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A prospective multisite severe malaria observational study in African children

Submission date
22/10/2024

Recruitment status
No longer recruiting

Registration date
01/11/2024

Overall study status
Ongoing

Last Edited
18/08/2025

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
In much of sub-Saharan Africa, malaria is the most common reason for children being admitted to the hospital and is a major cause of death in children under five. While it's believed that malaria rates have dropped due to control measures like bed nets and effective treatments, reports on hospital admission rates for malaria are mixed. Some show a decrease, while others show no change or an increase. This study aims to provide a clear picture of severe malaria admissions in children across multiple centers in Africa, using consistent definitions and data collected over several years.

Who can participate?
The study will include children aged 3 months to 15 years who are admitted to pediatric wards with malaria.

What does the study involve?
This study will take place in at least six sites across five countries. It will include two groups: 300 children per site with severe malaria (cases) and 100 children per site with non-severe malaria (controls). Basic data will also be collected from all other children admitted with non-severe malaria. Children already enrolled in this study or in a clinical trial will not be included.

Upon arrival at the pediatric ward, children with suspected malaria will be screened for severe malaria using a rapid diagnostic test and a malaria slide. Cases and controls will undergo a detailed clinical assessment and blood tests. An additional blood sample will be saved for future tests. Follow-up questionnaires and visits will be conducted at discharge, day 28, and day 180 to track outcomes like readmission and survival. No additional blood samples will be taken after enrollment, only malaria status will be checked during follow-up visits. For very sick children, verbal assent from parents/guardians will be sought, with written consent obtained once the child is stable.

What are the possible benefits and risks of participating?
Participants will not receive direct benefits from the study. However, the study will cover the cost of non-routine blood tests, and results will be available to the treating clinician. The study will also cover transport costs for follow-up visits, and parents/caregivers will be compensated

for their time. Any illnesses identified during follow-up visits will be treated or referred appropriately. Parents/guardians will receive health education during these visits. The study aims to improve understanding of severe malaria in children, which could lead to better care in the future.

Where is the study run from?
KEMRI Wellcome Trust Research Program in Kilifi, Kenya.

When is the study starting and how long is it expected to run for?
October 2019 to December 2025

Who is funding the study?
Wellcome (UK)

Who is the main contact?
Professor Kathryn Maitland, k.maitland@imperial.ac.uk

Contact information

Type(s)
Scientific, Principal Investigator

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Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Grant Number 209265/Z/17/Z

Study information

Scientific Title
Severe MAlaria A Research and Trials consortium: A protocol for a prospective observational study

Acronym
SMAART

Study objectives
The null hypothesis is that there will be no differences in the severity spectrum or outcomes from severe malaria across 6 sites across 5 African countries.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 26/10/2022, Imperial College Research Ethics Committee (Room 221 Medical School Building St Marys Campus, London, W2 1PG, United Kingdom; +44 (0)207 594 1872; researchethicscommittee@imperial.ac.uk), ref: 20IC5695

Study design
Prospective observational study

Primary study design
Observational

Secondary study design
Nested case-control study

Study setting(s)
Hospital

Study type(s)

Diagnostic, Other

Participant information sheet
Not available in web format, please use contact details to request patient information sheet

Health condition(s) or problem(s) studied
Severe Plasmodium falciparum malaria

Interventions
Current interventions as of 18/08/2025:

The primary aim is to characterise the contemporary epidemiology (including features at presentation, diagnostic and treatment pathway) of severe malaria in children in Africa presenting to hospital for admission, through conducting a prospective multicentre observational study across at least 6 sites in 5 countries. The study is enrolling (i) hospitalised children with severe malaria (cases): 300 per site and (ii) time-matched hospitalised children with non-severe malaria (controls): 100 per site. Both cases and controls will be followed over 6 months from admission. In addition, basic observation and in-hospital outcome data (but without follow up) will be collected from all other children admitted with non-severe malaria ('background').
This will also enable us to compare baseline characteristics of admitted children with severe and non-severe malaria; characterise time from presentation to the hospital 'gateway' to ward admission and time to first dose of parenteral artesunate to assess whether delays in definitive treatment may underpin malaria severity and estimate the incidence of significant post-discharge events to day-180 including readmission to hospital. In two sites in Uganda (Soroti Regional Referral Hospital and Dr Amboseli Hospital, Kalongo) admission samples (following consent) will be stored for batch genotyping for Kelch (PfK13) mutations of Plasmodium falciparum malaria (under the SMAART-CHARISMA substudy- see attached Protocol file v1.0 FINAL).

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Previous interventions:

The primary aim is to characterise the contemporary epidemiology (including features at presentation, diagnostic and treatment pathway) of severe malaria in children in Africa presenting to hospital for admission, through conducting a prospective multicentre observational study across at least 6 sites in 5 countries. The study is enrolling (i) hospitalised children with severe malaria (cases): 300 per site and (ii) time-matched hospitalised children with non-severe malaria (controls): 100 per site. Both cases and controls will be followed over 6 months from admission. In addition, basic observation and in-hospital outcome data (but without follow up) will be collected from all other children admitted with non-severe malaria ('background').
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hourly using malaria blood films and point of care lactate (Stat Strip Lactate Test Strips, BioNova) for the first 24 hours and 8 hourly thereafter until lactate levels < 2 mmols and malaria slides are negative to allow us to track artesunate antimalarial activity and clinical severity overtime.

Intervention Type
Other

Primary outcome measure
Measured using patient records:
1. Mortality: in-hospital or subsequently through 6 months post-discharge (all- cause) and
2. Readmission to hospital within 6 months of enrolment all-causes and with a positive malaria rapid diagnostic test (RDT)

Secondary outcome measures
1. New episodes of potential malaria, defined by self-reported anti-malarial use, self-reported positive malaria rapid diagnostic test (RDT), and self-reported febrile illnesses at follow up
2. In Soroti and Kalongo sites the prevalence of Kelch Mutations will be measured along with lactate clearance and parasite clearance of ring stage parasites

Overall study start date
06/10/2019

Completion date
31/12/2025

Eligibility

Key inclusion criteria
1. Children aged 3 months to 15 years
2. Admitted to hospital with P. falciparum malaria defined by a positive ParacheckTM rapid diagnostic test
3. History of fever by self-report or documented abnormal temperature at screening (fever or hypothermia, axillary temperature >37.5°C or <36°C)
4. Caregiver provides written informed consent, including for 6-month follow-up for severe malaria cases and non-severe malaria controls
5. Cases are defined as having either one or more of World Health Organization (WHO) Group 1 or 2 severity features or Teule Criteria
5.1. WHO clinical severity features include
5.1.1. Impaired consciousness: prostration (also Teule criteria) or coma
5.1.2. 2 or more convulsions within the last 24 hours
5.1.3. Respiratory distress (also Teule criteria)
5.1.4. Compensated or decompensated shock
5.1.4.1. Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension
5.1.4.2. Decompensated shock (hypotension) is defined as systolic blood pressure <70 mm Hg in children
5.1.5. Jaundice
5.1.6. Dark or cola coloured urine (blackwater fever)
5.2. WHO laboratory severity criteria, consisting of
5.2.1. Haemoglobin <5g/dl (also Teule criteria) (if routinely done)

5.3. Teule criteria consist of one or more of
5.3.1. HIV (standard test for all hospitalised children)
5.3.2. Impaired consciousness: prostration or coma (also WHO clinical criteria)
5.3.3. Respiratory distress (also WHO clinical criteria)
5.3.4. Haemoglobin <5g/dl (if routinely done) (also WHO clinical criteria)

For practicality, and to reduce potential bias, recruitment of controls (children admitted with malaria without the above features) will occur on Mondays and Thursdays only

Participant type(s)
Patient

Age group
Child

Lower age limit
3 Months

Upper age limit
15 Years

Sex
Both

Target number of participants
1800 cases (~300 per site) and 600 controls (100 per site)

Total final enrolment
1985

Key exclusion criteria
1. Already enrolled into a clinical trial
2. Previously enrolled in this observational study

Date of first enrolment
28/08/2021

Date of final enrolment
30/06/2024

Locations

Countries of recruitment
Ghana

Kenya

Mozambique

Uganda

Zambia

Study participating centre
St Pauls Hospital
Luapula Province
Nchelenge
Zambia
P.O. Box 71769

Study participating centre
Soroti Regional Hospital
Hospital Road
Soroti
Uganda
P.O. Box 289

Study participating centre
Dr Ambroseli Hospital
Hospital Road
Kalongo
Uganda
P.O. Box 47

Study participating centre
Kilifi County Hospital
KEMRI Wellcome Trust Research Programme,
Hospital Road
Kilifi
Kenya
P.O. Box 230

Study participating centre
Manhica Health Research Centre (CISM)
Av.Julius Nyerere, Estrada regional numero 470, Bairro Namuinho
Manhica
Mozambique
P.O. Box 1929

Study participating centre

Komfo Anokye Teaching Hospital (KATH)
Department of Child Health, Kwame Nkrumah University of Science and Technology, Bantama High Street
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P.O. Box 1934

Sponsor information

Organisation
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Sponsor type
University/education

Website
http://www.imperial.ac.uk/

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
Wellcome

Alternative Name(s)

Funding Body Type

Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
All publications and presentations relating to the study will be authorised by the study Management Group (SMG). The first publication of the study results will have named authors including at least the study's Chief and Site Investigators, Statisticians and Site Specific Coordinators. Authorship of parallel studies initiated outside of the SMG will be according to the individuals involved in the project but must acknowledge the contribution of the SMG and the Study Coordination Centre.

Imperial College and the SMG are the custodians of the data and specimens generated from SMAART study. Data are not the property of individual participating investigators or health care facilities where the data were generated.

During the course and following completion of the trial there will be publications, including manuscripts and abstracts for presentation at national and international meetings, as well as the preparation of manuscripts for peer-reviewed publication. In order to avoid disputes regarding authorship, we have established a consensus approach that will provide a framework for all publications derived in full or in part from this study.

In line with Wellcome policy that the results of publicly-funded research should be freely available, manuscripts arising from the study will be submitted to peer-reviewed journals which enable Open Access immediately, for example via UK PubMed Central (PMC). All publications will acknowledge the trial's funding sources.

The SMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, substudy reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing.

All headline authors in any publication arising from the main study or sub-studies must have a made a significant academic or project management contribution to the work that is being presented. "Significant" must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of patients who contributed data to any set of analyses contained in the manuscript, and /or the conduct of analyses (laboratory and statistical), leadership and

coordination of the project in the absence of a clear academic contribution.
Any requests for access to raw data will be welcomed as long as they are scientifically valid and do not conflict with the integrity of the study or ongoing analyses by the trial team.

Intention to publish date
30/05/2025

Individual participant data (IPD) sharing plan
We have a data sharing plan for investigator and external requests. Data from SMAART study will be shared according to a controlled access approach (outlined above) in accordance to Wellcome (the funders) policy based on the following principles:
No data should be released that would compromise an ongoing study.
There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers.
There sources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore, adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources. Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.1	10/10/2022	31/10/2024	No	No
Statistical Analysis Plan	version 1.0	20/10/2024	31/10/2024	No	No
Protocol file	version 1.0	28/07/2023	18/08/2025	No	No