

African Surgical Outcomes Study (ASOS)

**An African, multi-centre seven day evaluation of patient care and clinical
outcomes for patients undergoing surgery**

Study protocol version 1

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Introduction

The non-cardiac surgical population represents a major global public health burden with approximately 234 million major surgical procedures performed worldwide each year.¹ In unselected non-cardiac surgical patients, reports of early postoperative mortality vary between 2 and 4%,^{2,3} with an annual global mortality of 5 to 10 million. Surgery is a cost-effective intervention,⁴ even in low to middle income countries⁵ and as such it is considered a core component of health.⁶ The Lancet Commission on Global Surgery has been established to define safe surgery and develop strategies to ensure the adequate provision of safe surgery.^{6,7} Based on the global health burden of surgery, a call has recently been made to include perioperative mortality rate (POMR) as a global health metric.⁸ Two global health metrics have been proposed; death on the day of surgery, and death on hospital discharge or at 30 days.⁸ However although benchmarking between countries is important, what is really required to improve public health is an understanding of the determinants of surgical outcomes, so that risk factors for adverse outcomes can adequately addressed. Unfortunately, currently there is little data describing the determinants of surgical outcomes in lower and middle income countries and particularly in Africa. As such there remains little data on which factors need to be addressed to make surgery safer in this environment.

In contrast, surgical outcomes have been well described in Europe. The European Surgical Outcomes Study (EuSOS) is the largest prospective observational study to report outcomes following non-cardiac surgery in over 46000 patients who were 16 years or older across 28 European countries³ providing essential data for the Commission on Global Surgery.³ EuSOS showed that surgical outcomes vary tremendously between countries, with up to a 17 fold difference in in-hospital mortality between European countries.³ The fact that survival amongst patients who develop postoperative complications varies widely between hospitals, confirms both the potential and the need to improve clinical outcomes in the surgical population,⁹ and this may have important positive public health implications.

However, it is inappropriate to extrapolate data (such as EuSOS) to Africa. Firstly, consistent with other global health metrics, countries with a lower Human Development Index (HDI) (such as African countries) have a significantly higher postoperative mortality than countries with a high HDI.¹⁰ Secondly, the population morbidity and mortality patterns in Africa are different from Europe. The Global Burden of Disease Study¹¹ would suggest that in sub-Saharan Africa a larger patients with communicable diseases and injuries, and conversely a smaller proportion of patients with non-communicable diseases present for surgery when compared with Europe.¹² This has important implications for differences in surgical outcomes between Europe and Africa.

For example, approximately two-thirds of South African mortality is attributable to communicable diseases (driven predominantly by the HIV pandemic, 794 deaths per 100 000), a further quarter due to non-communicable disease (424 per 100 000) and the remaining mortality attributable to injuries (107 per 100 000).¹³ However, in the recently completed South Africa Surgical Outcomes Study (SASOS)¹⁴ two important principles are illustrated. Firstly, surgical mortality does not mirror the proportional national mortality as reported by the Global Burden of Disease Study.¹¹ Although HIV was the most common comorbidity in the South African Surgical Outcomes Study (and the leading cause of life years lost in sub-Saharan Africa),¹¹ it was not associated with in-hospital mortality following surgery. In SASOS, non-communicable diseases (metastatic cancers and stroke) have a larger proportional contribution to perioperative mortality than communicable diseases and injuries. Secondly, SASOS patients had a significantly higher burden of urgent and emergency surgery compared to EuSOS ($p < 0.0001$). Urgent or emergent surgery had the largest population-attributable risk for mortality of 25.5% (95% CI 5.1 - 55.8) in SASOS.¹⁴ These differences in the surgical characteristics and the predictors of morbidity between SASOS and EuSOS suggest that African surgical outcomes data is necessary to identify predictors of morbidity which could be targeted to make surgery safer in Africa, and potentially in other lower and middle income countries across the globe.

These points provide the rationale to conduct a surgical outcomes study in Africa, which is known as the African Surgical Outcomes Study (ASOS). Only once we understand the burden of morbidity and mortality associated with surgery in Africa will we be able to allocate resources appropriately and finally consider interventions to improve patient outcomes. This study therefore has important public health implications for Africa.

Research questions

Primary objective

To confirm the incidence of in-hospital postoperative complications in adult surgical patients in Africa

Secondary objectives

1. To confirm the rate of mortality on the day of surgery for patients undergoing surgery in Africa.
2. To confirm the in-hospital mortality rate for patients undergoing surgery in Africa.
3. To describe the relationship between postoperative complications and postoperative mortality.
4. To describe the proportional contribution of communicable, non-communicable diseases and traumatic injuries to in-hospital mortality and critical care admissions in Africa.

Methods

Seven day, African national multi-centre cohort study of adult (≥ 18 years) patients undergoing surgery. This study will be registered on ClinicalTrials.gov.

Inclusion criteria

All consecutive patients admitted to participating centres undergoing elective and non-elective surgery commencing during a seven day study cohort period with a planned overnight hospital stay following surgery. The recruitment week will run between February and March 2016.

Exclusion criteria

Patients undergoing planned day-case surgery or radiological procedures not requiring anaesthesia.

Centres

Our plan is to recruit as many centres as possible on an international basis and ask them to include all eligible patients in the study.

Number of centres.

We plan to recruit as many centres from each country for participation. Countries are expected to contribute data from at least 10 centres. Where countries have less than 10 centres performing surgery nationally, at least 50% of the surgical centres need to contribute data to ASOS.

Number of patients

Only centres which provide patient data on at least 90% of the eligible surgical cases for the recruitment week will be included in the data analysis. The selected recruitment week for a country will be decided by the National Leader.

Ethics approval

The requirement for patient consent is expected to vary according to regulations of the participating nations. The national leaders will ensure ethics approval is obtained from their respective countries and centres. Centres 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. We expect that in most, if not every country, that 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. This international precedent has already been set, as in the original EuSOS study, consent was waived in 27 of the 28 European countries participating,³ and seven of the eight ethics committees in the SASOS study.¹⁴

Data collection and collation

Data will be collected in individual centres on paper case record forms (CRFs) for every patient recruited. Paper CRFs will be stored within a locked office in each centre 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 an internet based electronic CRF. 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 centre 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 centres and the co-ordinating centre will be encrypted using a secure protocol (HTTPS/SSL 3.0 or better).

Where individual centres are unable to access the internet based case record form, pseudo-anonymised (coded) facsimile (fax) data transfer will be available to a secure, dedicated fax machine in the co-ordinating office. Pseudo-anonymised (coded) data may also be sent by mail to the coordinating centre if necessary.

Each centre will complete a screening log reporting the number of eligible surgical patients who had surgery during the recruitment week at the centre.

Each centre will maintain a secure trial file including a protocol, local investigator delegation log, ethics approval documentation and the patient list.

Once the local co-ordinator confirms data entry is complete for their hospital they will receive a spreadsheet of raw (un-cleaned) data, allowing further checks for data completeness and accuracy.

Dataset

A realistic data set will be fundamental to the success of the investigation, and this was confirmed in the EuSOS study where nearly complete data was available on 46 000 patients, and similarly in the SASOS study. We have therefore adopted core data variables from the EuSOS, International Surgical Outcomes Study (ISOS) and SASOS studies in order to achieve the study objectives. We believe that these key data points will encourage centres to participate as there will not be an excessive burden of data collection.

Centre co-ordinators may request the addition of a limited number of data points to support additional country specific data collection and for subsequent regional analyses. All additional data points must be discussed with the co-principal investigators and if necessary the steering committee.

Centre specific data will be collected once for each hospital including: university or non-university hospital, number of hospital beds, number of operating rooms, number and level of critical care beds and details about the reimbursement status of the hospital.

An ASOS case record form (CRF) will be completed for every eligible patient who undergoes surgery during the seven day cohort period (appendix 1). 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 whichever is the shorter period.

Sample size calculation

Our plan is to recruit as many centres as possible from each participating country and ask them to include all eligible patients in the study. A minimum of ten centres from any country will be required for participation (with the exception of countries which have less than 10 centres performing surgery nationally, where in this circumstance at least 50% of the surgical centres need to contribute data to ASOS). Only centres including data on at least 90% of eligible patients will be included in the data analysis. We do not have a specific sample size and statistical models will be adapted to the event rate provided by the sample recruited.

Statistical analysis

Data will be presented at a national level and in the following geographical regions: Northern, Western, Central, Eastern and Southern Africa. All institutional level data will be anonymised prior to publication. 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 inter-quartile 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 single final analysis is planned at the end of the study.

Primary outcome measure

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

Secondary outcome measures

1. Rate of mortality on the day of surgery for patients undergoing surgery in Africa.
2. The in-hospital mortality rate for patients undergoing surgery in Africa.

Organisation

The Steering Committee will be chaired by BB and TM. The study management team will be appointed by the Steering Committee and led by BB and TM. The duties of this team will include administration of all project tasks, communication between project partners (including funders, steering committee members, national and local co-ordinators, 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.

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, eCRF and other materials
- Ensure necessary regulatory approvals are in place prior to the start date
- Ensure good communication with the participating sites in his/her country

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 approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and assist with problem solving
- Act as guarantor for the integrity and quality of data collected

- Ensure timely completion of eCRFs
- Communicate with the relevant national coordinator

Data management and ownership

On behalf of the Steering Committee, the Anaesthetic Network of South Africa (ANSA) will act as custodian of the data. 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 conduct secondary analyses. 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 institutional and patient level data will be strictly anonymised. Individual patient data provided by participating hospitals remain the property of the respective institution. Once each local co-ordinator has confirmed the data provided from their hospital are both complete and accurate, they will be provided with a spreadsheet of the raw (un-cleaned) data for their hospital.

The complete ASOS dataset, anonymised with respect to participating patients and hospitals, will be made freely and publicly available two years following publication of the main scientific report. Prior to this, the steering committee is not under any obligation to release data to any collaborator or third party if they believe this is not in keeping with the wider aims of the ASOS project.

Publication plan

The steering committee will appoint a writing committee to draft the scientific report(s) of this investigation, which will be disseminated in a timely manner. The group will be known as 'The ASOS Investigators'. It is anticipated that a number of secondary analyses will be performed. ASOS 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. The steering committee will consider the scientific validity and the possible effect on the anonymity of participating centres prior to granting any such requests. Where necessary, a prior written agreement will set out the terms of such collaborations. The steering committee must approve the final version of all manuscripts including ASOS data prior to submission. In the event of disagreement within the steering committee, the co-principal investigators will make a ruling. Any analysis incorporating ASOS data from two or more study sites will be considered a secondary analysis and subject to these rules. The Steering Committee must approve the final version of all manuscripts prior to submission, whether they relate to part or all of the ASOS dataset.

References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008;**372**(9633):139-44.
2. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012;**307**(21):2295-304.
3. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012;**380**(9847):1059-65.
4. Chao TE, Sharma K, Mandigo M, et al. Cost-effectiveness of surgery and its policy implications for global health: a systematic review and analysis. *Lancet Glob Health* 2014;**2**(6):e334-45.
5. Grimes CE, Henry JA, Maraka J, et al. Cost-effectiveness of surgery in low- and middle-income countries: a systematic review. *World J Surg* 2014;**38**(1):252-63.
6. Dare AJ, Grimes CE, Gillies R, et al. Global surgery: defining an emerging global health field. *Lancet* 2014.
7. Meara JG, Hagander L, Leather AJ. Surgery and global health: a Lancet Commission. *Lancet* 2014;**383**(9911):12-3.
8. Watters DA, Hollands MJ, Gruen RL, et al. Perioperative Mortality Rate (POMR): A Global Indicator of Access to Safe Surgery and Anaesthesia. *World J Surg* 2014.
9. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med* 2009;**361**(14):1368-75.
10. 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.
11. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2095-128.
12. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2197-223.
13. WHO. www.who.int/healthinfo/statistics/bodgbddeathdalyestimates.xls (accessed 1.1.2012).
14. Biccard BM, Madiba TE. The South African Surgical Outcomes Study: A 7-day prospective observational cohort study. *SAMJ* 2015;**105**(6):465-75.

Appendix 1

African Surgical Outcomes Study (ASOS) case record form (CRF)

Appendix 2

African Surgical Outcomes Study (ASOS) Postoperative complications definitions