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.

Sub-study: Severity of pain in hospitalised patients in Africa

Statistical Analysis Plan (SAP)

Version 1.0
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Registration ClinicalTrials.gov - NCT06051526
Based on "ACIOS protocol version 2.0 HREC approved"

Persons contributing to the analysis plan	
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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 sub-study – "Severity of pain in hospitalised patients" – 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 – pain severity
Methodology	A prospective, international, multi-centre, observational study.
Research sites	Acute hospitals in African countries.
Objective	To determine the severity of self-reported pain in hospitalised patients across 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. To determine patients' self-reported severity of pain in the preceding 24 hours on a scale of 0 – 10. 2. To determine the association between severity of pain and critical illness in adult patients admitted to hospitals across Africa. 3. To determine the association between severity of pain and mortality in adult patients admitted to hospitals across Africa.
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

Introduction

Pain is poorly managed in hospitalised patients (Wu and Raja 2011). Uncontrolled pain in hospitalised patients is strongly associated with both short- and long-term complications. Patients are more likely to develop secondary complications such as sepsis, bleeding, and infarctions if their pain is not adequately managed (Brennan, Carr et al. 2007, van Boekel, Warlé et al. 2019). Further, pain of >7 on a visual analogue scale is strongly associated with an increased risk of persistent pain (Sinatra 2010). In high-income countries, up to 86% of hospitalised patients report having poorly managed pain (Wu and Raja 2011, Gan 2017). However, there is a paucity of the literature on the severity of acute pain in hospitalised patients in Africa. Therefore, this sub-study aims to determine the severity of self-reported pain in hospitalised patients across Africa; and the relationship between severity of pain and (1) critical illness and (2) mortality. This study falls under the ACIOS – African Critical Illness Outcome Study – parent study.

2. 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.

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 (version 4.2.1) in RStudio (RStudio Team 2019).

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 summary tables.

Objectives

1. To determine patients' self-reported severity of pain in the preceding 24 hours on a scale of 0 – 10.
2. To determine the association between severity of pain and critical illness in adult patients admitted to hospitals across Africa.
3. To determine the association between severity of pain and mortality in adult patients admitted to hospitals across Africa.

Statistical analysis plan for Objective 1 *"self-reported pain severity"*

Using the appropriate summary statistics, we will report patients' self-reported report pain severity in the preceding 24 hours from data collection on a scale of 0 – 10, where 0 is 'no pain' and 10 is 'the worst pain you can imagine'. We will report pain severity across all participants as well as for the following groups: patients with critical illness; patients without critical illness; patients who died; and patients who survived.

Some patients were unable to give pain ratings (e.g. patients who were unconscious at the time of data collection). Therefore, we will also present the number of patients who provided pain reports.

Dummy Table 1. Self-reported pain severity 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=?)
Pain severity (0 – 10) *[presented using the appropriate summary statistics]*					

Statistical analysis plan for Objective 2 *"association between severity of pain and critical illness"*

Data on 'critical illness' will be extrapolated from the parent study ACIOS.

We will conduct univariate and multivariate logistic regression models to determine the association between severity of pain (continuous variable) and critical illness (binary variable). Severity of pain will be the independent variable and critical illness will be the dependent variable. The independent patient associated with critical illness identified in the primary paper will be included in the multivariate model. We will follow best practice by using both visual data analysis and formal modelling to investigate this relationship. The specifics of the models will be determined by the data features to achieve the best fitting model that is interpretable.

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.

3.7 Statistical analysis plan for Objective 3 *"association between severity of pain and mortality"*

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.

We will conduct univariate and multivariable logistic regression models to determine the association between severity of pain (continuous variable) and mortality (binary variable). Severity of pain will be the independent variable and mortality will be the dependent variable. Additional patient factors identified in the primary paper to be independently associated with mortality will be included in the multivariate model. We will follow best practice by using both visual data analysis and formal modelling to investigate this relationship. The specifics of the models will be determined by the data features to achieve the best fitting model that is interpretable.

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.

A Kaplan-Meier graph will be constructed of the in-hospital mortality from Day 0 to Day 7 for patients with severe (>7 on VAS) pain and patients *without* severe pain (<7 on VAS). Time will be counted from recruitment to the study until discharge, death or censored. The graph will visualise 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.(Hosmer, Lemeshow et al. 2008)

Missing data: data from patients lost to follow up (missing outcome data) will be included in the statistical analysis without imputation and reported descriptively. Data from these patients will not be included in the mortality analysis (i.e. objective 3), but will be included in other analyses (i.e. objectives 1 and 2).

References

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