence for antibodies having been validated either by the authors, previous publications or manufacturers should also be provided in the table.

Flow cytometry

Authors should adhere to the Minimum Information about a Flow Cytometry Experiment (MIFlow Cyt; PMID 18752282), which establishes criteria for recording and reporting information about the flow cytometry experiment overview, samples, instrumentation and data analysis. Gating strategy should be demonstrated in supplementary data, together with raw data provided as an example for each experiment. For figures in the main manuscript, key flow cytometry data are sufficient (e.g. histograms, density plots).

ELISA

Details on intra- and inter-assay variability, lower limits of detection and linearity-of-dilution assessment for ELISAs should be provided in Supplementary Methods and referred to in Methods.

Large datasets

Large datasets for gene expression microarrays, SNP arrays, and high-throughput sequencing studies must be deposited in a public repository. Microarray data must be deposited in a MIAME-compliant public database. High-throughput sequencing data must be deposited in a MINSEQE-compliant public database. Provide the relevant accession numbers in the text of the main manuscript. Deposition of other types of large datasets in a public repository is strongly encouraged. Datasets should be made available to any interested reader on the publication date from the authors directly. Researchers who encounter a persistent refusal by an author of a paper to comply with these guidelines should contact the Editor-in-Chief.

Software

Commercially available software should be referenced, detailing software version number, company and location) Additionally, custom-written software should report the source code in the Supplemental Methods or detail how the software can be obtained.

Statistical Analysis

Many scientific manuscripts have flaws in design and statistical analysis. Statisticians should be involved in the design, analysis and reporting of most studies. Investigators should commit in writing to the statistical analysis plan prior to conducting a study. Certainly, this should be done prior to conducting analyses. Pre-publication of research protocols helps to promote rigour and allows other scientists to attempt replication or refutation. It is helpful to submit a date-stamped, ethics committee-approved protocol, containing the statistical analysis plan,

together with your submission. Specialist statistical expertise will be sought at editorial discretion, including, where applicable, to re-analyse original data. Authors must describe all statistical tests used in the Methods. Complete details of the statistical analyses should be reported in full in the Results section. Examples for reporting main statistical analyses are:

"...odds ratio, 1.22; 95% confidence interval, 1.06-1.39; $P=0.005$."

[Note: abbreviations for odds ratio (OR) and 95% confidence interval (95% CI) are acceptable provided they are defined in text/abstract].

"...lidocaine-group: 48 (23) mg (mean (SD)) vs placebo-group: 51(19) mg, $P=0.22$."

"...hazard ratio (HR) 0.65, 95% CI 0.49-0.84, $P=0.001$."

The distribution of data must meet the assumptions of the statistical test used. Authors must specify whether statistical tests are one-sided or two-sided. When making multiple comparisons on a single data set, authors should choose statistical tests that account for multiple groups (one-way, two-way or repeated measures ANOVA). The statistical analysis should also correct for repeated measures when comparing multiple measurements between groups.

Statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the report and results. Findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals and effect sizes provide more useful information for interpretation than a P value alone conveys. P values should be exact and provided to three decimal places (e.g. $P=0.123$) unless they are <0.001 . P values between 0.05 and 0.005 can generally be interpreted as providing suggestive evidence, whereas P values <0.005 generally provide more compelling evidence.

A sample size calculation should be performed before starting the study to determine the number of subjects needed in each group to detect a given change. Please note that a sample size calculation based on the primary endpoint will not necessarily be applicable to secondary measures. It is important to choose sample sizes for studies based on biologically or clinically important and realistic effect sizes. One of the most important weaknesses of scientific studies is that they do not include enough patients (or non-human animals). On the other hand, studies that are very large might yield statistically significant but clinically unimportant findings. There should be a separate section for Statistics in the Methods; all statistical tests used should be described in this section. It is helpful to provide brief rationale for these choices.

Results

Results should be presented in a logical order related to the aims and design of the study with appropriate statistical reporting and any pertinent negative findings. Description of experimental results should be concise. It is often useful to present the results in the order described in the Methods section. Data should not be repeated unnecessarily in text, tables and figures (see below). Unwarranted numbers of digits (false precision) should be avoided (Example: *the mean dose of propofol was 2.1 mg kg⁻¹ rather than 2.0897 mg kg⁻¹*). Precision of most biological measurements does not allow significant digits over two; use of more than this can imply false precision. It may not be necessary to provide all data from a complex study: only those values essential to the communication should be given. However, results should be presented in a manner so that the reader can check the statistical inferences. If the data are so numerous that this is not possible, Supplemental Data can be submitted as a separate file for on-line publication only. For example, in a pharmacokinetic study, more extensive sets of data can be included as an Appendix with the on-line version of the article. If authors wish to make use of this facility, they should state this in the submission letter and upload the data as a separate file. The Editor has the right to request the original data collected. The Results section should not include discussion of the findings, which should be included in the Discussion. Similarly, the Discussion should not restate the Results. SI units must be used. Means must be accompanied by SD in brackets; medians must be accompanied by 25-75th percentiles in brackets. Odds ratios (OR) must be accompanied by 95% confidence intervals (CI) in brackets. Negative index notation (e.g. mg kg⁻¹) **must** be used rather than solidus notation (e.g. mg/kg). Numbers in text and tables should always be provided if % is shown.

Tables and Figures

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