The African Critical Illness Outcomes Study (ACIOS)

A prospective, multi-country, multi-centre, observational study to determine the hospital point-prevalence and mortality rates of adult patients with critical illness in acute hospitals in Africa.

Statistical Analysis Plan (SAP)

Version 1.0
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Registration ClinicalTrials.gov - NCT06051526
Based on "ACIOS protocol version 1.0 HREC approved"

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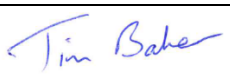
Signature	
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Remit of the SAP
The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper of the ACIOS study. It is important to set these out and to agree them 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 study analysis report.

Timing of the SAP
The SAP version 1.0 was written prior to the investigators having access to the data.

1. Study Summary

Short title	ACIOS
Methodology	A prospective, international, multi-centre, observational study.
Research sites	Acute hospitals in African countries.
Objective	To determine the hospital point-prevalence, and mortality rates of adult patients with critical illness in hospitals in Africa.
Number of patients	Not specified. All eligible patients in participating hospitals.
Inclusion criteria	All in-hospital patients aged 18 years or older in all departments and wards in participating hospitals in Africa.
Exclusion criteria	None
Patient follow-up	Until hospital discharge or death, censored at 7 days after inclusion.
Primary outcomes	1. The presence of critical illness 2. 7-day in-hospital mortality
Data collection duration	One day in each hospital in September-December 2023 plus 7 days follow-up in each hospital
Proposed start date	7th September 2023
Proposed end date	27th December 2023

2. Introduction

Critically ill patients – those in *a state of ill health with vital organ dysfunction, a high risk of imminent death if care is not provided, and the potential for reversibility*.[1] – have particular needs, and managing these needs is a core function of hospitals. Triage at admission and on the wards is needed to identify these patients with critical illness.[2,3] Critically ill patients need regular contact with health workers and close observation and frequent modifications to care, either in general wards, or in specialised locations such as Intensive Care Units (ICUs) and High Dependency Units (HDUs).[4] Rapid Response Teams of acute care specialists may be implemented in hospitals to provide care when called by ward staff.[5]

There are reports of gaps in the readiness and provision of critical care in hospitals in Africa.[6-8] Essential Emergency and Critical Care (EECC) has been developed and defined as the first-line care that should be provided to all critically ill patients.[9,10] Focusing on the first-line care in EECC is a strategy to address the gap in critical care. In our previous work an unmet need of EECC of 50-90% was found in hospitals in Malawi,[8] and there have been many calls to increase the coverage of EECC to address this gap.[9,11-13]

While it is accepted that critical illness and the underlying causes of critical illness are common, the number of patients with critical illness has not been accurately quantified.[14-16] In one region of Sweden we found 10.5% of hospital inpatients to be critically ill,[17] and in a Tanzanian university hospital's emergency unit, 10.7% of patients were critically ill at arrival.[18] Global estimates have been attempted by using the admission rates to ICUs but this method reflects national and local uses of ICUs which vary greatly even between high-income countries.[19] The indirect annual global estimate of 30-45 million adults made by extrapolating the incidence of common diseases leading to critical illness in North America is likely to be an underestimate as the burden of disease is greater in settings of lower resources.[20] Moreover, the mortality of critically ill patients has not been accurately quantified, with reports of 18-82% in-hospital mortality rates.[21-25]

A patient's vital signs (heart rate, respiratory rate, blood pressure, conscious level, body temperature, oxygen saturation) are commonly used measurements in hospital care. Deranged vital signs have been shown to correlate with negative outcomes such as admission to the ICU,[26,27] unexpected cardiac arrest,[27,28] and mortality,[27,29] and are pragmatic and useful as criteria for the identification of critical illness.[30,31]

This prospective, international, multi-centre, observational study of all adult in-patients in hospitals across Africa, is based on the methods we developed in the International Surgical Outcomes Study (ISOS),[32] European Surgical Outcomes Study (EuSOS),[33] African Surgical Outcomes Study (ASOS),[34] and African COVID-19 Critical Care Outcomes Study (ACCCOS)[22] studies. Using vital-signs based criteria, we will determine the hospital point-prevalence of critical illness. We will collect data on the care provided to patients, so to determine the coverage of essential emergency and critical care. We will follow the adult in-hospital patients for 7 days or until hospital discharge (whichever is sooner), allowing an estimate of the mortality rate and patients at increased risk who are critically ill in this population. The knowledge generated in the ACIOS study will assist in improving organisation of acute hospital services with the goal of averting substantial numbers of preventable deaths in African hospitals.

3. Statistical Analysis Plan

3.1 General analysis principles

Data will be presented at a continental African level. All institutional and national 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 (IQR) if not normally distributed. No comparisons between groups will be performed at a univariate level.

For the analysis of the objectives, we will present the following information:

- The number of patients included in each analysis.
- Summary statistics of the outcome (e.g. median (IQR), mean (SD), number (%), range).
- A point estimate, odds ratio or hazard ratio with 95% confidence intervals.
- A two-sided p-value with a significance level of <0.05 will be used where relevant.

For data that are not necessary for each objective, imputation of missing observations will not be made and will be reported descriptively. For data necessary for each objective – see sections 3.4 to 3.8 below.

Statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS) version 28.0.1.1 (SPSS Inc., Chicago, IL, USA).

3.2 Sample Size / Recruitment

As many sites as possible will be recruited in participating countries. All adult patients will be eligible for inclusion in the sites. A sensitivity analysis will be done for each objective including only data from hospitals that recruited >90% of eligible patients. We do not have a specific sample size and statistical models will be adapted to the event rates provided by the sample recruited. Participation in the study, and completeness of follow-up will be illustrated by a STROBE flow diagram.

Patient recruitment and description will be presented as follows:

- STROBE 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 described in Section 3.4 below.

3.3 Objectives

1. To establish the proportion of adult (18 years or older) inpatients in African hospitals that are critically ill.
2. To establish the mortality rate of the critically ill patients and those who are not critically ill.
3. To estimate the proportion of critically ill patients who receive EECC.
4. To investigate the association between the provision of EECC to critically ill patients and mortality.
5. To determine the availability of resources for EECC in African hospitals.

3.4 Statistical analysis plan for Objective 1 "*proportion of patients with critical illness*"

We will present the number and proportion of included patients who have critical illness, where critical illness is defined using the severely deranged vital sign criteria specified in the protocol.

We will present a breakdown of data by vital sign derangement, main category of admission (NCD, maternal, trauma, infection), by ward type (medical, surgical, maternal, other), by ward level (general ward, HDU, ICU), by urgency of admission (emergency, elective), by surgery during admission (yes/no), by known chronic disease/pregnancy, by treatment limitations (Y/N), age and sex. We will present the data in two tables (baseline characteristics of the cohort and vital signs and interventions) with three columns: all patients, critically ill patients, and non-critically ill patients.

Dummy Table 1. Baseline characteristics of the African Critical Illness Outcomes Study (ACIOS) patient cohort

	All patients (n=?)	Patients with critical illness (n=?)	Patients without critical illness (n=?)	Patients who died (n=?)	Patients who survived (n=?)
Age					
Mean (SD)					
Median (IQR)					
Sex					
Male	n/N (%)				
Female					
Known chronic illness or pregnancy					
Pregnant					
Hypertension					
Diabetes					
Cancer					
COPD/ Asthma					
Heart disease					
HIV/AIDS					
Tuberculosis					
Other					
Urgency of admission					
Elective					
Emergency/ acute					
Main category for admission					
Non-communicable					
Maternal health					
Trauma					
Infection					
Ward type					
Medical					
Surgical					
Maternal					

Other					
Ward level					
General ward					
High care ward					
Intensive care unit					

Data are n/N (%). Denominators vary with the completeness of the data. SD standard deviation, IQR interquartile range, HIV human immunodeficiency virus, AIDS acquired immunodeficiency syndrome

Dummy Table 2. Vital signs and essential emergency and critical care treatment interventions of the African Critical Illness Outcomes Study (ACIOS) patient cohort

	All patients (n=?)	Patients with critical illness (n=?)	Patients without critical illness (n=?)	Patients who died (n=?)	Patients who survived (n=?)
Position of patient					
Lying flat on back (<30°)					
Lying on side					
Head-up (30°-60°)					
Sitting (>60°)					
Head-down					
Other					
Airway patency					
Normal					
Partial obstruction					
Complete obstruction					
Conscious level (AVPU)					
Alert					
Responds to voice					
Responds to pain					
Unresponsive					
Heart rate					
Beats per minute					
Oxygen saturation					
Percentage					
Respiratory rate					
Breathes per minute					
Blood pressure					
Systolic blood pressure (mmHg)					

Diastolic blood pressure (mmHg)					
Current interventions					
Receiving intravenous fluids					
Receiving oxygen					
Receiving vasopressor or inotrope					
Airway intervention					

Data are n/N (%) or mean (SD). Denominators vary with the completeness of the data. SD standard deviation, IQR interquartile range, AVPU alert verbal pain unconscious, EECC essential emergency and critical care

Sensitivity analyses:
We will conduct a sensitivity analysis for the definition of critical illness whereby we include all of those in the primary definition of critical illness above, *plus* those who do not currently have a severely deranged vital sign but are receiving one of the EECC treatments specified in section 3.6 *or* receiving advanced critical care (e.g. receiving vasopressor/inotrope or treated in an ICU) – as the provision of these treatments may be masking a vital sign derangement.

We will conduct a sensitivity analysis where all patients with 'treatment limitations' (e.g. not for resuscitation) are removed.

We will conduct two sensitivity analyses for missing data required for an assessment of the presence of critical illness (e.g. a vital sign): a 'best case scenario' where missing data are imputed as normal (i.e. critical illness is not present), and a 'worst case scenario' where missing data are imputed as severely deranged (i.e. critical illness is present).

3.5 Statistical analysis plan for Objective 2 *"mortality"*

We will present the number and proportion of critically ill and non-critically patients who die in hospital within the 7 days of data collection. The defined time for the outcomes is from the point of inclusion of the patient into the study to hospital discharge or death, censored at 7-days. Patients discharged alive are not followed-up at home. Patients still in hospital receiving therapy at 7-days will be regarded as "alive" and included in the study.

In the patients who fulfil the criteria for critical illness, a univariate and multivariable logistic regression models will be constructed to determine the relationship between patient factors and mortality. The patient factors which will be entered into the model will include age, sex, category of admission, chronic diseases and pregnancy.

We will use a three-level generalized mixed model, with patients being at the first level, hospital at the second and country at the third level, to account for the expected correlation in outcomes within hospitals and countries. All factors will be entered into the model, unless the number of reported deaths is insufficient to provide 10 events (deaths) per variable. Should the events per variable be <10, then variables with a univariate association of $p<0.05$, and variables with biological plausibility and a low rate of missing data will be prioritized in the model. Collinearity will be assessed using the variance inflation factor. If collinearity is detected, then variables will either be excluded or combined. The model fit will be evaluated.

We will also present the risk of mortality in those with critical illness at the time of census, compared to those without critical illness using logistic regression. A univariate and multivariable logistic

regression models will be constructed to determine the relationship between patient factors and mortality. The patient factors which will be entered into the model will include age, sex, category of admission, chronic diseases and pregnancy. We will use a three-level generalized mixed model, with patients being at the first level, hospital at the second and country at the third level, to account for the expected correlation in outcomes within hospitals and countries. All factors will be entered into the model, unless the number of reported deaths is insufficient to provide 10 events (deaths) per variable. Should the events per variable be <10, then variables with a univariate association of $p<0.05$, and variables with biological plausibility and a low rate of missing data will be prioritized in the model. Collinearity will be assessed using the variance inflation factor. If collinearity is detected, then variables will either be excluded or combined. The model fit will be evaluated.

A Kaplan-Meier graph will be constructed of the in-hospital mortality from Day 0 to Day 7 for critically ill and non-critically ill patients. Time will be counted from recruitment to the study until discharge, death or censored. The graph will visualize how mortality risk changes over time. A log-rank test for equality of the survival functions will be performed if the assumptions necessary for using the test hold.[35]

Missing data: patients lost-to-follow-up (missing outcome data) will be included without imputation and reported descriptively. They will not be included in the mortality analysis, but will be included in other analyses.

3.6 Statistical analysis plan for Objective 3 *"receiving EECC"*

We will present the number and proportion of critically ill patients who are receiving EECC. In critically ill patients, we define three categories of 'receiving EECC': no intervention, partial intervention (where some critical ill systems are receiving an EECC intervention, and others are not receiving a EECC intervention), and complete EECC intervention (where all critical ill systems are receiving an EECC intervention).

Patients will be deemed to be receiving EECC if they are:

- critically ill due to the conscious level criterion ***and***:
  - are lying in the lateral position ***or***
  - have an oro-pharyngeal or naso-pharyngeal airway inserted in their pharynx ***or***
  - have an ongoing chin-life or jaw-thrust ***or***
  - have other airway protection.
- critically ill due to a respiratory criterion ***and***:
  - are receiving oxygen.
- critically ill due to a circulatory criterion ***and***:
  - are receiving intravenous fluids ***or***
  - are receiving a vasopressor or inotrope.

We will present a breakdown of data by vital sign derangement, the EECC treatment received, main category of admission, ward type, ward level, urgency of admission, surgery during admission, chronic diseases/pregnancy, treatment limitations (Y/N), age and sex.

Dummy Table 3. Baseline characteristics of critically ill patients in the African Critical Illness Outcomes Study (ACIOS) receiving 'essential emergency and critical care (EECC)'

	Critically ill patients (n=?)	Patients receiving no EECC intervention (n=?)	Patients receiving partial EECC intervention (n=?)	Patients receiving complete EECC intervention (n=?)
Airway patency				

Normal				
Partial obstruction				
Complete obstruction				
Conscious level (AVPU)				
Alert				
Responds to voice				
Responds to pain				
Unresponsive				
Heart rate				
Beats per minute				
Oxygen saturation				
Percentage				
Respiratory rate				
Breathes per minute				
Blood pressure				
Systolic blood pressure (mmHg)				
Diastolic blood pressure (mmHg)				
Current EECC interventions				
Receiving intravenous fluids				
Receiving oxygen				
Receiving vasopressor or inotrope				
Airway intervention				

Data are n/N (%). Denominators vary with the completeness of the data. SD standard deviation, IQR interquartile range, AVPU alert verbal pain unconscious, EECC essential emergency and critical care

We will conduct a sensitivity analysis whereby all patients receiving one of the EECC treatments as described above and yet the patient still has one or more severely deranged vital sign is regarded as *not* receiving EECC (as an interpretation that the treatment provided is not sufficient).

We will conduct two sensitivity analyses for missing data required for an assessment of the presence of critical illness (e.g. a vital sign): a 'best case scenario' where missing data are imputed as normal (i.e.

critical illness is not present), and a 'worst case scenario' where missing data are imputed as severely deranged (i.e. critical illness is present).

3.7 Statistical analysis plan for Objective 4 *"association between the provision of EECC and mortality"*

This objective will be addressed in a dedicated, separate manuscript. A separate SAP will be prepared for this analysis.

3.8 Statistical analysis plan for Objective 5 "availability of resources for EECC"

We will present the resources available for EECC in the hospitals through resource availability scores calculated for each hospital as the number of resources available divided by the total number of EECC resources. Summary measures for the hospitals will be presented. Domain resource availability scores will be calculated for each hospital using the same calculations with just the resources in each domain (equipment, consumables, drugs etc) and summary measures presented.

Missing data: items that are missing data required for an assessment of "resources for EECC" (e.g. a resource in a hospital) will not be included in the analysis.

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