

African Surgical Outcomes Study in Paediatric patients (ASOS-Paeds)

An African, international multi-centre fourteen-day evaluation of patient care and clinical outcomes for paediatric patients undergoing surgery

Protocol version 1.0

12 July 2021

A handwritten signature in black ink, appearing to be 'AT', enclosed within a large, loopy oval shape.

Alexandra Torborg

Chief Investigator

Chief Investigator contact details

Dr Alexandra Torborg

Perioperative Research Group,

Discipline of Anaesthesiology and Critical Care

Nelson R. Mandela School of Medicine

Private Bag 7, Congella, 4013

KwaZulu-Natal, South Africa

E-mail: alexandra@iafrica.com

Telephone: +27 (0)833850217

Steering committee

1. Alexandra Torborg MBChB FCA(SA), Discipline of Anaesthesiology and Critical Care Medicine, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa
2. Bruce Biccard MBChB FCA(SA) FFARC(I) MMedSci PhD, Professor and Second Chair, Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital and University of Cape Town, South Africa
3. Rupert Pearse MD(Res), Professor of Intensive Care Medicine, Queen Mary University of London, Royal London Hospital, London, E1 1BB, United Kingdom
4. Priyanka Naidu MBChB, Department of Research, Education, and Innovation, Operation Smile, Virginia Beach, Virginia, USA, Centre for Global Surgery, Department of Global Health, Stellenbosch University, Tygerberg, South Africa.
5. Hyla Kluyts DMed (Anaest), Department of Anaesthesiology, Sefako Makgatho Health Sciences University, South Africa
6. Mary T. Nabukenya MMED, FCA(ECSA), Lecturer, Makerere University College of Health Sciences, Paediatric anaesthesiologist, Mulago National Referral Hospital, Kampala, Uganda
7. Adesoji O Ademuyiwa, FACS, Professor of Surgery (Paediatric and Surgical Epidemiology), Department of Surgery, College of Medicine, University of Lagos and Lagos University Teaching Hospital, Lagos, Nigeria

Patient advocate

TBC

Funders

None as yet

Table of Contents

1. List of abbreviations	5
2. Summary	6
3. Introduction	7
4. Study objectives	8
4.1 Primary objective.....	8
4.2 Secondary objectives.....	8
5. Methods	8
5.1 Study design.....	8
5.2 Inclusion criteria	8
5.3 Exclusion criteria	9
5.4 Hospitals	9
5.5 Research Ethics and Informed Consent	9
5.6 Recruitment and screening	10
5.7 Data collection and collation.....	10
5.8 Dataset	11
5.9 Case record forms	12
5.10 Sample size calculation	12
5.11 Statistical analysis.....	12
5.12 Primary outcome measures	13
5.13 Secondary outcome measures	13
6. Study organisation and management	13
6.1 Study steering committee.....	13
6.2 Patient advocate	14
6.3 Country co-ordinators.....	14
6.4 Local co-ordinators	14
6.5 Training of investigators.....	15
7. Data management and ownership	15
8. Publication plan	15
9. References	16
10. Appendices	17

1. List of abbreviations

APRICOT	Anaesthesia PRactice in Children Observational Trial
ASOS	African Surgical Outcomes Study
ASOS-2	African Surgical OutcomeS-2 (ASOS-2) trial
EuSOS	European Surgical Outcomes Study
SAPSOS	South African Paediatric Surgical Outcomes Study

2. Summary

Short title	ASOS-Paeds
Methodology	A prospective international, multi-centre, African observational study
Research sites	Hospitals undertaking paediatric surgery in participating African countries.
Objective	To confirm the incidence of in-hospital postoperative complications in paediatric surgical patients aged < 18 years in Africa.
Number of patients	7000 patients
Inclusion criteria	All consecutive paediatric patients aged < 18 years admitted to participating hospitals undergoing elective and non-elective surgery
Exclusion criteria	Obstetric surgery
Statistical analysis	The primary outcome measure is in-hospital postoperative complications censored at 30 days postoperatively
Proposed start date	September 2021
Proposed end date	September 2022
Trial duration	Until hospital discharge, censored at 30 days

3. Introduction

Surgery is a cost-effective public health intervention. There are significant disparities in access to and the safety of surgical and anaesthesia services in low and middle-income countries (LMICs) compared to high-income countries (HICs).¹ There is a large burden of surgical disease in the paediatric surgical population with a large unmet need.^{2,3} In Africa, children comprise a significant proportion of the population with approximately 50% of the population being ≤ 19 years old.⁴

Postoperative complications are an important determinant of surgical morbidity and mortality. Limited data from Africa suggests the risk factors for, incidence and outcomes associated with paediatric surgical complications differ from HICs. In the prospective, observational South African Paediatric Surgical Outcomes Study (SAPSOS), the patients in this middle-income country (MIC),⁵ had double the incidence of complications⁶⁻⁸, and the types of complications differed from HICs, with a predominance of infective complications. Furthermore, the risk factors for complications (ASA physical status, urgency of surgery, severity of surgery and infective indication for surgery) were different from HICs, where risk factors include gestational age, ASA physical status >3 , a history of cardiovascular disease, and cardiovascular, neurological, or orthopaedic surgical procedures.⁹ Postoperative mortality was ten times higher in South Africa than in a prospective study in HICs.¹⁰ A prospective study of paediatric perioperative mortality in 24 Kenyan hospitals showed a 7 day postoperative mortality of 1.7%.¹¹, which is 17 times higher than that reported in HICs.

The African Surgical Outcomes Study (ASOS) has described surgical outcomes in adult patients in Africa.¹² Patients had a lower risk profile and fewer complications compared to those in HICs. However, the postoperative mortality was twice that of the global average.

There is a need to determine the burden of the complications in paediatric surgical patients in Africa, and the risk factors for and the type of complications experienced. If we do this, we will be able to target appropriate interventions to improve surgical outcomes for children in Africa. We have the capacity to do this important work, through the African Perioperative Research Group (APORG) group.

4. Study objectives

4.1 Primary objective

To determine the incidence of in-hospital postoperative complications up to 30 days post-surgery in paediatric surgical patients <18 years in Africa

4.2 Secondary objectives

In paediatric surgical patients < 18 years in Africa:

1. To determine the in-hospital postoperative mortality rate up to 30 days post-surgery,
2. To determine the incidence of intraoperative severe critical incidents,
3. To determine the association between pre-operative, intra-operative and facility factors with postoperative complications and death.

5. Methods

5.1 Study design

Fourteen-day, international African multi-centre prospective cohort study of paediatric patients (<18 years) undergoing surgery. This study will be registered on ClinicalTrials.gov.

5.2 Inclusion criteria

All consecutive patients < 18 years, admitted to participating hospitals during the study period who undergo elective and non-elective surgery. This will include day case surgery, operative procedures outside operating theatres where a general anaesthetic (GA) is performed. Recruitment will run for fourteen days, commencing on the date chosen by each participating hospital within the study cohort period of 01.09.2021 until 30.09.2022. Recruitment will start at 07h00 on day one and finish at 06h59 on the fourteenth day.

5.3 Exclusion criteria

1. Patients undergoing radiological or other procedures not requiring general anaesthesia, or where general anaesthesia is performed but no procedure is performed e.g. general anaesthesia during magnetic resonance imaging (MRI).
2. Patients having obstetric surgery.
3. Prior participation in the ASOS-Paeds.

5.4 Hospitals

We aim to recruit as many African hospitals as possible. Each hospital will receive an individual report allowing comparison of their dataset to that of the overall national cohort.

5.5 Research Ethics and Informed Consent

Research ethics and regulatory approvals will be sought before starting the study at each site, in accordance with national research legislation/guidelines for that country.

The national leaders will ensure the necessary ethics and regulatory approvals are obtained for the participating hospitals in their country. Hospitals will not be permitted to record data unless ethics approval or an equivalent waiver is in place.

This study is in effect a large-scale clinical audit and thus does not pose a significant risk to the study population. We expect that in most, if not every country, there will be no requirement for individual patient consent as all data will be anonymised and is already recorded as part of routine clinical care.

A precedent has already been set internationally. In the original EuSOS study, consent was waived in 27 of the 28 European countries participating¹³, in the ASOS study¹² and in the ASOS-2 trial consent was waived in the majority of hospitals. In previous African paediatric perioperative studies, written consent

was waived by six out of the eight ethics committees in the SAPSOS study⁵ and in a study in Kenya, written informed consent was waived in all 24 participating hospitals.¹¹

'Broadcasting' signage documents will be used at participating sites to ensure that all patients and parents/guardians are aware that the hospital is participating in the study. These broadcasting documents will be placed in key areas around participating hospitals explaining the study dates and the nature of the study. (Appendix 1)

5.6 Recruitment and screening

We expect all consecutive paediatric patients aged <18 years undergoing elective and non-elective surgery to be included in the study.

Broadcasting through appropriate hospital notices and signage will inform the patients, their parents/guardians and the public that the hospital is participating in the study.

Each hospital will be required to record and submit a screening log of all eligible patients.

5.7 Data collection and collation

Each individual hospital will collect and record data on either an electronic or paper case record form (CRF) for every patient recruited. Paper CRFs will be stored within a locked office in each hospital as they will include identifiable patient data in order to allow follow-up of clinical outcomes. Data will then be pseudo-anonymised by generation of a unique numeric code and transcribed by local investigators onto a secure, password protected internet based electronic CRF in the REDCap platform. Each patient will only be identified on the electronic CRF by their numeric code; thus, the co-ordinating study team cannot trace data back to an individual patient without contact with the local team. A participant (patient) list will be used in each hospital to match identifier codes in the database to individual patients in order to record clinical

outcomes and supply any missing data points. Access to the data entry system will be protected by username and password delivered during the registration process for individual local investigators. All electronic data transfer between participating hospitals and the co-ordinating centre will be encrypted using a secure protocol (HTTPS/SSL 3.0 or better).

Where individual hospitals are unable to access the internet-based case record form, pseudo-anonymised coded data may also be sent by facsimile (fax), by registered mail, e-mail or WhatsApp messaging to the coordinating centre if necessary.

Each hospital will maintain a secure study file including a protocol, local investigator delegation log, ethics approval documentation, the participant list, and other additional documentation such as study definitions.

A final summary printout of included patients with major variables should be produced for each hospital together with final data submission to double check for completeness and accuracy.

5.8 Dataset

A realistic data set will be fundamental to the success of the investigation, and this was confirmed in the EuSOS¹³, SASOS¹⁴ and SAPSOS⁵ studies where nearly complete data was available on patients. Based on the SAPSOS study of paediatric outcomes in 43 South African hospitals, we have adopted this dataset with minor changes to remove data which was found to be redundant, in order to develop a simple, lean and pragmatic data set. We believe that this simple data set will encourage hospitals to participate.

Hospital-specific data for each hospital will be collected once (Appendix 2) including: hospital level of care (first, second, third), number of operating rooms, number of specialists, number and level of critical care beds, equipment appropriate to paediatric surgery and anaesthesia, availability of medication and blood, details about the reimbursement status of the hospital and public holidays or other local factors affecting patient throughput during the study period.

5.9 Case record forms

An ASOS-Paeds CRF will be completed for every eligible patient who undergoes surgery during the cohort period (Appendix 3). Patients will be followed up until hospital discharge. This will be censored at thirty days i.e. patients will be followed up until discharge or for thirty days postoperatively if still in hospital, whichever is the shorter time period. The outcomes definition document is shown in Appendix 4.

5.10 Sample size calculation

Our plan is to recruit as many hospitals as possible from each participating country and ask them to include all eligible patients in the study. We do not have a specific sample size and statistical models will be adapted to the event rate provided by the sample recruited, in order to prevent overfitting of any logistic regression models.

5.11 Statistical analysis

The data to be collected are all collected as part of routine clinical care. Categorical variables will be described as proportions and will be compared using chi-square tests. Continuous variables will be described as mean and standard deviation if normally distributed or median and interquartile range if not normally distributed. Comparisons of continuous variables between groups will be performed using t-tests, one-way ANOVA or equivalent non-parametric tests as appropriate. Univariate analysis will be performed to test factors associated with postoperative complications, critical care admission and in-hospital death.

Single-level and hierarchical multi-level logistic regression models will be constructed to identify factors independently associated with these outcomes and to adjust for differences in confounding factors. Factors will be entered into the models based on their univariate relation to outcome ($p < 0.05$), biological plausibility and low rate of missing data.

Results of logistic regression will be reported as adjusted odds ratios (OR) with 95% confidence intervals. The models will be assessed through the use

of sensitivity analyses to explore possible interacting factors and examine any effect on the results. A statistical analysis plan will be written prior to analysis.

5.12 Primary outcome measures

Incidence of in-hospital postoperative complications in paediatric surgical patients in Africa.

5.13 Secondary outcome measures

- 1 a. The day of surgery mortality rate for patients < 18 years undergoing surgery in Africa.
 - b. The in-hospital mortality rate for patients < 18 years undergoing surgery in Africa censored at 30 days.
- 2 Risk factors associated with in-hospital complications
- 3 Time from first presentation to operation
- 4 Incidence of severe intraoperative critical incidents
- 5 Level of qualification of anesthesia and surgery providers and number of specialists per paediatric population.
- 6 Rate of admission to critical care.

6. Study organisation and management

6.1 Study steering committee

The Steering Committee will be chaired by AT. The study management team will be appointed by the Steering Committee and led by AT. The duties of this team will include administration of all project tasks, communication between project partners (including funders, Steering Committee members, national and local coordinators, etc.), data collation and management and preparation of reports for individual study sites. The Steering Committee is responsible for the scientific conduct and consistency of the project. The Steering Committee will ensure communication between the funder(s), study management team and co-ordinators as necessary.

6.2 Patient advocate

Patient advocate(s) will be appointed who will advise the Steering Committee on possible protocol amendments if required, based on patient concerns regarding delivery of the study or communication of the study.

6.3 Country co-ordinators

Country co-ordinators will be appointed by the steering committee to lead the project within individual countries and:

- Identify local co-ordinators in participating hospitals
- Assist with translation of study paperwork as required
- Ensure distribution of research manuals, and other research materials
- Ensure necessary regulatory and ethics approvals are in place prior to recruitment
- Ensure good communication with the participating sites in her/his country

6.4 Local co-ordinators

Local co-ordinators in individual institutions will have the following responsibilities:

- Provide leadership for the study in their institution
- Ensure all relevant regulatory and ethics approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and site recruitment and follow up management
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of electronic CRFs

- Communicate with the relevant national co-ordinator

6.5 Training of investigators

Training will be done using instructional videos placed on the study website. Each study site will be required to complete an online questionnaire as part of the site initiation, prior to starting data collection.

7. Data management and ownership

On behalf of the Steering Committee, the Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital and University of Cape Town will act as custodian of the data. The Steering committee will retain the right to use all pooled data for scientific and other purposes. Members of the ASOS-Paeds study group will have the right to access the pooled data for research purposes provided the research proposal has been reviewed and deemed appropriate by the Steering Committee. The primary consideration for such decisions will be the quality and validity of any proposed analysis. Only summary data will be presented publicly, and all institutions will be anonymised except in the individualised report provided to each institution at the end of the study. Individual patient data provided by participating sites remain the property of the respective institutions.

8. Publication plan

Data will be presented and disseminated in a timely manner. The Steering Committee will appoint a writing committee to draft the scientific report(s) of this investigation. The group will be known as 'The ASOS-Paeds Investigators'. It is anticipated that a number of secondary analyses will be performed. ASOS-Paeds investigators will be given priority to lead such analyses and are encouraged to do so. Participation and authorship opportunities will be based on contribution to the primary study. On request, hospitals will be provided with an individual report allowing comparison of their

individual hospital's summary data to that of their national cohort. In line with the principles of data preservation and sharing, the Steering Committee will, after publication of the overall dataset, consider all reasonable requests to make the dataset available in whole or part for secondary analyses and scientific publication. The Steering Committee will consider the scientific validity and the possible effect on the anonymity of participating hospitals prior to granting any such requests. Where appropriate, a prior written agreement will set out the terms of such collaborations. The Steering Committee will consider proposals for secondary analyses on the basis of the scientific quality of the proposal. The Steering Committee must approve the final version of all manuscripts prior to submission, whether they relate to part or all of the ASOS-Paeds dataset.

9. References

1. Bainbridge D, Martin J, Arango M, et al. Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. *Lancet* 2012;380(9847):1075-81. doi: 10.1016/s0140-6736(12)60990-8 [published Online First: 2012/09/25]
2. Bickler SW, Rode H. Surgical services for children in developing countries. *Bull World Health Organ* 2002;80(10):829-35. [published Online First: 2002/12/10]
3. Butler EK, Tran TM, Nagarajan N, et al. Epidemiology of pediatric surgical needs in low-income countries. *PLoS One* 2017;12(3):e0170968. doi: 10.1371/journal.pone.0170968 [published Online First: 2017/03/04]
4. 2014 World Population Data Sheet, 2014.
5. Torborg A, Cronje L, Thomas J, et al. South African Paediatric Surgical Outcomes Study: a 14-day prospective, observational cohort study of paediatric surgical patients. *Br J Anaesth* 2019;122(2):224-32. doi: 10.1016/j.bja.2018.11.015 [published Online First: 2019/01/29]
6. GlobalSurg C. Determinants of morbidity and mortality following emergency abdominal surgery in children in low-income and middle-income countries. *BMJ Glob Health* 2016;1(4):e000091. doi: 10.1136/bmjgh-2016-000091 [published Online First: 2017/06/08]
7. Weinberg AC, Huang L, Jiang H, et al. Perioperative risk factors for major complications in pediatric surgery: a study in surgical risk assessment for children. *J Am Coll Surg* 2011;212(5):768-78. doi: 10.1016/j.jamcollsurg.2011.02.006 [published Online First: 2011/03/26]
8. Saito JM, Chen LE, Hall BL, et al. Risk-adjusted hospital outcomes for children's surgery. *Pediatrics* 2013;132(3):e677-88. doi: 10.1542/peds.2013-0867 [published Online First: 2013/08/07]
9. Wood G, Barayan G, Sanchez DC, et al. Validation of the pediatric surgical risk assessment scoring system. *J Pediatr Surg* 2013;48(10):2017-21. doi: 10.1016/j.jpedsurg.2013.04.017 [published Online First: 2013/10/08]

10. Habre W, Disma N, Virag K, 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;5(5):412-25. doi: 10.1016/S2213-2600(17)30116-9 [published Online First: 2017/04/02]
11. Newton MW, Hurt SE, McEvoy MD, et al. Pediatric Perioperative Mortality in Kenya: A Prospective Cohort Study from 24 Hospitals. *Anesthesiology* 2019 doi: 10.1097/ALN.0000000000003070 [published Online First: 2019/12/07]
12. Biccard BM, Madiba TE, Kluyts HL, et al. Perioperative patient outcomes in the African Surgical Outcomes Study: a 7-day prospective observational cohort study. *Lancet* 2018;391(10130):1589-98. doi: 10.1016/S0140-6736(18)30001-1 [published Online First: 2018/01/08]
13. Pearse RM, Rhodes A, Moreno R, et al. EuSOS: European surgical outcomes study. *Eur J Anaesthesiol* 2011;28(6):454-6. doi: 10.1097/EJA.0b013e328344907b [published Online First: 2011/05/06]
14. Biccard BM, Madiba TE. The South African Surgical Outcomes Study: A 7-day prospective observational cohort study. *South African Medical Journal* 2015;105(6):465-75. doi: 10.7196/SAMJ.9435

10. Appendices

Appendix 1 – Broadcasting document

Appendix 2 – Hospital Information and site initiation record form

Appendix 3 – Case record form (CRF)

Appendix 4 – Outcomes definitions document