SMAART-MAP (ISRCTN 79071535) Statistical Analysis Plan

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Revision History

Version	Author	Date	Reason for Revision
0.1	Roisin Connon	11/12/2023	First draft, based on protocol v1.0.
0.2	Roisin Connon	11/12/2023	Incorporating edits from EG.
0.3	Roisin Connon	18/12/2023	Accepted changes from version 0.2.
0.4	Roisin Connon	14/10/2025	Updated after comments from SW.
0.5	Roisin Connon	15/10/2025	Further edits following discussion with EG.
0.6	Roisin Connon	4/11/2025	Updated following comments from KM.
1.0	Roisin Connon	4/11/2025	Accepted changes and upversioned from v0.6.

1. BACKGROUND

The overarching aim of the Severe Malaria Africa – A consortium for Research and Trials (SMAART) consortium is to improve outcomes from severe malaria by conducting better research studies faster. SMAART is an operational platform through which future research is coordinated efficiently, enabling evidence-based continuous updates of disease definitions and treatment guidelines for severe malaria.

Despite implementation of fast-acting effective antimalarial drugs (artemisinin-based combination treatment), in-patient mortality for severe malaria remains unacceptably high (~10%), and unlikely to improve without wider implementation of pre-referral artemisinin (Okebe and Eisenhut 2014) and better supportive treatments (John, Kutamba et al. 2010, Maitland 2015). Clinical trials addressing the safety and efficacy of adjuvant supportive therapies could close existing gaps in the severe malaria treatment algorithm and substantially improve outcomes.

Full details of the background, justification and rationale for each intervention are available in the protocol and domain-specific appendices.

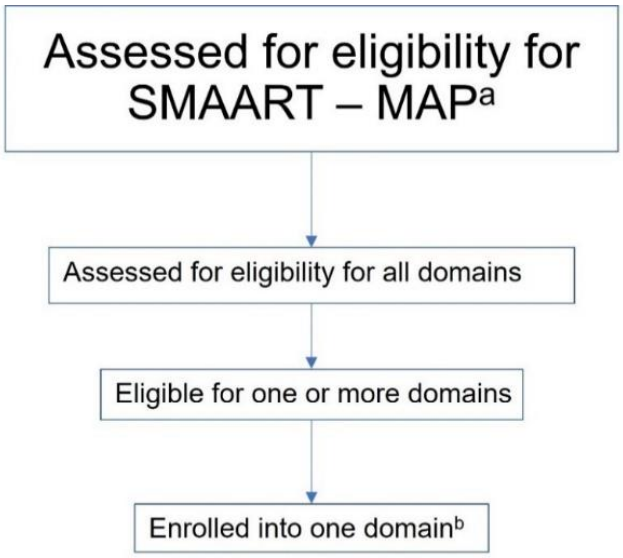
2. DESIGN

2.1 Overview of study design

SMAART-MAP is a multi-site adaptive phase II platform trial in hospitalised children with severe malaria. The trial consists of multiple domains, with each investigating specific randomised invention and comparator treatments for children enrolled to that domain. Primary outcomes are specific to the domain and detailed in sections 3-5.

The trial is being conducted in 7 sites in Uganda, Zambia, Ghana, Kenya, Democratic Republic of the Congo and Mozambique. Specific domains may not recruit in all sites.

2.2 Study flow diagram



[a] *Eligibility criteria: SMAART-MAP inclusion criteria: Aged >3 months and <12 years; admitted to the paediatric ward in last 24 hours; current or recent evidence of malaria (slide or RDT positive); guardian willing to provide consent.*

[b] *Recruitment to domains will be dynamically prioritised through predicted and active enrolment rates.*

2.3 Randomisation

Randomisation in each domain will be 1:1 stratified by site (additional stratification factors may be applied in specific domains, as specified in section 2.5). Randomisation lists, using permuted blocks of variable sizes, will be generated and kept at the MRC CTU. The lists will be hosted on an online randomisation system and accessed only by approved site staff. Eligible children will be screened and recruited during hospital admission. At enrolment, the site staff will access the online system to receive the randomisation allocation.

Enrolment within the SMAART-MAP trial is restricted to one domain per child. Recruitment to the different SMAART-MAP domains will be dynamically prioritised based on predicted and actual numbers randomised to each domain to achieve sample size targets across all domains.

2.4 Sample size

The sample size for each domain will be calculated to detect a difference in the primary outcome of that domain, see sections 3-5.

2.5 Current domains

2.5.1 Renal function

Population
Hospitalised children with severe malaria and creatinine>1.5xULN at presentation, and meeting one or more WHO severity criteria.

Interventions

1. High dose paracetamol (20mg/kg every 6 hours for 66 hours (last dose), given rectally, orally or via a nasogastric tube)
2. No or minimal paracetamol for fever reduction only (10mg/kg no more frequently than every 8 hours) (control)

2.5.2 Cerebral malaria

Population

Hospitalised children with severe malaria and either (i) a history of seizures in this illness and Blantyre Coma Score (BCS) ≤4 at screening, or (ii) BCS ≤2 at screening (regardless of history)

Interventions

1. 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 at this timepoint or had a temperature of >37.5°C within the preceding 12 hours, or has a Blantyre Coma Score of ≤4 at this timepoint)
2. Standard of care following national guidelines at each site (no prophylaxis, and treatment once a seizure is witnessed by clinical staff).

2.5.3 Anaemia

Population

Hospitalised children with severe malaria, haemoglobin <6g/dl and one or more severity signs (see below).

Interventions

1. Blood transfusion with whole blood (20mls/kg if temperature at screening is >37.5ºC, 30mls/kg if temperature is ≤37.5ºC)
2. Red cell concentrate (10mls/kg if temperature is >37.5ºC; 15mls/kg if temperature is ≤37.5ºC)

Randomisation

Screening temperature (≤37.5°C or >37.5°C) will be an additional randomisation stratification factor for this domain.

2.6 Selection of patients

2.6.1 Inclusion criteria

Patient inclusion criteria for SMAART-MAP trial:

1. Aged >3 months and <12 years
2. Admitted to the paediatric ward in the last 24 hours at screening
3. Current or recent evidence of malaria (slide or RDT positive in this admission)
4. Guardian willing to provide consent

Additional inclusion criteria for the renal function domain:

1. Creatinine > 1.5 x ULN on a 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 reclassification of severe malaria)

WHO Severity Criteria are as follows:

- Impaired consciousness: prostration or coma
- 2 or more convulsions within the last 24 hours
- Respiratory distress
- Compensated or decompensated shock:
    - Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension.
    - Decompensated shock (hypotension) is defined as systolic blood pressure <70 mm Hg in children
- Jaundice
- History or evidence of dark or cola coloured urine (blackwater fever)
- Haemoglobin <5g/dl (if routinely done)

The normal ranges for creatinine in children 1 month – 4 years are 13-39 µmol/L and in children 5-11 years are 29-53 µmol/L (Royal College of Paediatrics and Child Health 2016); corresponding to eligibility criteria of ≥60 and ≥80 µmol/L respectively.

Additional inclusion criteria for the 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

Additional inclusion criteria for the 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

2.6.2 Exclusion criteria

There are no exclusion criteria for the SMAART-MAP trial overall. Domain-specific exclusion criteria are listed below.

Exclusion criteria for the renal function domain:

1. Received paracetamol within 6 hours of screening or between screening and randomisation.
2. Known allergy to paracetamol
3. Severe malnutrition (MUAC<11.5cm)

Exclusion criteria for the 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.

Exclusion criteria for the anaemia domain:

1. Known congenital or valvular heart disease (not surgically corrected)

3. OUTCOMES FOR RENAL FUNCTION DOMAIN

3.1 Primary outcome

Area under the curve for creatinine levels calculated from measures taken at baseline, 24 hours, 48 hours and 72 hours. If any measurement is missed, e.g. through failure to store a plasma sample then multiple imputation will be used (see section 10.3). Children who die will have their last value carried forwards. Values within equally spaced windows around these timepoints after baseline will be assumed to have occurred at that timepoint.

3.2 Estimand

Estimand attribute	**Definition**
Population	Children with severe malaria and raised creatinine levels who present to hospital
Treatments	Intervention: Regularly dosed paracetamol (20mg/kg) for a total 72 hours exposure. Comparator: Paracetamol (10mg/kg) only if temperature >38.5°C during admission
Endpoint	Area under the curve of creatinine levels
Population level summary measure	Absolute difference between arms in mean area under the curve from baseline to 72 hours estimated with linear regression
Intercurrent events Any deviation from randomised strategy Deaths	 Treatment policy The last observation carried forwards will be used for children that have died

3.3 Secondary outcomes (domain specific)

- ALT and AST (liver enzymes) at 72 hours (change from baseline, adjusted for baseline)
- 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)
- Number of children with Acute Kidney Injury measured by the paediatric RIFLE criteria (Risk, Injury, Failure categories) (Akcan-Arikan, Zappitelli et al. 2007)
- AEs of any grade judged related to paracetamol
- AEs of any grade causing a change in paracetamol administration

3.4 Other outcomes (domain specific)

Urine samples will be stored and later assayed, where possible at sites, to calculate the creatinine:albumin ratio to further investigate changes in kidney function.

3.5 Sample size and power

75 children randomized per group provides 80% power to detect differences in area under the curve for creatinine levels between the groups of half the standard deviation (two-sided alpha=0.05), allowing for 15% missing data.

4. OUTCOMES FOR CEREBRAL MALARIA DOMAIN

4.1 Primary outcome

Number of witnessed seizures sufficient to start or change anticonvulsant medication up to 72 hours (or death if earlier).

4.2 Estimand

Estimand attribute	**Definition**
Population	Children with severe malaria and either seizures prior to admission and BCS ≤4, or Blantyre Come Score ≤2
Treatments	Intervention: IV levetiracetam over 72 hours Comparator: Standard of care
Endpoint	Number of seizures sufficient to start or change anticonvulsant medication up to 72 hours
Population level summary measure	Absolute difference in mean number of seizures sufficient to start or change anticonvulsant medication
Intercurrent events Any deviation from randomised strategy Deaths	 Treatment policy The highest number plus one of the maximum number of seizures sufficient to start or change anticonvulsant medication across all randomised children will be imputed for those who have died

4.3 Secondary outcomes (domain specific)

- Proportion of AEs of any grade judged related to anticonvulsants
- Proportion of solicited AEs
- Proportion of children with neurological sequalae at 28 days
- Proportion of children with neurological sequalae at 90 days
- Time to fully regain consciousness (BCS=5, the maximum possible score)

4.4 Sample size and power

Using unpublished data on children with a history of seizures from the SMAART observational study in severe malaria, we estimate that 66% of children in the control arm will not have any further fits, and 34% will have one or more fits in the 72 hours of observation time. This can be approximated by a Poisson distribution with rate parameter 0.41 (variance=rate), which asymptotically leads to 66%, 27%, 6%, 1% and <1% of children with 0, 1, 2, 3, 4+ fits in the 72 hours. 150 children randomised between control and intervention arms (75 per arm) provides 80% power to detect a reduction in this rate to 0.16 (10000 simulations), which asymptotically leads to 85% of children in the control arm having no further fits, with 14%, 1%, and 0.1% having 1, 2, or 3 fits.

5. OUTCOMES FOR ANAEMIA DOMAIN

5.1 Primary outcome

Change in haemoglobin at 24 hours (adjusted for baseline)

5.2 Estimand

Estimand attribute	Definition
Population	Children with severe anaemia and severe malaria that present to hospital
Treatments	Intervention: Whole blood transfusion Comparator: Red cell concentrate transfusion
Endpoint	Change in haemoglobin from baseline to 24 hours
Population level summary measure	Absolute difference in mean change from baseline at 24 hours between arms estimated with linear regression
Intercurrent events	
Any deviation from randomised strategy	Treatment policy
Deaths	Principal stratum strategy as those who died will not be included in the analysis, because no direct effect on mortality over the first 24 hours is expected from the intervention or comparator

5.3 Secondary outcomes (domain specific)

- Change in haemoglobin from baseline at 72 hours (adjusted for baseline)
- Number of additional transfusions in the acute admission
- Development of new profound anaemia (Hb<4g/dl) during acute admission or development of severe anaemia (Hb<6g/dl) post discharge
- AEs judged related to blood transfusion

5.4 Sample size and power

75 children randomized per group provides 80% power to detect differences in change in haemoglobin from baseline of half the standard deviation (SD) between two groups (two-sided alpha=0.05), allowing for 15% missing data.

6. COMMON OUTCOMES (ALL DOMAINS)

6.1 Secondary outcomes

- Proportion of deaths by 28 days from randomisation
- Proportion of deaths by 90 days from randomisation
- Proportion of children with readmissions by 28 days from randomisation
- Proportion of children with readmissions by 90 days from randomisation
- Proportion of children with grade 3 or 4 AEs during admission

7. DATA

Full details of data management procedures are provided in the Data Management Plan for the trial, which forms part of the Trial Master File.

7.1 CRF forms and variables

Full details of data collection and timing are described in the trial protocol. A copy of the CRFs are presented in the Trial Master File. Details of the variables are presented within the metadata which forms part of the Trial Master File.

7.2 Management of datasets

All clinical and laboratory data will be entered into a REDCap database (shared for all domains).

- For all analyses, datasets of all data will be extracted from REDCap. This will act as the frozen dataset. It is the responsibility of the statistician to accurately record the date of freezing and ensure all data is retrieved.
- For interim analyses, new data can continue to be entered onto the REDCap database. If any outstanding data queries are resolved during the analysis that relate to data in the frozen dataset (e.g. problems that are found during analysis or amended CRFs that are data entered post-freeze), the data should be changed at the start of the set of analysis programs using an auditable statistical program, separate from all other programs (by the Trial/Delegated Statistician). The main REDCap database will be amended in parallel at sites.

For the final analysis the Trial Statistician will be responsible for defining when the data are clean and ready for database lock.

7.3 Data verification

Data verification, consistency and range checks, as well as checks for missing data will be performed prior to analysis. Variables will be examined for unusual, outlying, unlabelled or inconsistent values. Details of these checks can be found in the Statistical Master File.

Any problems with trial data will be queried with the Trial Managers, Data Managers, or statisticians, as appropriate. For interim analyses, if possible, data queries will be resolved and amended, although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist.

7.4 Derivation of data for analysis

Definition of baseline

Baseline values for all measurements will be those recorded on the screening form and clinical evaluation form. For haemoglobin, the value on the screening form will be taken as baseline (to ensure consistency with inclusion criteria).

Definition of visit timepoint

Analyses of measurements at a given point in follow up will use the closest available measurement to that time point in evenly spaced windows. If there are two measurements that are equally close to the timepoint, the earliest measurement will be used.

Definition of censoring

For time-to-event analyses, participants not experiencing an event will be censored at their last trial assessment (including telephone visits). If participants are censored earlier due to loss to follow-up or withdrawal of consent, it will be assumed that such censoring is independent of the outcome.

Free text

Several fields are free text for other conditions. These will be categorised based on self-evident corrections, e.g. spelling. Adverse events and hospitalisations will be coded consistently (e.g. anaemia and malaria will be equivalent to malaria and anaemia) in consultation with the Chief Investigator.

Identification of severe malaria

Since children with severe malaria have clinical signs which overlap with other causes of severe febrile illness, such as sepsis, children with true severe malaria need to be differentiated from those with another aetiology and incidental parasitaemia (positive rapid diagnostic test (RDT)).

A subgroup of participants most likely to truly have severe malaria will be identified based on two additional laboratory criteria: a platelet count ≤150,000/μL and plasma pfHRP2 concentration >800 ng/ml.

8. STATISTICAL PRINCIPLES

8.1 Statistical software

All statistical analysis will be performed in Stata (updated and validated) unless otherwise specified.

8.2 Analysis populations and comparisons

The intention-to-treat (ITT) population will consist of all randomised participants excluding those demonstrably randomised in error; where randomisation in error will be judged by the participant meeting a major violation of the eligibility criteria, and will not depend on treatment allocation or post-randomisation follow-up.

SMAART-MAP will use the ITT population for the main analysis of each domain, with the groups defined according to the randomised allocation.

8.3 Statistical significance and p-values

All statistical tests will be two sided, with a p-value of 0.05 considered significant. Estimates will be presented with 95% confidence intervals. No adjustments will be made for multiple

testing. Appropriate transformations for all variables may be applied prior to analysis after inspection of the data.

8.4 Analysis methods

Descriptive statistics will be reported overall and by randomised group, and percentages will be of non-missing values, with the number of non-missing values given if data is not complete.

The primary analysis of each outcome will be stratified (Cox) or adjusted (other models) by site and adjusted for other domain-specific stratification factors where applicable. Where adjusted estimates of effect after marginalisation are presented, the p-value associated with this marginalised estimate will be presented.

Time to event analyses will consider time from randomisation until the earliest of the event date or censoring, presented as Kaplan Meier plots. Differences between groups will be tested using log rank tests and median survival time in each group will also be presented where this can be estimated (otherwise lower percentiles, eg 25^{th}). Cox proportional hazards models will be used to obtain adjusted hazard ratios. Where there are competing risks, time to event analyses will use Fine and Gray models to estimate subhazard ratios, and cumulative incidence curves will be plotted.

Count outcomes will be analysed using Poisson regression, with the time at risk under follow-up as the exposure. Children who died, withdrew or were lost to follow up before the end of the trial will be censored at the date last seen. The adjusted difference between groups will be summarised with by incidence rate ratios and estimated event rates per 100 person-years (marginalised over other factors) will be presented for each group.

Continuous outcome measures will be analysed using normal linear regression adjusted for baseline values. Mean values in each group (marginalised over other factors) and the adjusted difference between groups will be estimated.

Binary outcomes will be analysed by logistic regression. The adjusted proportions in each group (marginalised over other factors) and difference between groups will be presented. If there are fewer than 5 events in a group, Fisher's exact test will be used to estimate a p-value, and an estimate of effect will not be presented.

8.5 Missing data

Analyses will be based on observed data only unless otherwise specified.

8.6 Interim analyses

During the SMAART-MAP trial an independent Data Monitoring Committee (DMC) will meet regularly to review unblinded data for all domains. They will review data on enrolment, safety, adherence to randomised strategies, efficacy and safety at regular intervals and in strict confidence. The DMC will determine the frequency of their meetings, dependent on recruitment rates and any other factors they feel are important.

8.7 Statistical stopping rules

There are no formal statistical stopping rules as each domain is equivalent to a Phase II trial and rules based on very low p-values are unlikely to be useful.

9. ANALYSES FOR ALL DOMAINS

Analyses in this section will be conducted for all domains, comparing the intervention to the comparator.

All analyses will be presented in the final report. For interim reports to the DMC, only analyses in bold will be included.

9.1 Recruitment

- **Number randomised to each group by domain and site**
- **Graph of cumulative recruitment over time by domain and site**

9.2 Baseline characteristics

The following baseline characteristics will be summarised by the specified statistics. These will be presented separately by domain, and additionally by randomised group within the domain if there is a difference between groups with $p \leq 0.05$ (used as a flagging device for imbalance and expected for 1 in 20 characteristics by chance). P-values will be from rank-sum tests for continuous variables, and chi-squared tests for categorical variables, or Fisher's exact test if cell values are small.

- **Age at admission (months), weight (kg), respiration rate (breaths per minute), heart rate (bpm), axillary temperature (°C), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), oxygen saturation (%), capillary refill time (seconds), Blantyre Coma Score (total score), MUAC (cm): median (IQR)**
- **Conscious level: n (%) alert, voice, pain, coma**
- **Urine colour: n (%) normal, dark yellow, cola coloured, red, not done**
- **HIV test result: n (%) tested today positive, previously positive, tested today negative, previously negative, tested today invalid, not done**

Admission malaria tests

- **Malaria RDT, malaria blood film: n (%) positive, negative, invalid, not done**
- **Malaria pigment: n (%) yes, no, not done**
- **Malaria species: P. falciparum, P. ovale, P. malariae, P. vivax: n (% of those with malaria)**
- **pfHRP2 test result: n (%) positive, negative, invalid, not done**
- **Parasite count per μL: median (IQR)**
- pfHRP2 value (ng/ml): median (IQR)
- True severe malaria (platelet count ≤150,000/μL and plasma pfHRP2 concentration >800 ng/ml): n (%) yes, no

Severity features

- **Impaired consciousness, respiratory distress, clinical evidence of jaundice, history of convulsions in this illness, two or more convulsions in last 24h, evidence of compensated shock, evidence of decompensated shock, severe**

anaemia (Hb < 4g/dl, Hb<5g/dL, Hb<6g/dL), known HIV infection: n (%) yes, no
- **Weak radial pulse volume, temperature gradient: n (%) yes, no**

Lab results
- **Haemoglobin (g/dL), creatinine (mg/dL), platelets (10^3/μL), lactate (mmol/L), glucose (mmol/L),** white blood cells (**10^3/μL**), red blood cells (**10^6/μL**), haematocrit (%), lymphocytes (10^3/μL), neutrophils (10^3/μL), monocytes (10^3/μL), pfHRP2 (ng/ml): median (IQR)
- **Platelets > 150,000: n (%) yes, no, not done**
- pfHRP2 >800 ng/ml: n (%) yes, no, not done

9.3 Description of follow-up

The following will be tabulated by domain. Denominators will include those children who at the time of the data extract have been enrolled long enough ago for that visit to have occurred or to have completed follow up, including those who have been lost to follow up.

Completeness of follow up visits

- **Visits considered complete, defined as attended or died before the visit took place, at 28 and 90 days: n (%)**
- **Child status at 28 days and 90 days: n (%) visit done, died, lost to follow up, missed visit.**

9.4 Common secondary outcomes

The following outcomes will be analysed in each domain, comparing the intervention to the control group.

- **Proportion of deaths by 28 days from randomisation**
- **Proportion of deaths by 90 days from randomisation**

The number and proportion of deaths at 28 and 90 days will be tabulated by randomised group. The primary analysis will estimate the difference in adjusted proportions between groups using logistic regression marginalised over stratification factors as described in section 8.4. A secondary analysis will analyse time from randomisation to death using Cox models as described in section 8.4. Kaplan Meier plots will be plotted.

- **Proportion of children with readmissions by 28 days from randomisation**
- **Proportion of children with readmissions by 90 days from randomisation**

The number and proportion of children who are re-admitted, and the total number of readmissions, will be tabulated by randomised group. The primary analysis will estimate the difference in adjusted proportions between groups using margins after logistic regression as described in section 8.4.

A secondary analysis will estimate the differences between randomised groups in time from discharge to the first readmission, using competing risk methods counting death as a

competing risk as described in section 8.4. Subhazard ratios, 95% confidence intervals and p-values will be calculated from this model and cumulative incidence curves will be plotted.

- **Proportion of children with grade 3 or 4 AEs during admission**

The number and proportion of children having a grade 3 or 4 AE during admission will be tabulated, and the difference between groups will be estimated using logistic regression marginalised over stratification factors as described in section 8.4. The total number of events will also be presented.

9.5 Other analyses

- Validation of POC pfHRP2 test

If available, POC pfHRP2 test results will be compared with quantitative pfHRP2 concentrations determined retrospectively from batched testing in order to determine POC test performance (sensitivity, specificity, positive and negative predictive value, overall accuracy; particularly considering the 1000 ng/mL threshold). Receiver Operating Characteristics will also be calculated.

10. ANALYSIS FOR RENAL FUNCTION DOMAIN

The analyses in this section will only include children enrolled to the renal function domain, and will compare the intervention (high dose paracetamol) and control (no or minimal paracetamol) groups.

10.1 Completeness of data for primary outcome

- **Creatinine considered complete, defined as non-missing or died before time point, at 24, 48 and 72 hours individually, and at all time points: n (%) complete, not complete**

10.2 Treatment details

The following will be tabulated by randomised group.

- **Proportion of children who received paracetamol: n (%)**
- **Cumulative total dose of paracetamol during admission: median (IQR)**
  Cumulative total dose will be estimated by summing the doses given.

10.3 Missing data

Imputation will be used for missing creatinine data. Children who die before 72 hours will have their last value carried forwards. If values are missing for other reasons e.g. through failure to store a plasma sample or abscondment, multiple imputation by chained equations will be used to impute the value. Multiple imputation will be done separately by randomised group including all 4 creatinine values, indicators for whether dead or alive at each timepoint, and age and sex at randomisation.

10.4 Primary outcome

- **Area under the curve for creatinine levels calculated from measures taken from baseline, 24 hours, 48 hours and 72 hours.**

The area under the curve for creatinine levels over time will be calculated from the measurements using the trapezoid rule. If any measurement is missed, e.g. through failure to store a plasma sample then missing data methods will be used as above. Children who die before 72 hours will have their last value carried forwards. Values within equally spaced windows around these timepoints after baseline will be assumed to have occurred at that timepoint.

The mean area under the curve in each randomised group, and the difference between arms, will be estimated using normal linear regression, adjusted for baseline, site and blackwater fever.

- Secondary analysis

A secondary analysis will be carried out using Bayesian principles given the small sample size, using ACCEPT analyses (Clements, White et al. 2022).

- Subgroup analysis

Subgroup analyses will be performed for the following subgroups:

- Participants likely to have true severe malaria (as defined in section 7.4)

10.5 Secondary outcomes

- **ALT and AST (liver enzymes) at 72 hours**
- **Creatinine at 24 hours**
- **Creatinine at 48 hours**
- **Creatinine at 72 hours**

Changes in AST, ALT and creatinine at specific time points will be analysed using normal linear regression, adjusting for baseline values, site and blackwater fever. Mean change in each group and the mean difference between groups will be estimated and presented with 95% confidence intervals and p-values.

- **Number of children with Acute Kidney Injury measured by the paediatric RIFLE criteria (Risk, Injury, Failure categories) (Akcan-Arikan, Zappitelli et al. 2007)**

The number and proportion of children meeting the risk, injury and failure categories will be tabulated by randomised group. The difference between arms will analysed using ordered logistic regression adjusted for site and blackwater fever to obtain an odds ratio and p-value.

- **AEs of any grade judged related to paracetamol**
- **AEs of any grade causing a change in paracetamol administration**

The number and proportion of children having each outcome will be tabulated. Logistic regression adjusted for site and blackwater fever will be used to estimate the difference

between groups. The total number of events will also be presented. AEs will be counted as related to paracetamol if they are judged to be definitely, probably or possibly related.

10.6 Other outcomes

- **Creatinine:albumin ratio**

The number and proportion of children with normal and abnormal creatinine:albumin ratio will be tabulated by randomised group. The difference in proportion between groups will be estimated by marginalisation following logistic regression adjusted for site and blackwater fever.

- Time to fever clearance

The time from randomisation to temperature <37.5°C will be analysed for the children who had fever at baseline (temperature ≥37.5°C). A competing risks model adjusted for site and blackwater fever will be used, with death before fever clearance treated as a competing risk, as described in section 8.4. Subhazard ratios will be calculated from this model and cumulative incidence curves will be plotted.

11. ANALYSIS FOR CEREBRAL MALARIA DOMAIN

11.1 Completeness of data for primary outcome

- **Number of children with complete seizure data on bedside observations, defined as non-missing up to the 72 hours or time of death if before 72 hours: n (%) complete, LTFU before 72 hours, missing**

11.2 Treatment details

- **Number receiving levetiracetam: n (%)**
- **Number of doses of levetiracetam received: n (%) receiving 3, 4, and 5 doses**
- **Cumulative dose of levetiracetam (mg/kg) up to 48 hours by number of doses received: median (IQR) among children receiving 3, 4, and 5 doses**
  Cumulative total dose will be estimated by summing the doses given.

11.3 Missing data

Analysis of the primary outcome will use observed data only. Where the number of seizures at a timepoint has not been recorded, it will be assumed to be 0.

11.4 Primary outcome

- **Number of witnessed seizures sufficient to start or change anticonvulsant medication up to 72 hours (or death if earlier)**

The number and proportion of children having witnessed seizures, and the total number of such seizures, will be tabulated by randomised group. The primary outcome will be analysed using Poisson regression as described in section 8.4, including treatment arm as a covariate, and adjusted for site.

- Secondary analysis

A secondary analysis will be carried out using Bayesian principles given the small sample size, using ACCEPT analyses (Clements, White et al. 2022).

- Subgroup analysis

Subgroup analyses will be performed for the following subgroups:

- Participants likely to have true severe malaria (as defined in section 7.4)

11.5 Secondary outcomes

- **Proportion of AEs of any grade judged related to anticonvulsants**
- **Proportion of solicited AEs**

The number and proportion of children having each of event types will be tabulated, and the difference between groups will be estimated using logistic regression adjusted for site as described in section 8.4. The total number of events will also be presented. AEs will be counted as related to anticonvulsants if they are judged to be definitely, probably or possibly related.

- **Proportion of children with neurological sequalae at 28 days**
- **Proportion of children with neurological sequalae at 90 days**

The number and proportion of children having neurological sequalae at 28 and 90 days will be tabulated by randomised group. The difference between groups will be estimated using logistic regression adjusted for site as described in section 8.4.

- **Time to fully regain consciousness (BCS=5, the maximum possible score)**

The time in hours from randomisation to regaining consciousness will be compared between groups using time-to-event analysis, with death as a competing risk as described in section 8.4.

12. ANALYSIS FOR ANAEMIA DOMAIN

12.1 Completeness of data for primary outcome

- **Haemoglobin at 0 and 24 hours considered complete, defined as non-missing or died before the time point: n (%) complete, missing at 0 hours only, missing at 24 hours only, missing both 0 and 24 hours**

12.2 Treatment details

- **Number receiving blood transfusion: n (%) whole blood, red cell concentrate**
- **Total volume received (mls/kg): median (IQR) in groups with temperature ≤37.5ºC or >37.5ºC**

12.3 Missing data

Multiple imputation by chained equations will be used to impute missing haemoglobin values for the primary outcome, unless the value is missing due to death. Children that died before 24 hours will be excluded from analysis. Multiple imputation will be done separately by randomised group including any available haemoglobin values, age and sex at randomisation.

12.4 Primary outcome

- **Change in haemoglobin at 24 hours (adjusted for baseline)**

The change in haemoglobin from baseline to 24 hours will be estimated using normal linear regression, adjusted for baseline haemoglobin, and stratification factors (site and temperature ≤37.5ºC or >37.5ºC). Mean change in each group and the difference between groups will be presented with 95% confidence intervals.

- Secondary analysis

A secondary analysis will be carried out using Bayesian principles given the small sample size, using ACCEPT analyses (Clements, White et al. 2022).

- Subgroup analysis

Subgroup analyses will be performed for the following subgroups:

- Participants likely to have true severe malaria (as defined in section 7.4)

12.5 Secondary outcomes

- **Change in haemoglobin at 72 hours (adjusted for baseline)**

The change in haemoglobin from baseline to 72 hours will be estimated using normal linear regression, adjusted for baseline haemoglobin, and stratification factors (site and temperature ≤37.5ºC or >37.5ºC). Mean change in each group and the difference between groups will be presented with 95% confidence intervals.

- **Number of additional transfusions in the acute admission**

The number and proportion of children receiving additional transfusions during the initial admission, and the number of transfusions, will be tabulated by group. The number of additional transfusions will be analysed using ordered logistic regression and summarised with an odds ratio.

- **Development of new profound anaemia (Hb<4g/dl) during acute admission**
- **Development of severe anaemia (Hb<6g/dl) post discharge**

The number of children developing new profound anaemia (Hb<4g/dl) during acute admission and number of children developing severe anaemia (Hb<6g/dl) post discharge will be tabulated by randomised group. These will be analysed as binary outcomes, with exact tests used to test for difference between groups. The difference in proportion between

groups will be estimated by marginalisation following logistic regression adjusted for site and fever at admission.

- **AEs judged related to blood transfusion**

The number and proportion of children having an AE judged to be definitely, probably or possibly related to blood transfusion will be tabulated, and the difference between groups will be estimated using logistic regression adjusted for site and fever as described in section 8.4. The total number of events will also be presented.

13. REFERENCES

6.2 References to trial related documents (DMP, TMF, SMF)

The SMAART-MAP trial master file (TMF) is held at KEMRI-Wellcome Trust Research Programme Clinical Trial Facility. The Data Management Plan forms part of the TMF. The Statistical Master File (SMF) is held at MRC CTU.