Global Neuro-Infections Outcome Study (GNIOS)

An international multi-centre evaluation of surgical care and clinical outcomes for patients with central nervous system infections

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1. List of abbreviations

GNIOS	Global Neuro-Infections Outcome Study
ASOS	African Surgical Outcomes Study
ASOS-PAEDS	African Surgical Outcomes Study for Paediatric Patients
GNOS	Global Neuro-trauma Outcome Study
GHRGABSI	Global Health Research Group on Acquired Brain and Spine Injury
SAPSOS	South African Paediatric Surgical Outcomes Study
TBI	Traumatic Brain Injury
CNS	Central nervous system

2. Summary

Short title	GNIOS
Methodology	A prospective international, multi-centre, observational study
Research sites	Hospitals admitting patients, both adults and children, with *de novo* brain or spine (CNS) infection into surgical departments, in participating countries.
Objective	To map the burden and spectrum of disease and describe surgical management and outcome of patients with *de novo* CNS infections
Inclusion criteria	All consecutive patients admitted to participating hospitals with diagnosed *de novo* CNS infections and referred for surgical consult or management in the specified time-line.
Exclusion criteria	Prior inclusion to study. Iatrogenic post-surgical infections. Patients admitted with CNS infections but NOT referred for surgical consult and NOT undergoing surgical management.
Statistical analysis	The primary outcome measure is 30-day mortality (or to discharge).
Proposed start date	August 2024
Proposed end date	August 2026
Trial duration	Two year, open for recruitment in a two month window for each site (prospective). Open for recruitment in a one year window for each site (retrospective).

3. Introduction

Infections of the central nervous system (CNS) contribute significantly to the global burden of disease [1], especially in countries where infectious diseases are common. CNS infections are typically the most severe manifestation of infectious disease, associated with a high morbidity and mortality. The more severe cases may be associated with intracranial and intraspinal complications that require surgical intervention and treatment [2]; however, this is seldom discussed in the infectious diseases literature. The burden of these CNS infection complications and capacity of neurosurgical teams internationally to treat them is not well characterized [3]. While the medical treatment of CNS infections across the world has been studied in general terms, and post-surgical infections have been well documented in literature, there is less information about the impact these '*de novo'* infections on surgical services and their outcomes. While antimicrobial treatment is well characterised and there are large research projects that address infections in general, the burden of surgical complications of infectious diseases, especially in low- and middle-income countries (LMICs), is not well described. These include complications of bacterial meningitis or local bacterial infection (empyema and abscesses), tuberculosis (tuberculomas, TB abscesses), parasitic diseases (neurocystercercosis, hydatid disease, toxoplasmosis), and post-infectious hydrocephalus [4]. How these complications are treated is important to understand because untreated they almost always lead to death or significant neurological disability. Complications of trauma and infections are the greatest neurosurgical burden in LMICs and effective management often is limited by the unavailability of trained surgical staff and operating capacity in the areas of greatest need. Less is known about the surgical burden of infectious disease than trauma across the world and it is likely that the heterogeneity across different regions is even greater for infectious diseases.

Several factors contribute to differences between LMICs and high-income countries (HICs) in the volume and manifestation of CNS infections. Because of the greater overall burden of infectious diseases in LMICs, it is likely that the volume of

intracranial complications is greater. Due to a higher prevalence of underlying immunocompromise (for nutritional reasons and HIV), complicated and unusual manifestations may occur. Some diseases, such as tuberculosis, are endemic to some regions because they depend on community spread. Others, such as hydatid disease, are endemic because of interactions between humans and animals. It is also likely in LMICs that delayed primary treatment of infection results in more complications that require additional treatment and that may worsen outcome. These delays may be caused by reduced seeking or access to primary healthcare, limited antibiotic availability, lack of control of the primary site of infection, and diagnostic delays due to the lack of easily available imaging. Finally, once the diagnosis is made, there may be a relative lack of access to qualified surgical care in these regions. Even where surgical care is available, this may be constrained by the lack of high care and intensive care facilities needed to support care in patients who already have significant neurological compromise due to advanced disease.

This burden is poorly described and quantified in the literature. Retrospective studies have well-known limitations. Restricting studies to single regions when the manifestation and burden of disease is so geographically heterogenous produces poorly generalizable data. Moreover, the frequency of these cases and outcomes may be over- or under-represented due to the lack of consistent outcome and mortality measures [3]. Critical to providing better care and resources is understanding the burden of disease and the effectiveness of the interventions currently in place.

Similar studies have examined the surgical burden of specific conditions. For example, the Global Neurotrauma Outcome study (GNOS) described surgical outcomes for patients with traumatic brain injury (TBI) patients across a wide range of centres [5]. This generated valuable insights into the burden of TBI in different regions, the access to clinical care, and the outcomes. For all the above reasons, there is a similar need to map the burden of disease and surgical pathways for neurosurgically relevant *de novo* CNS infections across different regions. The results

are expected to inform potential strategies to address the burden of disease adapted to different regions. This knowledge is important because, while the epidemiology and medical management of infectious diseases is well-studied, we know little about the surgical needs and care of patients. Through the recently established Global Health Research Group on Acquired Brain and Spine Injury (GHRGABSI) group, we have a novel opportunity to co-ordinate studies across several different regions the world that encompass a variety of geographic and socio-economic environments.

4. Study objectives

4.1 Primary objective

To describe the profile of patients presenting with CNS infections who require neurosurgical management across a wide range of geographic and socio-economic environments (including patient demographics, baseline clinical characteristics, indications for surgery, surgical procedure, radiology, and microbiological diagnosis).

4.2 Secondary objectives

In patients with *de novo* CNS infections:

1. To describe the current referral, resource, and management pathways.
2. To determine the differences in current indications for conservative management vs surgery.
3. To compare outcomes for patients with *de novo* CNS infections between centers stratified according to the Human Development Index and adjusted for case mix [5].
4. To identify targets for future research and global health interventions.
5. To examine the relationship between seasonal fluctuation and incidence of CNS infection (in selected centers).

5. Methods

5.1 Study design

60-day, international multi-center prospective observational cohort study of patients *de novo* CNS infection (brain and spine) including both adults and children. Sites will be divided into category A and category B based on their

ability to conduct longer term follow-ups. Category A sites will report follow-up data of their patients to hospital discharge or 30 days post-referral. Category B sites will report follow-up data of their patients 6 months post-admission (sites are only eligible for category B if their loss to follow up rate is below 30%, and follow-up at 6 months is part of routine care).

Secondly, a retrospective, one year cohort (at selected sites that have capacity) to chart the seasonal variation of surgical cases.

5.2 Inclusion criteria

All consecutive patients with *de novo* CNS infections for whom 1) surgical consult is obtained or 2) who are admitted to a surgical unit within participating hospitals during the study period, whether or not a surgical procedure is undertaken. Patients will be recruited at each centre over any 60-day period of their choosing between 01.08.2024 through 31.8.2026 (anticipated).

5.3 Exclusion criteria

1. Previous neurological diagnosis
2. Previous neurosurgical procedure
3. Iatrogenic post-surgical infection
4. Patients with *de novo* CNS infection admitted during the chosen 60-day time window who do not require neurosurgery consult or surgical unit admission

5.4 Hospitals

We aim to recruit as many hospitals as possible utilizing the network established through the NIHR ABSI network. A previous study (GNOS) of

traumatic brain injury utilizing this network, published in Lancet Neurology, recruited 1635 patients from 159 hospitals in 57 countries.

5.5 Research Ethics and Informed Consent

Local research ethics and regulatory approvals will be sought before starting the study at each site, in accordance with national research legislation/guidelines for that country. Hospitals will not be permitted to record data unless ethics approval or an equivalent waiver is in place.

Local teams should follow local protocol and guidance to obtain approval from either their service evaluation, clinical audit, research department or head of department prior to commencing any data collection for this study.

This study is in effect a large-scale clinical audit and thus does not pose a significant risk to the study population. We expect that in most, if not every country, there will be no requirement for individual patient consent as all data will be anonymised and is already recorded as part of routine clinical care. This is aimed at maximising inclusion and avoiding bias.

Precedent has already been set internationally in similar prospective observational studies. In the ASOS study[6] and in the ASOS-2 trial consent was waived in the majority of hospitals. In the EuSOS study, consent was waived in 27 of the 28 European countries participating[7]. Written consent was waived by six out of the eight ethics committees in the paediatric version of the perio-operative outcomes study in South Africa (SAPSOS) [7] and in a study in Kenya, written informed consent was waived in all 24 participating hospitals[7]. The value of waiving consent for minimal risk studies is that *all* data are collected (due to consecutive inclusion) and not biased, and there is maximal inclusion of centers with varying capacity.

‘Broadcasting’ signage documents will be used at participating sites to ensure that all patients and parents/guardians are aware that the hospital is

participating in the study, we have made use of broadcasting documents which were previously approved for the ASOS-PAEDS study (HREC: 466/2021). These broadcasting documents will be placed in key areas around participating hospitals explaining the study dates and the nature of the study (Appendix 1,2).

5.6 Recruitment

We expect all consecutive patients admitted to a surgical department with diagnosed *de novo* CNS infection surgery to be included in the study, within a 60-day period.

Broadcasting through appropriate hospital notices and signage will inform the patients, their parents/guardians/ relatives, and the public that the hospital is participating in the study.

5.7 Data collection and collation

Each individual hospital will collect and record data on an electronic record form (eCRF) for every patient recruited using the Research Electronic Data Capture (REDCap) tools hosted by the University of Cape Town, who will act as the data custodian. All electronic data transfer between participating hospitals and the co-ordinating institution will be encrypted using a secure protocol (HTTPS/SSL 3.0 or better). Data will be anonymised during the transcription process. REDCap is a secure, web-based application designed to support databases and data capturing for research studies. Soft limits will be set for data entry, prompting investigators when data were entered outside these limits.

Each patient will only be identified on the eCRF by their numeric code which is generated and transcribed by local investigators; thus, the co-ordinating study team cannot trace data back to an individual patient without contact with the local team. Access to the data entry system will be protected by

username and password delivered during the registration process for individual local investigators.

Each hospital will maintain a secure study file including a protocol, local investigator delegation log, ethics approval documentation, and other additional documentation. The local study team at each site is required to have a senior clinician/ head of surgical unit to lead their group.

A final summary of included patients with aggregated data of patients, and outcomes will be produced for each hospital together with final data submission to double check for completeness and accuracy.

5.8 Dataset

A realistic data set will be fundamental to the success of the investigation, and this proposed study leans heavily on the experience of the EuSOS[6], SASOS[7] and SAPSOS[8] studies where nearly complete data was available on patients. Based on the SAPSOS study of paediatric outcomes in 43 South African hospitals, we have adopted this dataset with minor changes to remove data which was found to be redundant, in order to develop a simple, lean and pragmatic data set. We believe that this simple data set will encourage hospitals to participate.

5.9 Case record forms

A GNIOS eCRF will be completed for every eligible patient who undergoes surgery, and those who consult neurosurgery during the cohort period, based on routinely collected data. Category A sites will report follow-up data of their patients to hospital discharge or 30 days post-referral. Category B sites will report follow-up data of their patients 6 months post-admission. The eCRF document can be found in Appendix 3.

5.10 Sample size calculation

Our plan is to recruit as many hospitals as possible from each participating country and ask them to include all eligible patients in the study. We do not have a targeted sample size and statistical models will be adapted to the event rate provided by the sample recruited.

5.11 Statistical analysis

The data to be collected are all part of routine clinical care data recording. Continuous variables will be described as mean and standard deviation if normally distributed or median and interquartile range if not normally distributed.

Factors will be entered into the models based on their univariate relation to outcome ($p<0.05$), biological plausibility and low rate of missing data.

A statistical analysis plan will be written prior to analysis.

5.12 Primary outcome measure

Survival to discharge or 30 days after referral/ admission, whichever came first.

5.13 Secondary outcome measures

1 Functional outcome (GOS-E/ PGOS-E) at hospital discharge or 30 days, and at 6 months (for participating centres).

2 Length of hospital stay

3 In-hospital complications

4 Number and type of surgical procedures

6. Study organisation and management

6.1 Study steering committee

Prof Anthony Figaji will be principal investigator. There will be a study management team that will be appointed by him and led by him. The Steering Committee will be chaired by Prof Figaji. The duties of this team will include administration of all project tasks, communication between project partners (including funders, Steering Committee members, national and local coordinators, etc.), data collation and management and preparation of reports for individual study sites. The Steering Committee is responsible for the scientific conduct and consistency of the project. The Steering Committee will ensure communication between the funder(s), study management team and co-ordinators as necessary.

6.2 Local co-ordinators

Local co-ordinators in individual institutions will have the following responsibilities:

- Provide leadership for the study in their institution
- Ensure all relevant regulatory and ethics approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and site recruitment and follow up management
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of electronic CRFs
- Assist with translation of study paperwork as required

6.3 Training of investigators

Training will be done using instructional videos placed on the study website. Each study site will be required to complete an online questionnaire as part of the site initiation, prior to starting data collection.

7. Data management and ownership

On behalf of the Steering Committee, the Department of Surgery, Division of Neurosurgery and University of Cape Town will act as custodian of the data. The Steering committee will retain the right to use all pooled data for scientific and other purposes. Members of the GNIOS study group will have the right to access the pooled data for research purposes provided the research proposal has been reviewed and deemed appropriate by the Steering Committee. 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 institutions will be anonymised except in the individualized report provided to each institution at the end of the study. Individual patient data provided by participating sites remain the property of the respective institutions.

8. Publication plan

Data will be presented and disseminated in a timely manner. Participation and authorship opportunities will be based on contribution to the primary study. 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 make the dataset available in whole or part for secondary analyses and scientific publication. The Steering Committee will consider the scientific validity and the possible effect on the anonymity of participating hospitals prior to granting any such requests. Where appropriate, a prior written agreement will set out the terms of such

collaborations. The Steering Committee will consider proposals for secondary analyses on the basis of the scientific quality of the proposal. The Steering Committee must approve the final version of all manuscripts prior to submission, whether they relate to part or all of the GNIOS dataset.

9. References

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