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 7

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Contents

1. List of abbreviations

ASOS	African Surgical Outcomes Study
EuSOS	European Surgical Outcomes Study
ISOS	International Surgical Outcomes Study

2. Summary

Short title	ASOS-2 Trial
Methodology	An international, multicentre, African cluster randomised trial
Research sites	Hospitals undertaking adult surgery in participating countries.
Objectives	To determine whether increased postoperative surveillance in high-risk adult surgical patients reduces overall in-hospital mortality in surgical patients aged 18 years and over in Africa.
Number of patients	664 hospital clusters with a recruitment target of 100 patients per site (approximately 66,400 patients)
Inclusion criteria	All consecutive adult patients aged 18 years and over admitted to participating centres undergoing elective and non-elective surgery
Statistical analysis	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.
Recruitment start date	May 2019
Recruitment end date	March 2020
Trial duration	Until hospital discharge, censored at 30 days

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' after a postoperative complication partly due to an inadequacy of sufficient human resources necessary to identify postoperative surgical patients at risk. A potential 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 in high-risk adult surgical patients reduces overall in-hospital mortality in 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 in high-risk adult surgical patients reduces the overall incidence of the composite of severe in-hospital complications and mortality in 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

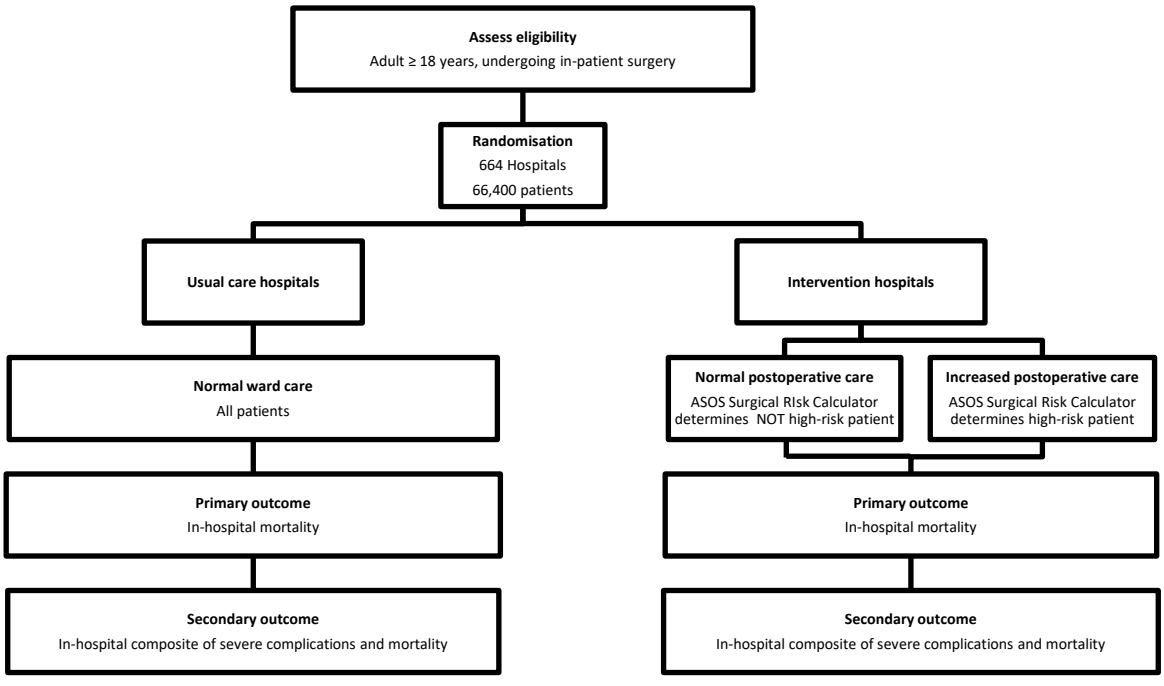
- Patients
  - All consecutive adult patients aged 18 years and over admitted to participating centres undergoing elective and non-elective surgery
- Participating surgical centres
  - Randomised according to a stratification based upon the level of the surgical facility and the surgical case load. Recruitment will run until March 2020.

We plan to randomise 664 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

- 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 surgent is a strong independent predictor of postoperative mortality in Africa.[8] 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 ("SOC"), or increased postoperative surveillance ("Intervention") in four recruitment blocks (calendar time blocks). Randomisation in each block will be stratified by country and by level of the surgical facility with a fixed block size of 2. The randomisation algorithm will seek to balance randomisation arms by simulating randomisations with an automated filter to screen out poorly balanced randomisations. In the second and subsequent recruitment blocks, the randomisation algorithm will use knowledge of the previous randomisations and a similar simulation and filtering approach to ensure reasonable balance across arms and across level of surgical facility. This approach was developed on the basis of a simulation model for the randomisation that was used to evaluate the probability of overall balance of randomisation arms and balance within level of care strata if randomising recruitment phases in waves. Results of 10,000 simulation runs indicated that a balanced simulation within the bounds described below would be obtained >50% of the time without the filtering step.

The algorithm is described briefly here:

For recruitment phase 1:

1. Simulate stratified block randomisation within country and level of facility
2. Check that simulated randomisation has percent SOC between [48% - 52%]
3. If NO, then repeat steps 1 and 2. If YES then use this randomisation.

For all other recruitment phases:

1. Simulate stratified block randomisation for this phase within country and level of facility
2. Combine this simulation with prior actual randomisations
3. Check that combined randomisation has percent SOC between [48% - 52%]
4. If NO, then repeat steps 1-3. If YES proceed to next check.
5. Check that combined randomisation has balance within level of care between [45% - 55%]
6. If NO, then repeat steps 1-5. If YES then use this randomisation.

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 Surgical Risk Calculator[9] stratification tool (also available at www.asos.org.za). Increased postoperative surveillance can include any 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 assigned to a bed in view of 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] This will be known as the 'Postoperative surveillance bedside guide' and will be placed at the bedside of every patient flagged as high-risk by the ASOS Surgical Risk Calculator.[9] This should be placed in a visible position at the patient's bedside e.g. posted on the wall above the patient's bed.

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),[3] and the International Surgical Outcomes Study (ISOS),[10] 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

Event/ visit	**Screening**	**Pre-op**	**Daily postop**	**Hospital discharge**
Inclusion/ exclusion criteria	X			
Demographic information		X		
Medical history		X		
Preoperative risk stratification, using the ASOS Surgical Risk Calculator[9]		X		
Review of postoperative surveillance			X	X
Outcome assessment				X
End of trial form				X

7. Statistical considerations

7.1. Sample size calculation

This is a cluster randomised trial of 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).[8] The variability of the individual patient outcomes explained by the cluster (or surgical site) is taken into account in these sample size calculations. The intra-cluster correlation coefficient (ICC) in ASOS was 0.01. For the sample size calculation, we have therefore used a conservative ICC of 0.015.

Based on ASOS, we estimate the coefficient of variance for a 4-week recruitment period to be 0.63. A 4-week recruitment period is defined as the following; i) hospitals stop recruiting at the end of the week in which they have exceeded 100 enrolled patients, and ii) if a site had not reached 100 enrolled patients after 4 weeks of recruiting, it would stop recruiting.

The incidence of mortality in ASOS was 2.1%.[8] 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 intra-cluster correlation coefficient (ICC) for the composite of severe complications and mortality in ASOS-2 of 1.5%, a coefficient of variance of 0.63, 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 64,200 patients, from 642 surgical centres across Africa (Table 1).[8] Based on a relative risk reduction of 25% in the intervention arm, the sample sizes for the primary outcome are shown in Table 1.

TABLE 1: Sample size calculations for the ASOS-2 Trial based on a power of 80%, 2-sided α = 0.05 and a mean cluster size of 100 patients

Primary outcome (in-hospital all-cause mortality)					
Control event rate	**Intervention arm**	**Relative risk**	**Intra-cluster correlation coefficient (ICC)**	**Coefficient of variance (CV)**	**Total clusters**
2.0%	1.5%	0.75	0.015	0	536
2.0%	1.5%	0.75	0.015	0.63	664
2.0%	1.6%	0.80	0.015	0.63	1068

During the trial an external auditor (Paul Myles) will check the event rate in the control arm of the study once 80% of all recruited patients have been captured on REDCap (practically this will take place around September 2019). The external auditor will use the event rate in the control arm to decide whether recruitment should continue beyond the target of 664 hospitals, and for how many months recruitment should continue. This specified interim analysis of data will not lead to adjustment of the prespecified alpha of 0.05.

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.

The detailed statistical analysis plan was added on 19 March 2020 and is attached as Appendix 6 to this document.

7.3. Secondary studies

The use of the ASOS-2 Trial data for secondary studies will be encouraged.

During the conduct of the ASOS-2 trial we will perform a concurrent process evaluation to gain insight into the implementation process. The process evaluation aims to:

1. Measure protocol compliance (fidelity of implementation)
2. Identify factors that influence success of implementation
3. Verify specified process steps that form part of the implementation of the protocol and logical framework of the trial
4. Generate contextual information about the trial setting

The questions asked by the process evaluation are:

1. Which factors determined fidelity of implementation at the local hospital level?
2. How did implementation of the intervention affect patient care?
3. Why does the intervention produce (or fail to produce) a change in patient morbidity and mortality?

The measurement tools used for the process evaluation are:

1. The post-education, REDCap based, online test
2. The individual participant case report form (CRF),
3. An online database, called the screening log, which is a REDCap application for participating hospitals to record the number of eligible patients daily,
4. Research fellows will perform selected site visits in order to verify specified process steps and perform structured interviews with a sample of stakeholders,
5. Telephonic structured interviews with a sample of stakeholders that cannot be reached by the two research fellows
6. A post-trial, semi-quantitative, REDCap based, online questionnaire built around the key components identified in the structured interviews and the pilot trial

Each member of the local hospital investigator team will be asked to complete the post-education online test prior to patient recruitment. The online test comprises eight short multiple-choice questions which checks comprehension of the key points from the education material.

The individual participant CRF (appendix 3) captures information that allows checking accuracy of risk stratification, fidelity of implementation, and differences in patient experience between non-high risk patients in the two arms.

The research fellows will visit specific sites during the trial on appointed days agreed upon by the local hospital investigators. They will visit sites during the initiation phase, the recruitment phase, and the follow-up phase of the trial. They will use standard site visit checklists to identify non-compliance, barriers and facilitators of implementation. During the follow-up phase they will interview a qualitative sample of stakeholders who indicate willingness to participate in an interview about their personal experience of the trial. Interviews will be recorded. Verbal consent will be obtained and recorded for each interviewee who agrees to participate. No personal identifying information will be recorded for interviewees. A semi-structured script will be used for the interviews. Recordings will be stored on a cloud base, password protected drive uploaded by the interviewers. Interviews will be analysed deductively by independent investigators using the Consolidated Framework for Implementation Research (CFIR) as a guide.

The post-trial questionnaire will be anonymous. At the start of the questionnaire respondents will be informed about its content and intent. Respondents will be given the opportunity to opt out, or to give consent prior to continuing to the questions.

Questions will test the CFIR constructs that were highlighted in the structured stakeholder interviews.

8. Research ethics

8.1 Ethical principles

The PI will ensure that this trial is conducted in accordance with the Principles of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008) and Fortaleza (2013) and adopted by the World Medical Association in 2017 as described at the following internet site: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ . In South Africa, the trial will be conducted according to the Department of Health guidelines: 'Ethics in Health Research: principles, processes and structures 2nd edition', published in 2015.

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.[11]

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 19.

However, an independent international advisor has been appointed to the ASOS-2 Trial (Prof Paul Myles). Should the recruitment target have not been met during the trial, his role will be to determine whether; i) hospital recruitment can continue after the planned recruitment window, and ii) whether an interim analysis would be required prior to continuing recruitment.

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, or conduct a remote electronic site initiation. The site initiation will include an induction to the trial protocol and procedures, the standardised assessment of outcome measures, and the trial database. When 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 low 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 provides 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, and all sites will recruit within a four-month window period. 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 within a four week period.

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 and public communication of trial results

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.

In order to inform the participating communities of the results, the ASOS-2 Trial results and possible interventions to improve postoperative surgical mortality will also be broadcast using appropriate signage at the facilities that participated in the trial.

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. doi: 10.1016/S0140-6736(08)60878-8 [published Online First: 2008/06/28]
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. doi: 10.1001/jama.2012.5502 [published Online First: 2012/06/19]
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. doi: 10.1016/S0140-6736(12)61148-9 [published Online First: 2012/09/25]
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. doi: 10.1016/s2214-109x(14)70213-x [published Online First: 2014/08/12]
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. doi: 10.1007/s00268-013-2243-y [published Online First: 2013/10/09]
6. Dare AJ, Grimes CE, Gillies R, et al. Global surgery: defining an emerging global health field. *Lancet* 2014;384(9961):2245-7. doi: 10.1016/S0140-6736(14)60237-3 [published Online First: 2014/05/24]
7. Meara JG, Leather AJ, Hagander L, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet* 2015;386(9993):569-624. doi: 10.1016/S0140-6736(15)60160-X
8. 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]
9. Kluyts HL, le Manach Y, Munlemvo DM, et al. The ASOS Surgical Risk Calculator: development and validation of a tool for identifying African surgical patients at risk of severe postoperative complications. *Br J Anaesth* 2018;121(6):1357-63. doi: 10.1016/j.bja.2018.08.005 [published Online First: 2018/11/18]
10. International Surgical Outcomes Study g. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *Br J Anaesth* 2016;117(5):601-09. doi: 10.1093/bja/aew316 [published Online First: 2016/11/02]
11. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010

Appendix 1

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

Definitions document

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Definitions of preoperative risk factors

What is the definition of neurosurgery?

Neurosurgical procedures are defined as involving the brain and cervical spine. Surgery on the thoracic and lumbar spine is defined as orthopaedic surgery in the CRF.

What should I do if some important medical co-morbidities are not included on the case record form (CRF)?

We realise that some patients may have important data which we have not asked for. The CRF has been designed to request only the most important patient data.

What are the definitions of the chronic co-morbid diseases?

We have not made any definitions for these diseases. We simply want doctors to give what they believe are the most appropriate answers. If the patient probably has the disease, then tick the box. If they probably do not have the disease, then leave it blank.

American Society of Anesthesiologists (ASA) score

I A normal healthy patient
II A patient with mild systemic disease which does not limit physical activity
III A patient with severe systemic disease which limits physical activity
IV A patient with severe systemic disease that is a constant threat to life
V A patient who is not expected to survive for 24 hours without the operation.

Urgency of surgery

Elective: Not immediately life-saving; planned within months or weeks.

Urgent: Planned surgery within hours or days of the decision to operate.

Emergency: As soon as possible; no delay to plan care; ideally within 24 hours.

Severity of the surgery

This is the category of surgery which indicates a combination of complexity and amount of tissue injury.

Minor surgery would include procedures lasting less than 30 minutes performed in a dedicated operating room which would often involve extremities or body surface or brief diagnostic and therapeutic procedures eg arthroscopy without intervention, removal of small cutaneous tumour, diagnostic proctology, biopsy of small lesions, etc.

Intermediate procedures are more prolonged or complex that may pose the risk of significant complications or tissue injury. Examples include laparoscopic cholecystectomy, arthroscopy with intervention, bilateral varicose vein removal, tonsillectomy, inguinal hernia repair, breast lump resection, haemorrhoidectomy, appendicectomy, partial thyroidectomy, cataract surgery, uvuloplasty, minimally invasive repair of vaginal prolapse, vaginal hysterectomy, tendon repair of hand, fixation of mandibular fracture, etc.

Major surgical procedures are expected to last more than 90 minutes and include major gut resection, major joint replacement, mastectomy, extensive head and neck tumour resection, abdominal aortic aneurysm repair, major vascular bypass procedure, procedures involving free flap to repair tissue defect, amputation, total thyroidectomy, cystectomy, trans-urethral resection of prostate, resection of liver tumour, carotid endarterectomy, nephrectomy, total abdominal hysterectomy, spinal discectomy, etc.

Definitions of postoperative care

Post anaesthesia care unit (PACU):

A postoperative recovery ward or unit which is dedicated to providing increased postoperative care during recovery (both in intensity of monitoring and in duration of care), when compared to normal postoperative recovery care.

High care ward:

A postoperative ward which is dedicated to providing increased postoperative care, when compared to the normal postoperative surgical ward.

Increased frequency of nursing observations:

Nursing observations which are conducted more frequently, than the normal frequency of observations on the postoperative ward.

Patient's bed in view of the nurses' station:

The patient is positioned in a bed close to the nursing station to ensure that the nurses can always see the patient from the nursing station.

Family members to stay with the patient in the ward:

If the family members are asked to stay with the patient on the ward, because of a concern that the patient is at increased risk of death of morbidity in the postoperative period.

Definitions of severe surgical complications

The following definitions and grading are provided for guidance where the nature and severity of a possible complication following surgery is uncertain. These definitions are based on the 'Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures'.[1]

Definition of a 'Severe Complication'

Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.

Surgical site infection (superficial)

Infection involving only superficial surgical incision which meets the following criteria:

1. Infection occurs within 30 days after surgery and

2. Involves only skin and subcutaneous tissues of the incision and

3. The patient has at least one of the following:

    a. purulent drainage from the superficial incision

    b. organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision and at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, or superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.

    c. diagnosis of a incisional surgical site infection by a surgeon or attending physician

Surgical site infection (deep)

An infection which involves both superficial and deep parts of surgical incision and meets the following criteria:

1. Infection occurs within 30 days after surgery if no surgical implant is left in place or one year if an implant is in place and

2. The infection appears to be related to the surgical procedure and involves deep soft tissues of the incision (e.g. fascial and muscle layers) and

3. The patient has at least one of the following:

a. purulent drainage from the deep incision but not from the organ/space component of the surgical site

b. a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or no cultures were taken whilst the patient has at least one of the following signs or symptoms of infection: fever (>38°C) or localized pain or tenderness. A culture-negative finding does not meet this criterion.

c. an abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathologic or radiologic examination

d. diagnosis of a deep incisional surgical site infection by a surgeon or attending physician

Surgical site infection (organ/space)

An infection which involves any part of the body excluding the fascia or muscle layers and meets the following criteria:

1. Infection occurs within 30 days after surgery and

2. The infection appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and

3. The patient has at least one of the following:

    a. purulent drainage from a drain that is placed through a stab wound into the organ/space

    b. organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space

    c. an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination

    d. diagnosis of an organ/space surgical site infection by a surgeon or attending physician

Bloodstream infection

An infection which is not related to infection at another site and which meets at least one of the following criteria:

1. Patient has a recognised pathogen cultured from blood cultures which is not related to an infection at another site

2. Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following:

    a. common skin contaminant cultured from two or more blood cultures drawn on separate occasions

    b. common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and a physician starts antimicrobial therapy

    c. positive blood antigen test

Acute Respiratory Distress Syndrome (ARDS)

Respiratory failure, or new or worsening respiratory symptoms, commencing within one week of surgery; and a chest radiograph or computed tomography scan which demonstrates bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules; and respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor is present.

Severity grading:
Severe: PaO2:FiO2 ≤100 mmHg with PEEP ≥5 cmH2O

Guidance:
If altitude is higher than 1000 m, a correction factor should be calculated as follows: (PaO2:FiO2 x [barometric pressure/760 mmHg]). PEEP, positive end-expiratory pressure; CPAP, non-invasive continuous positive airways pressure

Pneumonia

Chest radiographs with new or progressive and persistent infiltrates, or consolidation, or cavitation, and at least one of the following:

1. fever (>38°C) with no other recognized cause
2. leucopaenia (<4,000 white blood cells/mm^3) or leucocytosis (>12,000 white blood cells/mm^3)
3. for adults >70 years old, altered mental status with no other recognised cause;

and at least two of the following:

1. new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
2. new onset or worsening cough, or dyspnoea, or tachypnoea
3. rales or bronchial breath sounds
4. worsening gas exchange (hypoxaemia, increased oxygen requirement or increased ventilator demand)

Guidance: Two radiographs are required for patients with underlying pulmonary or cardiac disease. The definition may be used to identify ventilator associated pneumonia.

Urinary tract infection

An infection associated with at least one of the following signs or symptoms which should be identified within a 24 hour period; fever (>38 °C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognised cause,
and a positive urine culture of $\geq 10^5$ colony forming units/mL with no more than two species of microorganisms.

Acute Kidney Injury (AKI)

Acute Kidney Injury (AKI) Stage	**Serum creatinine**	**Urine output**
Severe	Increase of 3.0 times baseline within 7 days or increase in serum creatinine to ≥4.0 mg/dL (≥354 µmol/L) with an acute rise of >0.5 mg/dL (>44 µmol/L) or initiation of renal replacement therapy	≤0.3 ml/kg/h for 24 hours or Anuria for 12 hours

Guidance: Baseline serum creatinine must be measured before surgery but an estimated value can be used if the patient does not have chronic kidney disease.

Postoperative haemorrhage

Blood loss occurring within 72 hours after the end of surgery which would normally result in transfusion of blood.

Cardiac arrest

The cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. ECG changes may corroborate the incidence of cardiac arrest.

Other severe complications

If any of the following complications result in a significant prolongation of hospital stay and/or permanent functional limitation or death, then mark 'Other severe complication' as 'Yes'. Note that they will almost always requires clinical treatment.

Anastomotic breakdown

Leak of luminal contents from a surgical connection between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may

collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple-organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localised area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a sub-clinical leak.

Arrhythmia
Electrocardiograph (ECG) evidence of cardiac rhythm disturbance.

(Cardiogenic) pulmonary oedema
Evidence of fluid accumulation in the alveoli due to poor cardiac function.

Gastro-intestinal bleed
Unambiguous clinical or endoscopic evidence of blood in the gastro-intestinal tract. Upper gastrointestinal bleeding is that originating from the oesophagus, stomach and duodenum. Lower gastro-intestinal bleeding originates from the small bowel and colon.

Myocardial infarction
Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:

1. Symptoms of ischaemia

2. New or presumed new ST-segment or T-wave ECG changes or new left bundle branch block

3. Development of pathological Q-waves on ECG

4. Radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality

5. Identification of an intra-coronary thrombus at angiography or autopsy

Pulmonary embolism (PE)
A new blood clot or thrombus within the pulmonary arterial system.

Guidance: Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D-dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery.

Stroke
Embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).

Hospital resource use after surgery

We will collect some basic data to describe the treatment resources patients received after surgery.

Critical care admission to treat postoperative complications:

Postoperative complications requiring admission to critical care to treat the postoperative complications or provide critical care support necessitated by the severity of the postoperative complications.

Days in hospital after surgery: Total number of days in hospital after surgery.

Status at hospital discharge or 30th postoperative in-hospital day: The survival status of the patient at hospital discharge, or at the 30 in-hospital day (if the patient had not yet been discharged following surgery). The study is censored at the 30th in hospital postoperative day.

Reference

1. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015;32(2):88-105. doi: 10.1097/EJA.0000000000000118

Appendix 2

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

IMPORTANT PATIENT INFORMATION

ASOS-2 African Surgical OutcomeS-2 Trial

A research study is being conducted at .....Hospital.

The research is being done by Dr .... from the Department of ....

Why is this research study being done?

To understand if increasing monitoring following surgery, makes surgery safer.

Why are we telling you about this study?

All adult surgical patients in this hospital are part of the trial. It is a requirement that some details pertaining to your clinical care are entered into a trial folder. Information from this folder will be used anonymously to understand if increasing monitoring following surgery makes surgery safer.

Will this study affect my care while I am in hospital?

No. You will still receive the same care while you are in hospital.

Will my name or any personal details be recorded in this study?

No. Your name and personal details will not be recorded as part of this study. All information from the notes will be kept strictly confidential.

Are there any risks or benefits associated with this study?

No. There are no risks or direct benefits associated with this study.

Who should I contact if I have any questions or concerns?

Please contact Dr .... on telephone.....

If you have questions about your rights or welfare as a research participant, please contact the UCT Faculty of Health Sciences Human Research Ethics Committee on +27 (0)21 406 6338.

Appendix 3

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

ASOS-2
African Surgical OutcomeS-2 Trial

Age ☐☐ years   Sex ☐ M ☐ F

ASA ☐ I ☐ II ☐ III ☐ IV ☐ V

Chronic co-morbid disease (tick all that apply): ☐ Hypertension ☐ HIV / AIDS ☐ Diabetes mellitus ☐ COPD / Asthma

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

☐ Gynaecology ☐ Obstetrics ☐ Orthopaedic ☐ Ear, nose and throat ☐ Plastics or breast

☐ Urology ☐ Neurosurgery ☐ Gastro-intestinal or Hepato-biliary ☐ Cardiothoracic/ vascular ☐ Other

Indication for surgery:

☐ Non-communicable disease ☐ Caesarean section ☐ Trauma ☐ Infection

Urgency of surgery: ☐ Elective ☐ Urgent ☐ Emergency

Severity of surgery: ☐ Minor ☐ Intermediate ☐ Major

Start of surgery time (24h) & date: h h : m m   d d m m 2 0 1 9

Postoperative Follow Up

Indicate postoperative care given:

Higher care ward ☐ No ☐ Yes

Increased nursing observations ☐ No ☐ Yes

Assigned a bed in view of nurses' station ☐ No ☐ Yes

Family with patient in ward ☐ No ☐ Yes

Severe complications (tick *all* that apply): Superficial or deep surgical site, or body cavity infection ☐N ☐ Y Postop day ☐☐

Bloodstream infection or ARDS ☐N ☐ Y Postop day ☐☐   Pneumonia ☐N ☐ Y Postop day ☐☐

Urinary tract or AKI ☐N ☐ Y Postop day ☐☐   Postoperative bleed ☐N ☐ Y Postop day ☐☐

Cardiac arrest ☐N ☐ Y Postop day ☐☐   Other severe complication ☐N ☐ Y Postop day ☐☐

Days in hospital after surgery ☐☐

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

☐ Alive & discharged → if alive and discharged, was patient transferred to another facility for higher care? ☐ Yes ☐ No

If deceased, photo of clinical note of death uploaded: ☐ Yes   CRF completed and verified by............... on dd/mm/2019

ASOS-2 unique patient ID ☐☐☐☐☐☐☐☐☐☐   ASOS-2 Trial CRF v4 (Control arm)

✂ -

Patient name: ______________________   DOB d d m m y y y y

Patient hospital number : ____________   ASOS-2 unique patient ID ☐☐☐☐☐☐☐☐☐☐

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

ASOS-2
African Surgical OutcomeS-2 Trial

Age ☐☐☐ years (<30 points; 0 points/ 30-69 years; 1 point/ ≥70 years; 3 points) Sex ☐ M ☐ F

ASA ☐ I (0 points) ☐ II (2 points) ☐ III (5 points) ☐ IV (8 points) ☐ V (8 points)

Chronic co-morbid disease (tick all that apply): ☐ Hypertension ☐ HIV / AIDS ☐ Diabetes mellitus ☐ COPD / Asthma

Surgical procedure category (select *single* most appropriate): ☐ Gynaecology (minus 1 point) ☐ Obstetrics (minus 1 point)

☐ Orthopaedic (0 points) ☐ Ear, nose and throat (3 points) ☐ Plastics or breast (1 point) ☐ Urology (2 points)

☐ Neurosurgery(4 points) ☐ Gastro-intestinal or Hepato-biliary(3 points) ☐ Cardiothoracic/ vascular(3 points) ☐ Other(0 points)

Indication for surgery:

☐ Non-communicable disease (0 points) ☐ Caesarean section (minus 2 points) ☐ Trauma (1 point) ☐ Infection (2 points)

Urgency of surgery: ☐ Elective (0 points) ☐ Urgent (3 points) ☐ Emergency (4 points)

Severity of surgery: ☐ Minor (0 points) ☐ Intermediate (2 points) ☐ Major (4 points)

Start of surgery time (24h) & date: h h : m m d d m m 2 0 1 9

ASOS Surgical Risk Score points per risk factor:

☐ Age + ☐ ASA + ☐ Surgical procedure category + ☐ Indication for surgery + ☐ Urgency surgery + ☐ Severity surgery = ☐☐ points

Time that the ASOS Surgical Risk Score was calculated: ☐ Pre-op ☐ Intra-op ☐ Immediately post-op

Predicted ASOS Risk Score: ☐ Not high-risk patient (<10 points) ☐ High-risk patient (≥10 points)

Postoperative Follow Up

☐ Not high-risk patient: (*Indicate postoperative care given*): Higher care ward ☐ No ☐ Yes Increased nursing observations ☐ No ☐ Yes

Assigned a bed in view of nurses' station ☐ No ☐ Yes Family with patient in ward ☐ No ☐ Yes

☐ High-risk patient: (*Indicate all postop surveillance*)	Day 0	Day 1	Day 2	Day 3	Day 4+
Higher care ward	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Increased nursing observations	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Assigned a bed in view of nurses' station	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Family with patient in ward	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
'Postoperative surveillance bedside guide' at the patient's bedside?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Severe complications (tick *all* that apply): Superficial or deep surgical site, or body cavity infection ☐ N ☐ Y Postop day ☐☐

Bloodstream infection or ARDS ☐ N ☐ Y Postop day ☐☐ Pneumonia ☐ N ☐ Y Postop day ☐☐

Urinary tract or AKI ☐ N ☐ Y Postop day ☐☐ Postoperative bleed ☐ N ☐ Y Postop day ☐☐

Cardiac arrest ☐ N ☐ Y Postop day ☐☐ Other severe complication ☐ N ☐ Y Postop day ☐☐

Days in hospital after surgery ☐☐

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

☐ Alive & discharged → if alive and discharged, was patient transferred to another facility for higher care? ☐ Yes ☐ No

If deceased, photo of clinical note of death uploaded ☐ Yes CRF completed and verified by............... on dd/mm/2019

ASOS-2 unique patient ID ☐☐☐☐☐☐☐☐☐☐ ASOS-2 Trial CRF v4 (Intervention arm)

✂- -

Patient name: ______________________ DOB d d m m y y y y

Patient hospital number : ____________ ASOS-2 unique patient ID ☐☐☐☐☐☐☐☐☐☐

Appendix 4

ASOS-2 Surgical Risk Calculator Score Card

ASOS-2
African Surgical OutcomeS-2 Trial

The ASOS Surgical Risk Calculator Score card

The ASOS Surgical Risk Score is used to identify patients requiring 'increased postoperative surveillance'

How to calculate the ASOS Surgical Risk Score:

1. **Calculate score before surgery using the table below**
2. **ASOS Surgical Risk Score = Age (points) + ASA (points) + Surgery timing (points) + Surgery severity (points) + Indication for surgery (points) + Surgery (points)**
3. **High-risk patients have ASOS Surgical Risk Score ≥ 10 points**
4. **A high-risk patient has an ASOS Surgical Risk Score ≥ 10 points**
5. **If ≥ 10 points, then organize 'increased postoperative surveillance' after surgery**

Age	**Points**
18- 29	**0**
30-69	**+1**
≥ 70	**+3**
ASA	
ASA 1	**0**
ASA 2	**+2**
ASA 3	**+5**
ASA 4 and more	**+8**
Surgery timing	
Elective surgery	**0**
Urgent surgery	**+3**
Emergent surgery	**+4**
Surgery severity	
Minor	**0**
Intermediate	**+2**
Major	**+4**
Indication for surgery	
Non-communicable disease	**0**
Caesarean section	**-2**
Trauma	**+1**
Infection	**+2**
Surgery type	
Gynaecology/ obstetrics	**-1**
Plastics and breast	**+1**
Urology	**+2**
Ear, nose and throat, gastro-intestinal, hepato-biliary, cardiothoracic, vascular	**+3**
Neurosurgery	**+4**
All other types of surgery	**0**

Appendix 5

'Increased postoperative surveillance' bedside guide

'Increased postoperative surveillance' bedside guide

This is a 'high-risk' surgical patient

This patient requires 'increased postoperative surveillance' and is most likely to experience one of these complications postoperatively

'High-risk' patients most commonly experience the following complications.

Most common complications	Consider the following management
Cardiac arrest	Ensure staff know where the emergency drugs and defibrillator are stored
Surgical site infections	Swab wound for microbiology, and consider antibiotics
Bloodstream infections	Consider early blood cultures, and consider antibiotics
Pneumonia	Physiotherapy, mobilise early, sputum & blood cultures, & consider antibiotics
Acute kidney injury	Ensure adequate hydration, monitor the serum creatinine
Postoperative bleed	Look for signs of hypotension, and decreasing haemoglobin

If for any reason you are concerned about the patient's condition postoperatively,

then please look for these complications

Appendix 6

Statistical Analysis Plan

1. TRIAL OBJECTIVES

1.1. Primary effectiveness objective:

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

1.2. Secondary effectiveness objective:

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

2. TRIAL OUTCOME EVENTS

2.1. Primary effectiveness outcome for evaluation of increased postoperative surveillance for high-risk patients:

In-hospital death censored at 30 days if the patient is still alive and in-hospital.

2.2. Secondary effectiveness outcome:

Composite of severe in-hospital complications and death censored at 30 days if the patient is still alive and in-hospital.

Severe complications are:

I. Superficial or deep surgical site, or body cavity infection

II. Bloodstream infection or ARDS

III. Urinary tract or AKI

IV. Cardiac arrest

V. Pneumonia

VI. Postoperative bleed

VII. Other severe complications

The definitions of all the secondary outcomes are given in the Appendix 1: Definitions document.

3. STATISTICAL AND ANALYTICAL METHODS

3.1 Study design

The study design is a two arm, cluster randomised trial where randomisation was stratified by hospital level (tertiary, secondary, primary) and carried out in waves to permit ongoing recruitment of hospitals throughout the duration of the trial.

3.2. Analysis population

Primary analysis will be by modified intention to treat population which includes all patients recruited from randomised hospitals where the hospital reported any patient data. Hospitals that are randomised, but do not submit any patient data will be excluded from the modified intention to treat analysis on the presumption that there is no risk of exposure to the trial intervention. Patients will be analysed in the treatment group to which their hospitals were originally allocated.

Secondary analyses will include two analytic approached to two per protocol populations. Refer to table: Secondary analyses based on implementation fidelity. In the first per protocol analysis we will compare all patients from hospitals with data in the standard of care arm to all patients from hospitals with data in the intervention arm where the intervention hospital provided the intervention with fidelity to at least 80% of high-risk patients. Patients from hospitals in the intervention arm where the hospital delivered the intervention with fidelity to fewer than 80% of patients will be excluded from this analysis. In the second per protocol analysis we will compare all patients from hospitals with data in the standard of care arm to all patients from hospitals in the top two tertiles of implementation fidelity. Patients from intervention hospitals in the bottom tertile of implementation fidelity will be excluded from this analysis. At the hospital level we will report implementation fidelity as the proportion of high-risk patients who received the intervention with fidelity. We use two definitions for implementation fidelity; i) provision of at least the high-risk bedside guide plus one additional component of the intervention on days 0 and 1 postoperatively and ii) provision of at least 2 components of the intervention on days 0 and days 1 postoperatively, regardless whether the high-risk beside guide is one of the components.

Secondary analyses based on implementation fidelity		
	Fidelity = High-risk individuals exposed to the bedside guide plus at least 1 additional component of the intervention	Fidelity = High-risk individuals exposed to at least 2 components of the intervention, regardless whether one is the bedside guide
Intervention hospitals where >= 80% of high-risk patients received the intervention with fidelity	**Per protocol analysis 1**	**Per protocol analysis 3**
Top two tertiles of intervention hospitals ranked according to proportion of patients receiving the intervention with fidelity	**Per protocol analysis 2**	**Per protocol analysis 4**

3.2. Effectiveness analyses

3.2.1. Effectiveness analyses

Primary outcome

Relative risk of death in-hospital (within 30d) in the intervention arm vs death in-hospital (within 30d) in the standard of care arm, estimated by univariable generalised estimating equation under a binomial model with a log link and assuming an exchangeable correlation structure. Clustering will be assumed to be on hospitals within countries in a fully nested framework.

Secondary outcome

Relative risk of death in-hospital or severe complication (within 30d) in the intervention arm vs death in-hospital or severe complication (within 30d) in the standard of care arm. Analysis approach will be as in primary outcome.

3.2.2. Sensitivity and subgroup analyses on the effectiveness outcomes

Sensitivity analysis will investigate the potential for unobserved outcomes (transfer out or lost to follow up) to impact primary and secondary effectiveness estimates. Under the same model as the primary (secondary) effectiveness outcomes individuals with unobserved outcomes (lost to follow up) will alternately be assumed to be alive at discharge (censored at thirty days) or to have died in-hospital within 30 days. These estimates and confidence intervals will be plotted along with the primary (secondary) effectiveness estimates.

Primary and secondary endpoints will be analysed under the same model as the primary analysis for the following subgroups treated as stratification variables:

i) hospital level (primary, secondary, tertiary),

ii) duration of recruitment (1, 2 , 3 or 4 weeks)

iii) Calendar time (quarters)

iv) Income category of country (low or middle, according to the World Bank classification in 2020)

3.2.3. Patient risk factors and patient level analysis

A prespecified patient level analysis will be undertaken including all high-risk individuals with data in a standard of care hospital, and all high-risk individuals in an intervention arm who can be presumed to be exposed to the intervention (definition 1: poster and one other intervention on day 0 and day 1; definition 2: any 2 interventions on day 0 and day 1). The relative risk of experiencing the primary (secondary) outcome by exposure to intervention (as defined above) will be estimated in stratified models for the following individual characteristics:

I. age (years)

II. ASA status (1-5)

III. surgical procedure category (Gynaecologic, Obstetric, Neuro, ENT, Orthopaedic, Plastics and Breast, Urology, Gastrointestinal and Hepatobilliary, Cardiothoracics, Other)

IV. indication for surgery (non-communicable disease, caesarean section, trauma, infection)

V. urgency of surgery (elective, urgent, emergent)

VI. severity of surgery (minor, intermediate, major)

This concludes the pre-specified analyses for ASOS-2. Further exploration of the data will take place.