African Surgical OutcomeS-2 (ASOS-2) Trial

A cluster randomised trial to determine whether increased postoperative surveillance of adult African surgical patients reduces postoperative mortality

Trial protocol version 1
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1. **List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASOS</td>
<td>African Surgical Outcomes Study</td>
</tr>
<tr>
<td>EuSOS</td>
<td>European Surgical Outcomes Study</td>
</tr>
<tr>
<td>ISOS</td>
<td>International Surgical Outcomes Study</td>
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</table>
2. Summary

<table>
<thead>
<tr>
<th><strong>Short title</strong></th>
<th>ASOS-2 Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methodology</strong></td>
<td>An international, multicentre, African cluster randomised trial</td>
</tr>
<tr>
<td><strong>Research sites</strong></td>
<td>Hospitals undertaking adult surgery in participating countries.</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To determine whether increased postoperative surveillance reduces in-hospital mortality in high-risk adult surgical patients aged 18 years and over in Africa.</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>53,600 patients</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>All consecutive adult patients aged 18 years and over admitted to participating centres undergoing elective and non-elective surgery</td>
</tr>
<tr>
<td><strong>Statistical analysis</strong></td>
<td>The primary outcome measure is in-hospital mortality censored at 30 days of randomisation. The analysis will be conducted according to intention-to-treat principles; all participants with a recorded outcome will be analysed according to the treatment group to which they were randomised.</td>
</tr>
<tr>
<td><strong>Proposed start date</strong></td>
<td>March 2019</td>
</tr>
<tr>
<td><strong>Proposed end date</strong></td>
<td>April 2019</td>
</tr>
<tr>
<td><strong>Trial duration</strong></td>
<td>Until hospital discharge, censored at 30 days</td>
</tr>
</tbody>
</table>
3. 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 countries\(^5\) and as such it is considered a core component of health.\(^6\) The Lancet Commission on Global Surgery was established to define safe surgery and develop strategies to ensure the adequate provision of safe surgery.\(^7\)

Recently, the African Surgical Outcomes Study (ASOS) demonstrated, that despite a patient low risk profile and low complication rates, patients in Africa were twice as likely to die following surgery when compared to the global average.\(^8\) ASOS provides the most comprehensive data on surgical outcomes in Africa, comprising 25 countries, 247 hospitals, and data from over 11,000 patients.\(^8\) Importantly, 95\% of the deaths in ASOS occurred in the postoperative period, suggesting that many lives could be saved by effective surveillance for physiological deterioration amongst the patients who developed complications.\(^8\) In ASOS, the median number of combined anaesthesia, surgical and obstetric specialists was 0·7 (IQR 0·2-1·9) per 100,000 population,\(^8\) which is well below the documented inflection point of 20 to 40 specialists per 100,000 population necessary to significantly decrease surgical mortality.\(^7\)

It is likely that a major contributor to the high mortality in ASOS was ‘failure to rescue’ partly due to an inadequacy of sufficient human resources necessary to identify postoperative surgical patients at risk. The solution to improving surgical outcomes in Africa is identification of the high-risk surgical patient prior to further physiological deterioration.

The objective of this trial is to assess whether increased postoperative surveillance of surgical patients at increased risk of postoperative morbidity or mortality is associated with improved survival.
4. Trial objectives

4.1 Primary objective
To determine whether increased postoperative surveillance reduces in-hospital mortality in high-risk adult surgical patients aged 18 years and over in Africa.

4.2 Primary outcome measure
In-hospital mortality, censored at 30 days if the patient is still alive and in-hospital.

4.3 Secondary objective
To determine whether increased postoperative surveillance reduces the incidence of the composite of severe in-hospital complications and mortality in high-risk adult surgical patients aged 18 years and over in Africa.

4.4 Secondary outcome measure
Composite of severe in-hospital complications and mortality, censored at 30 days if the patient is still alive and in-hospital.

A full list of definitions is available in the ‘Definitions document’ in appendix 1.
5. Methodology

5.1 Study design
ASOS-2 is an African, international, multicentre, cluster randomised trial.

5.2 Inclusion criteria
- Patients
  - All consecutive adult patients aged 18 years and over admitted to participating centres undergoing elective and non-elective surgery
- Participating surgical centres
  - Randomised according to a stratification based upon the level of the surgical facility and the surgical case load. Recruitment will run in early 2019.

We plan to randomise 536 hospitals to either increased postoperative surveillance or standard care for high-risk adult (≥18 years) surgical patients. The follow up is in-hospital. This study will be registered on ClinicalTrials.gov.

5.3 Exclusion criteria
- Patient refusal
- Prior participation in ASOS-2

5.4 Study flow diagram
6. Trial procedures

6.1 Recruitment and screening
This is a pragmatic trial. It is an African, international cluster randomised controlled trial in several African countries. Participating surgical sites will be randomised to either increased postoperative surveillance or usual postoperative care. We expect all consecutive adult patients aged 18 years and over admitted to participating centres undergoing elective and non-elective surgery to be included in the trial. ‘Broadcasting’ through appropriate hospital notices and signage will inform the patients and the public that the hospital is participating in the cluster randomised trial.

6.2 Informed consent and trial participation
The requirement for informed 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 prior to participation.

We will apply to all ethics committees for a waiver of consent for participating trial sites for the following reasons. Firstly, more than 50% of surgery in Africa is urgent or emergent, and urgent or emergent surgery is a strong independent predictor of postoperative mortality in Africa. Attempts to obtain traditional consent in the preoperative period in predominantly urgent and emergent surgery, which may include patients with a decreased level of consciousness may lead to non-consecutive patient enrolment in the ASOS-2 Trial. It is likely that this would lead to a biased sample, with artificially low estimates of adverse outcomes in African surgical patients, and data following the trial which are not generalisable to the majority of African surgical patients. Secondly, for these reasons, a waiver of consent is increasingly common around the world in both interventional and observational research involving time-sensitive procedures, such as surgery. Thirdly, generating biased and poorly generalizable data would not address the research question, and thus would dishonour the contributions of the other included patients, and would be wasteful research, in a resource limited environment. Fourthly, we believe that the trial intervention is low risk. Furthermore, the patients in the control arm will receive the current standard postoperative care. The intervention group will receive a low risk intervention which is only aimed at increasing surveillance of at-risk patients. Finally, we would use ‘broadcasting’ at participating sites to ensure that all patients and family members were aware that the surgical site was a participating surgical trial site, through appropriate signage (appendix 2).
6.3. **Randomisation**
Participating sites will be randomised to normal postoperative care, or increased postoperative surveillance. Randomisation will be stratified according to the level of the surgical facility and the expected weekly surgical case-load.

6.4. **Trial intervention**
The intervention arm to which each participating site is randomised will be offered to all eligible surgical patients for the duration of the trial.

**Intervention arm**
Participating sites which have been randomised to increased surveillance will need to provide increased surveillance to surgical patients with a predicted increased postoperative risk as determined by the ASOS risk stratification tool. Increased postoperative surveillance can include either of the following; i) admission to a higher care ward than had been planned at the time of surgery, ii) an increase in the frequency of nursing observations in the postoperative period, iii) ensuring that the patient is placed in closer proximity to the nursing station, and not in a remote location in the postoperative ward, or iv) allowing family members to stay with the patient in the ward in the postoperative period. The nature of the offered increased postoperative surveillance will be left to the discretion of the healthcare workers and the participating sites. However, all sites will be encouraged to include more than one of the increased postoperative surveillance intervention. The healthcare providers will also receive information on the leading causes of postoperative mortality in African surgical patients as documented in ASOS; surgical site infections, bloodstream infection and acute respiratory distress syndrome, pneumonia, acute kidney injury, postoperative bleeding, and cardiac arrest.8

**Control arm**
Participating sites randomised to the control arm will provide usual postoperative care to patients. The care will be left to the discretion of the healthcare providers.

6.5. **Data collection and collation**

**Dataset**
This is a pragmatic trial in a resource limited environment. As a result, a realistic data set will be fundamental to the success of the trial. We are confident that the proposed data set will achieve this objective, as it is smaller than the data sets used in ASOS,8 the
European Surgical Outcomes Study (EuSOS), and the International Surgical Outcomes Study (ISOS), and these studies successfully achieved follow up on >95% of patients despite requiring data on all surgical patients at each participating centre for a week of surgery. We believe that these key data points will encourage centres to participate as there will not be an excessive burden of data collection.

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-2 case record form (CRF) will be completed for every eligible patient who undergoes surgery during the trial (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 whichever is the shorter period.

6.6. **Predefined protocol violation**
A protocol violation will be defined as patients who were randomised to increased surveillance, but did not get any of the planned increased postoperative surveillance interventions.

6.7. **Follow up procedures**
Follow-up data will be collected by a site trial investigator. Investigators will review a participant’s in-hospital medical records (paper or electronic) up to hospital discharge.

6.8. **Schedule of assessment**

<table>
<thead>
<tr>
<th>Event/visit</th>
<th>Screening</th>
<th>Pre-op</th>
<th>24 hrs postop</th>
<th>Hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/ exclusion criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic information</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASOS preoperative risk stratification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of postoperative surveillance</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of trial form</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
7. Statistical considerations

7.1. Sample size calculation
This is a cluster randomised trial of approximately hospitals in Africa. We will match hospitals on expected surgical volume in a week of surgery. This varied tremendously across the ASOS group; with a median number of surgical procedures per hospital for the study week in ASOS of 29 (IQR 10-71). The variability of the individual patient outcomes explained by the cluster (or surgical site) is taken into account in these sample size calculations. The inter-cluster correlation coefficient (ICC) in ASOS was 0.01. For the sample size calculation, we have therefore used a conservative ICC of 0.015.

The incidence of mortality in ASOS was 2.1%. We expect a 25% relative risk reduction in mortality through increased surveillance of postoperative surgical patients at high-risk of severe complications or in-hospital mortality. Based on the inter-class correlation coefficient (ICC) for the composite of severe complications and mortality in ASOS-2 of 1.5%, and stratification for the level of the surgical facility, and the volume of procedures per week, a trial for efficacy of increased postoperative surveillance would require 53,600 patients, from 536 surgical centres across Africa (Table 1). Based on a relative risk reduction of 25% in the intervention arm, the power for the secondary outcome, based on the sample sizes for the primary outcome are also shown in Table 1.

<table>
<thead>
<tr>
<th>Primary outcome (in-hospital all-cause mortality and severe complications)</th>
<th>Power (2-sided ( \alpha = 0.05 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control event rate</td>
<td>Intervention arm</td>
</tr>
<tr>
<td>2.0%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

7.2. Statistical analysis
Outcomes will be presented at a continental level. 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.

The primary outcome will be in hospital mortality. Overall differences in in-hospital mortality will be compared between the intervention and control clusters. All analyses
will account for clusters. A list of baseline risk factors (the risk factors in the ASOS Surgical Risk Calculator) will be included in the analysis. We will use logistic regression model to estimate the effect of increased postoperative surveillance, on the primary and secondary outcomes. We will calculate the odds ratios and their associated 95% confidence intervals. We will infer statistical significance if the computed 2-sided p-value is < 0.05. A single final analysis is planned at the end of the study.

7.3. **Subgroup analyses**
An a priori decision has been taken to conduct the following subgroup analyses; i) between high and low outcome hospitals, ii) between district hospitals and higher-level hospitals, iii) between low and high human resourced surgical hospitals, iv) between low-income countries and middle-income countries, and v) between the different types of postoperative surveillance.

7.4. **Secondary studies**
The use of the ASOS-2 Trial data for secondary studies will be encouraged.
8. Research ethics

8.1 Ethical principles


Research ethics and regulatory approvals will be sought before starting the trial at each site, in accordance with national research legislation/guidelines for that country. This may require the translation of the trial protocol and ‘broadcasting’ documents. Other trial documents will be translated at the discretion of the national lead investigator. Full approval by the Research Ethics Committee will be obtained prior to starting the trial and fully documented by letter to the Chief Investigator naming the trial site, local PI (who may also be the Chief Investigator) and the date on which the ethics committee deemed the trial as permissible at that site. All members of the trial steering committee will declare conflicts of interest before joining the study group. These will be listed on any publications arising from the trial.
9. Data handling and record keeping

Data will be collected in individual centres on paper case record forms (CRFs). 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. Data were anonymised during the transcription process using REDCap (Research Electronic Data Capture) tools hosted by Safe Surgery South Africa. REDCap is a secure, web-based application designed to support data capture for research studies.10

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 co-ordinating centre if necessary.

Each centre will complete a screening log reporting the number of eligible surgical patients who had surgery during the trial 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.
10. Monitoring and auditing

The Sponsor will have oversight of the trial conduct at each site. The trial team will take day-to-day responsibility for ensuring compliance with the requirements of GCP in terms of quality control and quality assurance of the data collected as well as safety reporting. The ASOS-2 Trial Management Group will communicate closely with individual sites and the Sponsor’s representatives to ensure these processes are effective. A Data and Safety Monitoring Board (DSMB) will be not be appointed for this trial. The reasons for this decision are discussed in section 11.3 on page 18.

10.1 Training of investigators

All investigators will complete training consistent with their national regulations for clinical research, as well as those in the country of the trial sponsor (RSA). A representative of the national coordinating centre for that country will conduct a site initiation at each site before patient recruitment commences. The site initiation will include an induction to the trial protocol and procedures, the standardised assessment of outcome measures, and the trial database. Where new investigators join the research team at a particular site during the course of the trial, the responsibility for induction training will fall to the local principal investigator.

10.2 Monitoring the safety and wellbeing of trial participants

Systems are in place to ensure that all PIs and designees are able to demonstrate that they are qualified by education, training or experience to fulfil their roles and that procedures are in place that assures the quality of every aspect of the trial.

Based on the expected rapidity of completion of the trial from initiation, it will not be possible to terminate the trial early. We believe that this is acceptable considering the loss risk of the trial intervention. Day to day management and monitoring of individual sites will be undertaken via the Trial Management Group composed of the Chief Investigator and supporting staff. They will meet on a regular basis to discuss trial issues.
11. Trial management and committees

11.1 Trial management group
Day-to-day trial management will be co-ordinated by a trial management group consisting of the Chief Investigator and his/her support staff.

11.2 Trial Steering Committee
The Trial Steering Committee will oversee the trial and will consist of:

- several independent clinicians and trialists
- co-investigators (including a representative of each participating nation)

Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

- approving the final trial protocol;
- major decisions such as a need to change the protocol for any reason;
- monitoring and supervising the progress of the trial;
- reviewing relevant information from other sources;
- informing and advising on all aspects of the trial

11.3 Data and Safety Monitoring Board
The principle responsibility of a Data and Safety Monitoring Board (DSMB) is to safeguard the interests of trial participants, including assessing the safety of the intervention, reviewing relevant new external evidence, and monitoring the overall conduct of the trial. A DSMB provide recommendations about stopping, modifying or continuing the trial to the Trial Steering Committee.

The ASOS-2 Trial will not appoint a DSMB. The reasons for not appointing a DSMB are the following: i) the intervention is considered of a low risk (and the DSMB functions primarily to identify increased adverse events associated with the intervention), and ii) the trial is expected to be completed within two months of initiation at a site. It is therefore unlikely that sufficient data will be available to allow for an interim analysis and a decision to be made on the analysis, prior to the completion of the trial. We are confident that the trial could be completed within two months, as in ASOS the median surgical volume was 29 patients per week,\(^8\) and each hospital in the ASOS-2 Trial is expected to recruit 100 patients.
12. Data management and ownership

On behalf of the Steering Committee, Safe Surgery South Africa (SSSA) 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-2 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-2 project.
13. 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-2 Investigators’. It is anticipated that a number of secondary analyses will be performed. ASOS-2 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-2 data prior to submission. In the event of disagreement within the steering committee, the Chief Investigator will make a final ruling. Any analysis incorporating ASOS-2 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-2 dataset.
References


Appendix 1

African Surgical OutcomeS-2 (ASOS-2) Trial: Definitions document
Appendix 2

African Surgical OutcomeS-2 (ASOS-2) Trial: Hospital 'broadcasting' signage
Appendix 3

African Surgical OutcomeS-2 (ASOS-2) Trial: Case Record Form (CRF)