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Severe malaria in African children: A randomised clinical trial with an adaptive design

Submission date
11/12/2023

Recruitment status
Recruiting

Registration date
11/01/2024

Overall study status
Ongoing

Last Edited
17/12/2024

Condition category
Infections and Infestations

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

Plain English Summary
Background and study aims
Severe malaria remains a common cause of child hospitalisations and deaths in African children. Even on the best anti-malarial treatments (injectable artesunate) many African children with severe malaria have poor outcomes with most deaths occurring within 24 hours of arrival at hospital. Children with the complications of altered consciousness and seizures (cerebral malaria), impaired renal function, or anaemia have poor outcomes. We have identified supportive (adjunctive therapies) for each of the complications and would like to test these in a multicentre Phase II trial using a platform trial design (master protocol with multiple domains). The objective of the trial is to identify promising adjunctive therapies to take forward into a large Phase III trial in severe malaria. The adaptive platform design enables additional domains to be added so a range of adjunctive therapies can be tested, across multiple clinical presentations of severe malaria, in a timely manner.

Who can participate?
The target population for the trial is children, aged >3 months and <12 years who are hospitalised with severe malaria in 7 sites in 6 countries (Uganda, Zambia, Ghana, Kenya, Democratic Republic of the Congo and Mozambique).

What does the study involve?
Each domain (renal, cerebral, or severe anaemia) will enrol 150 children, randomising them 1:1 to an experimental intervention versus standard of care or control.
A computer programme will assign a child to receive either the adjunctive treatment or the standard of care at that site within a domain at random (like the flip of a coin). Each child can only be enrolled to one domain and thus possibly receive one adjunctive treatment through the trial. Each child will be monitored through bedside observations and depending on the domain they may need some additional tests. This information will help us compare how children receiving the adjunctive therapy and receiving standard of care are responding to their treatment.

What are the possible benefits and risks of participating?
Benefits:
All patients will be closely monitored so that clinical deteriorations can be identified at the

earliest opportunity and appropriate therapy initiated. In general, the trial sites have considerable experience with this population, and this will serve to minimise the risks to the patients and the trial. All routine non-trial medications required by the hospital to treat the child will be made available. Hospital bills for participants older than 5 years will be covered by the study (covering the costs for standard treatment for severe malaria and related complications). The parents or guardians for the children will be asked to return for a follow up clinic visit at day 28 and day 90 and thus will be offered continuing care for concurrent illness, including any investigations or blood tests that are clinically indicated.
Risks:
The trial is being performed in children who may potentially benefit from treatment. The children in this trial will have an additional full blood sample taken compared to a child outside of a trial. This will be used to obtain a full blood count (which in most countries is standard practice in severely ill children as it helps with patient management). The children will already have a cannula inserted for clinical management (for giving intravenous antimalarials, antibiotics, fluids and transfusions) and no additional cannula would be inserted. The risks of cannula insertion and blood drawing include pain, infection at the site of the cannula and thrombophlebitis. These will be minimised by careful technique according to a standard SOP, cannula site inspection and replacement or removal where necessary. No more than 1ml/kg of blood will be drawn for research at any one time. The other blood tests used to monitor children are point-of-care tests (for haemoglobin or creatinine for example) and thus need only a pinprick of blood, as does the POC pfHRP2 test for severe malaria which we propose to validate within this trial.

Where is the study run from?
1. Imperial College London (UK)
2. KEMRI-Wellcome Trust Clinical Trials Facility in Kilifi (Kenya)

When is the study starting and how long is it expected to run for?
November 2023 to October 2026

Who is funding the study?
Wellcome Trust (UK) (grant number 209265/Z/17/Z)

Who is the main contact?
The chief investigator is Kathryn Maitland (k.maitland@imperial.ac.uk)
The trial manager is Emmanuel Oguda (e.oguda@kemri-wellcome.org)

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
209265_Z_17_Z

Study information

Scientific Title
Severe Malaria A Research and Trials consortium - Multisite Adaptive Platform trial: SMAART-MAP trial

Acronym
SMAART MAP

Study hypothesis
We are using an adaptive platform design to test whether a number of adjunctive therapies directed at treating the complications (domains) of severe malaria in African children improves outcome either of surrogate biomarker or by clinical assessment at 24-72 hours compared standard or control. The adaptive design allow the addition of domains to be added so a range

of adjunctive therapies can be tested, across multiple clinical presentations of severe malaria, in a timely manner.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. Approved 21/06/2024, Imperial College Research Ethics Comittee (Joint Research Compliance Office,Imperial College London Room 215,Level 2, Medical School Building, Norfolk Place, London, W2 1YN, United Kingdom; +44 20 7594 1872; r.nicholson@imperial.ac.uk), ref: 6887850

2. Approved 17/07/2024, Scientific and Ethics Review Unit (SERU) Kenya Medical Research Institute (PO Box 5440 00200, Nairobi, 54400020, Kenya; +254 722205901; seru@kemri.go.ke), ref: CGMR-C/213/4952

3. Approved 16/05/2024, Infectious Diseases Institute Research Ethics Committee (College of Health Sciences, Makerere University, IDI-McKinnell Knowledge Centre, Kampala, P.O. Box 22418, Uganda; +256-31-2211422; research@idi.co.ug), ref: JCRC-2024-67

4. Approved 05/09/2024, National Health Research Ethics Board (Chalala Office Lot No 18961/M, Off Kasama Road, Lusaka, PO Box 30075, Zambia; +260 211250309; info@tdrc.org.zm), ref: TDREC/169/07/24

5. Approved 16/08/2024, Committee on Human Research Publication and Ethics. College of Health Science (Kwame Nkrumah University of Science and Technology. Room7 Block J, School of Medical Sciences, University Post office, Kumasi, Uni PO, Ghana; +233 20 5453785; chrpe.knust.kath@gmail.com), ref: GHS-ERC:023/06124

6. Submitted 18/12/2023, CISM Internal BioethicsCommittee for Health (Saúde do Centro de Investigação em Saúde da Manhiça, 12th Street, Manhica, CP 1929, Mozambique; +258 21 81 01 81; secretariado.cibs@manhica.net), ref: Reference number not provided

Study design
Multicentre interventional phase III randomized platform trial

Primary study design
Interventional

Secondary study design
Platform trial

Study setting(s)
Hospital

Study type(s)
Treatment, Safety, Efficacy

Participant information sheet
To follow

Condition

Severe malaria

Interventions
In each domain (i.e. renal, cerebral, or severe anaemia complications of malaria) participants will be randomised 1:1 using an online tool to either:

1. High dose paracetamol (20mg/kg every 6 hours for 66 hours (last dose), given rectally, orally or via a nasogastric tube) compared to no or minimal paracetamol for fever reduction only (10mg /kg no more frequently than every 8 hours) (control) for those with impaired renal function (renal domain)

2. Parenteral levetiracetam (40 mg/kg loading dose and then 30mg/kg at 12 hours and 24 hours for all children, with doses at 36 hours and 48 hours only if the child has a temperature of >37.5° C or had a temperature of >37.5°C within the preceding 12 hours, or has a Blantyre Coma Score of ≤4) as prophylaxis to prevent further seizures compared to standard of care following national guidelines at each site (no prophylaxis) for children in the cerebral malaria domain

3. Blood transfusion with whole blood (20mls/kg if temperature at screening is >37.5ºC, 30mls /kg if temperature is ≤37.5ºC) compared to red cell concentrate (10mls/kg if axillary temperature is >37.5ºC; 15mls/kg if axillary temperature is ≤37.5ºC) for those with severe anaemia (severe anaemia domain)

Intervention Type
Mixed

Primary outcome measure
Primary outcome is specific to each domain:

Renal Domain: Area Under the Curve (AUC) for creatinine over the first 72 hours from Randomisation. Creatinine will be measured by a laboratory biochemistry machine on stored plasma samples taken at randomisation (treated as time 0/baseline), 24, 48 and 72 hours. The AUC will be calculated from these measurements.

Cerebral Malaria domain: the number of witnessed seizures by medical staff which result in starting or changing anticonvulsant medication by 72 hours. The child will have regular scheduled, and where clinically indicated non-scheduled, assessments by the trial team which will assess for witnessed seizures since the last assessment and will be recorded in the CRF.

Severe Anaemia domain: change in haemoglobin at 24 hours (adjusted for baseline). Haemoglobin will be measured using a point-of-care analyser (HaemoCue ® Hb 301 System, AngleHolm, Sweden) at randomisation (treated as time 0/baseline) and at 24 hours.

Secondary outcome measures
For all domains are readmissions to hospital and mortality to day 28 and day 90; grade 3 or 4 adverse events (AEs) during admission ascertained by questionnaire to parental/carer .

Renal domain outcomes:
1. Creatinine at 24 hours (change from baseline, adjusted for baseline); Creatinine at 48 hours (change from baseline, adjusted for baseline); Creatinine at 72 hours (change from baseline, adjusted for baseline). Measurement are on laboratory biochemistry machines (real time or on stored plasma samples).

Renal domain safety outcomes:
2. Change in Alanine transaminase (ALT) or Aspartate transaminase (AST) (liver enzymes) at 72 hours (adjusted for baseline) measured on biochemistry machines (real time or on stored plasma samples)
3. Adverse events (AEs) of any grade judged related to paracetamol assessed by the clinician
4. AEs of any grade causing a change in paracetamol administration

Cerebral malaria domain outcomes:
1. Time to fully regain consciousness (BCS 5 (the maximum score)) assessed by the clinician on the clinical coma score assessment
2. Adverse events (AEs) of any grade judged related to anticonvulsants assessed by the clinician
3. Solicited AEs
4. Neurological sequelae by day 28 and day 90 assessed by the clinician using structure clinical assessment

Severe anaemia domain outcomes:
1. Change in haemoglobin at 72 hours (measured by HaemoCue ® Hb 301 System, AngleHolm, Sweden)
2. Number of additional transfusions in the acute admission (recorded on prescription chart and case report forms)
3. Development of new profound anaemia (Hb<4g/dl) during acute admission or development of severe anaemia (Hb<6g/dl) post discharge measured by HaemoCue ® Hb 301 System, AngleHolm, Sweden)

Overall study start date
01/11/2023

Overall study end date
30/10/2026

Eligibility

Participant inclusion criteria
For all domains:
1. Aged >3 months and <12 years
2. Admitted to the paediatric ward in the last 24 hours
3. Current or recent evidence of malaria (slide or rapid diagnostic test (RDT) positive in this admission)
4. Guardian willing to provide consent

Additional domain-specific inclusion criteria:

Renal domain:
1. Creatinine >1.5xULN on point-of-care assay or laboratory test at screening
2. Meet one of the current WHO severity criteria (clinical or laboratory (where these tests are done routinely)) (Group 1 and 2 from the recent WHO reclassification of severe malaria))

Cerebral malaria domain:
EITHER
1. One or more reported seizures in the current episode of illness and altered consciousness (BCS≤4) at screening

OR
2. Presence of coma (BCS ≤2) at screening regardless of history

Severe anaemia domain:
1. Hb <6g/dl
2. One or more or the following severity signs: Hb<4g/dl, prostration, impaired consciousness, respiratory distress, history of passing red or coca-coloured urine in this illness

Participant type(s)
Patient

Age group
Child

Lower age limit
3 Months

Upper age limit
11 Years

Sex
Both

Target number of participants
150 per domain ie 450 in total

Participant exclusion criteria
Renal domain:
1. Received paracetamol within 6 hours of screening or between screening and randomisation
2. Known allergy to paracetamol
3. Severe malnutrition (middle upper arm circumference MUAC<11.5cm)

Cerebral malaria domain:
1. Received an anticonvulsant within 6 hours of screening or between screening and randomisation.
2. Known cerebral palsy or significant neuro-development delay

Severe anaemia domain:
1. Known congenital or valvular heart disease (not surgically corrected)

Recruitment start date
01/11/2024

Recruitment end date
30/10/2026

Locations

Countries of recruitment
Congo, Democratic Republic

Ghana

Kenya

Mozambique

Uganda

Zambia

Study participating centre
Mbale Clinical Research Institute (MCRI)
Mbale Regional Referral Hospital Pallisa Road Zone
Mbale
Uganda
P.O Box 921

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

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

Study participating centre
Kilifi County Hospital
Hospital Road
Kilifi
Kenya
PO Box 230

Study participating centre
Hospital Central de Quelimane
Av.Julius Nyerere, Estrada regional numero 470. Bairro Namuinho

Manhica
Mozambique
PO BOX 1929

Study participating centre
Komfo Anokye Teaching Hospital
Bantama High Street
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PO Box 1934

Study participating centre
St Pauls Mission Hospital
Hospital Road
Nchelenge, Luapula Province,
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P.O Box 71769

Study participating centre
Universite de Kinshasa
Campus UNIKIN, Lemba
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Sponsor information

Organisation
Imperial College London

Sponsor details
Joint Research Compliance Office, Imperial College London Room 215, Level 2, Medical School Building Norfolk Place
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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 Trial Management Group (TMG). The first publication of the trial results will have named authors including at least the trial's Chief and Site Investigators, Statisticians and Site Specific Coordinators. Members of the TMG and the Data Monitoring Committee will be listed, and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

The SMAART-MAP TSC is the custodian of the data and specimens generated from the SMAART-MAP trial; SMAART-MAP trial 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, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the publication policies used in other clinical trials:

All publications are to be approved by the TMG and Trial Steering Committee (TSC) before submission for publication. Any publication arising before the end of the trial (not by randomised groups) will also be approved by the DMC in order to ensure that the primary objective of the trial (the randomised comparison) is not compromised. In particular, no analyses by randomised group of any outcome (primary, secondary or other) in either the main trial or associated substudies will be conducted or presented before the end of the trial, other than those for interim review by the DMC. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.

In line with Wellcome policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial 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.

For all publications, the TMG will nominate a chairperson or approve an individual’s request to chair a manuscript writing committee. The chair will usually be the primary or senior author. The chairperson is responsible for identifying fellow authors and for determining with that group the order of authorship that will appear on the manuscript. The TSC will resolve any problems of authorship and maintain the quality of publications.

The TMG 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.

The data derived from this clinical trial are considered the property of the SMAART-MAP Trial Steering Committee. The presentation or publication of any data collected by the participating investigators on patients entered into this trial is under the direct control of the TMG and TSC (and the DMC before the end of the trial). This is true whether the publication or presentation is concerned directly with the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC (and the IDMC before the end of the trial), they will be encouraged to develop sub-studies or propose

analyses subject to the approval by the TMG and TSC (and the DMC before the end of the trial). 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 trial or ongoing analyses by the trial team.

Outcome data by randomised group will not be revealed to the participating investigators until the data collection phase and primary full analysis of the trial has been completed. This policy safeguards against possible bias affecting the data collection. The DMC will be monitoring the outcome results and may recommend that the trial be stopped for safety reasons or if a definitive answer is reached earlier than the scheduled end of the trial.

Intention to publish date
30/10/2026

Individual participant data (IPD) sharing plan
We have a data sharing plan for investigator and external requests. Data from SMAART-MAP trial 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 trial or 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 InformationGovernance and DataSecurity Policies in all of the relevant countries.

IPD sharing plan summary
Available on request