‘5 Rs to Rescue’

A cluster trial with an embedded process evaluation

Multi-centre, cluster trial with a baseline assessment to evaluate the efficacy of the ‘5 Rs to Rescue’ quality improvement intervention. The trial will incorporate a mixed-methods process evaluation of the trial intervention in 20 centres in 4 countries (Ethiopia, South Africa, Tanzania and Uganda)

Study

To evaluate whether implementation of the ‘5 Rs to Rescue’ quality improvement intervention increases surveillance for patients at risk of ‘failure to rescue’ after surgery in hospitals in Africa.

Statistical Analysis Plan (SAP)

Version 1.0

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Based on ‘5 Rs to Rescue’ protocol version 1.0 HREC approved”

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Remit of the SAP

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the paper of the 5 Rs study documenting the processes involved in the delivery of the quality improvement intervention in African hospitals. It is important to set these out and to agree them in advance of inspecting the outcome data for the study, so that data derived decisions in the analysis are avoided. Any exploratory, post hoc, or unplanned analysis will be clearly identified as such in the statistical analysis report.

Timing of the SAP

The SAP version 1.0 was written prior to analysis and prior to those writing the SAP having access to the trial data.

1. Study Summary

Short title	**'5 Rs to Rescue': A cluster trial with an embedded process evaluation**
Methodology	A multi-centre cluster trial.
Research sites	Surgical wards in 20 centres in 4 countries (Ethiopia, South Africa, Tanzania, and Uganda).
Primary objective and outcomes	To evaluate whether implementation of the '5 Rs to Rescue' quality improvement intervention increases surveillance for patients at risk of 'failure to rescue' after surgery in hospitals in Africa.
Secondary objective and outcomes	1. 30 day in-hospital mortality 2. Duration of hospital stay
Number of patients	All eligible patients within the year of recruitment. The maximum sample size required for the primary efficacy outcomes is 539 per group.
Inclusion criteria	Hospitals: 1. Sufficient volume of high-risk patients (ASOS Surgical Risk Calculator Score >10) having surgery, defined as ≥7 high risk patients having surgery per week 2. Confirmed engagement with the surgical and nursing teams on target surgical wards Patients: Patients aged 18 years and older undergoing any surgery, who receive postoperative care on a participating ward.
Exclusion criteria	Hospitals: 1. Insufficient volume of high-risk patients having surgery. 2. No confirmed engagement with surgical and nursing teams. 3. Participation in similar improvement programmes within previous 12 months (Ward level only exclusion criteria). Patients: 1. Patients who opt out of trial participation. 2. Patients receiving end of life care.

Trial design	Multi-centre, cluster trial with a baseline assessment to evaluate the efficacy of the '5 Rs to Rescue' quality improvement intervention. The trial will incorporate a mixed-methods process evaluation of the trial intervention.
Patient follow-up	Until hospital discharge or 30 days from surgery, whichever occurs first
Data collection duration	The duration of the entire study was twelve months starting with a 'Set-up' Phase lasting three months, followed by a six-month 'Adaptation' Phase and ending with a three-month 'Sustainability' Phase. All patients were followed until hospital discharge or censored at 30 days
Proposed start date	The first site to start recruited started in August 2024.
Proposed end date	The last site to start recruitment is expected to end on 11 March 2026.

2. Introduction

'Failure to rescue' describes the preventable death of a patient following a complication after surgery. Patients who develop complications after surgery, such as haemorrhage or infection, begin to deteriorate physiologically and become acutely unwell. This is usually identified by careful monitoring of the patient's basic 'vital signs' which include pulse rate, respiratory rate, oxygen saturation, blood pressure and consciousness level. However, if physiological deterioration is not identified and treated in a timely manner, it will progress and lead to organ dysfunction and then organ failure. This will ultimately lead to cardio-respiratory arrest and the death of the patient.

'Failure to rescue' can be used as a key concept in delivering safe and effective perioperative care as well as a healthcare quality metric in general. The first African Surgical Outcomes Study (ASOS-1) showed that 'failure to rescue' is the mode of death in 19 out of 20 deaths following surgery across Africa.[1] Hospitals in high-income countries use early warning systems to monitor patients after surgery and trigger the escalation of care for patients who are critically ill to ensure prompt treatment. However, these systems do not exist in many resource-poor African hospitals where nurse: patient ratios can be as high as 1:35 and limit capacity-to-rescue within the system. Furthermore, in many African hospitals they do not use early warning systems to monitor patients following surgery. These factors contribute to the higher mortality post-surgery in Africa compared to high-income countries.

As patient outcomes tend to improve when enhanced monitoring increases the identification and treatment of critically ill patients,[2-4] we have co-produced a complex intervention with healthcare staff, community engagement and involvement (CEI) partners, and the Institute for Health Improvement (IHI) across four African countries (Ethiopia, South Africa, Tanzania and Uganda) to improve the capacity-to-rescue. This complex quality improvement intervention focuses on improving five main areas of patient management following surgery: 1) Risk assessment, 2) Recognition of patient deterioration, 3) Response to patient deterioration, 4) Reassessment following intervention to manage deterioration, and 5) Reflection on care provided following a patient's death. The complex quality improvement (QI) intervention is known as '5 Rs to Rescue'. Ultimately, we intend to conduct a large international cluster randomised trial of the '5 Rs to Rescue' intervention comparing patient important outcomes for patients undergoing major surgery between intervention and usual care hospitals. We hope to demonstrate that the '5 Rs to Rescue' intervention can decrease 'failure to rescue' in Africa, and improve postoperative survival.

However, to inform the large international cluster randomised trial, we need to i) determine the efficacy of the intervention in demonstrating positive change to clinical management and ii) understand the factors which are either positively or negative impacting on the processes involved in the delivery of the quality improvement intervention. We will therefore undertake a pilot cluster trial to assess intervention efficacy with an embedded process evaluation.

2.1 Aim

We intend to conduct a large international cluster randomised trial of the '5 Rs to Rescue' intervention comparing patient important outcomes for patients undergoing major surgery between intervention and usual care hospitals. We hope to demonstrate that the '5 Rs to Rescue' intervention can decrease 'failure to rescue' in Africa, and improve postoperative survival.

2.2.1 Primary objectives

To evaluate whether implementation of the '5 Rs to Rescue' quality improvement intervention increases surveillance for patients at risk of 'failure to rescue' after surgery in hospitals in Africa.

2.2.2 Secondary objectives

To evaluate the effect of the trial intervention on:

1. 30 day in-hospital mortality.
2. Duration of hospital stay.

2.3.1 Cohort

The cohort include any patient 18 years and older undergoing any surgery, who received postoperative care on a participating ward.

2.3.2 Outcomes

2.3.2.1 Primary outcomes

1. The number of ASOS Surgical Risk Calculator Scores documented.
2. The number of completed Early Warning Scores (EWS) within the first 72 hours after surgery.
3. The number of physician patient encounters within the first 72 hours after surgery.

2.3.2.2 Secondary outcomes

1. All-cause in-hospital mortality within 30 days of surgery.
2. Duration of hospital stay (number of days from day of surgery until hospital discharge).

2.3.2.3 Baseline characteristics of the cohort

Patient-specific covariates include:

- Age

- ASA status
- Co-morbidities
- Surgical procedure category
- Indication for surgery
- Urgency of surgery
- Severity of surgery

Hospital-specific covariates include:

- Hospital level
- Number of postoperative beds in wards
- Surgical specialities
- Number of doctors in wards
- Number of ward rounds per day
- Number of nurses during the day
- Number of nurses at night
- Doctor on site at night
- EWS system in ward

2.3.3 Definitions

1. **72 hours after surgery**: 72 hours from the patient's arrival on the ward postoperatively

2. **Documented African Surgical Outcomes Study (ASOS) Score**: ASOS score written in an appropriately visible location on the patients notes / ward charts

3. **Completed Early Warning Scores (EWS)**: This is dependent on the EWS chart chosen.

Each score requires a set of measured and documented vital signs that includes all the following:

- Conscious level (AVPU Scale)
- Respiratory rate per minute
- Oxygen saturation (%)
- Heart rate per minute
- Systolic blood pressure (mmHg)
- Plus documentation of the aggregate score (e.g. for NEWS) or documentation of any out-of-range vital signs (e.g. for the VSDT)

4. **Physician encounters**: any documented reviews of a patient by a physician

5. **Hospital population**: all adult patients aged 18 years or over who have been admitted for inpatient care in any department or ward in participating hospitals on the day of data collection

6. **In-hospital mortality**: Death in-hospital within 30 days of surgery. Patients discharged alive are not followed-up at home.

3. Trial design

The trial will commence with a three-month 'Set-up' Phase which will serve as the control Phase providing baseline data and preparation for change associated with quality improvement. This will be followed by a six-month 'Adaptation' Phase where local clinical teams will receive education and training to implement the '5 Rs to Rescue' quality improvement intervention. This will be supported by Improvement Advisors from the Institute for Health Improvement. We will collect data during this Phase, but this will not be used to describe intervention efficacy. The trial will conclude with a three-month 'Sustainability' Phase to build a learning system for adoption and sustainability of the '5 Rs to Rescue' quality improvement intervention. The 'Sustainability' Phase will provide efficacy outcomes data. Further adaptations to the complex intervention by the quality improvement teams are permissible during this Phase. It is not essential for all clusters to commence the trial on the same date.

The '5 Rs to Rescue' clinical intervention is a complex intervention which comprises five key postoperative care processes designed to reduce 'failure to rescue':

1. Risk assessment: use of the ASOS Surgical Risk Calculator Score for all surgical patients.

For those patients deemed high risk by the ASOS Surgical Risk Calculator Score (>10) or where the clinical team deems the patient high-risk:

2. Recognition of patient deterioration: regular, protocolised vital signs monitoring plus use of an Early Warning Score (EWS) system.
3. Response to deterioration: protocolised escalation based upon EWS plus protocolised care pathways for common complications (e.g. hypoxia, hypovolaemia, sepsis).
4. Reassessment following deterioration: protocolised re-assessment based upon the EWS.
5. Reflection on care provided using structured review tools for daily ward 'huddles' and regular scheduled 'reflection meetings' to discuss patients who deteriorate and/ or died.

Further adaptations to the complex intervention by the quality improvement teams are permissible during the trial. Any adaptions will be described as part of the embedded process evaluation.

4. Statistical Analysis Plan

4.1 Recruitment / Sample size

This is an international trial in four African countries. We included consecutive patients admitted to eight participating hospitals and undergoing surgery. The basis for participation in this trial was opt out i.e., patients were included unless they asked not to be included. All adult patients undergoing surgery were eligible for inclusion in the trial.

The sample size determination is based on four countries contributing approximately five hospitals each to the study.

One-level clustering has been assumed, not accounting for clustering by countries separately. As no intra-cluster correlations (ICC) estimates are available, a high within cluster ICC is assumed (being conservative).

All sample size calculations are for a one-sample proportion tests, testing against a fixed value and accounting for clustering. The fixed values are based on baseline estimates, however, choosing target values might be preferable. System optimisation step rates assumed not used in analyses.

The sample size determination is based on four countries contributing approximately five hospitals each to the study. The sample size calculations for the three co-primary outcomes are the following:

1. Documentation of the ASOS Surgical Risk Calculator Score postoperatively.

Calculation based on i) a control rate from the pilot study of 25%, with ii) a post intervention (a 'Sustainability Phase') compliance of 90%.

alpha	power	K	M	N	delta	p0	pa	rho	CV_cluster
.05	.9	20	.15	3	.65	.25	.9	.1	1.5
.05	.9	20	.1	2	.65	.25	.9	.2	1.5
.05	.9	20	.1	2	.65	.25	.9	.3	1.5
.05	.9	20	.1	2	.65	.25	.9	.4	1.5
.05	.9	20	.1	2	.65	.25	.9	.5	1.5

2. The number of completed early warning scores (EWS) within the first 72 hours postoperatively (high-risk patients only).

Calculation based on a post intervention (a 'Sustainability Phase') compliance of 80% of patients across all sites.

alpha	power	K	M	N	delta	p0	pa	rho	CV_cluster
.05	.9	20	8.3	166	.2	.6	.8	.1	1.5
.05	.9	20	11.45	229	.2	.6	.8	.2	1.5
.05	.9	20	14.55	291	.2	.6	.8	.3	1.5
.05	.9	20	26.95	539	.2	.6	.8	.4	1.5
.05	.9	20	.	.	.2	.6	.8	.5	1.5

3. The number of patients who have documented physician patient encounters within the first 72 hours postoperatively (all postoperative patients).

Calculation will be based on i) control rate of number of physician encounters per patient over 72 hours (1 physician encounter per day), and ii) a post intervention (a 'Sustainability Phase') physician encounter increase of 30% from the baseline rate over 72 postoperative hours.

alpha	power	K	M	N	delta	p0	pa	rho	CV_cluster
.05	.9	20	.25	5	.65	.1	.75	.1	1.5
.05	.9	20	.25	5	.65	.1	.75	.2	1.5
.05	.9	20	.25	5	.65	.1	.75	.3	1.5
.05	.9	20	.25	5	.65	.1	.75	.4	1.5
.05	.9	20	.25	5	.65	.1	.75	.5	1.5

To minimise contamination of control data by the intervention, the baseline data for the 'Set-up Phase' will be from the beginning of the trial to the end of the on-site 3-day intervention training period (also known as the 'Jump Start'). All patients from the 3-month 'Sustainability Phase' (efficacy outcome) will be compared to this baseline period.

A sensitivity analysis will be conducted comparing the sample from the initial three-month 'Set-up Phase', with the final 3-month 'Sustainability Phase' for the efficacy outcomes, as described in the original protocol. It is likely that the full three-month 'Set-up Phase' will be heavily contaminated by the intervention, as the 'Jump Start' occurred during the 'Set-up Phase'.

Participation in the study, and completeness of follow-up will be illustrated by a CONSORT flow diagram.

Patient recruitment and description will be presented as follows:

- CONSORT flow diagram including i) countries, ii) number of eligible patients, iii) patients included and excluded.
- The number of participating hospitals, hospital characteristics and patients at each hospital level will be reported in a table. Detailed hospital characteristics will be provided in a Supplementary Table.
- The patient characteristics of the cohort will be presented in the table.

4.2 Analysis

Outcomes will be presented for the whole cohort. Categorical variables will be described as the number (n/N) and proportions and will be compared using chi-square tests. We will describe continuous variables as either mean and standard deviation or median and inter-quartile range (IQR) based on the data distribution. Comparisons of continuous variables between groups will be performed using t-tests, one-way ANOVA or equivalent non-parametric tests as appropriate.

Basic statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS) version 28.0.1.1 (SPSS Inc., Chicago, IL, USA) and R statistical software: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing (2024) using Studio: Integrated Development Environment for R. Boston, MA: RStudio, Inc. (2024).

4.2.1 Tables

Table 1. Patient characteristics

	All patients (n=?)	**Set-up Phase (n=?)**	**Adaptation Phase (n=?)**	**Sustainability Phase (n=?)**	**P-value**
Age (mean (SD)/median (IQR))					
ASA status - I - II - II - IV - V					
Co-morbidities - Hypertension - HIV/AIDS - Diabetes - Asthma/COPD - Other					
Surgical procedure category - Gynaecology - Obstetrics - Orthopaedic - Ear, nose and throat - Plastics or breast - Urology - Neurosurgery - Gastro-intestinal or hepato-biliary - Cardiothoracic/vascular - Other					

Indication for surgery - NCD - Trauma - Infection - Caesarean section					
Urgency of surgery - Elective - Urgent - Emergency					
Severity of surgery - Minor - Intermediate - Major					

Table S1: Hospital characteristics

	Resources and activities
Hospital level - Primary - Secondary - Tertiary	
Number of postoperative beds in wards (mean (SD)/median (IQR))	
Number of doctors in wards (mean (SD)/median (IQR))	
Number of ward rounds per day (mean (SD)/median (IQR))	
Number of nurses during the day (mean (SD)/median (IQR))	
Number of nurses at night (mean (SD)/median (IQR))	
Doctors on site at night - Yes - No	
EWS system in ward - Yes - No	

Table 2: Primary and secondary outcome characteristics

	All patients (n=?)	Set-up Phase (n=?)	Sustainability Phase (n=?)	P-value
Primary outcomes				
Number of ASOS Surgical Risk Calculator Scores documented (mean (SD)/median (IQR))				
Number of completed Early Warning Scores (EWS) within the first 72 hours after surgery (mean (SD)/median (IQR))				
Number of physician patient encounters within the first 72 hours after surgery (mean (SD)/median (IQR))				
Secondary outcomes				
30-day in-hospital mortality - Dead - Alive				
Duration of hospital stay (mean (SD)/median (IQR))				

Table S2: Patient characteristics stratified by country

	All patients (n=?)	Country 1 (n=?)	Country 2 (n=?)	Country 3 (n=?)	Country 4 (n=?)	P-value
Age (mean (SD)/median (IQR))						
ASA status - I - II - II - IV - V						
Co-morbidities - Hypertension - HIV/AIDS - Diabetes - Asthma/COPD - Other						
Surgical procedure category - Gynaecology - Obstetrics						

- Orthopaedic - Ear, nose and throat - Plastics or breast - Urology - Neurosurgery - Gastro-intestinal or hepato-biliary - Cardiothoracic/vascular - Other						
Indication for surgery - NCD - Trauma - Infection - Caesarean section						
Urgency of surgery - Elective - Urgent - Emergency						
Severity of surgery - Minor - Intermediate - Major						

5. References

1. 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]
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3. O'Cathain A, Croot L, Duncan E, et al. Guidance on how to develop complex interventions to improve health and healthcare. *BMJ Open* 2019;9(8):e029954. doi: 10.1136/bmjopen-2019-029954 [published Online First: 20190815]
4. Johnston M, Arora S, King D, et al. Escalation of care and failure to rescue: a multicenter, multiprofessional qualitative study. *Surgery* 2014;155(6):989-94. doi: 10.1016/j.surg.2014.01.016 [published Online First: 20140207]