SMAART-MAP trial

Severe Malaria A Research and Trials consortium - Multisite Adaptive Platform trial

Master protocol

Main Sponsor:
Imperial College London

Collaborating groups:

Version:	**1.3**
Date:	**5th June 2024**
ISRCTN #:	**ISRCTN79071535**
PACTR #:	PACTR202312551082722

Authorised by:

Name:	Kathryn Maitland
Role:	Chief Principal Investigator
Signature:	
Date:	5th June 2024

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GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 10.0. The CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the SMAART-MAP trial, coordinated by the Kenya Medical Research Institute (KEMRI)-Wellcome Trust Kilifi Clinical Trials Facility, and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. **This master protocol should be used alongside each appendix protocol for specific domains of the SMAART-MAP trial**.

Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be available to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the trial team to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2) and other applicable national regulations.

SPONSOR

Imperial College London is the Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity at r.nicholson@imperial.ac.uk.

Joint Research Compliance Office, Imperial College London Room 215, Level 2, Medical School Building Norfolk Place London, W2 1PG Tel: 020 7594 1872

Imperial College has delegated responsibility for the overall management of the SMAART-MAP trial to the KEMRI-Wellcome Trust Clinical Trials Facility in Kilifi, Kenya.

FUNDING

Funding is provided by Wellcome as part of the grant to the SMAART Consortium (209265/Z/17/Z).

AUTHORISATIONS AND APPROVALS

This trial was approved by [*Insert Info when approved*].

TRIAL REGISTRATION

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN79071535 and with PACTR where it is identified as PACTR202312551082722.

SAE REPORTING

Within 24 hours of becoming aware of an SAE, submit a completed SAE Form to KEMRI Wellcome Trust Kilifi by email to SMAART@kemri-wellcome.org
Tel: +254 715461761 or +254 726957045

TRIAL ADMINISTRATION

Please direct all queries to the Emmanuel Oguda, SMAART-MAP clinical project manager at KEMRI Wellcome Trust programme Clinical Trial Facility in the first instance; clinical queries will be passed to the Chief Investigator via the SMAART-MAP clinical project manager.

Trial Monitoring

The trial will be monitored from the KEMRI Wellcome Trust Clinical Trial Facility. This trial will be monitored according to a Monitoring and Quality Management Plan.

COORDINATING CENTRE

KEMRI Wellcome Trust Programme Clinical Trial Facility		Switchboard: Mobile:	+254 417 522063/522535 +254 715 461761 (Trial administrator)
PO Box 230, Kilifi, Kenya		Email:	SMAART@kemri-wellcome.org
KEMRI WELLCOME TRUST RESEARCH PROGRAMME, STUDY AND TRIAL MANAGEMENT GROUP Kilifi Clinical Trials Unit, PO Box 230, Kilifi			
Principal Investigator:	Prof Kathryn Maitland MBBS PhD	Mobile: Email:	+254 733 411022 kathryn.maitland@gmail.com
Trial Administrator	Phyles Maitha Dip.Business.Mgt	Tel: Mobile: Email:	+254 417 525453 (switchboard) +254 715 461761 PMaitha@kemri-wellcome.org
Clinical Project Manager:	Emmanuel Oguda Dip.Clin.Med.Chir	Tel: Mobile: Email:	+254 417 525453 (switchboard) +254 726957045 EOguda@kemri-wellcome.org
Data Manager:	Christabel Mogaka BSc	Tel: Email:	+254715811661 CMogaka@kemri-wellcome.org
KILIFI: CLINICAL GROUP			
Lead Investigator	Prof Mainga Hamaluba MBCHB, MRCP	Mobile: Email:	+254 709983946 MHamaluba@kemri-wellcome.org

Coinvestigators	Prof Thomas Williams MBBS, PhD	Mobile: Email:	+254 733 411021 tom.n.williams@gmail.com
Coinvestigators	Prof Phillip Bejon MBBS, PhD	Mobile: Email:	+254 724 45743 PBejon@kemri-wellcome.org

IMPERIAL COLLEGE

Division of Medicine Room 1030 Level 10 St Mary's Campus Norfolk Place London W2 1PG			
Principal Investigator:	Prof Kathryn Maitland MBBS PhD	Tel: Email:	+44 207 670 4905 kmaitland@imperial.ac.uk
Centre Administrator	Tony Tarragona-Fiol	Tel: Email:	+44 20 3312 6230 t.tarragona@imperial.ac.uk

MRC CTU AT UCL

MRC Clinical Trials Unit at UCL Institute of Clinical Trials and Methodology 90 High Holborn, 2nd Floor, London WC1V 6LJ			
Principal Investigator:	Prof Diana M Gibb MD MSc	Tel: Email:	+44 207 670 4905 diana.gibb@ucl.ac.uk
Statistician:	Dr Elizabeth George PhD MSc	Tel: Email:	+44 207 670 4931 elizabeth.george@ucl.ac.uk
Statistician:	Prof Ann Sarah Walker PhD MSc	Tel: Email:	+44 207 670 4726 rmjlasw@ucl.ac.uk
Statistician:	Roisin Connon MSc	Email:	r.connon@ucl.ac.uk

MORU

Mahidol Oxford Tropical Medicine Research Unit 420/6 Rajvithi Road, Tungphyathai, Bangkok 10400, Thailand			
Co-Lead Investigator:	Prof Nicholas Day, MBBS PhD	Tel: Email:	+66 870 118990 nickd@tropmedres.ac

Co-Lead Investigator:	Prof Arjen Dondorp, PhD	Tel: Email:	+66 818 015675 arjen@tropmedres.ac
Data Manager:	Naomi Waithera, MSc	Email:	Naomi@tropmedres.ac

STUDY SITES AND INVESTIGATORS

UGANDA: Country Principal Investigator Prof Peter Olupot Olupot			
Mbale Regional Referral Hospital, Mbale Clinical Research Institute (MCRI) Pallisa Road Zone, P.O Box 921, Mbale			
Site Investigator:	Prof Peter Olupot Olupot MBChB, MPH	Tel: Mobile: Email:	+256 77 2457217 +256 77 2457217 polupotolupot@yahoo.com
Study Site Coordinator:	To be appointed	Tel: Mobile: Email:	
Soroti Regional Hospital, P.O Box 289, Soroti			
Site Investigator:	Dr Florence Aloroker, MBChB, MMed	Tel: Email:	+256 45 4461382 alaroflorence@gmail.com
Study Site Coordinator:	Denis Amorut, BsHSM, RCN	Tel: Mobile: Email:	+256 45 4461382 +256 77 4573911 damoruts@gmail.com
Dr. Ambrosoli Hospital, Kalongo, P.O Box 47 Agago District			
Site Investigator:	Dr Okao Maurice, MD, MMED Paediatrics	Tel: Email:	+ 256 779066157 maurice.okao@gmail.com
Study Site Coordinator:	Dr Modester Akite MD	Email:	modesterakite@gmail.com

KENYA:			
Kilifi County Hospital, Hospital Road, PO Box 230, Kilifi			
Co Lead investigator:	Prof Mainga Hamaluba MBCHB, MRCP	Tel: Email:	+254 709983946 MHamaluba@kemri-wellcome.org
Co-Lead investigator::	Prof Kathryn Maitland MBBS PhD	Tel: Email:	+254710508749 Kathryn.maitland@gmail.com

MOZAMBIQUE:			
Hospital Central de Quelimane, Av.Julius Nyerere, Estrada regional numero 470. Bairro Namuinho Manhica Health Research Centre (CISM) PO BOX 1929 Manhica			
Co-Lead investigator:	Dr Pedro Aide, MD, MSc, PhD	Tel: Email:	+258 2181 0181 pedro.aide@manhica.net
Co-Lead investigator:	Dr Rosauro Varo, MD, MSc, PhD, Paediatrician	Email:	rosauro.varo@isglobal.org
Co-investigator:	Professor Quique Bassat, MD, MSc, PhD	Email:	quique.bassat@isglobal.org
Co-investigator:	Dr David Torres, MD, MSc, Paediatrician.	Email:	david.torres@isglobal.org

GHANA:			
Komfo Anokye Teaching Hospital, Bantama High Street PO Box 1934 Kumasi Department of Child Health, Kwame Nkrumah University of Science and Technology, Kumasi			
Principal investigator:	Professor Daniel Ansong, MBCHB MSc	Tel: Email:	+233 208 168767 dansong@kathhsp.org
Co-investigator:	Prof Tsiri Agbenyega, PhD	Tel: Email:	+233 208 113848 tsiri@ghana.com
Co-investigator	Dr Justice Sylverken, MBCHB	Tel: Email:	+233 208 113715 jsylverken@gmail.com

ZAMBIA			
St Pauls Mission Hospital, Nchelenge, Luapula Province and Tropical Diseases Research Centre 6th and 7th Floor of Ndola Teaching Hospital building P.O Box 71769, Ndola			
Principal Investigator:	Dr Mike Chaponda, MSc, MBChB, MSc, DTMH	Tel: Email:	+260 212 620737 mikechaponda@yahoo.com
Co-investigator:	Dr Sam Miti, MBChB, MMed	Tel: Email:	+260 212 620737 drsammiti@gmail.com
Co-investigator	Dr Jonathan Gwasupika, MBChB	Tel: Email:	+260 212 620737 gwagwejo@gmail.com

DEMOCRATIC REPUBLIC OF THE CONGO			
Kinshasa School of Public Health, Kin I School of Medicine Universite de Kinshasa, Campus UNIKIN, Lemba, BP 11850 Kinshasa, DRC			
Principal Investigator:	Prof Marie Onyamboko, MD, DPhil	Tel: Email:	+243990024201 marie.onyamboko@unikin.ac.cd
Co-investigator:	Dr Catarina Fanello, PhD	Email:	Caterina@tropmedres.ac

For full details of all trial committees, please see **Section 14**.

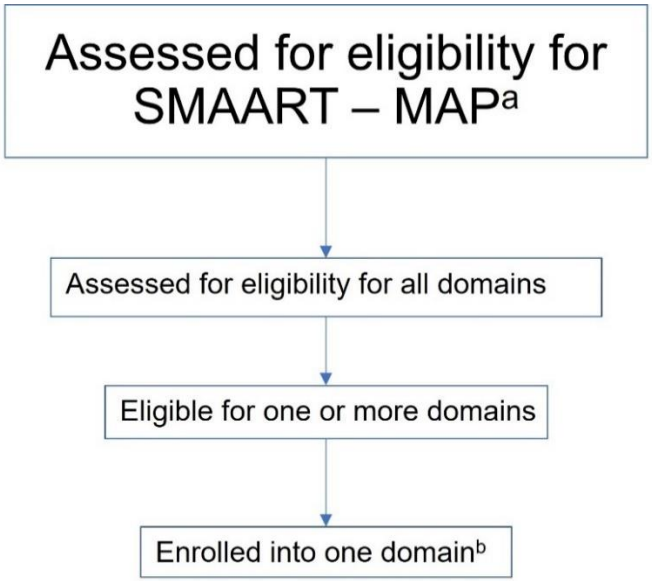
SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym or short title	SMAART-MAP trial
Long Title of Trial	Severe Malaria a Research and Trials consortium – Multisite Adaptive Platform trial
Version	1.3
Date	5th June 2024
ISRCTN # /PACTR #	ISRCTN79071535 / PACTR202312551082722
Study Design	Multi-site adaptive phase II platform trial with multiple domains
Setting	Hospitals in Uganda, Zambia, Ghana, Kenya, Democratic Republic of the Congo and Mozambique
Type of Participants to be Studied	Hospitalised children with severe malaria
Ancillary Studies/Substudies	Comparison of quantitative vs a point of care (POC) test for plasmodium falciparum histidine rich protein 2 (pfHRP2), a potential severity marker. Any other ancillary study will be detailed in each domain appendix where applicable.
Sponsor	Imperial College London
Funder	Wellcome
Chief Investigator	Professor Kathryn Maitland
Randomisation for each domain	1:1 randomisation using randomised permuted blocks stratified by site. Additional stratification may be applied in specific domains.
Number of Participants to be Studied in each domain	The sample size for the number of children enrolled within each domain will be calculated to detect a difference in the primary outcome of that domain.
Duration	24 months
Eligibility criteria for SMAART-MAP (all domains)	Inclusion criteria: • Aged >3 months and <12 years • Admitted to the paediatric ward in the last 24 hours at screening • Current or recent evidence of malaria (slide or rapid diagnostic test (RDT) positive in this admission) • Guardian willing to provide consent Exclusion criteria: • Enrolment into the SMAART-MAP trial on a previous admission Domains may also have additional domain-specific inclusion and/or exclusion criteria.
Outcomes for SMAART-MAP	Primary outcomes will be specific to each domain. Secondary outcomes for all domains will include readmissions and mortality to day 28 and day 90; grade 3 or 4 adverse events (AEs); and AEs judged related to domain-specific interventions or their

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	comparators during admission as detailed in the domain-specific appendices.

TRIAL SCHEMA

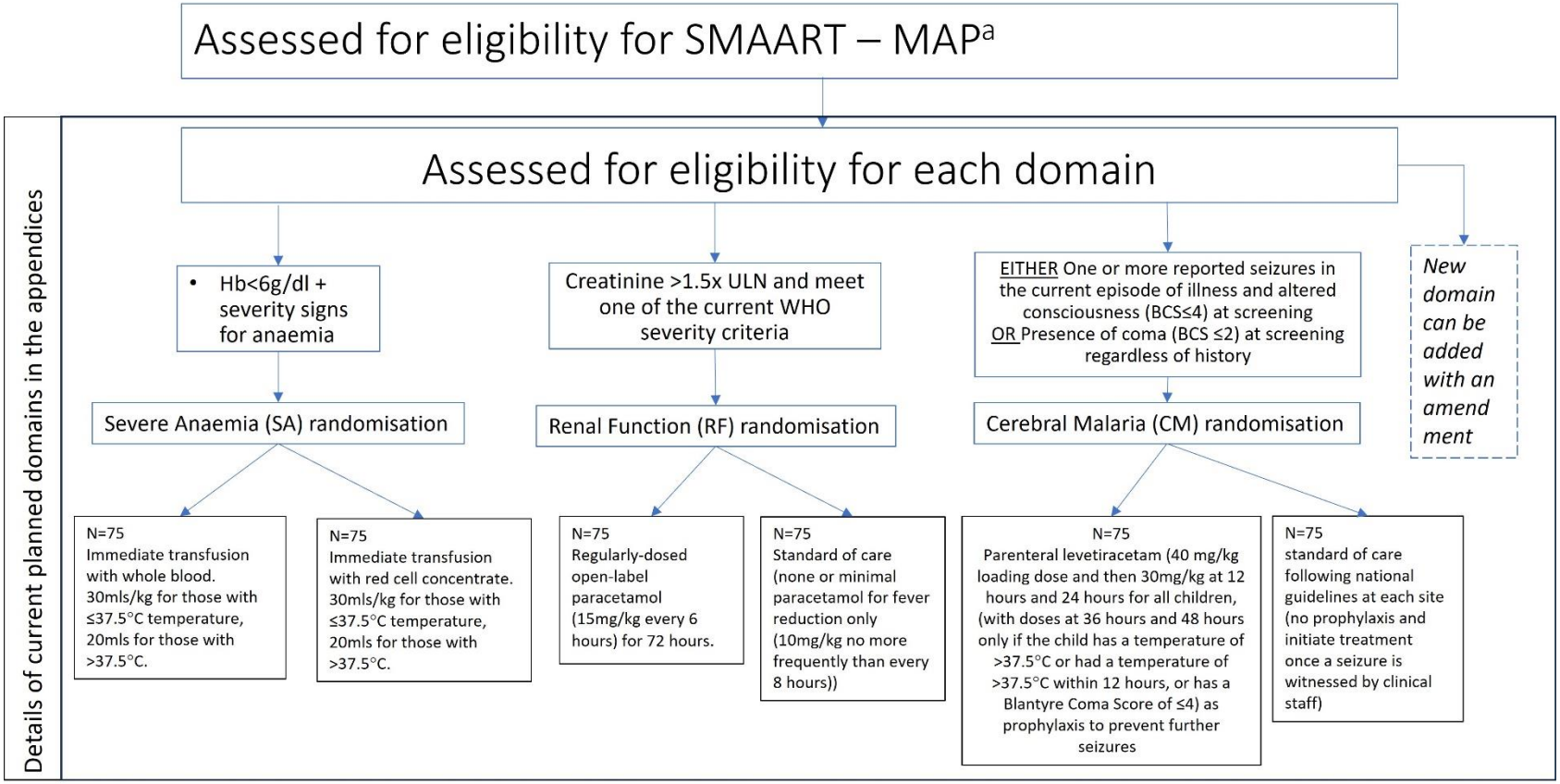
Figure 1: Trial Entry, Randomisation and Treatment



[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.*

Figure 2: Overview of planned domains for the SMAART-MAP trial



[a]*Eligibility criteria: SMAART-MAP inclusion criteria: Aged >3 months and <12 years admitted to the paediatric ward; current or recent evidence of malaria (slide or RDT positive); positive on a POC PfHRP2 RDT test (indicating >1000 PfHRP2 ng/ml); guardian willing to provide consent*

TRIAL ASSESSMENT SCHEDULE

TABLE 1: Trial Assessment Schedule: common assessments

Assessment	Admission/ screening	Random-isation	3 hrs (±1 hr)	12 hrs (±3 hrs)	24 hrs (±3 hrs)	48 hrs (±3 hrs)	72 hrs (±3 hrs)	Dis-charge	28±7 days	90±14 days
SMAART-MAP all domains										
Clinical assessment[1]	x		x	x	x	x	x[7]		x	x
Point-of-care tests (0.2-0.3ml)[2]	x		x		x	x	x		x	x
Weight[3]	x								x	x
Malaria RDT, and thick and thin malaria slide (if available at site) (0.2ml)	x								x	x
Informed consent process[4]	x									
Randomisation		x								
Full Blood Count[5] (1ml)		x								
Urine dipstick		x[6]								
Plasma storage for quantitative pfHRP2 (1mls)		x								
POC pfHRP2 test (when available) (0.2ml)		x								
Ascertainment of all treatments given during admission (anticonvulsants, antimalarials, antipyretics, antibiotics and transfusions)								x		
Ascertainment of vital status, readmissions, potential malaria episodes, and neurological sequalae									x	x
Total Blood draws (mls). (Total across whole admission and 2 follow ups is 3.4-3.7mls)	0.4-0.5ml	2.2mls	0	0	0	0	**0**	**0**	0.4-0.5ml	0.4-0.5ml

[1] Clinical assessment: heart rate, oxygen saturation (pulse oximetry), respiratory rate, respiratory distress, axillary temperature, blood pressure, capillary refill time, and consciousness level (as measured by the Blantyre Coma Score (BCS)).

[2] Lactate, glucose and haemoglobin (hb) as point-of-care tests (lactate & glucose only at 3hrs as hb will be done at first domain specific timepoint, hb only at 28 and 90 days).

[3] Weight: assessed at screening or as soon as possible after enrolment depending on status.

[4] This could be informed consent or emergency verbal assent followed by deferred consent dependant on the child's condition – please see section 3.5 for details.

[45]Full blood count: haemoglobin, white blood cells (and differential if available as standard at site), platelets. Values from a blood draw taken for clinical reasons (i.e. not for the trial) at any time in this admission before randomisation should be used if available, rather than re-bleeding the child, as eligibility requires all children to be within 24 hr of admission at screening.

[6] This should be done when the first urine sample is available after enrolment.

[7] If the child is discharged prior to 72 hours then these assessments should be done at discharge. However, caregivers should be encouraged to stay until 72 hours wherever possible.

These assessments will be performed for all children enrolled in any SMAART-MAP domain. Domains may also have additional domain-specific assessments, tests or sample storage (e.g. to ascertain domain-specific primary or secondary outcomes) or additional domain-specific timepoints (e.g. relating to dosing), see domain-specific appendices for details. Additional assessments can also be done where clinically required and will be recorded on an appropriate case report form (CRF).

LAY SUMMARY

Children with severe malaria come to hospital very sick and need urgent care. Despite the introduction of the malaria vaccine in some areas of Africa and increased bednet use, severe malaria is still causing child deaths and hospitalisations. Even on the best anti-malarial treatments many African children with severe malaria have poor outcomes with including deaths which tend to occur on the first day of arrival to hospital. One of the bad things that happen in severe malaria is that red blood cells that are infected with malaria parasites stick to the very deep parts of our blood vessels. This occurs throughout the body and affects vital places such as the brain or kidneys. Thus, children come to hospital with different symptoms such as in a coma or with fits or with anaemia. They will be treated immediately with anti-malarials and may also receive antibiotics. Other treatments targeted at symptoms or specific areas of the body may also help them recover (called adjunctive therapy).

The World Health Organisation has developed guidelines for treatment of severe malaria but much of the information used to develop the recommendations on adjunctive therapy are based on expert opinion and not data from clinical trials and studies which are a better source of evidence. The SMAART-MAP trial aims to identify adjunctive therapies that will help children with severe malaria get better faster in the short term (within 3 days of coming to hospital) and that could then be studied further in larger numbers to see if they are able to reduce the number of children who die or return to hospital.

The trial has been designed to look at the impact of these adjunctive therapies on different symptoms or body areas. In the trial these different areas are called ‘domains’. One adjunctive therapy will be investigated within each domain of the trial. It is called an adaptive trial as new domains can be added to the structure of the trial after it has started, and all domains have some joint processes and will be run by the same staff. This document is the master protocol which outlines those joint processes and explains the main objective of the trial. Appendices describe the adjunctive therapies within each domain in more detail.

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.

CONTENTS

ABBREVIATIONS

ABBREVIATION	EXPANSION
AE	Adverse event
AR	Adverse reaction
BCS	Blantyre Coma Score
CI	Chief Investigator
CI	Confidence interval
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTF	Clinical Trials Facility
CTU	*See MRC CTU at UCL*
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSUR	Developmental Safety Update Report
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IRB	Institutional Review Board
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
KEMRI-Wellcome Trust Kilifi CTF	Kenya Medical Research Institute – Wellcome Trust Kilifi Clinical Trials Facility (also generally abbreviated to CTF)
MedDRA	Medical Dictionary for Regulatory Activities

ABBREVIATION	EXPANSION
MOP	Manual of Operations
MRC	Medical Research Council
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London (also generally abbreviated to "CTU")
NIMP	Non-investigational-medicinal product
PI	Principal Investigator
pfHRP2	Plasmodium falciparum histidine rich protein 2
PK	Pharmacokinetics
POC	Point of care
RCT	Randomised controlled trial
RDT	Rapid Diagnostic Test
REC	Research Ethics Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Standard deviation
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
WHO	World Health Organization

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. A 2-day inception meeting brought together a multidisciplinary group of scientists, with track records of successful high quality research in low-income settings in severe malaria from three Wellcome major overseas programmes (KEMRI Wellcome Trust Programme, Kenya; Malawi-Liverpool-Wellcome Trust Unit, Malawi; and the Mahidol Oxford Tropical Medicine Research Unit, Thailand), specialists in clinical trials (MRC CTU at UCL) and African clinician scientists from existing or new collaborations (Kenya, Uganda, Mozambique, Malawi, Zambia, and Ghana). The overarching aim was to establish the main priorities for a future research agenda. The key specific goals were to establish the current burden of severe malaria (review of the literature); and update the current understanding of the clinical spectrum of disease and identify better tools for accurate diagnosis in order to establish best practice and identify research gaps. The final aim of the inception meeting was to review the current status of clinical trial evidence for practice guidelines and discuss key targets for future clinical trials, including pathophysiological research underpinning these, and potential trial methodologies and approaches to an integrated trial platform. These are discussed in more detail below.

BURDEN OF SEVERE MALARIA

Models suggest that across sub-Saharan Africa, the scale-up of anti-malarial control efforts has led to substantial reductions in the incidence of malaria morbidity and mortality since 2000 (Bhatt, Weiss et al. 2015, Gething, Casey et al. 2016). However, there is increasing evidence from detailed hospital studies that this has not been a universal phenomenon; hospital admissions for malaria have been increasing in some areas and the disease pattern and age-phenotype is changing (Okiro, Al-Taiar et al. 2009, Okiro, Alegana et al. 2010, Roca-Feltrer, Carneiro et al. 2010, Okiro, Bitira et al. 2011). Strategies to control or prevent malaria (including vaccines) have so far offered limited short-term protection (RtsS Clinical Trials Partnership 2015) and are under threat from emerging artemisinin resistance in Southeast Asia (Woodrow and White 2017) and alarming rates of insecticide resistance (Maitland 2016). Furthermore, 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.

IDENTIFYING CHILDREN WITH SEVERE MALARIA?

Identifying children with severe malaria remains challenging; whilst malaria rapid diagnostic tests (RDTs) have transformed immediate malaria diagnosis in many settings, clinical criteria alone fail to distinguish those with severe malaria at greatest risk of poor outcomes. We considered several point-of-care (POC) tests that might be valuable to identify children with 'true' severe malaria more accurately, as well as identify high-risk subgroups with specific complications. The most promising test to identify accurately children with severe malaria (including those progressing to severe malaria) from those with incidental parasitaemia who are less likely to benefit from malaria-specific

supportive therapies is for plasma Plasmodium falciparum histidine-rich protein2 (pfHRP2), a proxy for total body parasite burden (Chinkhumba, Skarbinski et al. 2010, Sinha, Ekapirat et al. 2015). In addition, a recent analysis of 2,649 patients enrolled in four studies of severe malaria in three countries (Kenya, Uganda and Bangladesh) identified that platelet counts and plasma pfHRP2 concentration increased the specificity of a diagnosis of severe malaria in African children, and concluded that studies of severe falciparum malaria could be improved by including only children with platelet counts ≤150,000/µL and plasma pfHRP2 concentrations ≥800 ng/mL (Watson, Uyoga et al. 2022, White, Watson et al. 2022). In these studies, mortality in 'true' severe malaria was consistent across the African sites at ~10%. The main challenge is being able to conduct these tests (especially pfHRP2 concentration) at the point of enrolment into a clinical trial - a point of care test for pfHRP2 is now being developed but has not yet been validated for widespread use. Nevertheless, these data could be collected in future trials and used in their final analysis to compare intervention effects in those most likely to truly have severe malaria as opposed to another cause of severe illness with incidental parasitaemia.

EVIDENCE REVIEW AND POTENTIAL INTERVENTIONS FOR EVALUATION

The second aim of the inception meeting was to discuss key targets for future clinical trials, including pathophysiological research underpinning these, and potential trial methodologies and approaches to an integrated trial platform. The group examined current WHO management guidelines for severe malaria along with their levels of supporting evidence and other briefing documents including a published systematic review of evidence for supportive or adjunctive care in severe malaria (Maitland 2015, Varo, Crowley et al. 2018). It is important to highlight that most recommendations in the current WHO guidelines for the management of severe malaria are based on expert opinion, including controversial recommendations regarding several seemingly simple elements such as treatment thresholds for transfusion or correcting hypoglycaemia (World Health Organisation 2014). The paucity of clinical trial data was stark; even at times when over a million African children were dying annually from malaria, only 33 clinical trials of adjunctive (supportive) treatments had been conducted globally since 1980 (Warrell, Looareesuwan et al. 1982) and none showed benefit (Maitland 2015). Over 60% of trials involved children and 15 specifically focused on cerebral malaria. The majority were single-centre Phase I or II trials involving few participants, with a number stopped prematurely for harm. Promising results from several early-phase studies were not reproduced in larger Phase III controlled trials, including phenobarbitone for seizure prophylaxis (Crawley, Waruiru et al. 2000) and fluid boluses for shock (Maitland, Kiguli et al. 2011). The only recent trial which has shown improved outcomes is a large pragmatic multicentre transfusion trial (TRACT ISRCTN 84086586) which enrolled children with severe anaemia (haemoglobin, Hb <6/dl) and included 2050/3196 (64%) children with severe malaria (Mpoya, Kiguli et al. 2015). Key findings have reinforced the evidence base for current guidelines recommending no immediate transfusion for children with Hb 4-6g/dl with no signs of severity (Maitland, Kiguli et al. 2019). The volumes (20 versus 30mls/kg whole blood equivalent) of transfusion recommended should be guided by fever status at the time of issuing blood as a life-saving strategy (Maitland, Olupot-Olupot et al. 2019).

A search of the clinical trial registration sites Trials.gov and ISCTRN for planned or on-going trials of supportive therapies in severe malaria (May 2023) identified no Phase III trials, and only five Phase I or II trials, four of which are designed and run by SMAART investigators and collaborators.

- Phase I trial of prophylactic anticonvulsant levetiracetam with a non-invasive biphasic curass for 30 children with cerebral malaria in one site in Kenya (NOVICE_M) (ISCRTN 76942974)

- Phase I safety and dose-finding trial of a new anti-rosetting agent sevuparin in 20 children with severe malaria in two countries (Kenya and Zambia) (SEVUSMART) (ISCRTN 32271864)
- Phase II trial investigating the pharmacokinetics of paracetamol in 40 children with acute kidney injury in severe malaria in one site in Uganda (PARIST) (ISCRTN 84974248)
- Phase II trial investigating the effect of paracetamol on kidney function in severe malaria (PROTECtS) in 460 children in The Democratic Republic of the Congo (ClinicalTrials.gov Identifier: NCT04251351)
- Phase II trial investigating the use of whole blood as a source of platelets in 132 Zambian children with thrombocytopaenia (platelet count ≤75,000/µL) and low haemoglobin (6-9 g/dl) (PLATFORM) (ClinicalTrials.gov Identifier: NCT05711485)

We concluded that there was little prospect for further reducing the substantial mortality burden from severe malaria within the foreseeable future based on the limited amount of ongoing research and that a flexible adaptive trial was needed to ensure proper evaluation of any adjunctive therapy that could be beneficial, prior to conducting a large Phase III trial in this area.

The consortium also considered both high priority risk factors and missed opportunities to improve short and long-term outcomes which could be prioritised and investigated through a Phase II platform trial. The group identified several high-priority candidates for testing, covering targeted treatments and complications with high mortality, with primary endpoints based on mechanisms of action. These candidates were also further discussed by investigators in Kilifi in January 2023 and ranked by all present at the meeting on feasibility and importance.

Background, justification and rationale for each intervention will be presented in detail in each domain-specific appendix protocol.

1.1 OBJECTIVES

The objective of the SMAART-MAP trial is to identify promising adjunctive therapies to take forward into a large Phase III trial in severe malaria with a mortality endpoint. 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.

1.1.1 PRIMARY OBJECTIVE(S)

To explore within each domain the therapeutic efficacy of the intervention using an early indicator such as a biomarker or clinical assessment at 24-72 hours.

1.1.2 SECONDARY OBJECTIVE(S)

- To assess the impact of the interventions on clinical outcomes (readmission and mortality) on all children 28 days and 90 days after randomisation
- To assess the impact of the interventions on Grade 3 or 4 adverse events, and adverse events of any grade related to the interventions or comparators.

- To assess the impact of proposed definitions for severe malaria based on platelet counts ≤150,000/µL and plasma pfHRP2 concentrations ≥800 ng/mL on differences between randomised groups
- In a substudy, to determine the performance characteristics of a POC pfHRP2 test compared with quantitative plasma pfHRP2 concentrations determined from plasma.

2 SELECTION OF SITES/CLINICIANS

The trial Sponsor has overall responsibility for site and investigator selection. The Sites included in the SMAART-MAP trial are all part of the Severe Malaria a Research and Trials Consortium group.

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

To participate in the SMAART-MAP trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been agreed by the SMAART-MAP Trial Management Group (TMG) and are defined below.

Sites where a previous serious protocol breach has occurred will be visited and thoroughly reviewed before allowing participants to enter the trial.

Those sites that meet the criteria will be issued with the SMAART-MAP Trial Master File (TMF) documentation for their Site-specific Approval.

2.1.1 PI'S QUALIFICATIONS & AGREEMENTS

1. The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, the IRB, and/or the regulatory authorities.

2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s) (if appropriate, as described in the protocol, in the current Investigator Brochure, in the product information and in other information sources provided by the Sponsor.

3. The investigator should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators.

4. The investigator/site should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authorities.

5. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

6. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

7. The investigator should maintain a delegation log of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

8. The investigator should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.1.2 ADEQUATE RESOURCES

1. The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (that is, the investigator regularly treats the target population).

2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5. The site should have sufficient data management resources to allow prompt data return to the KEMRI-Wellcome Kilifi Clinical Trials Facility (CTF). Sites that have previously participated in trials coordinated by KEMRI-Wellcome Kilifi CTF should have a proven track record of good data return.

2.1.3 SITE ASSESSMENT

Each selected clinical trial site must complete the SMAART-MAP Accreditation Form, which includes the Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Investigator Statement verifies that the site is willing, and able to comply with the requirements of the trial. This will be signed by the Principal Investigator at the site. In addition, and in compliance with the principles of GCP, all site staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the KEMRI-Wellcome Trust Kilifi CTF. The CTF must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Investigator Site File at the site and the TMF at KEMRI-Wellcome Trust Kilifi CTF.

2.2 APPROVAL AND ACTIVATION

The SMAART-MAP trial is scheduled to run for 18-24 months. It will start after scientific and ethical approval, approximately July 2024. Site training will be performed prior to the activation of the site and will include all processes for the trial, including but not limited to protocol training, data management procedures, procedures for handling of investigational medicinal product, adverse event reporting procedures, procedures for laboratory samples, and frequency and expectations for any monitoring visits. A log of attendees will be kept in the TMF as a record of participants present at all types of training events.

Before a site can open to recruitment, formal Sponsor Site Green light/Accreditation will be completed in order to document that the site has met all the requirements to participate in the trial. Written confirmation of site activation will be sent to the PI.

A list of activated sites may be obtained from the Trial Manager.

3 SELECTION OF PATIENTS

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the child.

The eligibility criteria are the standards used to ensure that only medically appropriate children are considered for this study. Patients not meeting the criteria should not join the study. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the trial.

Children will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

3.1 PATIENT INCLUSION CRITERIA FOR THE 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

Domains may also have additional domain-specific inclusion and/or exclusion criteria, see domain-specific appendices for details.

The restriction of time since admission to 24 hours is because all children recruited in this trial will be treated with artesunate based antimalarials, which would be expected to be effective within 24 hours if malaria were the underlying cause; later clinical manifestations may have other causes unrelated to severe malaria.

3.2 PATIENT EXCLUSION CRITERIA FOR THE SMAART-MAP TRIAL

1. Enrolled into the SMAART-MAP trial on a previous admission to hospital.

Individual domains may also have domain-specific exclusion criteria.

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.

3.3 NUMBER OF PATIENTS

The sample size for each domain will be calculated to detect a difference in the primary outcome of that domain.

3.4 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in **Section 4.3**.

3.5 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

On arrival at the paediatric ward, the clinical team will immediately screen for *P. falciparum* (by RDT) as part of routine clinical practice. This will also determine eligibility for the SMAART-MAP trial. In some cases, positivity may be determined by a malaria slide (also part of routine clinical practice). All thick and thin malaria slides from children enrolled in SMAART-MAP will be stored for future review and quality control.

Potentially eligible children (RDT/slide positive) will be identified by the nurse and clinician on duty and registered in the eligibility screening log. A member of the trial team will then perform a rapid structured assessment (comprising only clinical parameters routinely assessed at admission) of heart rate, oxygen saturation (pulse oximetry), respiratory rate, axillary temperature, blood pressure, markers of shock (capillary refill time, pulse volume and assessment of lower limb temperature) and confirm whether the child has had any seizures in this illness. Weight will also be recorded (part of standard of care as many drug doses are weight dependent). Additional assessments as part of routine care and as recommended by the WHO malaria treatment guidelines may involve taking finger pricks of blood, for example for haemoglobin, lactate, glucose and creatinine tests with a point of care analyser or at the laboratory.. All children will have a cannula inserted for administration of IV antimalarial treatment; this will be used for any blood collection wherever possible.

Details of those fulfilling the SMAART-MAP entry criteria will be entered onto a screening form for all domains, while reasons for non-eligibility will be added to the eligibility screening log. It is anticipated that this process will take approximately 5 minutes.

Children who are eligible for more than one domain will only be enrolled into one domain. Enrolment into one domain over another for a child eligible for both will be directed by the Trial Management Team (TMT) following predicted and actual recruitment rates into each domain.

INFORMED CONSENT

Prospective written, informed consent will be sought from parents or guardians of children who are considered to be sufficiently stable. Parents or guardians will be given an information sheet in their usual language containing details of the trial. The sheet will be read aloud to those who are unable to read. Parents and guardians will be encouraged to ask questions about the trial prior to signing the consent form. It must be made completely and unambiguously clear that the parent or guardian of the child is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of their child. The right of the parent or guardian to refuse to participate without giving reasons must be respected.

CHILD ASSENT

Older children should give assent to trial participation, if applicable and at an age determined by the country of enrolment. This will be recorded on a dedicated signed assent form.

Signed consent forms (and assent forms where applicable) must be kept by the investigator and documented in the Case Report Form (CRF), and a copy of the signed consent form (and assent form where applicable) given to the family.

EMERGENCY VERBAL ASSENT FOLLOWED BY DEFERRED CONSENT

A number of children will present as emergencies where delay in study enrolment, and thus treatment, through a consent procedure would be unacceptable. For the FEAST trial we developed and received ethical approval to use a two stage consent process in this circumstance (Maitland, Molyneux et al. 2011). Verbal assent will be sought from parents or guardians by the admitting medical team, if it is considered that the full consent process would significantly delay treatment allocation, and consequently could be detrimental to the child's health. Full consent will be sought once the child's clinical condition has been stabilised. Caregivers will be provided with a brief verbal description of the trial and will be given the opportunity to "opt out" of clinical research. The clinician will later sign the verbal assent form which will be filed with the consent form. If written consent is not provided following verbal consent, the child will be excluded from analyses from the time consent is refused. If the child dies before written consent is obtained, written consent will not be sought to avoid distress to the parents/guardians, but the child will be included in the analysis to ensure this important clinical outcome is recorded.

After verbal or written consent, all children should have a urine dipstick, a full blood count, and a blood draw to store plasma for quantitative pfHRP2 testing. Urine dipstick will be done on the first available urine sample, so may be after randomisation depending on the child's status. Blood draws will be done through the cannula already inserted to give IV antimalarials in all children. If blood has previously been taken as part of clinical practice and full blood count performed within this admission, these values should be used rather than taking additional blood. When POC pfHRP2 tests are available on site, either part of the admission draw or a fingerprick (0.1ml) test will be used to conduct this POC test for comparison with the quantitative pfHRP2 concentration (which will be batch processed at the end of the trial).

4 REGISTRATION & RANDOMISATION

4.1 RANDOMISATION PRACTICALITIES

Randomisation lists, using variable block sizes, stratified by site, will be generated and hosted on an online randomisation system accessed by approved site staff. To facilitate protocol adherence, a maximum number to be enrolled per day per site will be agreed upon (for example up to 2 children per day). This approach was very successful with respect to protocol adherence and the quality of data generated in the TRACT trial.

4.2 CO-ENROLMENT GUIDELINES AND REPORTING

Patients will not ordinarily be permitted to participate in any other clinical intervention trial or research protocol for adjunctive therapy while in the SMAART-MAP trial. Participation in other studies that do not involve an intervention such as observational studies may be acceptable but should be discussed with the SMAART-MAP Trial Management Group (TMG).

5 DATA MANAGEMENT

5.1 DATA STORAGE

All clinical and laboratory data will be recorded in the CRF and stored with a unique serial number identifier. Data will be entered onto REDCap® 10.5.1. The trial site staff assigned data entry responsibilities will be trained on REDCap application and each will be assigned an user access account. Sharing of user login details will NOT be allowed. Each user will always be required to use their own account while accessing the system. All electronic data will be regularly backed up and backup copies stored in both on and off site. Paper records will be archived in locked cabinets. These cabinets will have limited access with prior authorisation. Archive documents will be sent for long term storage (up to 15 years) at an appropriate facility according national policies.

5.2 DATA MANAGEMENT AND ANALYSIS

Please refer to the detailed Data Management Plan (Appendix 3) which includes country specific requirements. For statistical analysis see section 10 and Statistical Analysis Plan (Appendix 4).

6 TREATMENT OF PATIENTS

6.1 INTRODUCTION

Each domain has specific randomised intervention and comparator treatments for children enrolled into that domain. Please see domain-specific appendices for more detail.

Standard of care for all children enrolled into SMAART-MAP will include antimalarials, antipyretics and antibiotics following national guidelines in each country.

6.2 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, parents or guardians of children are consenting to trial treatment, trial follow-up and data collection. However, a child may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- Any change in the child's condition that justifies the discontinuation of treatment in the clinician's opinion
- Withdrawal of consent for treatment by the parent or guardian of the child

As the child's participation in the trial is entirely voluntary, their parent or guardian may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled, and this will not be considered a protocol deviation. Although the parent or guardian is not required to give a reason for discontinuing trial treatment, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

Early cessation of any randomised treatment (intervention or comparator) should be recorded on the relevant trial CRF(s) and flagged within the trial database, along with any accompanying information as appropriate.

6.3 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in **Section 4.3**.

7 ASSESSMENTS & FOLLOW-UP

7.1 TRIAL ASSESSMENT SCHEDULE

The trial assessment schedule is presented in **Table 1**. The assessments are designed to be aligned between domains and thus efficacy measures will be done at the same time points (i.e. 24 hours, 48 hours and 72 hours). If the child is discharged prior to 72 hours, then a clinical assessment should be done at discharge. However, caregivers should be encouraged to stay until 72 hours wherever possible. These follow-up assessments are the same for all children enrolled in the SMAART-MAP trial; however, some domains may have additional assessment timepoints where these are important for ascertaining domain-specific outcomes (see domain-specific appendices).

7.2 PROCEDURES FOR ASSESSING EFFICACY

Each domain has primary and secondary outcomes specific to that domain (details in domain-specific appendices). Deaths during the follow up period will be recorded, as will readmissions (ascertained from caregivers during follow up visits), for all children in the SMAART-MAP trial.

7.3 PROCEDURES FOR ASSESSING SAFETY

All adverse event (AE) and Serious Adverse Event (SAE) reporting will follow the same procedure across the domains for all children enrolled in the SMAART-MAP trial. Domain may have specific additional solicited AEs (details in domain-specific appendices).

7.4 EARLY STOPPING OF FOLLOW-UP

As detailed in **Section 6.2**, if a parent or guardian chooses to discontinue their child's treatment in the trial, they should always be encouraged to continue with follow-up as per the trial assessment schedule. It should be made clear to the parent or guardian that continuing to provide follow-up data is important for the success of the trial, regardless of their decisions around their child's treatment. However, as the child's participation in the trial is entirely voluntary, their parent or guardian may choose to discontinue trial follow-up at any time without penalty or loss of benefits to which they are otherwise entitled; if the parent or guardian does not wish their child to remain on trial follow-up, their decision must be respected, and this will not be considered a protocol deviation.

It should be clear to the parent or guardian and recorded in the child's notes exactly which aspect(s) of the trial that the parent or guardian is discontinuing their participation for. These could include:

- Withdrawal from further treatment (Section 6.2)
- Withdrawal from further collection of trial samples
- Withdrawal from further trial follow-up assessments or visits

Information on the specific level of the child's discontinuation should be recorded on the relevant trial Case Report Form(s) and flagged within the trial database, along with any accompanying information as appropriate (and this will not be considered a protocol deviation). Although the

parent or guardian is not required to give a reason for discontinuing trial follow-up, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

To ensure that important trial outcomes are compared in the population randomised and hence balanced by design (the principle of “intention-to-treat”), previously collected and de-identified data from children who stop follow-up early (i.e. data collected before the point of withdrawal) will be kept and included in analysis, in line with the General Data Protection Regulation (GDPR) exemption which states that the ‘right to erasure’ of data does not apply where data processing is necessary for the performance of a task in the public interest in the area of public health, with the appropriate safeguards in place.

Parents and guardians may change their minds about stopping trial follow-up at any time and re-consent to their child’s participation in the trial.

Children who stop trial follow-up early will not be replaced because the primary outcomes for each domain are calculated over the first 24-72 hours when losses to follow-up are expected to be very small.

7.5 LOSS TO FOLLOW-UP

Any child lost to follow-up before 90 days will be traced for vital status. In order to minimise losses to follow-up, locator data (maps and identifiable landmark) and mobile phone numbers will be taken as soon as possible after admission, and at minimum on discharge, and verified at every review. During the 90 day study period, if a child does not attend a scheduled visit, then attempts should be made to contact the parents or guardians via phone (if available) and to follow up with home visits, if at all possible. This led to minimal lost to follow up in previous trials such as FEAST and TRACT.

7.6 COMPLETION OF PROTOCOL FOLLOW UP

The protocol follow up will end after the last scheduled follow-up visit of the last randomised participant in the last domain. Sites will be closed once data cleaning is completed and the database undergone its final lock; the regulatory authorities and ethics committee will be informed of the trial closure as required by local regulations.

8 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. **Section 8.1** lists definitions, **Section 8.2** gives details of the investigator responsibilities and **Section 8.3** provides information on study coordination centre responsibilities.

8.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial protocol. These definitions are given in **Table 2**.

Table 2: Definitions

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect ▪ Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

8.1.1 MEDICINAL PRODUCTS

An investigational medicinal product (IMP) is defined as the tested investigational medicinal product and the comparators used in the study (EU guidance ENTR/CT 3, April 2006 revision). These are defined in the domain-specific appendices.

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

8.1.2 ADVERSE EVENTS

Adverse Events include:

- An exacerbation of a pre-existing illness
- Laboratory abnormalities which are judged clinically significant (hence meet the definition of untoward medical occurrence in **Table 2** above)
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected only after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

Adverse Events do **not include**:

- Medical or surgical procedures; however, the condition that leads to the procedure is the adverse event (and that should be captured in the CRF)
- Laboratory abnormalities which are not judged clinically significant (hence do not meet the definition of untoward medical occurrence, e.g. isolated abnormal measurement without clinical signs or consequence)
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g. social admissions
- Overdose of medication without signs or symptoms. Overdoses with clinical symptoms will be reported as AEs (and SAEs if 'seriousness' criteria are met).

The domain-specific appendices will list any adverse events that will be specifically solicited for children enrolled into that domain.

8.2 INVESTIGATOR RESPONSIBILITIES

AEs judged by the investigator as being related to the intervention or its comparators (any grade), solicited AEs (any grade), grade 3/4 AEs and SAEs should be recorded in an appropriate CRF. SAEs should be notified to the study coordination centre within 24 hours of the investigator becoming aware of the event. Other AEs should be reported as part of routine CRF submission and data entry.

Assessing safety is important, however all patients eligible for the SMAART MAP trial are critically ill and due to the complexity of their condition are at increased risk of experiencing AEs as defined in **Section 8.1**. Consequently, Grade 1 and 2 AEs occurring as a result of the patient's medical condition or standard hospital treatment will not be reported on CRFs. Pre-existing conditions identified before trial drug administration do not qualify as AEs unless they worsen (**Section 8.1.2**) but should be documented in the child's medical notes.

8.2.1 SERIOUSNESS

When an AE or AR occurs, the investigator responsible for the care of the child must first assess whether or not the event is serious using the definition given in **Table 2**. If the event is serious, then an SAE Form must be completed, and the study coordination centre notified within 24 hours.

8.2.1.A Severity or Grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings from Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (https://evs.nci.nih.gov/ftp1/CTCAE/About.html).

8.2.1.B Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial intervention or its comparator using the definitions in **Table 3**. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

Table 3: Assigning Type of SAE Through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition, other concomitant treatments).	SAR
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient's clinical condition, other concomitant treatment).	Unrelated SAE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE

8.2.1.C Expectedness

If there is at least a possible involvement of the trial treatment (or comparator), the investigator may make an initial assessment of the expectedness of the event; however, the Sponsor has the overall responsibility for determination of expectedness. An unexpected adverse reaction is one not previously reported in the appropriate current Reference Safety Information for the specific domain located in the Investigator's Brochure or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in **Table 2**.

8.2.1.D Notification

The study coordination centre should be notified of all SAEs within 24 hours of the investigator becoming aware of the event.

At each clinical review the clinician or nurse will check for potential SAEs, grade 3 or 4 AEs, AEs judged by the investigator as being related to the intervention or its comparator and any solicited AEs. All SAEs will be reported on SAE forms. All grade 3 or 4 events (regardless of causality), AEs judged by the investigator as being related to the intervention or its comparator and all solicited AEs (any grade) will be reported on the CRFs. The reporting procedure is captured within the safety reporting SOP. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance via email or by telephone. SAEs will be reviewed immediately by a designated physician (SAE reviewer) in Kilifi.

8.2.2 Notification Procedure

1. SAEs will be reported to the study coordination centre, using an SAE form, which should be completed, scanned and sent electronically to the study coordination centre within 24 hours. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should determine the causality of the event. Additional information should be sent within 5 days if the event has not resolved at the time of reporting.

2. The SAE Form must be scanned and sent by email to SMAART@kemri-wellcome.org

3. Follow-up: children must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised and no further change is expected. Follow-up should continue after completion of protocol treatment if necessary. A further SAE form, indicated as 'Follow-up', should be completed and emailed to the study coordination centre as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The child must be identified by trial number, date of birth and initials only. The child's name should not be used on any correspondence and should be deleted from any test results.

4. Staff should also follow their institution's procedure and national reporting guidelines for local notification requirements to national ethics and regulatory bodies.

SAE REPORTING
Within 24 hours of becoming aware of an SAE, submit a completed SAE Form to the study coordination centre by email to
SMAART@kemri-wellcome.org
Tel: +254 715461761 or +254 726957045

8.3 STUDY COORDINATION CENTRE RESPONSIBILITIES

Medically-qualified staff at the study coordination centre and/or the Chief Investigator (or a medically-qualified delegate) will review all SAE reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The study coordination centre has been delegated the duties of trial Sponsor in regards to the reporting of SUSARs and other SARs to the regulatory authorities of the countries in which the trial is taking place, and the research ethics committees, as appropriate. Fatal and life-threatening SUSARs must be reported to the competent authorities within the designated timeframe for the country in which the site is located.

The study coordination centre will also keep all investigators informed of any safety issues that arise during the course of the trial.

The study coordination centre, as delegate of the Sponsor, will submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) to competent authorities (Regulatory Authority and Ethics Committee) in the countries for which this applies.

9 QUALITY ASSURANCE & CONTROL

9.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled.

9.2 CENTRAL MONITORING AT THE STUDY COORDINATION CENTRE

Each site will be responsible for its own data entry and local trial management. Data will be entered into the web-enabled trial database directly at the site. The site will retain the original CRF. Data stored on the central database will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, the site will be contacted and asked to verify or correct the entry. Changes will be made on the original CRF and entered into the database at the site. Kilifi CTF will also send reminders for any overdue and/or missing data with the regular inconsistency reports of errors.

Other essential trial issues, events and outputs will be detailed in the Monitoring Plan that is based on the trial-specific Risk Assessment.

9.3 ON-SITE OR REMOTE MONITORING

9.3.1 MONITORING

Quality processes will be in place using a risk-based approach to monitor all trial sites. Monitoring will be conducted by clinical study monitors at the KWTRP. Monitoring will include but will not be limited to ensuring clinical and laboratory processes are conducted as outlined in the protocol and standard operating procedures. The frequency, type and intensity for routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring Plan. The Monitoring plan will also detail the procedures for review and sign-off.

On-site or remote monitoring may be used through the course of the trial. Site staff may be asked to scan and send anonymised form sections to the study coordination centre for remote verification or asked to complete forms to confirm compliance with protocol procedures.

Monitoring will be conducted according to ICH-GCP and WHO Good Clinical Laboratory Practice (GCLP) for laboratories. The individuals responsible for monitoring the study will have access to all records necessary to ensure the integrity and validity of the recorded data and will periodically review the progress of the study. The monitor will contact the site prior to the start of the study to discuss the protocol and data collection procedures with the site personnel.
The investigator and site teams must allow the monitor direct access to all relevant documents and

allocate time to the monitor to discuss findings and any emerging issues. Additional site visits may be made as the monitoring plan is a living document and will be adjusted based on site performance and findings. The plan will outline the proposed visit schedule, timings and planned source data verification processes.

Training sessions on GCP, GCLP and on protocol implementation will be organised for the investigators and all trial staff, as appropriate to their role, prior to recruitment start. A Manual of Operations will be distributed to all the trial sites and laboratories.

9.3.2 DIRECT ACCESS TO PATIENT RECORDS

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Parent or guardians' consent for this must be obtained.

9.3.3 CONFIDENTIALITY

We plan to follow the principles of the UK Data Protection Act (DPA) regardless of the countries where the trial is being conducted.

9.3.4 PROTOCOL DEVIATIONS

Protocol deviations are defined as any change, divergence or departure from study design or procedures as defined in ICH E3 Q&A R1. Further details on identifying protocol deviations and actions to be taken will be outlined in the monitoring plan which will follow a risk-based approach. Thus the focus for establishing protocol deviations will be on assessing the meaningfulness of the difference from the protocol, with emphasis on the impact on the scientific integrity of the trial and on patient safety, and where actions could have been taken to prevent them, rather than for example deviations due to patient choice (such as missed visits) or external circumstances (clotted blood means test results not available although blood taken).

9.4 SOURCE DATA

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data are contained in source documents and are defined by EU guidelines as all information in original records that are used for the reconstruction and evaluation of the clinical trial. Source documents are the first place where the source data are recorded. These can include hospital records, clinical and office charts, laboratory notes, X-rays, and pharmacy dispensing records.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail). Each data element should only have one source.

A source data plan will be agreed with each site as part of the green light process. This plan will define the source documents and the data therein. The document will also specify for each site where the CRF will be the source data. **For this trial, the CRFs may be the source document for data elements including but not limited to:**

- clinical signs and symptoms

- trial samples

The following data should all be verifiable from source documents, which may include paper notes and electronic health records:

- signed consent forms
- dates of visits including dates any trial samples were taken and processed in the laboratory
- eligibility and baseline values
- dates IMP dispensed and (if necessary) drugs returned
- pharmacy or clinic IMP accountability and prescription logs
- adverse events of any grade judged related to the trial interventions or comparators
- severe (grade 3/4) adverse events
- serious adverse events

10 STATISTICAL CONSIDERATIONS

Each domain of the SMAART-MAP trial is a parallel two-arm design comparing outcomes in children randomised to intervention vs comparator in that domain.

Statistical considerations that are specific to each domain will be outlined in the appropriate domain-specific appendix. Considerations that will apply across all domains are outlined below.

10.1 METHOD OF RANDOMISATION

Randomisation will be 1:1 stratified by site. 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.

10.2 SAMPLE SIZE

The sample size for each domain will be calculated to detect a difference in the primary outcome of that domain with 80% power and a two-sided alpha=0.05. Further assumptions for each sample size are detailed in the domain appendices.

10.3 INTERIM CHECKING & 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. 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.

10.4 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 RDT). Previous studies have suggested that identification of severe falciparum malaria can be refined by two additional laboratory criteria, namely a platelet count ≤150,000/µL and plasma pfHRP2 concentrations ≥800 ng/mL (Watson, Uyoga et al. 2022, White, Watson et al. 2022). The final analysis of each domain will include subgroup analyses based on this definition to compare intervention effects in those most likely to truly have severe malaria as opposed to another cause of severe illness with incidental parasitaemia.

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.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

Sites will comply with the principles of GCP as laid down by the ICH topic E6 (R2) and other applicable national regulations.

11.1.2 SITE COMPLIANCE

An agreement will be in place between the site and the KEMRI Kilifi CTF, setting out respective roles and responsibilities (see **Section 13 - Finance**).

11.1.3 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for a minimum of 15 years after the end of the trial. During this period, all data should be accessible, with suitable notice, to the competent or equivalent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations. The data may be subject to an audit by the competent authorities. Medical files of trial participants should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.

11.2 ETHICAL CONDUCT

11.2.1 ETHICAL CONSIDERATIONS

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 reason we want all children to have full blood count is so we can obtain platelet counts which have been proposed as a key laboratory marker to improve the accuracy of identification of severe malaria. We also need a small blood sample for plasma, which will be stored, and batch processed to quantify PfHRP2 (which refines the case-definition of severe malaria) and for any other domain-specific laboratory tests.

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.

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.

Prior to the start, the dedicated study teams will undergo detailed training on management of severe malaria and its complications and on the administration of all interventions.

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.

Compensation

Families will not incur any costs from participation in this study. Travel expenses for attending the visits on Day 28 and Day 90 will be paid, for all children enrolled in the study, based on the cost of public transport to and from the participant's home and compensation for out-of-pocket expenses using standard rates. At follow up visits snacks and drinks will be provided for children enrolled in the trial.

11.2.2 Favourable Ethical Opinion

The Study Coordination Centre will obtain approval from the Imperial College Research Ethics Committee. This trial will also be submitted for approval by Research Ethics Committees/Institutional Review Boards and by all required regulatory authorities in participating countries.

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (Note for Guidance on GCP) and applicable national regulations.

The rights of the parent of guardian to refuse to participate in the trial without giving a reason must be respected. After the child has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the child, and this will not be considered a protocol deviation. The reason for doing so, however, should be recorded; the child will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the parent or guardian must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

11.3 COMPETENT AUTHORITY APPROVALS

This protocol will be submitted to the national competent or equivalent authority as appropriate in each country where the trial will be run.

The progress of the trial and safety issues will be reported to the competent authority, regulatory agency or equivalent in accordance with local requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARS will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

11.4 OTHER APPROVALS

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the local R&D approval (or other relevant approval as above) and of the Patient Information Sheet and Consent Form on local headed paper should be forwarded to the study coordination centre before children are entered.

11.5 END OF TRIAL AND COMPARISON CLOSURE

The SMAART-MAP trial will be closed when the last enrolled child to any domain has been followed up for 90 days, or the last child has been declared lost to follow up.

12 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies, which apply to this study. There will be additional site-specific insurance where required.

13 FINANCE

The trial is supported by grant funding from Wellcome, UK (Grant Number 209265/Z/17/Z). The trial will be coordinated by Imperial College. A written agreement with the site principal investigator and/or the investigator's institution and Imperial College will outline the funding arrangements to sites. The TSC will meet and review the financial aspects of the trial at least 12-monthly and report to the sponsor. Terms of reference will be developed for this activity.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below.

14.1 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the Kilifi CTF. The TMG will be responsible for the day-to-day running and management of the trial.

14.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair. The Chair for the TSC for this trial will be Prof Elizabeth Molyneux, and members will be Prof William Macharia and Dr Irene Lubega. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

14.3 INDEPENDENT DATA MONITORING COMMITTEE (DMC)

An independent Data Monitoring Committee (DMC) will be formed. The DMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the DMC will be produced by the CTU statisticians. The DMC will meet within 6 months of the trial opening; the frequency of subsequent meetings will be determined by the DMC as specified in the DMC charter. The DMC will consider data using the statistical analysis plan (see domain-specific appendices) and will advise the TSC. The DMC can recommend premature closure or reporting of the trial, or that recruitment to any domain be discontinued. The DMC for this trial will be Prof Tim Peto, and independent members will be Prof Philippa Musoke and Prof Jim Todd.

Further details of DMC functioning, and the procedures for interim analysis and monitoring are provided in the DMC Charter.

14.4 ROLE OF STUDY SPONSOR

Imperial College London will act as the Sponsor for this study and delegates this responsibility to the KEMRI CTF, Kilifi, and MRC CTU to oversee the implementation of the study by ensuring that arrangements are put into place for adequate management, monitoring, analysis and reporting of the trial.

Any Intellectual property rights that arise from the work will be safeguarded according to national policies. The scientific and intellectual contributions of all persons involved in the research will be appropriately acknowledged in all publications and presentations arising from the work.

15 PUBLICATION AND DISSEMINATION OF RESULTS

All publications and presentations relating to the study will be authorised by the Trial Management Group. 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 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.

16 DATA AND/OR SAMPLE SHARING

Data from all domains of the SMAART-MAP trial will be shared according to a controlled access approach, 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.
- The resources 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.

Data will be available for sharing after the primary analysis of the trial is complete. Researchers wishing to access SMAART-MAP data should contact the Trial Management Group in the first instance.

Please refer to the Data Management Plan (Appendix 3) which provides further details of any country-specific requirements for data sharing.

17 PROTOCOL AMENDMENTS

None to date.

Protocol	Date	Amendments from previous version
1.01	11th January 2024	Updated details for a coinvestigator and added ISRCTN Number
1.02	9th February 2024	Updated details for investigators
1.1	22nd April 2024	• Exclusion criteria added – no re-enrolment into the trial • Additional wording for notification of SAEs to national regulatory authorities in section 8.2.2 • Co-enrolment restricted to observational studies only (section 4.2) • Addition of POC haemoglobin and RDT for malaria at day 28 and day 90 follow up visits
1.2	8th May 2024	• Added in informed consent row to schedule of assessments • Added in row indicating total volume of blood drawn for common assessments • Further guidance on clinical reasons for stopping treatment given in section 6. • Expected duration and timeline given in section 2.2 • Further detail added to 10.2 sample size section
1.3	5th June 2024	• Addition of overview schema including domains

18 LIST OF APPENDICES

1) Trial Domain Appendices
2) Patient Information Sheet, Consent and Child Assent
3) Data Management Plan
4) Statistical Analysis Plan

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SM AART
Severe Malaria in Africa:
A Research and Trials Consortium

Main Sponsor:
Imperial College London

Collaborating groups:

Appendix C to the Severe Malaria A Research and Trials Consortium – Multisite Adaptive Platform (SMAART-MAP) trial

For management of those enrolled into the Cerebral Malaria domain

Version: 1.2
Date: 8th May 2024

ISRCTN #: ISRCTN79071535
PACTR #: PACTR202312551082722

Authorised by:
Name: Professor Kathryn Maitland
Role: Chief Principal Investigator
Signature:

Date: 8th May 2024

wellcome trust

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GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 10.0. The CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the SMAART-MAP trial cerebral malaria domain, coordinated by the Kenya Medical Research Institute (KEMRI)-Wellcome Trust Kilifi Clinical Trials Facility, and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. This protocol should be used alongside the Master protocol for the SMAART-MAP trial.

Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be available to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the trial team to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, and the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2).

Sites will comply with the principles of GCP as laid down by the ICH topic E6 (R2) and other applicable national regulations.

SPONSOR

Imperial College London is the trial Sponsor and has delegated responsibility for the overall management of the SMAART-MAP trial to the KEMRI-Wellcome Trust Clinical Trials Facility in Kilifi, Kenya.

FUNDING

Funding is provided by Wellcome as part of the grant to the SMAART Consortium (209265/Z/17/Z).

AUTHORISATIONS AND APPROVALS

This trial was approved by **[*Insert Info when approved*]**.

TRIAL REGISTRATION

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN79071535. It has also been registered with the PACTR, where it is identified as PACTR202312551082722.

SAE REPORTING
Within 24 hours of becoming aware of an SAE, submit a completed SAE Form to KEMRI Wellcome Trust Kilifi [by email to **SMAART@kemri-wellcome.org**
Tel: +254 715461761 or +254 726957045

TRIAL ADMINISTRATION

Please direct all queries to Emmanual Oguda the SMAART-MAP clinical project manager at KEMRI Wellcome Trust – Kilifi in the first instance; clinical queries will be passed to the Chief Investigator via the SMAART-MAP clinical project manager.

COORDINATING CENTRE

KEMRI Wellcome Trust Programme	Switchboard: Mobile:	+254 417 522063/522535 +254 715 461761 (Trial administrator)
Clinical Trial Facility	Fax:	+254 417 522390
PO Box 230, Kilifi, Kenya	Email:	SMAART@kemri-wellcome.org

KEMRI WELLCOME TRUST RESEARCH PROGRAMME, STUDY AND TRIAL MANAGEMENT GROUP
Kilifi Clinical Trials Unit, PO Box 230, Kilifi

Principal Investigator:	Prof Kathryn Maitland MBBS PhD	Mobile: Email:	+254 733 411022 kathryn.maitland@gmail.com
Trial Administrator	Phyles Maitha Dip.Business.Mgt	Tel: Mobile: Email:	**+254 417 525453 (switchboard)** +254 715 461761 PMaitha@kemri-wellcome.org
Clinical Project Manager:	Emmanuel Oguda Dipl.Clin.Med.Chir	Tel: Mobile: Email:	+254 417 525453 (switchboard) +254 726957045 EOguda@kemri-wellcome.org
Data Manager:	Christabel Mogaka BSc	Tel: Email:	+254715811661 CMogaka@kemri-wellcome.org

KILIFI: CLINICAL GROUP

Lead Investigator	Prof Mainga Hamaluba MBCHB, MRCP	Mobile: Email:	+254 709 983946 MHamaluba@kemri-wellcome.org
Coinvestigators	Prof Thomas Williams MBBS, PhD	Mobile: Email:	+254 733 411021 tom.n.williams@gmail.com

Coinvestigators	Prof Phillip Bejon MBBS, PhD	Mobile: Email:	+254 724 45743 PBejon@kemri-wellcome.org
Coinvestigators	Prof Charles Newton, MBChB, MA, MD	Email:	CNewton@kemri-wellcome.org

IMPERIAL COLLEGE

Division of Medicine Room 1030 Level 10 St Mary's Campus Norfolk Place London W2 1PG			
Principal Investigator:	Prof Kathryn Maitland MBBS PhD	Tel: Email:	+44 207 670 4905 kmaitland@imperial.ac.uk
Centre Admininstrator	Tony Tarragona-Fiol	Tel: Email:	+44 20 3312 6230 t.tarragona@imperial.ac.uk

MRC CTU AT UCL

MRC Clinical Trials Unit at UCL Institute of Clinical Trials and Methodology 90 High Holborn, 2nd Floor, London WC1V 6LJ			
Principal Investigator:	Prof Diana M Gibb MD MSc	Tel: Email:	+44 207 670 4905 diana.gibb@ucl.ac.uk
Statistician:	Dr Elizabeth George PhD MSc	Tel: Email:	+44 207 670 4931 elizabeth.george@ucl.ac.uk
Statistician:	Prof Ann Sarah Walker PhD MSc	Tel: Email:	+44 207 670 4726 rmjlasw@ucl.ac.uk
Statistician	Roisin Connon MSc	Email:	r.connon@ucl.ac.uk

MORU

Mahidol Oxford Tropical Medicine Research Unit 420/6 Rajvithi Road, Tungphyathai, Bangkok 10400, Thailand			
Co-Lead Investigator:	Prof Nicholas Day, MBBS PhD	Tel: Email:	+66 870 118990 nickd@tropmedres.ac
Co-Lead Investigator:	Prof Arjen Dondorp, PhD	Tel: Email:	+66 818 015675 arjen@tropmedres.ac
Data Manager:	Naomi Waithera, MSc	Email:	Naomi@tropmedres.ac

STUDY SITES AND INVESTIGATORS

UGANDA: Country Principal Investigator Prof Peter Olupot Olupot			
Mbale Clinical Research Institute (MCRI) Mbale Regional Referral Hospital Pallisa Road Zone, P.O Box 921, Mbale, Uganda			
Site Investigator:	Prof Peter Olupot Olupot MBChB, MPH	Tel: Mobile: Fax: Email:	+256 77 2457217 +256 77 2457217 + 256 45 4435894 polupotolupot@yahoo.com
Study Site Coordinator:	To be appointed.	Tel: Mobile: Email:	
Soroti Regional Hospital, P.O Box 289, Soroti, Uganda			
Site Investigator:	Dr Florence Aloroker MBChB, MMed	Tel: Email:	+256 45 4461382 alaroflorence@gmail.com
Study Site Coordinator:	Denis Amorut	Tel: Mobile: Fax: Email:	+256 45 4461382 +256 77 4573911 +256 45 4461382 damoruts@gmail.com
Dr. Ambrosoli Hospital, Kalongo, P.O Box 47 Agago District, Uganda			
Site investigator:	Dr Okao Maurice MD, MMED Paediatrics	Tel: Email:	+ 256 779066157 maurice.okao@gmail.com
Study Site Coordinator	Modester Akite	Email:	modesterakite@gmail.com

KENYA:			
Kilifi County Hospital, Hospital Road, PO Box 230, Kilifi			
Co-Lead investigator:	Prof Mainga Hamaluba MBCHB, MRCP	Tel: Email:	+254 709983946 MHamaluba@kemri-wellcome.org
Co-Lead investigator:	Prof Kathryn Maitland MBBS PhD	Tel: Email:	+254710508749 Kathryn.maitland@gmail.com

MOZAMBIQUE:			
Hospital Central de Quelimane, Av.Julius Nyerere, Estrada regional numero 470. Bairro Namuinho Manhica Health Research Centre (CISM) PO BOX 1929 Manhica			
Co-Lead investigator:	Professor Quique Bassat, MD, MSc, PhD	Tel: Email:	Quique.bassat@isglobal.org
Co-Lead investigator:	Dr Rosauro Varo, MD, MSc, PhD	Tel: Email:	rosauro.varo@isglobal.org
Co-investigator:	Dr Pedro Aide, MD, MSc, PhD	Tel: Email:	+258 2181 0181 pedro.aide@manhica.net
Co-investigator:	Dr David Torres, MD, MSc	Email:	david.torres@isglobal.org

GHANA:			
Komfo Anokye Teaching Hospital, Bantama High Street PO Box 1934 Kumasi Department of Child Health, Kwame Nkrumah University of Science and Technology, Kumasi			
Principal investigator:	Professor Daniel Ansong, MSc	Tel: Email:	+233 208 168767 dansong@kathhsp.org
Co-investigator:	Prof Tsiri Agbenyega, PhD	Tel: Email:	+233 208 113848 tsiri@ghana.com
Co-investigator	Dr Justice Sylverken, MBCHB	Tel: Email:	+233 208 113715 jsylverken@gmail.com

ZAMBIA			
Tropical Diseases Research (TDR) Centre, 6th and 7th Floor of Ndola Teaching Hospital building P.O Box 71769, Ndola, Zambia and St Pauls Mission Hospital, Nchelenge, Luapula Province			
Principal Investigator:	Dr Mike Chaponda, MSc, MBChB, MSc, DTMH	Tel: Email:	+260 212 620737 mikechaponda@yahoo.com
Co-investigator:	Dr Sam Miti, MBChB, MMed	Tel: Email:	+260 212 620737 drsammiti@gmail.com
Co-investigator	Dr Jonathan Gwasupika, MBChB	Tel: Email:	+260 212 620737 gwagwejo@gmail.com

DEMOCRATIC REPUBLIC OF THE CONGO			
Kinshasa School of Public Health Universite de Kinshasa, Campus UNIKIN, BP 11850, Lemba, Kinshasa, DRC			
Principal Investigator:	Prof Marie Onyamboko, MD, DPhil	Tel: Email:	+243990024201 akatshimarie@yahoo.fr
Co-investigator:	Dr Catarina Fanello, PhD	Email:	Caterina@tropmedres.ac

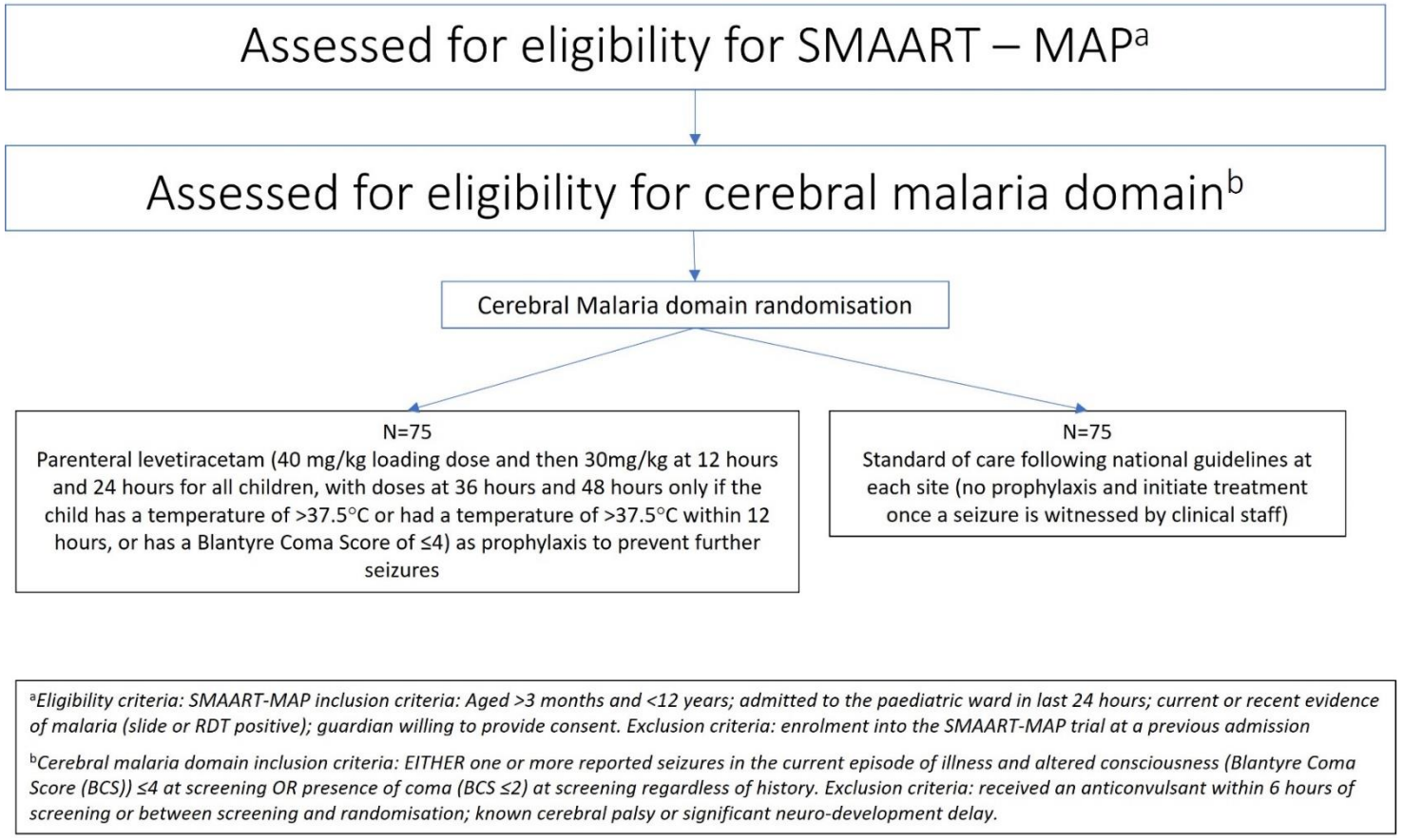
SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym	SMAART – MAP Cerebral Malaria
Long Title of Trial	Severe Malaria A Research and Trials Consortium – Multisite Adaptive Platform trial: Cerebral Malaria domain
Version	1.2
Date	8th May 2024
ISRCTN # **PACTR #**	ISRCTN79071535 PACTR202312551082722
Study Design	Parallel arm multi-site Phase II trial
Setting	Hospitals in Uganda, Zambia, Ghana, Kenya, Democratic Republic of the Congo and Mozambique
Type of Participants to be Studied	Hospitalised children with severe malaria and either a history of seizures in this illness and Blantyre Coma Score (BCS) ≤4 at screening, or BCS ≤2 at screening (regardless of history)
Ancillary Studies/Substudies	Retinal device for diagnosis of severe malaria
Sponsor	Imperial College London
Interventions to be Compared	Parenteral levetiracetam as prophylaxis to prevent further seizures compared to standard of care following national guidelines at each site (no prophylaxis, and treatment once a seizure is witnessed by clinical staff). All children randomised to levetiracetam should receive a 40 mg/kg loading dose and then 30mg/kg at 12 hours and 24 hours. Doses at 36 hours and 48 hours should be given only to a child with a Blantyre Coma Score of ≤4 at these timepoints, or, if they are conscious, should be considered for those with a temperature of >37.5°C or had a temperature of >37.5°C within the preceding 12 hours.
Study Hypothesis	Standard practice is to give anticonvulsants once a seizure is witnessed during an admission for severe malaria. Levetiracetam is an anticonvulsant which has fewer respiration side effects and has been shown to be safer than phenobarbitone. It is also given in UK emergency departments as the first-line treatment for seizures. Giving it to children in coma or who have had seizures in their current episode of severe malaria could prevent further seizures during admission and prevent development of neurological sequelae.
Eligibility criteria	**For SMAART-MAP:** **Inclusion criteria** • Aged >3 months and <12 years • Admitted to the paediatric ward in the last 24 hours at screening • Current or recent evidence of malaria (slide or rapid diagnostic test (RDT) positive in this admission) • Guardian willing to provide consent

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	Exclusion criteria • Enrolment into the SMAART-MAP trial on a previous admission **For this domain:** **Inclusion criteria** EITHER • One or more reported seizures in the current episode of illness and altered consciousness (BCS≤4) at screening OR • Presence of coma (BCS ≤2) at screening regardless of history **Exclusion criteria** • Received an anticonvulsant within 6 hours of screening or between screening and randomisation. • Known cerebral palsy or significant neuro-development delay.
Primary Outcome Measure(s)	Number of witnessed seizures sufficient to start or change anticonvulsant medication by 72 hours
Secondary Outcome Measure(s)	<u>Cerebral malaria domain outcomes</u> • Time to fully regain consciousness (BCS 5 (the maximum score)) • Adverse events (AEs) of any grade judged related to anticonvulsants • Solicited AEs • Neurological sequalae by day 28 and day 90 <u>SMAART-MAP outcomes:</u> • Day 28 and Day 90 readmissions and mortality • Grade 3 or 4 AEs during admission
Randomisation	1:1 randomisation using randomised permuted blocks, stratified by site.
Number of Participants to be Studied	150 children, 75 per arm
Duration	24 months
Funder	Wellcome
Chief Investigator	Professor Kathryn Maitland

TRIAL SCHEMA

Figure 1: Trial Entry, Randomisation and Treatment



[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. Exclusion criteria: enrolment into the SMAART-MAP trial at a previous admission*

[b]*Cerebral malaria domain inclusion criteria: EITHER one or more reported seizures in the current episode of illness and altered consciousness (Blantyre Coma Score (BCS)) ≤4 at screening OR presence of coma (BCS ≤2) at screening regardless of history. Exclusion criteria: received an anticonvulsant within 6 hours of screening or between screening and randomisation; known cerebral palsy or significant neuro-development delay.*

TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule

Assessment	Admission/ Screening	Random-isation	3 hrs (± 1hr)	12 hrs (± 1hr)	24 hrs (±3 hrs)	36 hrs (±3 hrs)	48 hrs (±3 hrs)	72 hrs (±3 hrs)	Discharge	28 (±7) days	90 (±14) days
Clinical assessment[1]	x		x	x	x	x	x	x[8]		x	x
Point-of-care tests (0.2-0.3ml) [2]	x		x		x	x	x	x		x	x
Record witnessed seizures	x		x	x	x	x	x	x[8]			
Weight[3]	x									x	x
Malaria RDT, and thick and thin malaria slide (if available at site) (0.2ml)	x									x	x
Informed consent process[4]	x										
Randomisation		x									
Full Blood Count[5] (1ml)		x									
Urine dipstick[6]		x[4]									
Plasma storage for quantitative pfHRP2 (1ml)		x									
POC pfHRP2 test (when available) (0.2mls)		x									
Dosing of levetiracetam (levetiracetam group only)		x		x	x	(x[7])	(x[7])				
Pharmacokinetics blood sample on filter paper (0.2mls) (levetiracetam group only)			x	x[7]	x[7]						
Ascertainment of all treatments given during admission (anticonvulsants, anti-malarials, antibiotics and transfusions)									x		
Ascertainment of readmissions, potential malaria episodes, and neurological sequalae										x	x
Optional substudy: Retispot examination[10]		x									
Total blood draw (mls) (total across study 4.6-5.3mls)	0.4-0.5	2.2	0.2-0.3	0.2-0.3	0.2-0.3	0.2-0.3	0.2-0.3	0.2-0.3	0	0.4	0.4

Note: greyed cells indicate assessments common to all SMAART-MAP domains from the master protocol.

[1] Clinical assessment: heart rate, oxygen saturation (pulse oximetry), respiratory rate, respiratory distress, axillary temperature, blood pressure, capillary refill time, consciousness level (as measured by the Blantyre Coma Score (BCS)).

[2] Lactate, glucose and haemoglobin (hb) as point-of-care tests (lactate and glucose only at 3hrs, haemoglobin only at 28 and 90 days).

[3] Weight: assessed at screening or as soon as possible after enrolment depending on status.

[4] This could be informed consent or emergency verbal assent followed by deferred consent dependant on the child's condition – please see section 3.7 for details.

[5] Full blood count: haemoglobin, white blood cells, platelets (and differential if available as standard at site). Values from a blood draw taken for clinical reasons (i.e. not for the trial) at any time in this admission before randomisation should be used if available, rather than re-bleeding the child, as eligibility requires all children to be enrolled within 24 hr of admission at screening.

[6] This should be taken when the first urine sample is available.

[7] These doses are only given if a child has a temperature >37.5°C, has had a temperature >37.5°C within the 12 hours preceeding the assessment or has a Blantyre Coma Score (BCS) of ≤4

[8] If the child is discharged prior to 72 hours then these assessments should be done at discharge. However, caregivers should be encouraged to stay until 72 hours wherever possible.

[9] Blood sample taken prior to dose being given.
[10] Optional consent will be sought for this substudy, see Section 11.1. As soon as possible after written consent is obtained, the child may be given myriaditic eye drops, if needed for the device and as required as standard procedure for eye examinations, and the ocular fundus of each eye will be examined with the RetiSpot module.

LAY SUMMARY

Children with severe malaria can be very sick and be unconscious (unable to be wakened) due to the malaria parasites in their body. This inceases their risk of fits (also called seizures) and is also known as cerebral malaria. Children who have had seizures in their current illness also have an increased risk of futher seizures, especially if they have a fever. They also have a higher chance of dying or developing longer term complications affecting their development and normal mobility (called neurocognitive sequelae).

Treatment of seizures follows national guidelines which are based on recommendations from the World Health Organization and what drugs (called anticonvulsants) are available in each country. Sometimes treatments have side effects; for these kinds of drugs this means that although they may stop the seizures, they may make the child more deeply unconscious for longer and also lower their breathing rate and ability to breath effectively. If we could stop a child from having a seizure by giving an anticonvulsant to prevent, rather just treat, seizures this might improve outcomes in these children.

Levetiracitam is an anticonvulsant medication designed to treat seizures effectively. Unlike some previous anticonvulsants, it is very safe and has very few side effects (including those above) making it a good drug to give both to stop seizures and to prevent further seizures. It is given to children in hospitals around the world as the initial treatment of fits and has been given safely to children with cerebral malaria before in Malawi. It can be given as a liquid to be drunk, or to go to a child's stomach through a tube if they are unable to drink, or by an intravenous (IV) line – where it goes straight into the blood stream. In this trial we are using an IV line to give it most effectively. In this trial we will be giving leveteracitam to children with malaria who are at greatest risk of having seizures to prevent the seizures from happening.

A computer programme will assign a child to receive either levetiracitam or standard of care at random (like the flip of a coin). If they are assigned to receive levetiracitam then they will be given a first dose as soon as possible and then further doses every 12 hours whilst their conscious level is reduced or whilst they have a fever for up to 3 days. If they are not assigned to levetiracitam then they will be treated following national guidelines which give anticonvulsations to treat any further seizures during admission. Trial staff will be monitoring all the children very closely to see if they have any further seizures that lead to treatment being given. These will be recorded to check if those that receive leveteracitam have fewer seizures compared to those receiving care following national guidelines.

CONTENTS

ABBREVIATIONS

ABBREVIATION	EXPANSION
AE	Adverse event
AI	Artificial intelligence
AR	Adverse reaction
AUROC	Area under the Receiver Operator Curve
BCS	Blantyre Coma Score
CF	Consent Form
CI	Chief Investigator
CI	Confidence interval
CM	Cerebral Malaria
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTF	Clinical Trial Facility
CTU	*See MRC CTU at UCL*
DM	Data Manager
DMC	Data Monitoring Committee
DSUR	Developmental Safety Update Report
EEG	Electroencephalogram
GCP	Good Clinical Practice
Hb	Haemoglobin
IB	Investigator Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ISRCTN	International Standard Randomised Controlled Trial Number

ABBREVIATION	EXPANSION
KEMRI-Wellcome Trust Kilifi CTF	Kenya Medical Research Institute – Wellcome Trust Kilifi Clinical Trials Facility (also generally abbreviated to CTF)
MAF	Malaria attributable fraction
MOP	Manual of Operations
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London (also generally abbreviated to "CTU")
NGT	Naso-gastric tube
PfHRP2	Plasmodium falciparum histidine rich protein 2
PI	Principal Investigator
POC	Point of Care
RCT	Randomised controlled trial
RDT	Rapid Diagnostic Test
REC	Research Ethics Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Standard deviation
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
WHO	World Health Organization

1 BACKGROUND

Neurological involvement in African children presenting to hospital with severe malaria is very common. Typically, it manifests following a short febrile illness with seizures, altered consciousness, with or without signs of brain-stem involvement. The spectrum of neurological involvement in severe malaria includes decreased conscious level, which may result from a variety of metabolic (hypoglycaemia) and haemodynamic (shock) complications, seizures, posturing and profound and sustained coma (known as cerebral malaria) (Maitland and Molyneux 2004). For epidemiological purposes, cerebral malaria is strictly defined as an unrousable coma (equating to inability to localise a painful stimulus) persisting >1 hour post-seizure (irrespective of anticonvulsant medication) as many children may regain full consciousness following a convulsion. The Blantyre Coma Scale (BCS) is the most widely used paediatric classification of impaired consciousness in sub-Saharan Africa. This was developed as a practical tool for children who are too young to speak (Molyneux, Taylor et al. 1989, Newton, Chokwe et al. 1997). Coma (and hence cerebral malaria (CM)) is classified as a BCS of 2 or less (out of a possible 5). More recently, ophthalmoscopy (in temporarily-dilated pupils) to assess for malaria retinopathy has been used to improve the precision of the clinical diagnosis of cerebral malaria and is recommended for use in intervention studies to refine the diagnosis of cerebral malaria (Lewallen, Harding et al. 1999). The observation of a specific malaria retinopathy is supported by autopsy evidence of intracerebral parasite sequestration in a study of 27 Malawian children with fatal cerebral malaria (Taylor, Fu et al. 2004).

Seizures are the most common neurological complication of acute *P. falciparum* malaria, manifesting as either simple tonic-clonic or partial convulsive episodes (Molyneux 1989) to clinically silent electrical status (Birbeck, Molyneux et al. 2010). The most common seizures in severe malaria are focal motor or generalised tonic-clonic convulsions (Bondi 1992). However, around 25% of seizures are subtle or sub-clinical (detected with EEG), frequently manifesting as eye deviation, an irregular respiratory pattern or drooling (Crawley, English et al. 1998). In a prospective study in Kenyan children with malaria, 15.8% had a history of seizures or witnessed seizures at admission to hospital (Waruiru, Newton et al. 1996). Only 25% of malaria-related epileptic seizures were associated with cerebral malaria (BCS <=2). Moreover, there was no relationship with fever with 54% of observed seizures occurring at rectal temperatures below 38°C. During hospital admission, multiple seizures typically occurred in over 50% of these cases, with 22% having a prolonged seizure episode (>30 minutes). Whilst short-lived seizures frequently occur in many young children with febrile illnesses, with limited prognostic significance, the aetiological relatedness in acute malarial illness or the malarial attributable fraction (MAF) was explored in a prospective study (Kariuki, Ikumi et al. 2011). Children that had two or more seizures in 24 hours prior to hospital admission with malaria had very high MAFs, suggesting that acute malaria was the chief cause of convulsions (Kariuki, Ikumi et al. 2011).

Current management recommendations for seizures

The current treatment algorithm for managing children with seizures is a weight-adjusted dose of intravenous or intramuscular diazepam (0.15-0.2mg/kg) to treat a prolonged seizure (>5 minutes). This can be repeated once; for further seizures intravenous loading of phenobarbitone (15mg/kg) (or phenytoin) is recommended as second-line followed by a maintenance dosage (10mg/kg/day) until the child is seizure free. Since convulsions are common in severe malaria, in particular in the sub-group with cerebral malaria, and are associated with adverse outcomes including death and neurological sequelae (in children), routine administration of anti-epileptics to prevent seizures may have potential benefits.

Trials of prophylactic anticonvulsant therapy in severe malaria

In a double-blind controlled trial conducted in Thailand in the early 1990s, both children and adults with cerebral malaria were randomised to receive either a single dose of phenobarbitone or placebo. There was a lower seizure rate in the phenobarbitone group at 12% (3/24) compared to 54% (13/24) in the placebo group (p = 0.006) (White, Looareesuwan et al. 1988). There was no evidence of an effect on mortality, with deaths occurring in 8 (33%) vs 5 (21%) participants respectively. Based on this small study, at that time the authors recommended that guidelines should advocate that all patients with cerebral malaria should receive a single intramuscular loading dose of phenobarbitone.

Anticonvulsants in African children

Phenobarbitone

A large single centre paediatric placebo-controlled trial conducted in 340 Kenyan children with cerebral malaria, designed to provide the evidence for this new recommendation, examined a single intramuscular dose of phenobarbitone (20mg/kg) versus placebo. As expected the phenobarbitone group had a lower rate of seizures (defined as three or more seizures of any duration) than the placebo group (18 [11%] vs 46 [27%], odds ratio 0·32 [95% CI 0·18–0·58]) but mortality was more than double in the phenobarbitone group (30 [18%] compared to 14 [8%] placebo deaths; relative risk 2·39 [95% CI 1·28–4·64]) (Crawley, Waruiru et al. 2000). The main mode of death in those receiving phenobarbitone was respiratory arrest. Following this trial, the guidelines changed and no longer recommend phenobarbitone prophylaxis in cerebral malaria.

Fosphenytion

A further placebo-controlled trial, conducted at the same centre in Kenya, in non-traumatic encephalopathy (including a cerebral malaria subgroup, n=110) investigated the use of fosphenytoin (a drug often used for seizure prophylaxis in neuro-trauma that has minimal cardiorespiratory side effects). This trial was terminated due to slow recruitment/futility. At least one seizure (monitored clinically and by electroencephalogram) occurred in 33/83 (40%) children receiving fosphenytoin versus 32/88 (36%) receiving placebo (P=0.73) (Gwer, Idro et al. 2013). In the cerebral malaria sub-group, 20 (37%) children in the fosphenytoin group had seizures; identical to the placebo group (21, 38%). Overall, 18 children treated with fosphenytoin (21%) died compared with 15 (17%) in the placebo group (P=0.49). In survivors, rates of neurologic sequelae at 3 months were the same (10%) in both groups (Gwer, Idro et al. 2013).

Levetiracetam (sold as Keppra or other brand names)

Owing to its favourable properties, levetiracetam is increasingly the drug for choice in children with status epilepticus (Dahlin, Wide et al. 2010). However, previously the cost of intravenous formulations was prohibitive and thus some investigators have considered the oral formulation (dosed via an nasogastric tube) owing to its favourable enteral bioavailability, and likelihood that this could be adopted into future guidelines if shown to result in improved disability-free survival. Two linked studies (Phase I and Phase II) have been undertaken in Blantyre, Malawi in children with cerebral malaria with a history of seizures.

A Phase I Dose-Escalation, Safety And Feasibility Study Of Enteral Levetiracetam For Seizure Control In Pediatric Cerebral Malaria (NCT01660672) (Birbeck, Herman et al. 2019)

The overarching aim of this trial was to provide optimal dosing recommendations and preliminary efficacy data to determine whether to proceed with the Phase II randomised clinical trial of levetiracetam. It was designed to start with a 40 mg/kg loading dose followed by 30mg/kg every 12 hours via nasogastric tube for 3 days, which is the standard recommended dose. If the primary

outcome (see below) was not reached, then the dose was planned to be escalated to 150%, 225%, and 300% standard, as needed. Levetiracetam doses of ~3 times the standard dose have been successfully used for other seizure-related conditions. Levetiracetam was escalated based upon efficacy and toxicity endpoints. Efficacy was defined as seizure freedom in 75% of children during the 24 hours following the initial loading dose of levetiracetam compared to the pretrial experience of approximately 20% of children remaining seizure free after admission with CM (and a history of seizures) receiving standard antiepileptic treatment. Safety assessments included side-effects of nasogastric tube (NGT) placement and medication delivery, laboratory parameters at 24 hours and 7 days post levetiracetam, and overall case fatality rates to day 7 compared to the consistent historical average case-fatalities rates for CM. Pharmacokinetic (PK) samples were collected to estimate the absorption and elimination of levetiracetam in CM as the experience with enteral formulations was limited in critically ill children (with none in malaria).

Seven children were enrolled with a mean age of 40.8 months (range 27-71 months). All children were free from seizures (7/7) to 72 hours (the primary efficacy endpoint). However, 6 children required additional antiepileptic drugs. There were no toxicity events reported (these included no vomiting aspiration, complications related to NGT, fatal events or lab abnormal laboratory parameters). The PK studies examined the range of levetiracetam concentrations at 8 time points post levetiracetam administration to 72 hours. The mean (and full range) of levetiracetam concentrations was 35 (20-50) micrograms/mL. Since the primary endpoint (seizure control) was achieved in all participants (although there is uncertainty why children received additional antiepileptic drugs) there was no dose escalation.

The LVT2 Phase II trial (NCT01982812) (Birbeck, Herman et al. 2019)
Treatment of seizures in this follow-on Phase II trial was by using oral levetiracetam administered via NGT at an initial dosage of 40mg/kg followed by 30mg per kg 12 hourly (twice daily) compared to standard of care with phenobarbitone as required. Children randomised to 'standard of care' received 20mg/kg phenobarbitone with additional doses at the managing clinicians' discretion (a protocol amendment in 2015 restricted the maximum standard of care daily dose to 20mg/kg).

The study was conducted between January 2015 to June 2016. Eligible children were aged 24-83 months, with BCS <=2, *P. falciparum* positive (slide or RDT) and a history of a seizure in the proceeding 24 hours. Children with a plasma creatinine >2mg/dL were excluded as were children on HIV or tuberculosis medications. The main outcomes were electroencelephogram (EEG)-defined seizure control over 72 hours. Secondary endpoints included safety, survival and neurological outcomes. In the levetiracetam group, 4/23 had breakthrough seizures, mean 165 min duration (SD 266; IQR 26–305; maximum 563). In the usual care group, 5/21 had breakthrough seizures after phenobarbital, mean 465 min (SD 639; IQR 42–734; maximum 1473). There was no statistical evidence of differences in minutes with seizure, coma duration, need for alternate treatment, neurologic sequelae at discharge or death. Phenobarbitone was discontinued in 3/15 due to respiratory side effects.

Research Gap
Orally dosed levetiracetam has been demonstrated to be safe and reduce seizures in children with cerebral malaria in a previous single centre study in Malawi (Birbeck, Herman et al. 2019). It has also been shown to be given safely intravenously to critically ill children (Abend, Monk et al. 2009, Appleton, Rainford et al. 2020) and is very commonly used in high-income countries to prevent and treat seizures. Based on the emerging evidence, we hypothesise that prophylactic anticonvulsant medication could avert 'spikes' of intracranial pressure during repeated seizure events, thus giving it to children that have had seizures in their current episode of severe malaria but prior to admission,

or to those in coma at admission, could prevent further seizures during admission and prevent development of neurological sequelae. Since the studies conducted in Malawi, the cost of levetiracetam across sub-Saharan Africa has substantially reduced and the availability of the intravenous formulation has improved. It is increasingly becoming an attractive alternative for treatment of status epileptic in Africa and is being considered by WHO to be included in the essential drugs lists (personal communication Professor Charles Newton).

1.1 OBJECTIVES

1.1.1 PRIMARY OBJECTIVE(S)

Our primary objective is to test whether that levetiracetam given to children with seizures in their current episode of malaria will help prevent further seizures.

1.1.2 SECONDARY OBJECTIVE(S)

Our secondary objective is to assess the impact of levetiracetam on other outcomes including mortality and readmission at 90 days and to investigate its safety profile in this patient population by grade 3 and 4 adverse events (AEs), solicited AEs, and AEs of any grade related to anticonvulsants.

An additional objective is to store blood spots on filter papers, in order to further assess the pharmacokinetics of levetiracetam in this patient population.

2 SELECTION OF SITES/CLINICIANS

The trial Sponsor has overall responsibility for site and investigator selection. The Sites included in the SMAART-MAP trial are all part of the Severe Malaria - a Research and Trials Consortium group. The site/investigator inclusion criteria and steps for approval and activation are outlined in the Master Protocol.

3 SELECTION OF PATIENTS

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

The eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this study. Patients not meeting the criteria should not join the study. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the trial.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

3.1 PATIENT INCLUSION CRITERIA FOR THE SMAART-MAP TRIAL

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

The restriction of time since admission to 24 hours is because all children recruited in this trial will be treated with artensunate based antimalarials, which would be expected to be effective within 24 hours if malaria were the underlying cause; later clinical manifestations may have other causes.

3.2 PATIENT EXCLUSION CRITERIA FOR THE SMAART-MAP TRIAL

1. Enrolment into the SMAART-MAP trial on a previous admission

3.3 ADDITIONAL PATIENT INCLUSION CRITERIA FOR THE CEREBRAL MALARIA DOMAIN

1. EITHER one or more seizures in the current episode of illness and BCS ≤4 at screening OR presence of coma (BCS ≤2) at screening

3.4 ADDITIONAL PATIENT EXCLUSION CRITERIA FOR THE CEREBRAL MALARIA DOMAIN

1. Received an anti-convulsant within 6 hours of screening or between screening and randomisation.
2. Known cerebral palsy or significant neuro-development delay.

3.5 NUMBER OF PATIENTS

75 per arm. 150 in total.

3.6 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in **Section 4.2**.

3.7 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

On arrival at the paediatric ward, the clinical team will immediately screen for *P. falciparum* (by RDT) as part of routine clinical practice. This will also determine for eligibility for the SMAART-MAP trial. In some cases, positivity will be determined by a slide (also part of routine clinical practice).

Potentially eligible children (RDT/slide positive) will be identified by the nurse and clinician on duty and registered in the eligibility screening log. A member of the trial team will then perform a rapid structured assessment (comprising only clinical parameters routinely assessed at admission) of heart rate, oxygen saturation (pulse oximetry), respiratory rate, axillary temperature, blood pressure, markers of shock (capillary refill time, pulse volume and assessment of lower limb temperature) and confirm whether the child has had any seizures in this illness. Information on the presence of any seizures in this illness will be taken from the caregiver or parent. Weight will be measured as standard of care and in preparation for any weight-based dosing of medications. Additional assessments as part of standard of care and as recommended by the WHO malaria treatment guidelines may involve taking finger pricks of blood, for example forhaemoglobin, lactate, glucose and creatininetests with a point of care analyser or at the laboratory. Details of those fulfilling the entry criteria will be entered onto a screening form, while reasons for non-eligibility will be added to the eligibility screening log. Entry criteria for this domain will be based on clinical assessment alone. It is anticipated that this process will take approximately 5 minutes.

INFORMED CONSENT

Prospective written, informed consent will be sought from parents or guardians of children who are considered to be sufficiently stable. If a wearable device for monitoring seizures is available, consent for use of the device will be sought separately. Parents or guardians will be given an information sheet in their usual language containing details of the trial. The sheet will be read aloud to those who are unable to read. Parents and guardians will be encouraged to ask questions about the trial prior to signing the consent form. It must be made completely and unambiguously clear that the parent or guardian of the child is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of their child. The right of the parent or guardian to refuse to participate without giving reasons must be respected. Older children should give assent to trial participation, if applicable and at an age determined by the country of enrolment. This will be recorded on a signed assent form.

EMERGENCY VERBAL ASSENT FOLLOWED BY DEFERRED CONSENT

A number of children will present as emergencies where delay in study enrolment, and thus treatment, through a consent procedure would be unacceptable. For the FEAST trial we developed and received ethical approval to use a two stage consent process in this circumstance (Maitland, Molyneux et al. 2011). Verbal assent will be sought from parents or guardians by the admitting medical team, if it is considered that the full consent process would significantly delay treatment allocation, and consequently could be detrimental to the child's health. Full consent will be sought once the child's clinical condition has been stabilized. Caregivers will be provided with a brief verbal

description of the trial and will be given the opportunity to “opt out” of clinical research. The clinician will later sign the verbal assent form which will be filed with the consent form. If written consent is not provided following verbal consent, the child will be excluded from analyses from the time consent is refused. If the child dies before written consent is obtained, written consent will not be sought to avoid distress to the parents/guardians, but the child will be included in the analysis to ensure this important clinical outcome is recorded.

Signed consent forms (and signed assent forms where applicable) must be kept by the investigator and documented in the CRF and a copy given to the family.

4 REGISTRATION & RANDOMISATION

4.1 RANDOMISATION PRACTICALITIES

Randomisation lists, using variable block sizes, stratified by site, will be generated and hosted on an online randomisation system accessed by approved site staff. To facilitate protocol adherence, a maximum enrolled per day per site will be agreed upon (for example up to 2 children per day). This approach was very successful with respect to protocol adherence and the quality of data generated in the TRACT trial.

4.2 CO-ENROLMENT GUIDELINES AND REPORTING

Patients will not ordinarily be permitted to participate in any other clinical intervention trial or research protocol for adjunctive therapy while in the SMAART-MAP trial. Participation in other studies that do not involve an adjunctive therapy intervention, such as observational studies, may be acceptable but should be discussed with the SMAART-MAP Trial Management Group (TMG). Enrolment within the SMAART-MAP trial is restricted to one domain.

5 TREATMENT OF PATIENTS

5.1 INTRODUCTION

All trial patients will receive standard of care including antibiotics, antipyretics and anti-malarial drugs (parenteral then oral) following national guidelines, based on WHO syndromic patient management (World Health Organisation 2022). All children enrolled in the trial should remain admitted to the ward until after the 72 hour clinical assessment and tests have been conducted wherever possible.

5.2 LEVETIRACETAM PROPHYLAXIS ARM

5.2.1 TREATMENT SCHEDULE

Children randomised to this arm will receive parenteral levetiracetam as a 40mg/kg loading dose then 30mg/kg given at 12 and 24 hours. Thereafter 30mg/kg should be given every 12 hours up to 48 hours (i.e at 36 and 48 hours, 5 doses in total) if the child is not fully conscious (BCS≤4) at these timepoints. If the child is conscious, these doses should be considered if the child continues to have evidence of fever, suggesting that they remain at risk of febrile seizures that the intervention could potentially prevent, that is have a temperature of >37.5°C, or have had a previous temperature (within 12 hours) of >37.5°C.

5.2.2 DISPENSING & STORAGE

Open-label levetiracetam for use in the trial will be stored in the site pharmacy and dispensed to study staff.

5.2.3 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

Any difficulties with the IV line used to give the levetiracetam and any other reason for difficulties in administration of the medication will be recorded on the appropriate treatment CRF. If a child develops a seizure which clinicians judge needs treatment, then additional anticonvulsants can be given at therapeutic doses in accordance with national guidelines. These may include diazepam, phenobarbitone, phenytoin, midazolam or sodium valproate depending on response to previous treatments and availability at site and in accordance with national guidelines (which may vary from country to country).

5.2.3.A Stopping Drug Early

Additional doses of levetiracetam should not be given if two or more doses of diazapam (any route) have been administered to the child. In addition if the child experiences/displays any neuropsychiatric side effects (hallucinations) or delirium then further doses should be stopped (and this should be reported on the SAE CRF). Other discontinuation criteria are considered in **Section 5.4.**

5.2.4 ACCOUNTABILITY & UNUSED DRUGS/DEVICES

Accountability must be maintained for all levetiracetam dispensed to participants. Any diluted product that has been dispensed from pharmacy must be destroyed if not used for the treatment of a trial participant. Expired products should be quarantined prior to destruction according to local procedures and recorded in the appropriate trial-specific log. Logs may be collected centrally for monitoring purposes. More information on accountability and pharmacy procedures, including destruction procedures, can be found in the trial manual of operations (MOP).

5.2.5 COMPLIANCE & ADHERENCE

Data on compliance with administration of levetiracetam by study staff at site at the dose and times indicated above will be collected on a treatment CRF. Other measures of adherence are not needed as the intervention is given by study staff rather than parents or children.

5.3 NO LEVETIRACETAM PROPHYLAXIS ARM (CONTROL)

5.3.1 TREATMENT SCHEDULE

Children randomised to this arm will not receive levetiracetam unless it is in the site's guidelines for treatment of witnessed seizures during admission. The site staff will be monitoring children closely and if a child develops a seizure which clinicians judge needs treatment, then anticonvulsants can be given in accordance with national guidelines. Standard treatment may include diazepam, phenobarbitone, phenytoin, midazolam or sodium valproate depending on response to previous treatments and availability at site and in accordance with national guidelines (which may vary from country to country).

5.3.2 DISPENSING & STORAGE

No medication will be dispensed or stored specifically for the trial for this arm as it is following standard of care.

5.3.3 COMPLIANCE & ADHERENCE

Data on all systemic medications given to children in the trial will be recorded on a relevant CRF, including any levetiracetam given to children in this arm.

5.4 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, parents or guardians of children are consenting to trial treatment, trial follow-up and data collection. However, a child may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- Any change in the child's condition that justifies the discontinuation of treatment in the clinician's opinion
- Withdrawal of consent for treatment by the parent or guardian of the child

As the child's participation in the trial is entirely voluntary, their parent or guardian may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled, and this will not be considered a protocol deviation. Although the parent or guardian is not required to give a reason for discontinuing trial treatment, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

Early cessation of levetiracetam treatment should be recorded on the relevant trial CRF(s) along with any accompanying information as appropriate.

Children for which levetiracetam treatment is stopped early should be encouraged to continue follow-up as per the trial assessment schedule, unless the parent or guardian expressly withdraws

their consent to be followed up or to provide any further data. If this occurs, see **Section 6.4** for further details.

5.5 COMPLIANCE & ADHERENCE

All children entering this trial will be severely ill and medical personnel will be responsible for administering the interventions. Site staff compliance will be regularly checked from CRF and data entry by trial staff.

5.6 TREATMENT DATA COLLECTION

Data will be collected on the dose and timing of all levetiracetam given during the trial on an appropriate CRF.

5.7 NON-TRIAL TREATMENT

All non-trial systemic treatment given in the course of the admission will be recorded on a CRF. Such concomitant medication would include anti-malarials, other anticonvulsants, antipyretics, and antibiotics following national guidelines. Any fluids, including blood transfusions, given during the admission would also be recorded. If required, maintenance fluids will be run at 3-4 mls/kg per hour irrespective of age until the child can drink and retain oral fluids. Antipyretics and treatment for hypoglycaemia will be administered according to nationally agreed protocols.

Patients who receive non-trial treatment will remain in the trial, following the same visit schedule where possible, for the purposes of follow-up and data collection (unless they withdraw their consent from all stages of the trial).

5.7.1 TREATMENT AFTER TRIAL EVENT

Treatment will be at the discretion of the responsible physician and following national guidelines and protocols.

6 ASSESSMENTS & FOLLOW-UP

Children will be monitored on the day of admission by the clinical team, and then reviewed daily by the study team until discharge (**Table 1**). If the child is discharged prior to 72 hours then a clinical assessment should be done at discharge. However, caregivers should be encouraged to stay until 72 hours wherever possible. Locator maps and contact numbers will be obtained as soon as possible after admission, and at a minimum on discharge to facilitate follow-up. All participants will then be seen at 4 weeks (28 days) and 3 months (90 days) from the date of randomisation, at outpatient clinics attached to each centre for evaluation of morbidity, and toxicity. During the 90 day study period, if a child does not attend a scheduled visit, then attempts should be made to contact the parents or guardians via phone (if available) and to follow-up with home visits, if at all possible.

6.1 TRIAL ASSESSMENT SCHEDULE

The trial assessment schedule is outlined in **Table 1**.

6.2 DOMAIN-SPECIFIC PROCEDURES FOR ASSESSING EFFICACY

Children in both arms will be regularly monitored for seizures. Children will have regular scheduled, and where clinically indicated non-scheduled, assessments by the trial team which will assess for vital signs, temperature, witnessed seizures since the last assessment and level of consciousness which will be recorded in the CRF. Staff will also ask parents/guardians to notify them if they have any concerns that their child vital status has changed or had seizure movements so they can perform an unscheduled clinical assessment. Information on any anticonvulsants prescribed including dosage will be recorded on a CRF to assess total number of doses given and changes in medications. If available, wearable devices to monitor seizures may be used to provide additional data, but this would not inform clinical management.

6.3 DOMAIN-SPECIFIC PROCEDURES FOR ASSESSING SAFETY

Levetiracetam is a safe and well-tolerated anti-epileptic medication (Birbeck, Herman et al. 2019). AEs judged by the investigator as being related to anticonvulsants (any grade) and solicited AEs (see below, any grade) should be recorded on the appropriate CRF and sent to the study coordination centre, in addition to safety reporting applicable to all domains (grade 3/4 AEs and SAEs, see Master protocol).

6.3.1 SOLICITED AES

Any development of aggressive behaviour will be recorded during admission and follow up as this has been identified in a previous small study (McTague, Kneen et al. 2012).

6.4 EARLY STOPPING OF FOLLOW-UP

As the child's participation in the trial is entirely voluntary, their parent or guardian may choose to discontinue trial follow-up at any time without penalty or loss of benefits to which they are otherwise entitled. As detailed in **Section 5.4**, if a parent or guardian chooses to discontinue their child's treatment in the trial, they should always be encouraged to continue with follow-up as per

the trial assessment schedule. It should be made clear to the parent or guardian that continuing to provide follow-up data is important for the success of the trial. However, regardless of their decisions around their child's treatment, if the parent or guardian does not wish their child to remain on trial follow-up, their decision must be respected, and this will not be considered a protocol deviation.

It should be clear to the parent or guardian and recorded in the child's notes exactly which aspect(s) of the trial that the parent or guardian is discontinuing their participation for. These could include:

- Withdrawal from further treatment (as addressed in **Section 5.4**)
- Withdrawal from further collection of trial samples
- Withdrawal from further trial follow-up assessments or visits

Information on the specific level of the child's discontinuation should be recorded on the relevant trial Case Report Form(s) and flagged within the trial database, along with any accompanying information as appropriate (and this will not be considered a protocol deviation). Although the parent or guardian is not required to give a reason for discontinuing trial follow-up, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

To ensure that important trial outcomes are compared in the population randomised and hence balanced by design (the principle of "intention-to-treat"), previously collected and de-identified data from children who stop follow-up early (i.e data collected before the point of withdrawal) will be kept and included in analysis, in line with the General Data Protection Regulation (GDPR) exemption which states that the 'right to erasure' of data does not apply where data processing is necessary for the performance of a task in the public interest in the area of public health, with the appropriate safeguards in place.

Parents or guardians may change their minds about stopping trial follow-up for their child at any time and re-consent to participation in the trial.

Children who stop trial follow-up early will not be replaced because the primary endpoint is calculated over the first 72 hours when losses to follow-up are expected to be very small.

6.5 LOSS TO FOLLOW-UP

Any child lost to follow-up before 3 months will be traced for vital status. In order to minimise losses to follow-up, locator data (maps and identifiable landmark) and mobile phone numbers will be taken as soon as possible after admission, and at minimum on discharge, and verified at every review. During the 90 day study period, if a child does not attend a scheduled visit, then attempts should be made to contact the parents or guardians via phone (if available) and to follow up with home visits, if at all possible.

6.6 COMPLETION OF PROTOCOL FOLLOW UP

The protocol follow up will end after the last scheduled follow-up visit of the last randomised participant. Sites will be closed once data cleaning is completed and the database undergone its final lock; the regulatory authorities and ethics committee will be informed of the trial closure as required by local regulations.

7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are the same across all domains of the SMAART-MAP trial and are described in the Safety Reporting section of the Master protocol. Sites will follow national reporting guidelines for notification requirements to national ethics and regulatory bodies.

8 QUALITY ASSURANCE & CONTROL

Details regarding the risk assessment, central monitoring, on-site or remote monitoring, source data and protocol deviations are outlined in the Master protocol.

9 STATISTICAL CONSIDERATIONS

This domain of the SMAART-MAP trial is a parallel arm design comparing outcomes in children that have had seizures in this illness prior to presentation at hospital and received levetiracetam to those that receive standard of care.

9.1 METHOD OF RANDOMISATION

Randomisation will be stratified by centre. Randomisation lists, using permuted blocks of variable sizes, will be generated and 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.

9.2 OUTCOME MEASURES

Primary outcome:

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

Secondary outcomes:

- 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)

SMAART-MAP outcomes:

- Proportion of deaths by 28 days from randomisation
- Proportion of children with readmissions by 28 days from randomisation
- Proportion of deaths by 90 days from randomisation
- Proportion of children with readmissions by 90 days from randomisation
- Proportion of children with Grade 3 or 4 adverse events

9.3 SAMPLE SIZE

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.

9.4 ESTIMANDS

The primary estimand for the primary endpoint is described in Table x below.

Table X: 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

9.5 INTERIM CHECKING & ANALYSES

During the SMAART-MAP trial an independent Data Monitoring Committee would 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. 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.

9.6 ANALYSIS PLAN (BRIEF)

The analyses are described fully in the Statistical Analysis Plan. In brief, the primary analysis for the trial will describe baseline parameters and compare primary and secondary endpoints by trial arm, adjusted for the stratification factors. The primary analysis will follow the Estimand described above and measure the absolute difference in the mean number of seizures sufficient to start or change anticonvulsant medications in each arm.

The primary outcome will be analysed using Poisson regression including treatment arm as a covariate, adjusted for baseline and for the stratification factors. Analysis of mortality will use time-

to-event methods through to day 28 and 90. Readmissions will be analysed using competing risk methods counting death as a competing risk. The secondary outcome of time to regaining consciousness in those with BCS≤4 will be compared between arms using time-to-event analysis in hours, with death as a competing risk to regaining consciousness.

A secondary analysis will be carried out using Bayesian principles given the small sample size, using ACCEPT analyses (Clements, White et al. 2022). This will enable estimation of the probability that one arm is superior to the other, based on a continuous range of efficacy thresholds, and is more powerful than frequentist approaches when sample sizes are small due to the use of priors giving additional information.

10 ANCILLARY STUDIES

10.1 ANCILLARY STUDY 1: LOW-COST 3D-PRINTED MOBILE IMAGING DEVICE AS A SCREENING TOOL FOR RETINAL PATHOLOGY IN CHILDREN WITH CEREBRAL MALARIA (CM)

10.1.1 STUDY SUMMARY

Smartphone-based portable devices empowered by Artificial Intelligence (AI) provide new capabilities for medical diagnosis and patient management at the point-of-care. MultiSpot is a digital platform which consists of a mobile application to acquire multimodal medical data and results using a range of smartphone sensors and external devices. This system includes a specific module, RetiSpot, consisting of a low-cost retina screening device with 3D printed material which can hold a lens, and can be attached to a mobile phone. The device includes connection to MultiSpot that enables the mobile phone to acquire retinal images and/or videos. It has been designed to be used by non-specialists to acquire images of the retinal fundus of adults and children.

Such a low-cost mobile retinal screening device could be applied to endemic diseases in low-income countries, such as malaria. This combined or validated with other types of data, such as RDT results or microscopy, could create a useful potential tool for the management of these patients. In this particular disease, it may help to confirm the diagnosis of cerebral malaria, due to the pathognomonic particularities of malarial retinopathy. This device could enable rapid and accurate recognition of patients with CM in low-resource settings where the implementation of retinopathy is difficult and not universal, thereby reducing neuropathology, cognitive sequelae and ultimately avoidable deaths. In addition, this device could also facilitate the implementation of clinical trials in children with cerebral malaria by a better identification of misdiagnosed patients.

We propose to conduct a substudy within the cerebral malaria domain using the RetiSpot module, aiming to: (1) identify children with true cerebral malaria (2) describe the different retinal findings in children with cerebral malaria and then (3) use this information to develop a more accurate diagnostic protocol for CM in addition to clinical information and laboratory data (including parasite biomass markers such as Plasmodium falciparum histidine rich protein 2 (PfHRP-2)).

10.1.2 ANCILLARY STUDY INVESTIGATORS

Principal Investigators
Quique Bassat (1) (2)
Rosauro Varo (1) (2)
Miguel Luengo-Oroz (3)
Elena Dacal (3)

Other Investigators
David Torres (1) (2)
Jessica Dalsuco (1)
Justina Bramugy (1)
Maria Postigo Camps (3)
Jaime García-Villena (3)
Daniel Cuadrado (3)

Alexander Vladimirov (3)
Nuria Díez (3)
Ramón Vallés-López (3)
Laura Beltran Agullo (4)
Olivia Pujol (4)

1. Centro de Investigação em Saúde de Manhiça (CISM), Manhiça, Mozambique.
2. Barcelona Institute for Global Health (ISGLOBAL), Barcelona, Spain.
3. Spotlab, Madrid, Spain.
4. Institut Català de Retina, Barcelona, Spain.

10.1.3 INTRODUCTION

Background and rationale

The diagnosis of cerebral malaria (CM) currently follows WHO criteria, requiring a Blantyre coma score ≤2 (i.e. coma) and the presence of *Plasmodium falciparum* parasites in peripheral blood. However, this diagnosis is frequently inaccurate, as was evidenced by an autopsy study where 23% of children that had been diagnosed with CM following WHO criteria lacked sequestration of *Plasmodium falciparum* infected erythrocytes in brain vessels and an alternative cause of death was identified for each one (Taylor, Fu et al. 2004). The high inaccuracy of the CM diagnosis is caused by: (1) the non-specificity of the clinical features of malaria coma compared to other causes of coma; and (2) the high proportion of children in malaria endemic areas with detectable circulating *Plasmodium falciparum* parasitaemia in the absence of any clinical symptoms (as high as 50%) (O'Meara, Bejon et al. 2008). Moreover, CM diagnosis is frequently confounded by other lethal infectious diseases like bacterial meningitis (4-14%); or is accompanied by other invasive infections, with an important increase in the case fatality rate of those patients (Berkley, Mwangi et al. 1999, Aipit, Laman et al. 2014).

CM is an exclusion diagnosis, thus requiring ruling out other common causes of coma, such as meningitis, septicaemia, hypoglycaemia, acidosis, severe anaemia, or a transient post-ictal state. Indeed, CM can only be confirmed in the presence of coma which persists longer than one hour after a seizure, irrespective of anticonvulsant medications (World Health Organisation 2014). An accurate diagnosis of CM is challenging, but is important in terms of patient management and epidemiological surveillance, but also to enrol patients in clinical studies targeting CM. The detection of malaria retinopathy is considered the 'gold standard' for CM diagnosis, since it is highly predictive of malaria-caused versus non-malaria-caused coma in children and greatly improves the sensitivity and specificity of a clinical diagnosis. When retinopathy is combined with the levels of pHRP2 (a *P. falciparum* protein that is easily detectable in plasma), the area under the ROC curve (AUROC) was 0.90-0.9816 compared to parasite detection alone, with an AUROC of 0.5817. Visualizing any of the changes typical of what is known as malarial retinopathy (patchy retinal whitening, focal changes of vessel colour, white-centered retinal haemorrhages or papilledema) can contribute to the confirmation of CM (Beare, Lewallen et al. 2011). Unfortunately, although the diagnosis of these retinal changes is relatively straightforward, the lack of specialized ophthalmology resources in low-income countries hampers such diagnosis. The implementation of this test presents difficulties in malaria endemic areas since it requires expensive equipment and specialized skills from clinicians (acquisition of retinal images with a direct ophthalmoscope after the use of a short-acting mydriatic to dilate the pupils, or an alternative imaging strategy that considers non-mydriatic retinography); and the identification of those features compatible with CM. Therefore, there is an urgent need for a low cost, easy to use, retinal-screening device that could be implemented easily in those places where it would be most needed. Rates of screening of ocular diseases could be increased drastically

with the availability of a portable, low-cost medical device which could enable capturing retinal images and or videos, allowing their interpretation by specialists through distance tele-diagnosis methods.

Mobile retinal device

RetiSpot is a retinal image or video acquisition module composed of a device attached to a mobile phone. This module incorporates a lens and an application. The 3D printed functional prototype has a calculated production cost under 1€ (excluding lens and smartphone), and can become available after 6 printing hours. Prototypes enable the correct alignment of the cell phone camera, cell phone flash, lens, and eye, required for a correct visualization of the retina (Figure 2). Importantly, the app is designed to capture the retinal images or videos through the mobile phone (the images or videos would be inverted due to the lens effect) and automatically de-inverts the images or videos, so that the person obtaining can intuitively understand what is being portrayed in the phone screen.

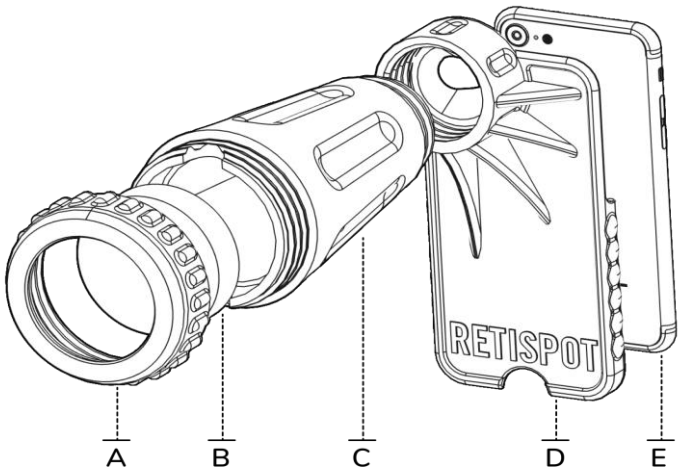


Fig 2. Hardware 3D-printed plastic structure. A: Cover for attaching the lens to the structure. B: Ophthalmic lens (Pan Retinal Lens, Volk 2.2). C: Cone for ophthalmic lens attachment and external light isolation. D: Case for attachment of the mobile phone. E: Smartphone

The main difference from RetiSpot to available commercial devices is that it leverages mobile phones, 3D printing and original image processing algorithms to create a portable and low-cost screening device. The prototype device was initially based on an open-source design by oDocs Eye Care. Since then, several design changes have been made to improve functionality and usability and the final design has been validated in a previous study in Mozambique (Varo, Postigo et al. 2023). The pilot study evaluated the functionality and usability of this tele-retinography system for the detection of retinal pathology, based on a low-cost portable retinal scanner, manufactured with 3D printing and controlled by a mobile phone with an application designed ad-hoc. The study was conducted at the Manhiça Rural Hospital in southern Mozambique. General practitioners, with no specific knowledge of ophthalmology or previous use of retinography, performed digital retinographies on 104 hospitalized patients, for whom there was no previous ophthalmological information (Varo, Postigo et al. 2023). The study concluded that the images taken were of a good quality and that the device was easy to use by healthcare personnel without specialized ophthalmological knowledge, and could be applied for the screening and initial diagnosis of retinal pathology.

The RetiSpot module and device is currently a research tool and has not yet been registered as a medical device. However devices and applications on mobile phones for eye screening have been

certified as medical devices such as Smartscope Pro (Optomed, Oulu, Finland), Epicam M (Epipole), VersaCamTM DS-10 (Nidek, Gamagori, Japan) or Horus DEC 200 (MiiS, Hsinchu, Taiwan),(Quellec, Bazin et al. 2016). In addition there are some more prototypes under development including by Epipole (Dunfermline, UK) and IDx (Iowa City, IA) (Abramoff, Lou et al. 2016). Others are being developed using Smartphones for image acquisition and processing such as Peek Vision (Nesta, London, UK)(Bastawrous, Giardini et al. 2016), PanOptic -iExaminer (Welch Allyn, Skaneateles Falls, NY), and D-Eye (D-EYE, Padova, Italy)(Rajalakshmi, Prathiba et al. 2021). More sophisticated adapters are also available on the market, including for instance the Remidio FOP-NM (Bangalore, India)(Sengupta, Sindal et al. 2019), Volk iNview and Vistaview (Volk Optical, Mentor, OH, USA) (Chalam, Chamchikh et al. 2022), Cellscope Retina which is 3D-printed (University of Michigan, MI, USA)(Kim, Aaberg et al. 2021), MII Retcam (Coimbatore, India)(Kaur, Singh et al. 2020) and Phelcom Eyer (São Carlos, Brazil) (Malerbi, Andrade et al. 2022).

10.1.4 SUBSTUDY OBJECTIVES

Substudy primary objective

- To characterise the different retinal findings in children with severe and cerebral malaria

Substudy secondary objectives

- To use this information to develop a more accurate diagnostic protocol for CM in addition to clinical information and laboratory data (including parasite biomass markers as pHRP-2)

10.1.5 METHODS

Sites

This ancillary study will aim to recruit from all SMAART-MAP sites.

Inclusion/exclusion criteria

All children eligible for and randomised into this domain of the SMAART-MAP trial will be eligible for this ancillary study – there are no additional inclusion or exclusion criteria.

Sample size

As this study's objectives are exploratory there is no formal sample size; however sites will be encouraged to enrol as many children randomised into this domain as possible throughout recruitment.

Ancillary study procedures

Parents or guardians of children randomised into this ancillary study will be offered enrolment into this ancillary study at the point where they sign the informed consent form (that is, consent for this ancillary study will not be sought as part of verbal consent for randomisation in this domain, but only as part of the written consent procedure). By definition this will be at a point in the child's clinical management when the child is stable. Written information about the ancillary study will be included in the main participant information sheet for parents and guardians, as the aim is to recruit as many children randomised into this domain into the ancillary study as possible. This written information will include details about data processing (see next paragraph). However, consent for the ancillary study is optional and not required to be randomised within the domain.

As soon as possible after written consent is obtained, the child will be given myriaditic eye drops, if required for the device as standard procedure for eye examinations, and the ocular fundus of each eye will be examined with the RetiSpot module. Minor side effects are related to blurred vision which is transitory and short-term. Videos of 30-60 seconds each will be taken of each eye and saved

onto the mobile phone on a secure platform accessed through a dedicated application on the phone and stored under the trial number. Images taken from the videos will then be sent via the application to a team of retinal experts based in Spain for specialized assessment. The RetiSpot app uses privacy by design specifications to minimize the potential risks.

Results of this assessment will be sent back to the study team within 24 hours, and a detailed report including the images captured (even if normal) will be prepared. A direct benefit for the patient will be to have their images reviewed by a specialized ophthalmologist. In case of identification of a treatable ocular disease, this information will be communicated to the clinician and the patient will be managed according to the national guidelines.

11 REGULATORY & ETHICAL ISSUES

11.1 ETHICAL CONSIDERATIONS

Additional risks to those outlined in the Master protocol.

Levetiracetam has been found to be a safe treatment for children with cerebral malaria and with seizures. Risks from having a cannula inserted for administration of IV levetiracetam are given in the Master protocol. A small study noted an increase in aggressive behaviour in children given levetiracetam but further research is needed to confirm any link. Children will be monitored closely and data on any neurological changes including behaviour will be collected by study staff during admission and follow up.

Benefits to children in this domain are outlined in the Master protocol

All further detail on regulatory and ethical issues are found in the Master protocol including compliance, other ethical considerations including compensation, competent authority and other approvals and end of trial and comparison closure.

12 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies, which apply to this study. There will be additional site-specific insurance where required.

13 FINANCE

The trial is supported by grant funding from Wellcome, UK (Grant Number 209265/Z/17/Z). The trial will be coordinated by Imperial College. A written agreement with the site principal investigator and/or the investigator's institution and Imperial College will outline the funding arrangements to sites. The TSC will meet and review the financial aspects of the trial at least 12-monthly and report to the sponsor. Terms of reference will be developed for this activity.

14 OVERSIGHT & TRIAL COMMITTEES

All oversight and trial committees will oversee all domains of the SMAART-MAP trial. These committees and the relationship between them are described in detail in the Master Protocol.

15 PUBLICATION AND DISSEMINATION OF RESULTS

Details on publication and dissemination of results can be found in the Master protocol as these will be the same across all domains of the SMAART-MAP trial.

16 DATA AND/OR SAMPLE SHARING

Details on data sharing are outlined in the SMAART-MAP Master protocol.

17 PROTOCOL AMENDMENTS

Protocol	Date	Amendments to protocol
1.01	11th January 2024	Added ISRCTN number and updated investigator details Added clarification of requirements for dosing at 36 and 48 hours
1.1	22nd April 2024	• Edited secondary objective to remove words 'where possible' • Addition of exclusion criteria for SMAART-MAP trial so that no child can be re-enrolled. • The trial will use just IV levetiracetam and so the option of oral and IM has been removed from Section 5. • Further detail on recording of anticonvulsants received during admission has been added to Section 6 under 'domain specific procedures for assessing efficacy' to fit with measurement of our primary outcome. • Removal of words 'prior to admission' from study hypothesis in Trial Summary and in Section 1.1.1 Primary objective. • Co-enrolment restricted to observational studies only (section 4.2) • Addition of a sentence in Section 7 to highlight reporting to ethics and regulatory bodies to follow guidelines. • Addition of a POC test for haemoglobin and malaria RDT at day 28 and day 90 follow up visits
1.2	8th May 2024	• Addition of total blood draw across the whole study in schedule of assessment table • Addition of consent process into schedule of assessment table • Clarification of analysis of measurement of primary outcome in the Statistical Considerations section • Correction of reference in section 5.2 • Further information on clinical stopping criteria for treatment given in Section 5. •

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Appendix S to the Severe Malaria A Research and Trials Consortium – Multisite Adaptive Platform (SMAART-MAP) trial

For management of those enrolled into the Severe Anaemia Domain

Main Sponsor:
Imperial College London

Collaborating groups:

Version: **1.2**
Date: **8th May 2024**

ISRCTN #: **ISRCTN79071535**
PACTR #: **PACTR202312551082722**

Authorised by:
Name: Prof Kathryn Maitland
Role: Chief Principal Investigator
Signature:

Date: 8th May 2024

This protocol has been produced using MRC CTU at UCL Protocol Template version 10.0. The template, but not any study-specific content, is licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). Use of the template in production of other protocols is allowed, but MRC CTU at UCL must be credited.

GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 10.0. The CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the SMAART-MAP trial Severe Anaemia domain, coordinated by the Kenya Medical Research Institute (KEMRI)-Wellcome Trust Kilifi Clinical Trials Facility, and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. This protocol should be used alongside the Master protocol for the SMAART-MAP trial.

Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be available to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the trial team to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2), and other applicable national regulations.

SPONSOR

Imperial College London is the trial Sponsor and has delegated responsibility for the overall management of the SMAART-MAP trial to the KEMRI-Wellcome Trust Clinical Trials Facility in Kilifi, Kenya.

FUNDING

Funding is provided by the Wellcome Trust as part of the grant to the SMAART Consortium (209265/Z/17/Z).

AUTHORISATIONS AND APPROVALS

This trial was approved by **[*Insert Info when approved*].**

TRIAL REGISTRATION

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN79071535. It has also been registered with PACTR, where is identified as PACTR202312551082722.

SAE REPORTING
Within 24 hours of becoming aware of an SAE, submit a completed SAE Form to KEMRI Wellcome Trust Kilifi by email to SMAART@kemri-wellcome.org
Tel: +254 715461761 or +254 726957045

TRIAL ADMINISTRATION

Please direct all queries to Emmanuel Oguda, Clinical project manager at KEMRI Wellcome Trust Programme Clinical Trial Facility in the first instance; clinical queries will be passed to the Chief Investigatorvia the SMAART clinical project manager.

COORDINATING CENTRE

KEMRI Wellcome Trust Programme Clinical Trial Facility		Switchboard: Mobile:	+254 417 522063/522535 +254 715 461761 (Trial manager)
PO Box 230, Kilifi, Kenya		Email:	SMAART@kemri-wellcome.org
KEMRI WELLCOME TRUST RESEARCH PROGRAMME, STUDY AND TRIAL MANAGEMENT GROUP Kilifi Clinical Trials Unit, PO Box 230, Kilifi			
Principal Investigator:	Prof Kathryn Maitland MBBS PhD	Mobile: Email:	+254 733 411022 kathryn.maitland@gmail.com
Trial Administrator	Phyles Maitha Dip.Business.Mgt	Tel: Mobile: Email:	+254 417 525453 (switchboard) +254 715 461761 PMaitha@kemri-wellcome.org
Clinical Project Manager:	Emmanuel Oguda Dip.Clin.Med.Chir	Tel: Mobile: Email:	+254 417 525453 (switchboard) +254 726957045 EOguda@kemri-wellcome.org
Data Manager:	Christabel Mogaka BSc	Tel: Email:	+254715811661 CMogaka@kemri-wellcome.org
KILIFI: CLINICAL GROUP			
Lead Investigator	Prof Mainga Hamaluba MBCHB, MRCP	Mobile: Email:	+254 709 983946 MHamaluba@kemri- wellcome.org
Coinvestigators	Prof Thomas Williams MBBS, PhD	Mobile: Email:	+254 733 411021 tom.n.williams@gmail.com

Coinvestigators	Prof Phillip Bejon MBBS, PhD	Mobile: Email:	+254 724 45743 Pbejon@kemri-wellcome.org

IMPERIAL COLLEGE

Division of Medicine Room 1030 Level 10 St Mary's Campus Norfolk Place London W2 1PG			
Principal Investigator:	Prof Kathryn Maitland MBBS PhD	Tel: Email:	+44 207 670 4905 kmaitland@imperial.ac.uk
Research Manager	Tony Tarragona-Fiol	Tel: Email:	+44 20 3312 6230 t.tarragona@imperial.ac.uk

MRC CTU AT UCL

MRC Clinical Trials Unit at UCL Institute of Clinical Trials and Methodology 90 High Holborn, 2nd Floor, London WC1V 6LJ			
Principal Investigator:	Prof Diana M Gibb MD MSc	Tel: Email:	+44 207 670 4905 diana.gibb@ucl.ac.uk
Statistician:	Dr Elizabeth George PhD MSc	Tel: Email:	+44 207 670 4931 elizabeth.george@ucl.ac.uk
Statistician:	Prof Ann Sarah Walker PhD MSc	Tel: Email:	+44 207 670 4726 rmjlasw@ucl.ac.uk

MORU

Mahidol Oxford Tropical Medicine Research Unit 420/6 Rajvithi Road, Tungphyathai, Bangkok 10400, Thailand			
Co-Lead Investigator:	Prof Nicholas Day, MBBS PhD	Tel: Email:	+66 870 118990 nickd@tropmedres.ac
Co-Lead Investigator:	Prof Arjen Dondorp, PhD	Tel: Email:	+66 818 015675 arjen@tropmedres.ac
Data Manager:	Naomi Waithera, MSc	Email:	Naomi@tropmedres.ac

STUDY SITES AND INVESTIGATORS

UGANDA: Country Principal Investigator Prof Peter Olupot Olupot			
Mbale Clinical Research Institute (MCRI) Mbale Regional Referral Hospital Pallisa Road Zone, P.O Box 921, Mbale, Uganda			
Site Investigator:	Prof Peter Olupot Olupot MBChB, MPH	Tel: Mobile: Fax: Email:	+256 77 2457217 +256 77 2457217 +256 45 4435894 polupotolupot@yahoo.com
Study Site Coordinator:	To be appointed.	Tel: Mobile: Email:	
Soroti Regional Hospital, P.O Box 289, Soroti, Uganda			
Site Investigator:	Dr Florence Aloroker MBChB, Mmed	Tel: Email:	+256 45 4461382 alaroflorence@gmail.com
Study Site Coordinator:	Denis Amorut, BsHSM, RCN	Tel: Mobile: Fax: Email:	+256 45 4461382 +256 77 4573911 +256 45 4461382 damoruts@gmail.com
Dr. Ambrosoli Hospital, Kalongo, P.O Box 47 Agago District, Uganda			
Site Investigator	Dr Okao Maurice, MD, MMED Paediatrics	Tel: Email:	+ 256 779066157 maurice.okao@gmail.com
Study Site Coordinator	Dr Modester Akite	Email:	modesterakite@gmail.com

KENYA:			
Kilifi County Hospital, Hospital Road, PO Box 230, Kilifi			
Co-Lead investigator:	Prof Mainga Hamaluba MBCHB, MRCP	Tel: Email:	+254 709 983946 Mhamaluba@kemri-wellcome.org
Co-Lead investigator:	Prof Kathryn Maitland MBBS PhD	Tel: Email:	+254710508749 Kathryn.maitland@gmail.com

MOZAMBIQUE:			
Hospital Central de Quelimane, Av.Julius Nyerere, Estrada regional numero 470. Bairro Namuinho Manhica Health Research Centre (CISM) PO BOX 1929 Manhica			
Co-Lead investigator:	Dr Pedro Aide, MD, MSc, PhD	Tel: Email:	+258 2181 0181 pedro.aide@manhica.net
Co-Lead investigator:	Dr Rosauro Varo, MD, MSc, PhD, Paediatrician	Tel: Email:	rosauro.varo@isglobal.org
Co-investigator:	Professor Quique Bassat, MD, MSc, PhD	Email:	quique.bassat@isglobal.org
Co-investigator:	Dr David Torres, MD, MSc, Paediatrician.	Tel: Email:	david.torres@isglobal.org

GHANA:			
Komfo Anokye Teaching Hospital, Bantama High Street PO Box 1934 Kumasi Department of Child Health, Kwame Nkrumah University of Science and Technology, Kumasi			
Principal investigator:	Professor Daniel Ansong, MSc	Tel: Email:	+233 208 168767 dansong@kathhsp.org
Co-investigator:	Prof Tsiri Agbenyega, PhD	Tel: Email:	+233 208 113848 tsiri@ghana.com
Co-investigator	Dr Justice Sylverken, MBCHB	Tel: Email:	+233 208 113715 jsylverken@gmail.com

ZAMBIA			
Tropical Diseases Research (TDR) Centre, 6th and 7th Floor of Ndola Teaching Hospital building, P.O Box 71769, Ndola, Zambia St Pauls Mission Hospital, Nchelenge, Luapula Province, Zambia			
Principal Investigator:	Dr Mike Chaponda, MSc, MBChB, MSc, DTMH	Tel: Email:	+260 212 620737 mikechaponda@yahoo.com
Co-investigator:	Dr Sam Miti, MBChB, Mmed	Tel: Email:	+260 212 620737 drsammiti@gmail.com
Co-investigator	Dr Jonathan Gwasupika, MBChB	Tel: Email:	+260212620737 gwagwejo@gmail.com

DEMOCRATIC REPUBLIC OF THE CONGO			
Kinshasa School of Public Health Universite de Kinshasa, Campus UNIKIN, Lemba, BP 11850, Kinshasa, DRC			
Principal Investigator:	Prof Marie Onyamboko, MD, Dphil	Tel: Email:	+243990024201 akatshimarie@yahoo.fr
Co-investigator:	Dr Catarina Fanello, PhD	Email:	Caterina@tropmedres.ac

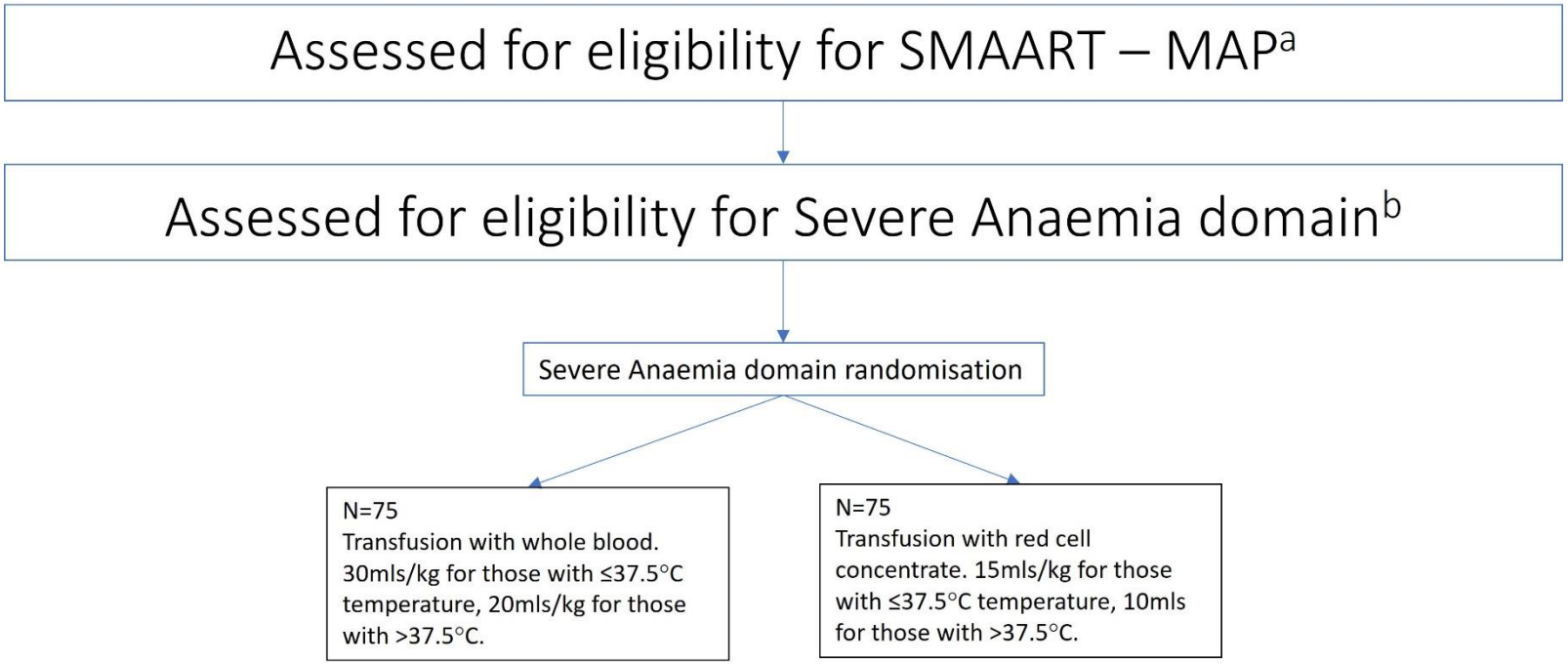
SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
[Acronym or short title]	SMAART – MAP Severe Anaemia
Long Title of Trial	Severe Malaria A Research and Trials Consortium – Multisite Adaptive Platform trial: Severe anaemia domain
Version	1.2
Date	8th May 2024
ISRCTN # **PACTR #**	ISRCTN79071535 PACTR202312551082722
Study Design	Parallel arm multi-site Phase II trial
Setting	Hospitals in Uganda, Zambia, Ghana, Kenya, Democratic Republic of the Congo and Mozambique
Type of Participants to be Studied	Hospitalised children with severe malaria and haemoglobin <6g/dl
Ancillary Studies/Substudies	None
Sponsor	Imperial College London
Interventions to be Compared	Blood transfusion with whole blood (20mls/kg if temperature at screening is >37.5^{o}C, 30mls/kg if temperature is ≤37.5^{o}C) compared to red cell concentrate (10mls/kg if temperature is >37.5^{o}C; 15mls/kg if temperature is ≤37.5^{o}C)
Study Hypothesis	There were no adverse effects of giving children whole blood in the TRACT trial and, in a post hoc observational analysis, whole blood transfusion was associated with improved haemoglobin recovery and fewer second transfusions compared to red cell concentrate. We hypothesise that whole blood transfusions in this trial will lead to improved haemoglobin recovery. This could provide further evidence that whole blood should be given to children with severe anaemia and would remove pressure for blood transfusions associations to prepare red cell concentrates, saving money and resource in the blood transfusion services.
Eligibility criteria	**For SMAART-MAP:** **Inclusion criteria** • Aged >3 months and <12 years • Admitted to the paediatric ward in the last 24 hours • Current or recent evidence of malaria (slide or rapid diagnostic test (RDT) positive in this admission) • Guardian willing to provide consent **Exclusion criteria** • Enrolment into this trial on a previous admission **For this domain:** **Inclusion criteria** • Hb <6g/dl

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	• 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 **Exclusion criteria** • Known congenital or valvular heart disease (not surgically corrected)
Primary Outcome Measure(s)	Change in haemoglobin at 24 hours (adjusted for baseline)
Secondary Outcome Measure(s)	<u>Severe anaemia domain outcomes:</u> • Change in haemoglobin at 72 hours • 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 • Adverse Events (AEs) judged related to blood transfusion <u>SMAART-MAP outcomes:</u> • Day 28 and Day 90 readmissions and mortality • Grade 3 or 4 AEs during admission
Randomisation	1:1 randomisation using randomised permuted blocks stratified by site and screening temperature (≤37.5°C or >37.5°C)
Number of Participants to be Studied	150 children, 75 per arm
Duration	24 months
Funder	Wellcome
Chief Investigator	Professor Kathryn Maitland

TRIAL SCHEMA

Figure 1: Trial Entry, Randomisation and Treatment



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

[b] *Severe Anaemia domain inclusion criteria: Haemoglobin <6g/dl and one or more severity signs (haemoglobin <4/dl; prostration; impaired consciousness; respiratory distress; history of passing red or coca-cola coloured urine in this illness). Exclusion criteria: known congenital or valvular heart disease (non-surgically corrected)*

TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule

Assessment	Admission/ screening	Random-isation	3hrs (±1 hr)	8hrs[2] (±2 hrs)	12 hrs (±3 hrs)	24 hrs (±3 hrs)	48 hrs (±3 hrs)	72 hrs (±3 hrs)	Dis-charge	28 (±7) days	90 (±14) days
Clinical assessment[1]	x		x	x	x	x	x	x[8]		x	x
Point-of-care tests (0.2-0.3ml) [3]	x		x	x		x	x	x			
Weight	x									x	x
Malaria RDT, and thick and thin malaria slide (if available at site) (0.2mls)	x									x	x
Informed consent process[4]	x										
Randomisation		x									
Full Blood Count[5] (1ml)		x									
Urine dipstick		x[6]									
Plasma storage for quantitative pfHRP2 (1ml)		x									
POC pfHRP2 test (when available) (0.2mls)		x									
Point of care (POC) haemoglobin test (0.5mls)[7]	x			x		x	x	x[8]	(x[8])	x	x
Ascertainment of all treatments given during admission (anticonvulsants, anti-malarials, antibiotics and transfusions)									x		
Ascertainment of vital status, readmissions, potential malaria episodes, and neurological sequalae										x	x
Total amount of blood drawn (mls) (mls) (total across study 8.2-8.9mls)	0.9-1.0	2.2	0.2-0.3	0.7-0.8		0.7-0.8	0.7-0.8	0.7-0.8	0.7-0.8	0.7	0.7

Note: grayed cells indicate assessments common to all SMAART-MAP domains from the master protocol.

[1] Clinical assessment: heart rate, oxygen saturation (pulse oximetry), respiratory rate, respiratory distress, axillary temperature, blood pressure, capillary refill time, consciousness level (as measured by the Blantyre Coma Score (BCS)).

[2] Assessment and POC Hb to follow algorithm for severe anaemia management developed from the TRACT trial (Maitland, Kiguli et al. 2021).

[3] Lactate and glucose as point-of-care tests.

[4] This could be informed consent or emergency verbal assent followed by deferred consent dependant on the child's condition – please see section 3.7 for details.

[5] Full blood count: haemoglobin, white blood cells, red blood cells, platelets (and differential if available as standard at site). Values from a blood draw taken for clinical reasons (i.e. not for the trial) at any time in this admission before randomisation should be used if available, rather than re-bleeding the child, as eligibility requires all children to be within 24 hr of admission at screening.

[6] This should be done when the first urine sample is available after enrolment.

[7] Additional POC Hb can be performed at other time points if clinically indicated.

[8] If the child is discharged prior to 72 hours then the POC hb and clinical assessment should be done at discharge. However, caregivers should be encouraged to stay until 72 hours wherever possible

LAY SUMMARY

Severe anaemia is when a measure of the strength of blood called a haemoglobin level is very low. Children who come to hospital with malaria often also have severe anaemia and it is a common symptom of severe malaria. The low level indicates that child needs to have a blood transfusion. Most blood transfusions given in sub-Saharan Africa are with whole blood (blood that is directly from a donor). But international guidelines, including the Blood Transfusion Safety Programme for the World Health Organisation, recommend component preparation, where donated blood is separated into different parts (eg red cell concentrates (sometimes also called packed cells), plasma and platelets). This means blood transfusion services are increasingly moving towards giving red cell concentrates for transfusions, rather than whole blood. Component preparation requires additional resources, including staff time and equipment, compared to providing whole blood for transfusion. In Zimbabwe, it is estimated to cost 16% more per pack for red cell concentrates compared to whole blood. Also there is very little evidence to support the use of red cell concentrates over whole blood in children and pregnant women, who are the main users of blood transfusion in African countries.

One argument for component use is that it makes the most of a single donation of blood, allowing different components to be used for different patients with different needs. This is useful in high-income countries, where the main people who get blood transfusions are those with cancer or having surgery. However, the main people who get blood transfusions in sub-Saharan Africa are very different and include children with severe malaria and severe anaemia where what needs to be replaced is whole blood. Another concern has been that whole blood transfusions in children could increase the risk of complications linked to the amount of fluid transfused. But previous research has suggested that use of whole blood in children with severe anaemia did not lead to too much fluid in the child's body.

In another study, researchers looked at the two different types of blood transfusion (red cell concentrates compared to whole blood) within data collected as part of a trial looking at transfusions in children with severe anaemia in Uganda and Malawi (the Transfusion and Treatment of severe Anaemia in African Children Trial, TRACT). This showed that children who received whole blood had better haemoglobin recovery at 8 hours, were discharged from hospital sooner and were less likely to need a second transfusion. This was not the main objective of the clinical trial and so higher quality evidence is needed to support any move towards or away from component preparation in these settings for children.

In this study, a computer programme will assign an eligible child at random (like the flip of a coin) to receive either whole blood or red cell concentrate transfusions during admission. The volume that is given will follow an algorithm developed using evidence from the TRACT trial and is linked to a child's temperature on admission. The volumes given will be 30mls per kg whole blood or 15mls per kg red cell concentrate if a child's temperature is ≤37.5°C when they arrive at hospital, and 20mls per kg whole blood or 10mls per kg red cell concentrate if a child's temperature is >37.5°C. Their haemologbin will be measured by a point-of-care test on the ward at regular intervals and will be compared at 24 hours to look for a difference between those that received whole blood and those that received red cell concentrates.

CONTENTS

ABBREVIATIONS

ABBREVIATION	EXPANSION
AE	Adverse event
AR	Adverse reaction
BCS	Blantyre Coma Score
CF	Consent Form
CI	Chief Investigator
CI	Confidence interval
CRF	Case Report Form
CTF	Clinical Trial Facility
CTU	*See MRC CTU at UCL*
DMC	Data Monitoring Committee
DSUR	Developmental Safety Update Report
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
KEMRI-Wellcome Trust Kilifi CTF	Kenya Medical Research Institute - Wellcome Trust Kilifi Clinical Trials Facility (also generally abbreviated to “CTF”)
MOP	Manual of Operations
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London (also generally abbreviated to “CTU”)
PfHRP2	Plasmodium falciparum histidine rich protein 2
POC	Point of Care
RDT	Rapid Diagnostic Test

ABBREVIATION	EXPANSION
RCT	Randomised controlled trial
REC	Research Ethics Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Standard deviation
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
TMT	Trial Management Team
TRACT	Transfusion and Treatment of severe Anaemia in African Children
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
WHO	World Health Organization

1 BACKGROUND

INTRODUCTION

Most transfusions given in sub-Saharan Africa are with whole blood (World Health Organisation 2017). Reflecting international practice, blood transfusion services across sub-Saharan Africa are increasingly moving towards a wider provision of red cell concentrates, despite clear differences in the patient populations requiring transfusion in sub-Saharan Africa vs high income countries (Ala, Allain et al. 2012) and a lack of evidence from Africa-relevant clinical research. Although more costly and time-consuming to prepare, this change to providing red cell concentrates has largely been justified on the grounds of maximizing the utility of a single donation of blood (https://www.who.int/bloodsafety/processing/en/). In high income countries, the plasma remaining after preparation of red cell concentrates can be used for transfusion or fractionated into blood products, but the capacity to do this in low and middle-income countries is very limited. Also, much of the separated plasma in sub-Saharan Africa is not of suitable quality to undergo fractionation (World Health Organisation 2015) and evidence for the use of plasma in many settings is lacking (Yang, Stanworth et al. 2012). Thus, the potential benefits from maximising utility of a single donation are lost.

TRANSFUSION REQUIREMENTS IN SSA

Data on requirements for blood components is minimal for most African countries. Studies published on this subject tend to be biased towards blood transfusion services (Butler, Hume et al. 2015, Mafirakureva, Khoza et al. 2015), and may not represent the needs of less well-resourced hospital blood banks. A recent review examined the published literature on the use of blood and blood products in sub-Saharan Africa (Kohli, Bhaumik et al. 2019). From 37 included studies across 14 countries, the review confirmed that pediatric malaria, obstetric haemorrhage and sickle cell anaemia were the leading disease conditions for blood transfusion (Kohli, Bhaumik et al. 2019). In the 9 paediatric studies, 64% of blood products were used for children with severe malaria. This is likely due to severe anaemia being a common phenotype of severe malaria, with for example the WHO criteria for severe malaria including haemoglobin <5g/dl. These requirements differ from those in many high-income countries where oncology and surgery are the biggest users of transfusion components.

Thus transfusions required by patient groups in sub-Saharan Africa are largely for emergency management, where the deficit to be replaced is whole blood (Hassell, Bates et al. 2012). There is also evidence that it is safe to use whole blood in African children hospitalised with severe anaemia, and that this does not lead to fluid overload events (Olupot-Olupot, Engoru et al. 2014).

Transfusion services in sub-Saharan Africa often experience stock-outs and shortages of blood, or blood banks are located far from hospitals and there is a transportation delay. They also differ from services in high-income countries in terms of the demand and patterns of blood use along with technical, logistical and financial constraints they face (Kohli, Bhaumik et al. 2019).

RED CELL CONCENTRATES

Red cell concentrates are created when most of the plasma is removed from whole blood, either by centrifugation or by gravity; they may also have an additive solution added. They may also be

referred to as packed red cells or settled red cells. In this protocol the term 'red cell concentrates' will be used to refer to any preparation of red cells when plasma has been removed.

An analysis of clinical practice guidelines published in 2019 concluded that evidence for transfusions with red cell concentrates was virtually non-existent in sub-Saharan Africa; thus it is unclear whether policies promoting red cells over whole blood are clinically appropriate (Kohli, Bhaumik et al. 2019). The review included 32 guidelines from 15 countries, but only 7 justified their recommendation for using red cell concentrates or whole blood and none had any supporting citations. Only one study out of 33 full-text papers reviewed compared red cell concentrates and whole blood and that was a single-centre study in post-partum haemorrhage which retrospectively reviewed case notes of women in the USA (Alexander, Sarode et al. 2009). Since that review there also has been a study comparing red cell concentrates to whole blood in a paediatric population following spinal surgery. This study randomised 65 children to either whole blood or component transfusions and found that children receiving whole blood had shorter duration of oxygen dependence (36.43 hours vs 43.45 hours; p=0.03) and shorter high dependence unit stay (40.6 hours vs 46.5 hours; p=0.02) (Vasan, Rajasekaran et al. 2021). With respect to international guidelines for paediatric transfusion in critically ill children, the international Transfusion and Anemia Expertise Initiative (TAXI) developed consensus recommendations for red cell transfusion in 2018 (Doctor, Cholette et al. 2018). The guideline group noted the general paucity of published paediatric data to justify their recommendations. Moreover, there were no specific recommendations on the use of whole blood versus red cell concentrates.

TRACT TRIAL ANALYSIS

Recently, there has been a post-hoc analysis of the multi-centre open-label Transfusion and Treatment of severe Anaemia in African Children (TRACT) trial (Maitland, Olupot-Olupot et al. 2019), involving 3992 transfusions, 1632 (41%) whole blood and 2360 (49%) red cell concentrate transfusions. The type of blood issued by the blood bank was not prespecified on the request form, and was not part of the randomisation, hence this comparison is observational. These transfusions were given to 3196 children with severe anaemia on admission to four different hospitals in Uganda and Malawi. The analysis of haemoglobin recovery by pack type (whole blood versus packed cells or settled cells) at 8 hours showed superior recovery in children initially receiving whole blood (p<0.0001) (George, Uyoga et al. 2022). This superior recovery also remained until at least 48 hours (**Figure 1** reproduced from George at al). There was no evidence of effect of the age of the blood being transfused or of the pack haemoglobin.

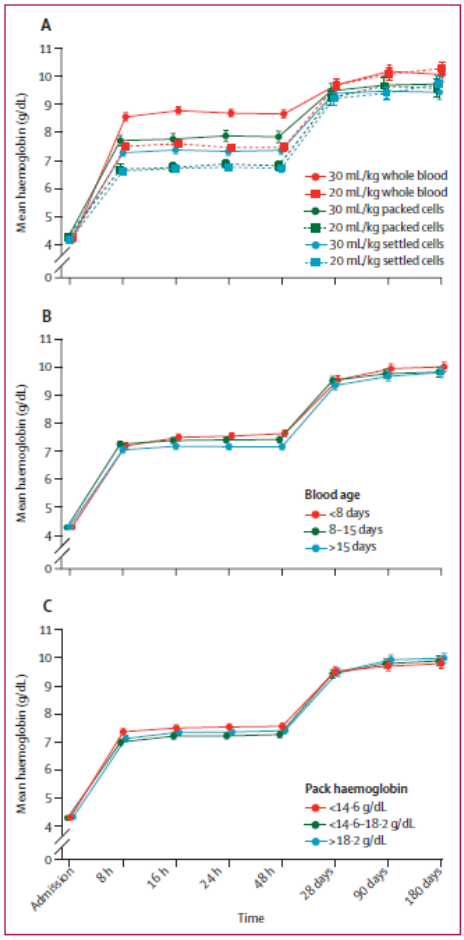


Figure 1: **Haemoglobin recovery over time by blood pack characteristics**
Bars indicate 95% CIs. Haemoglobin recovery over time by type of first blood pack in first transfusion (A); by age of first blood pack in first transfusion (B); and by haemoglobin of first blood pack (C).

In addition to this finding, children who were initially transfused with red cell concentrates had significantly more second transfusion episodes (349/1784 (19.5%) vs 147/1404 (10.5%) in children who received whole blood) and longer hospital stays compared to children who received whole blood initially (time to discharge hazard ratio 0.94 (95%CI 0.81-1.10) for packed cells compared to whole blood and 0.86 (95%CI 0.79-0.94) for settled cells compared to whole blood; thus time to discharge is slower in those receiving packed or settled cells (both red cell concentrates) vs whole blood). Transfusion-related adverse events related to volume overload were rare and unrelated to pack type. There were no demonstratable safety benefits from transfusion with red cell concentrates. The trial recruited 2040/3196 (64%) children with severe malaria and results in this subgroup were similar to the analyses in all children as published in the paper appendix.

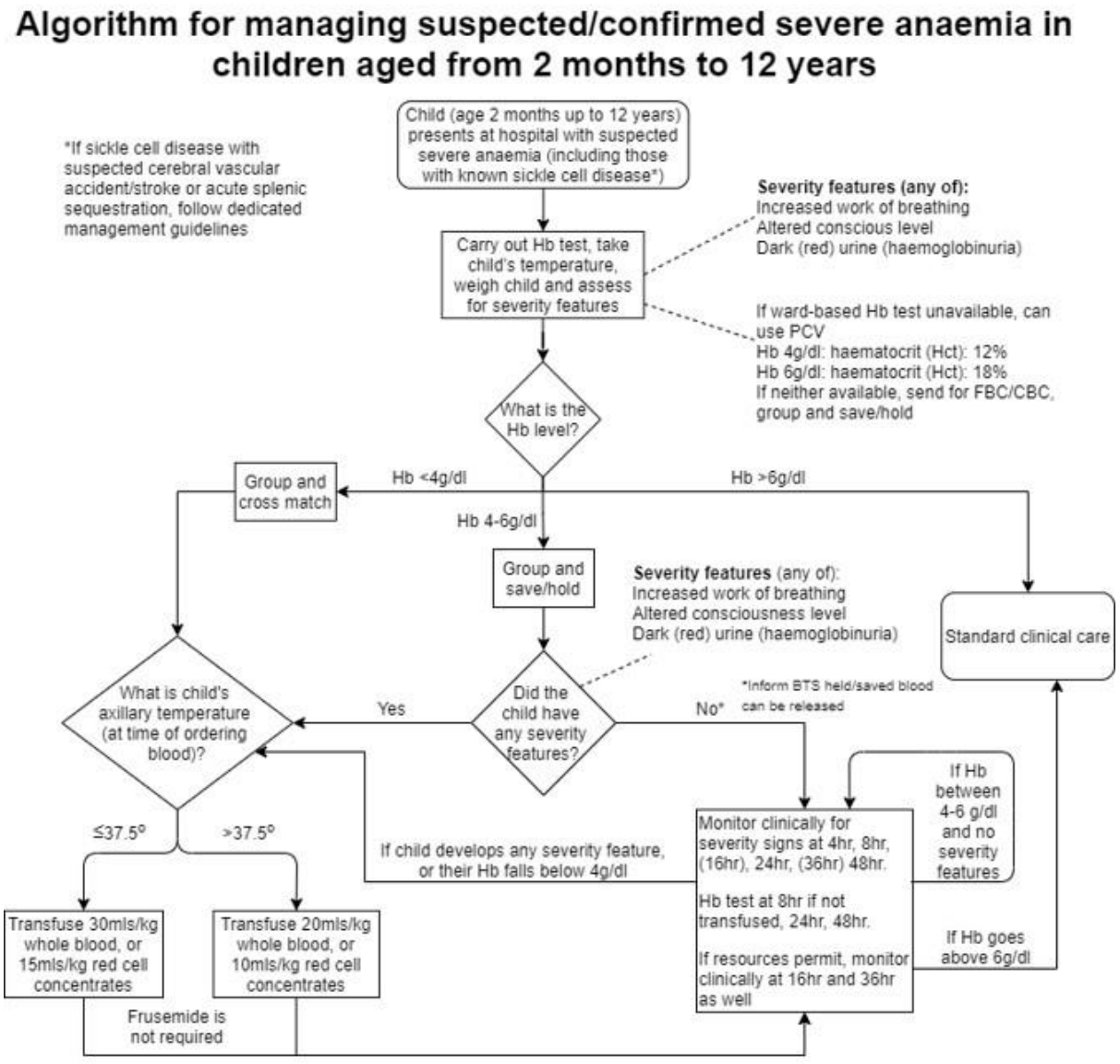
Each time a child receives a transfusion there is a risk of receiving a transfusion-transmitted infection. Targeted screening of blood for pathogens to reduces this risk but may be limited in scope (Kasirye, Hume et al. 2022). There is also the risk of adverse reactions to receiving the transfusion. The post-hoc analysis described above demonstrated a reduced risk of these events in those receiving whole blood. Blood is also a limited resource in these settings and thus a reduction in requirements for additional transfusions would enable better availability for all children with severe malaria and anaemia.

TRACT TRIAL ALGORITHM

The TRACT trial demonstrated that an increased volume of blood given to children with severe anaemia and with an axillary temperature of ≤37.5°C at presentation reduced mortality but that the

standard amount was suitable for those with a temperature of >37.5°C at presentation (Maitland, Olupot-Olupot et al. 2019). Although the trial included children without severe malaria, there were 2050 children with malaria and the evidence from the malaria group supported the main findings. This evidence will inform the transfusion management of the children in this trial through a published algorithm devised with stakeholders at the meeting following the trial results publication (**Figure 2**).

Figure 2: Algorithm developed from the TRACT trial (Maitland, Kiguli et al. 2021).



Thus in this trial, 30mls/kg whole blood or 15mls/kg red cell concentrate will be given to those with an axillary temperature of ≤37.5°C at the time when blood is requested, and 20mls/kg whole blood or 10mls/kg red cell concentrate will be given to those with <37.5°C. Haemoglobin monitoring subsequent to the initial transfusion and clinical signs for additional transfusions will also follow the published algorithm.

1.1 OBJECTIVES

1.1.1 PRIMARY OBJECTIVE

Our primary objective is to test whether giving a whole blood transfusion compared to red cell concentrates in children with severe malaria and severe anaemia leads to improved haemoglobin recovery and reduces the need for secondary transfusions.

1.1.2 SECONDARY OBJECTIVE

Our secondary objective is to assess the impact of whole blood vs red cell concentrate transfusions on other clinical outcomes such as mortality and readmission at 90 days and to understand the safety profile of both types of transfusions further by comparing grade 3 and 4 adverse events (AEs) and AEs of any grade related to the transfusions.

2 SELECTION OF SITES/CLINICIANS

The trial sponsor, Imperial College London, has overall responsibility for site and investigator selection. The sites included in the SMAART-MAP trial are all part of the Severe Malaria a Research and Trials Consortium group. The site/investigator inclusion criteria and steps for approval and activation are outlined in the Master protocol.

3 SELECTION OF PATIENTS

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

The eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this study. Patients not meeting the criteria should not join the study. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

3.1 PATIENT INCLUSION CRITERIA FOR THE SMAART-MAP TRIAL

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

The restriction of time since admission to 24 hours is because all children recruited in this trial will be treated with artesunate based antimalarials which would be expected to be effective within 24 hours if malaria were the underlying cause; later clinical manifestations may have other causes.

3.2 PATIENT EXCLUSION CRITERIA FOR THE SMAART-MAP TRIAL

1. Enrolment into this trial at a previous admission

3.3 ADDITIONAL PATIENT INCLUSION CRITERIA FOR THE SEVERE ANAEMIA DOMAIN

1. Haemoglobin <6g/dl
2. One or more WHO anaemia severity feature (haemoglobin <4g/dl, prostration, impaired consciousness, or respiratory distress, history of passing red or coca-cola coloured urine in this illness)

3.4 ADDITIONAL PATIENT EXCLUSION CRITERIA FOR THE SEVERE ANAEMIA DOMAIN

1. Known congenital or valvular heart disease (non-surgically corrected)

3.5 NUMBER OF PATIENTS

75 per arm, 150 in total.

3.6 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in **Section 4.2**.

3.7 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

Each day the clinical team will check with the transfusion services the quantities of blood available for transfusion and whether both red cell concentrates and whole blood are available. Screening and enrolment to this domain will not be conducted on days when supplies are critical or when either type is not available. Numbers of patients enrolled each day will vary from site to site and depend upon blood stocks and requirement by non-study children.

Eligible children will be identified by the nurse and clinician on duty and registered in the eligibility screening log. A member of the trial team will then perform a rapid structured assessment of heart rate, oxygen saturation (pulse oximetry), respiratory rate, axillary temperature, blood pressure, markers of shock (capillary refill time, pulse volume and assessment of lower limb temperature) and severity (conscious level and respiratory distress). Weight will also be recorded (part of standard of care blood transfusions and many drug doses are weight dependent). Children with suspected severe anaemia will have had a point of care (POC) haemoglobin test as part of clinical care. For children with a haemoglobin < 6g/dl, admitting clinicians will enquire about a history of passing dark or red urine in this illness. Details of those fulfilling the entry criteria will be entered onto a screening form, while reasons for non-eligibility will be added to the eligibility screening log.

INFORMED CONSENT

Prospective written, informed consent will be sought from parents or guardians of children who are considered to be sufficiently stable. Parents or guardians will be given an information sheet in their usual language containing details of the trial. The sheet will be read aloud to those who are unable to read. Parents and guardians will be encouraged to ask questions about the trial prior to signing the consent form. It must be made completely and unambiguously clear that the parent or guardian of the child is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of their child. The right of the parent or guardian to refuse to participate without giving reasons must be respected. Older children should give assent to trial participation, if applicable and at an age determined by the country of enrolment. This will be recorded on a signed assent form.

EMERGENCY VERBAL ASSENT FOLLOWED BY DEFERRED CONSENT

A number of children will present as emergencies where delay in study enrolment, and thus treatment, through a consent procedure would be unacceptable. For the FEAST trial we developed and received ethical approval to use a two stage consent process in this circumstance (Maitland, Molyneux et al. 2011). Verbal assent will be sought from parents or guardians by the admitting medical team, if it is considered that the full consent process would significantly delay treatment allocation, and consequently could be detrimental to the child's health. Full consent will be sought once the child's clinical condition has been stabilized. Caregivers will be provided with a brief verbal description of the trial and will be given the opportunity to "opt out" of clinical research. The clinician will later sign the verbal assent form which will be filed with the consent form. If consent is withdrawn later no data from the subject will be used. If written consent is not provided following verbal consent, the child will be excluded from analyses from the time consent is refused. If the child dies before written consent is obtained, written consent will not be sought to avoid distress to the parents/guardians, but the child will be included in the analysis to ensure this important clinical outcome is recorded.

Signed consent forms (and signed assent forms where applicable) must be kept by the investigator and documented in the CRF and a copy given to the family.

4 REGISTRATION & RANDOMISATION

4.1 RANDOMISATION PRACTICALITIES

Randomisation lists, using variable block sizes, stratified by site and by temperature at screening (≤37.5°C or >37.5°C), will be generated and hosted on an online randomisation system accessed by approved site staff. To facilitate protocol adherence, a maximum enrolled per day per site will be agreed upon. This approach was very successful with respect to protocol adherence and the quality of data generated in the TRACT trial. It will also put less pressure on the blood banks.

4.2 CO-ENROLMENT GUIDELINES AND REPORTING

Patients will not ordinarily be permitted to participate in any other clinical intervention trial or research protocol while in the SMAART-MAP trial. Participation in other studies that do not involve an adjunctive therapy intervention such as observational studies may be acceptable, but should be discussed with the SMAART-MAP Trial Management Group (TMG). Enrolment within the SMAART-MAP trial is restricted to one domain.

5 TREATMENT OF PATIENTS

5.1 INTRODUCTION

All trial patients will receive standard of care including antibiotics (iv or oral) and anti-malarial drugs following national guidelines, based on WHO syndromic patient management (World Health Organisation 2013). We will collect data on all administered drugs. Antipyretics, anticonvulsants and treatment for hypoglycaemia will be administered according to nationally agreed protocols. If required, maintenance fluids will be run at 3-4 mls/kg per hour irrespective of age until the child can drink and retain oral fluids.

5.2 TRANSFUSIONS

5.2.1 WHOLE BLOOD TRANSFUSION

Once the randomisation allocation has been given and the axillary temperature of the child taken, a clinician or medical officer will prescribe the blood and request the whole blood from blood transfusion services. The clinician will calculate, using a calculator, the volume of whole blood required (20mls/kg for those with axillary temperature>37.5°C or 30mls/kg if axillary temperature is ≤37.5°C).

5.2.2 RED CELL CONCENTRATES TRANSFUSION

Once the randomisation allocation has been given and the axillary temperature of the child taken, a clinician or medical officer will prescribe the blood and request red cell concentrates from the blood transfusion services. The clinician will calculate, using a calculator, the volume of red cell concentrates required (10mls/kg for those with axillary temperature>37.5°C or 15mls/kg if axillary temperature is ≤37.5°C).

5.2.3 TREATMENT SCHEDULE

The request form must specify patient's first and last name, date of birth, randomised blood pack type (whole blood or red cell concentrates), volume of blood requested, date and time of request. Once the blood has been cross-matched and the blood pack for transfusion is ready for collection, the health worker who collects the donor blood for transfusion will complete the blood collection log. The blood pack will be weighed on the ward when the blood is received and the weight recorded on the appropriate log.

Transfusions will be administered in gauged blood burettes; an initial drop will be taken from this and spotted onto a haemocue POC test to record the haemoglobin of donor blood. Whole blood should be run over 3-4 hours and red cell concentrates should be administered over 2-3 hours.

Additional transfusion management during hospital admission

An additional transfusion (s) will be permitted for children who still have any of the following:

(i) Profound anaemia Hb <4g/dl, irrespective of other signs of severity
(ii) Severe anaemia 4-6g/dl and one or both *de novo* signs of severity (respiratory distress or impaired consciousness)

5.2.4 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

A transfusion should be stopped and necessary clinical interventions instituted in the following situations:
Rise in temperature: If the participant is noted to have a rise in temperature of more than 1^0C during the blood transfusion, consider a reaction to the blood product and as an immediate measure first stop the blood and record the vitals and time and attempt to lower the temperature by tepid sponging. Continue monitoring for any further increase in temperature and for any signs that may suggest a transfusion reaction.

Suspected allergic reaction (see MOP for details): If the participant shows signs of a suspected allergic reaction (see MOP for more details) then stop the blood, record the vitals and time and complete the Serious Adverse Reaction and SAE CRFs.

Suspected Cardiac Overload or Respiratory event (see MOP for details): If the participant shows signs of a suspected allergic reaction (see MOP for more details) then stop the blood, record the vitals and time, treat accordingly and complete the SAE CRFs.

If a decision is made to continue transfusion after a suspected adverse reaction with a different blood pack, the volume requested should be a balance i.e what has already been received subtracted from the initial prescribed volume. The different blood pack should be the same as the randomised blood pack type.

5.3 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, parents or guardians of children are consenting to trial treatment, trial follow-up and data collection. However, a child may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- Any change in the child's condition that justifies the discontinuation of treatment in the clinician's opinion
- Withdrawal of consent for treatment by the parent or guardian of the child

As the child's participation in the trial is entirely voluntary, their parent or guardian may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled, and this will not be considered a protocol deviation. Although the parent or guardian is not required to give a reason for discontinuing trial treatment, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

Early cessation of a transfusion should be recorded on the relevant trial Case Report Form(s) and flagged within the trial database, along with any accompanying information as appropriate.

Children for which a transfusion is stopped early should be encouraged to continue follow-up as per the trial assessment schedule, unless the parent or guardian expressly withdraws their consent to be followed up or to provide any further data. If this occurs, see Section 6.4 for further details.

5.4 ACCOUNTABILITY

The trial coordinator at each site will maintain accountability logs for transfusions. These will be kept securely until verified by the external monitors and for the duration of the trial.

5.5 COMPLIANCE & ADHERENCE

All children entering this trial will be severely ill and medical personnel will be responsible for administering the interventions. Any non-compliance will likely be a consequence of the intervention itself (e.g. lack of matched blood). To minimise wastage of blood, digital weighing scales will be provided for the blood transfusion laboratories to ensure accurate volumes are being issued and this will also be checked at a clinical level by use of gauged blood burettes.

5.6 TREATMENT DATA COLLECTION

Data will be collected on the quality of each blood pack provided (for example, pack weight, volume, haemoglobin and haematocrit of the blood). Data will also be collected on the transfusion and whether it was completed, or if there were any delays or interruptions to the transfusion. Basic data will be collected on whether any pack of blood supplied was rejected by the clinical team and requiring a repeat request to be made eg wrong blood to right patient (wrong blood group or pack type), wrong blood to wrong patient or evidence of haemolysis (red plasma).

5.7 NON-TRIAL TREATMENT

All non-trial systemic treatment given in the course of the admission will be recorded on a CRF. Concomitant medication would include anti-malarials, antipyretics, anticonvulsants, antibiotics and other treatments such as steroids. Any fluids given during the admission would also be recorded.

Patients who receive non-trial treatment will remain on trial, following the same visit schedule where possible, for the purposes of follow-up and data collection (unless they withdraw their consent from all stages of the trial).

5.7.1 TREATMENT AFTER TRIAL EVENT

Treatment will be at the discretion of the responsible physician and follow national guidelines and local protocols.

6 ASSESSMENTS & FOLLOW-UP

Children will be monitored on the day of admission by the clinical team, and during any transfusion and then reviewed daily by the study team until discharge, with Hb performed at 8 hours, 24, 48 and then at the earliest of 72 hours or discharge. (**Table 1**). Additional POC Hb measurements can be taken at other times if clinically indicated. Locator maps and contact numbers will be obtained to facilitate follow-up. All participants will then be seen at 4 weeks (28 days) and 3 months (90 days) from the date of randomisation, at outpatient clinics attached to each site for evaluation of morbidity, Hb, and toxicity. Any patient not returning for a study visit will be traced for vital status ascertainment (consent will be sought for this at recruitment).

6.1 TRIAL ASSESSMENT SCHEDULE

The trial assessment schedule is outlined in **Table 1**.

6.2 DOMAIN-SPECIFIC PROCEDURES FOR ASSESSING EFFICACY

Haemoglobin will be measured at 8, 24, 48 and then at the earliest of 72 hours from randomisation or discharge. Additional transfusions will be recorded on CRFs along with any clinical observations that fulfilled the criteria for prompting an additional transfusion.

6.3 DOMAIN-SPECIFIC PROCEDURES FOR ASSESSING SAFETY

Children will be closely monitored during the transfusion for any transfusion reactions.

Serious, solicited and grade 3 or 4 adverse events will be reported as and when the doctor becomes aware of them (see Safety Reporting section in the Master protocol). The details reported will include bedside observations, laboratory data, and additional clinical narrative.

For this domain within the SMAART-MAP trial the solicited adverse events that will be routinely capture and reported include suspected events related to transfusion:

- Acute transfusion reaction
- Haemolytic transfusion reaction (acute or delayed)
- Transfusion related acute lung injury
- Post transfusion purpura
- Transfusion transmitted infection
- Transfusion associated circulatory overload (see Trial Standard Operating procedures (SOP) for details)
- Pulmonary oedema.

6.4 EARLY STOPPING OF FOLLOW-UP

As the child's participation in the trial is entirely voluntary, their parent or guardian may choose to discontinue trial follow-up at any time without penalty or loss of benefits to which they are otherwise entitled. As detailed in **Section 5.3**, if a parent or guardian chooses to discontinue their child in the trial, they should always be encouraged to continue with follow-up as per the trial

assessment schedule. It should be made clear to the parent or guardian that continuing to provide follow-up data is important for the success of the trial. However, if the parent or guardian does not wish their child to remain on trial follow-up, their decision must be respected, and this will not be considered a protocol deviation.

It should be clear to the parent or guardian and recorded in the child's notes exactly which aspect(s) of the trial that the parent or guardian is discontinuing their participation for. These could include:

- Withdrawal from further treatment (as addressed in **Section 5.3**)
- Withdrawal from further sample collections
- Withdrawal from further trial follow-up visits

Information on the specific level of the child's discontinuation should be recorded on the relevant trial Case Report Form(s) and flagged within the trial database, along with any accompanying information as appropriate. Although the parent or guardian is not required to give a reason for discontinuing trial follow-up, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

To ensure that important trial outcomes are compared in the population randomised and hence balanced by design (the principle of "intention-to-treat"), previously-collected and de-indentified data on children who stop follow-up early will be kept and included in analysis, in line with the General Data Protection Regulation (GDPR) exemption which states that the 'right to erasure' of data does not apply where data processing is necessary for the performance of a task in the public interest in the area of public health, with the appropriate safeguards in place.

Parents or guardians may change their minds about stopping trial follow-up for their child at any time and re-consent to participation in the trial.

Children who stop trial follow-up early will not be replaced because the primary endpoint is calculated at 24 hours when losses to follow-up are expected to be very small.

6.5 LOSS TO FOLLOW-UP

Any child lost to follow-up before 90 days will be traced for vital status. In order to minimise losses to follow-up, locator data (maps and identifiable landmark) and mobile phone numbers will be taken on discharge and verified at every review. During the 90 day study period, if a child does not attend a scheduled visit, attempts should be made to contact the parents or guardians via phone (if available) and to follow-up with home visits, if at all possible.

6.6 COMPLETION OF PROTOCOL FOLLOW UP

The protocol follow up will end after the last scheduled follow-up visit of the last randomised participant. Sites will be closed once data cleaning is completed and the database undergone its final lock; the regulatory authorities and ethics committee will be informed of the trial closure as required by local regulations.

7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are the same across all domains of the SMAART-MAP trial and are described in the Safety Reporting section of the Master protocol. Sites will follow national reporting guidelines for notification requirements to national ethics and regulatory bodies.

8 QUALITY ASSURANCE & CONTROL

Details regarding the risk assessment, central monitoring, on-site or remote monitoring, source data and protocol deviations are outlined in the Master protocol.

9 STATISTICAL CONSIDERATIONS

This domain of the SMAART-MAP trial is a parallel arm design comparing outcomes in children that receive whole blood transfusions to those that receive red cell concentrate transfusions.

9.1 METHOD OF RANDOMISATION

Randomisation will be stratified by site and screening temperature (≤37.5°C or >37.5°C) as this determines the volume of each type of blood (additional stratification factor for this domain only). Randomisation lists, using permuted blocks of variable sizes, will be generated and 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.

9.2 OUTCOME MEASURES

9.2.1 PRIMARY OUTCOME

Change in haemoglobin from baseline by 24 hours (adjusted for baseline)

9.2.2 SECONDARY OUTCOMES

Severe anaemia domain outcomes:

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

SMAART-MAP outcomes:

- Proportion of children that died by 28 days from randomisation
- Proportion of children with readmissions by 28 days from randomisation
- Proportion of children that died by 90 days from randomisation
- Proportion of children with readmissions by 90 days from randomisation
- Proportion of children with Grade 3 or 4 adverse events (AEs)

9.3 SAMPLE SIZE

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. In the TRACT trial (George, Uyoga et al. 2022), in those with severe malaria receiving whole blood, the SD for the change from baseline haemoglobin was 1.96, meaning the detectable difference between the arms would be 1g/dl. The difference at 8 hours in those with severe malaria in the TRACT trial was 1.1g/dl for packed cells vs whole blood, 1.1g/dl

for settled cells vs whole blood in the 20mls/kg arm, and 2.2g/dl and 1.2g/dl respectively in the 30mls/kg arm (George, Uyoga et al. 2022).

9.4 ESTIMANDS

The primary estimand for change in haemoglobin from baseline by 24 hours is described in Table 2 below.

Table 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

9.5 INTERIM CHECKING & ANALYSES

During the SMAART-MAP trial an independent Data Monitoring Committee 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. 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.

9.6 ANALYSIS PLAN (BRIEF)

The analyses will be described fully in the Statistical Analysis Plan. In brief, the primary analysis for the trial will describe baseline parameters and compare primary and secondary endpoints by trial arm, adjusted for the stratification factors. The primary analysis will follow the Estimand framework described above.

The primary outcome will be analysed using normal linear regression, adjusted for baseline and for the stratification factors. Analysis of mortality will use time-to-event methods through to day 28 and 90. Readmissions will be analysed using competing risk methods counting death as a competing risk. Number of additional transfusions received during initial admission will be compared with ordinal logistic regression, 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 compared with logistic regression and exact tests as binary outcomes.

A secondary analysis will be carried out using Bayesian principles given the small sample size, using ACCEPT analyses (Clements, White et al. 2022). This will enable estimation of the probability that one arm is superior to the other, based on a continuous range of efficacy thresholds, and is more powerful than frequentist approaches when sample sizes are small due to the use of priors giving additional information.

10 ANCILLARY STUDIES

There are no planned ancillary studies.

11 REGULATORY & ETHICAL ISSUES

11.1 ETHICAL CONSIDERATIONS

Additional risks to those outlined in the Master protocol.

There are known risks from blood transfusions that are the same for transfusion with whole blood or red cell concentrates (eg infections in/failure to correctly cross-match transfused blood). The trial team is working with the local blood transfusion services to make sure blood used in this study as safe as possible and to reduce risks of incorrectly cross-matched or infected transfused blood (since donors blood is routinely screened for transfusion transmitted infections by the blood transfusion services as part of the quality control). One other risk is a reaction from the blood transfusion, but staff will monitor children closely as per standard guidelines for blood transfusions at this hospital and will treat children quickly should this happen.

Benefits to children in this domain are outlined in the Master protocol

All further detail on regulatory and ethical issues are found in the Master protocol including compliance, other ethical considerations including compensation, competent authority and other approvals and end of trial and comparison closure.

12 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies, which apply to this study. There will be additional site-specific insurance where required.

13 FINANCE

The trial is supported by a Collaborative Grant in Science from Wellcome, UK (grant number 209265/Z/17/Z). The trial will be coordinated by Imperial College. A written agreement with the site principal investigator and/or the investigator's institution and Imperial College will outline the funding arrangements to sites. The Trial Steering Committee (TSC) will meet and review the financial aspects of the trial at least 12-monthly and report to the sponsor. Terms of reference will be developed for this activity.

14 OVERSIGHT & TRIAL COMMITTEES

All oversight and trial committees will oversee all domains of the SMAART-MAP trial. These committees and the relationship between them are described in detail in the Master protocol.

15 PUBLICATION AND DISSEMINATION OF RESULTS

Details on publication and dissemination of results can be found in the Master protocol as these will be the same across all domains of the SMAART-MAP trial.

16 DATA AND/OR SAMPLE SHARING

Details on data sharing are outlined in the SMAART-MAP Master protocol.

17 PROTOCOL AMENDMENTS

Protocol	Date	Amendments to previous version
1.01	11th January 2024	Added ISRCTN Number and updated investigator details
1.02	9th February 2024	Updated investigator details
1.1	22nd April 2024	• Edit to drug accountability section (5.4) to remove mention of 'destruction'. • Addition of exclusion criteria for SMAART-MAP trial so that no child can be re-enrolled. • Co-enrolment restricted to observational studies only (section 4.2). • Addition of a sentence in Section 7 to highlight reporting to ethics and regulatory bodies to follow guidelines. • Addition of a malaria RDT at day 28 and day 90 follow up visits
1.2	8th May 2024	• Added in informed consent row to schedule of assessments • Added in row indicating total volume of blood drawn for common assessments • Added in further details on stopping transfusion for clinical reasons to section 5.

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SM AART
Severe Malaria in Africa:
A Research and Trials Consortium

Main Sponsor:
Imperial College London

Collaborating groups:

Appendix R to the Severe Malaria A Research and Trials Consortium – Multisite Adaptive Platform (SMAART-MAP) trial

For management of those enrolled into the Renal Function domain

Version: 1.3
Date: 5th June 2024

ISRCTN #: ISRCTN79071535
PACTR #: PACTR202312551082722

Authorised by:
Name: Prof Kathryn Maitland
Role: Chief Principal Investigator
Signature:

Date: 5th June 2024

This protocol has been produced using MRC CTU at UCL Protocol Template version 10.0. The template, but not any study-specific content, is licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). Use of the template in production of other protocols is allowed, but MRC CTU at UCL must be credited.

GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 10.0. The CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the SMAART-MAP trial Renal function domain, coordinated by the Kenya Medical Research Institute (KEMRI)-Wellcome Trust Kilifi Clinical Trials Facility, and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. This protocol should be used alongside the Master protocol for the SMAART-MAP trial.

Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be available to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the trial team to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, and the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2).

Sites will comply with the principles of GCP as laid down by the ICH topic E6 (R2) and other applicable national regulations.

SPONSOR

Imperial College London is the trial Sponsor and has delegated responsibility for the overall management of the SMAART-MAP trial to the KEMRI-Wellcome Trust Clinical Trials Facility in Kilifi, Kenya.

FUNDING

Funding is provided by the Wellcome as part of the grant to the SMAART Consortium (Grant Number 209265/Z/17/Z).

AUTHORISATIONS AND APPROVALS

This trial was approved by **[*Insert Info when approved*]**.

TRIAL REGISTRATION

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN79071535. It is also registered with PACTR, where it is identified as PACTR202312551082722 .

SAE REPORTING
Within 24 hours of becoming aware of an SAE, submit a completed SAE Form to KEMRI Wellcome Trust Kilifi by email to SMAART@kemri-wellcome.org
Tel: +254 715461761 or +254 726957045

TRIAL ADMINISTRATION

Please direct all queries to Emmanuel Oguda, SMAART clinical project manager at KEMRI Wellcome Trust – Kilifi in the first instance; clinical queries will be passed to the Chief Investigator via the SMAART clinical project manager.

COORDINATING CENTRE

KEMRI Wellcome Trust Programme	Switchboard: Mobile:	+254 417 522063/522535 +254 715 461761 (Trial manager)
Clinical Trial Facility	Fax:	+254 417 522390
PO Box 230, Kilifi, Kenya	Email:	SMAART@kemri-wellcome.org

KEMRI WELLCOME TRUST RESEARCH PROGRAMME, STUDY AND TRIAL MANAGEMENT GROUP Kilifi Clinical Trials Unit, PO Box 230, Kilifi			
Principal Investigator:	Prof Kathryn Maitland MBBS PhD	Mobile: Email:	+254 733 411022 kathryn.maitland@gmail.com
Trial Administrator	Phyles Maitha Dip.Business.Mgt	Tel: Mobile: Email:	+254 417 525453 (switchboard) +254 715 461761 PMaitha@kemri-wellcome.org
Clinical Project Manager:	Emmanuel Oguda Dipl.Clin.Med.Chir	Tel: Mobile: Email:	+254 417 525453 (switchboard) +254 726957045 EOguda@kemri-wellcome.org
Data Manager:	Christabel Mogaka BSc	Tel: Email:	+254715811661 CMogaka@kemri-wellcome.org
KILIFI: CLINICAL GROUP			
Lead Investigator	Prof Mainga Hamaluba MBCHB MRCP	Mobile: Email:	+254 709983946 MHamaluba@kemri- wellcome.org

Coinvestigators	Prof Thomas Williams MBBS, PhD	Mobile: Email:	+254 733 411021 tom.n.williams@gmail.com
Coinvestigators	Prof Phillip Bejon MBBS, PhD	Mobile: Email:	+254 724 45743 PBejon@kemri-wellcome.org

IMPERIAL COLLEGE

Division of Medicine Room 1030 Level 10 St Mary's Campus Norfolk Place London W2 1PG			
Principal Investigator:	Prof Kathryn Maitland MBBS PhD	Tel: Email:	+44 207 670 4905 kmaitland@imperial.ac.uk
Centre Administrator	Tony Tarragona-Fiol	Tel: Email:	+44 20 3312 6230 t.tarragona@imperial.ac.uk

MRC CTU AT UCL

MRC Clinical Trials Unit at UCL Institute of Clinical Trials and Methodology 90 High Holborn, 2nd Floor, London WC1V 6LJ			
Principal Investigator:	Prof Diana M Gibb MD MSc	Tel: Email:	+44 207 670 4905 diana.gibb@ucl.ac.uk
Statistician:	Dr Elizabeth George PhD MSc	Tel: Email:	+44 207 670 4931 elizabeth.george@ucl.ac.uk
Statistician:	Prof Ann Sarah Walker PhD MSc	Tel: Email:	+44 207 670 4726 rmjlasw@ucl.ac.uk

MORU

Mahidol Oxford Tropical Medicine Research Unit 420/6 Rajvithi Road, Tungphyathai, Bangkok 10400, Thailand			
Co-Lead Investigator:	Prof Nicholas Day, MBBS PhD	Tel: Email:	+66 870 118990 nickd@tropmedres.ac
Co-Lead Investigator:	Prof Arjen Dondorp, PhD	Tel: Email:	+66 818 015675 arjen@tropmedres.ac
Data Manager:	Naomi Waithera, MSc	Email:	Naomi@tropmedres.ac

STUDY SITES AND INVESTIGATORS

UGANDA: Country Principal Investigator Prof Peter Olupot Olupot			
Mbale Clinical Research Institute (MCRI) Mbale Regional Referral Hospital Pallisa Road Zone, P.O Box 921, Mbale, Uganda			
Site Investigator:	Prof Peter Olupot Olupot MBChB, MPH	Tel: Mobile: Fax: Email:	+256 77 2457217 +256 77 2457217 + 256 45 4435894 polupotolupot@yahoo.com
Study Site Coordinator:	to be appointed	Tel: Mobile: Email:	
Soroti Regional Hospital, P.O Box 289, Soroti, Uganda			
Site Investigator:	Dr Florence Aloroker MBChB, MMed	Tel: Mobile: Email:	+256 45 4461382 alaroflorence@gmail.com
Study Site Coordinator:	Denis Amorut, BsHSM, RCN	Tel: Mobile: Fax: Email:	+256 45 4461382 +256 77 4573911 +256 45 4461382 damoruts@gmail.com
Dr. Ambrosoli Hospital, Kalongo, P.O Box 47 Agago District, Uganda			
Site investigator:	Dr Okao Maurice MD, MMED Paediatrics	Tel: Email:	+ 256 779066157 maurice.okao@gmail.com
Study Site Coordinator	Modester Akite	Email:	Modesterakite@gmail.com

KENYA:			
Kilifi County Hospital, Hospital Road, PO Box 230, Kilifi			
Co-Lead investigator:	Prof Mainga Hamaluba MBCHB, MRCP	Tel: Email:	+254 709983946 MHamaluba@kemri-wellcome.org
Co-Lead investigator:	Prof Kathryn Maitland MBBS PhD	Tel: Email:	+254710508749 Kathryn.maitland@gmail.com

MOZAMBIQUE:			
Hospital Central de Quelimane, Av.Julius Nyerere, Estrada regional numero 470. Bairro Namuinho Manhica Health Research Centre (CISM) PO BOX 1929 Manhica			
Co-Lead investigator:	Dr Pedro Aide, MD, MSc, PhD	Tel: Email:	+258 2181 0181 pedro.aide@manhica.net
Co-Lead investigator:	Dr Rosauro Varo, MD, MSc	Tel: Email:	 Rosauro.varo@isglobal.org
Co-investigator:	Professor Quique Bassat, MD, MSc, PhD	Tel: Email:	 quique.bassat@isglobal.org
Clinical coordinator:	Dr David Torres, MD, MSc	Tel: Email:	 David.torres@isglobal.org
GHANA:			
Komfo Anokye Teaching Hospital, Bantama High Street PO Box 1934 Kumasi Department of Child Health, Kwame Nkrumah University of Science and Technology, Kumasi			
Principal investigator:	Professor Daniel Ansong, MSc	Tel: Email:	+233 208 168767 dansong@kathhsp.org
Co-investigator:	Prof Tsiri Agbenyega, PhD	Tel: Email:	+233 208 113848 tsiri@ghana.com
Co-investigator	Dr Justice Sylverken, MBChB	Tel: Email:	+233 208 113715 jsylverken@gmail.com

ZAMBIA			
St Pauls Mission Hospital, Nchelenge, Luapula Province and Tropical Diseases Research (TDR) Centre, 6th and 7th Floor of Ndola Teaching Hospital building, P.O Box 71769, Zambia			
Principal Investigator:	Dr Mike Chaponda, MSc, MBChB, MSc, DTMH	Tel: Email:	+260 212 620737 mikechaponda@yahoo.com
Co-investigator:	Dr Sam Miti, MBChB, MMed	Tel: Email:	+260 212 620737 drsammiti@gmail.com
Co-investigator	Dr Jonathan Gwasupika, MBChB	Tel: Email:	+260212620737 gwagwejo@gmail.com

DEMOCRATIC REPUBLIC OF THE CONGO			
Kinshasa School of Public Health Universite de Kinshasa, Campus UNIKIN, Lemba, BP 11850, Kinshasa, DRC			
Principal Investigator:	Prof Marie Onyamboko, MD, DPhil	Tel: Email:	+243990024201 akatshimarie@yahoo.fr
Co-investigator:	Dr Catarina Fanello, PhD	Email:	Caterina@tropmedres.ac

SUMMARY OF TRIAL

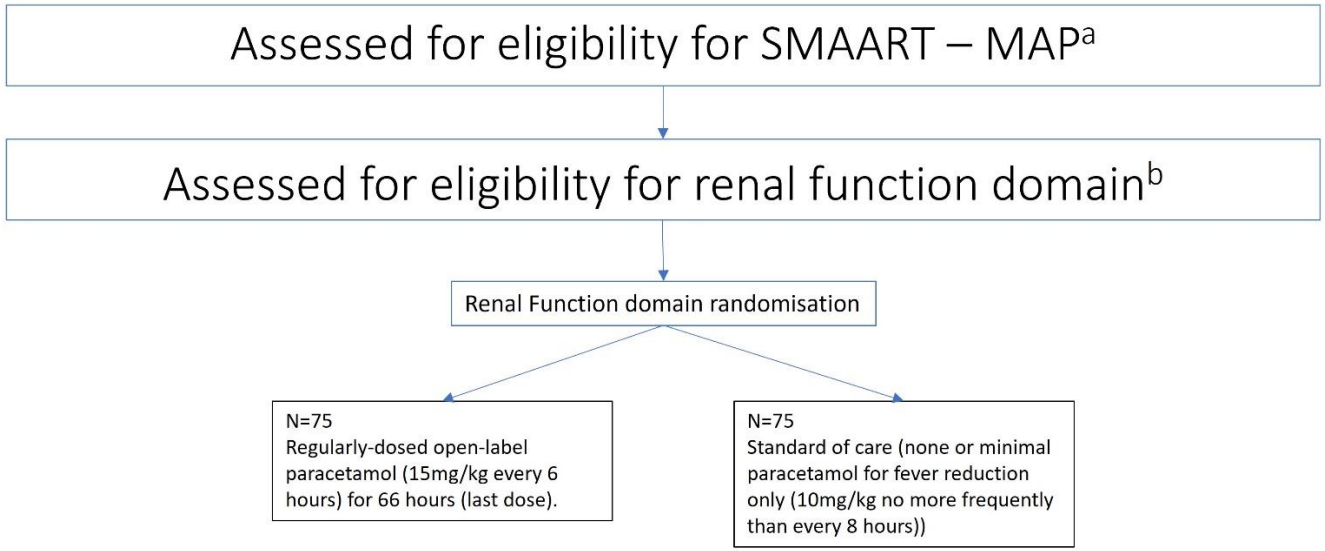
SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym	SMAART – MAP Renal function
Long Title of Trial	Severe Malaria A Research and Trials Consortium – Multisite Adaptive Platform trial: Renal function domain
Version	1.3
Date	5th June 2024
ISRCTN # **PACTR #**	ISRCTN79071535 PACTR202312551082722
Study Design	Parallel arm multi-site Phase II trial
Setting	Hospitals in Uganda, Zambia, Ghana, Kenya, Democratic Republic of the Congo and Mozambique
Type of Participants to be Studied	Hospitalised children with severe malaria and creatinine>1.5xULN at presentation
Ancillary Studies/Substudies	None
Sponsor	Imperial College London
Interventions to be Compared	High dose paracetamol (15mg/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)
Study Hypothesis	Kidney dysfunction occurs in up to 25% of paediatric severe malaria cases and is a strong predictor of mortality. Regularly-dosed paracetamol (at a higher dose than used for fever control) will reduce kidney dysfunction (evidenced by raised creatinine) and improve renal outcomes by inhibiting cell-free haem-mediated oxidative damage
Eligibility criteria	SMAART MAP inclusion criteria: • Aged >3 months and <12 years • Admitted to the paediatric ward in the last 24 hours at screening • Current or recent evidence of malaria (slide or rapid diagnostic test (RDT) positive in this admission) • Guardian willing to provide consent SMAART-MAP exclusion criteria: • Enrolment into this trial on a previous admission Domain specific inclusion criteria: • Creatinine >1.5xULN on point-of-care assay or laboratory test at screening • Meet one of the current WHO severity criteria (clinical or laboratory (where these tests are done routinely)) (Group 1

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	and 2 from the recent WHO 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)* Exclusion criteria for the renal domain: • Received paracetamol within 6 hours of screening or between screening and randomisation • Known allergy to paracetamol • Severe malnutrition (middle upper arm circumference (MUAC) <11.5cm, or weight-for-length score <-3 for children <6 months) • Known history of hepatic or renal impairment
Primary Outcome Measure(s)	Area Under the Curve (AUC) for creatinine over the first 72 hours from randomisation based on measurements assayed retrospectively on stored plasma samples taken at randomisation (treated as time 0/baseline) 24, 48 and 72 hours
Secondary Outcome Measure(s)	<u>Renal domain outcomes:</u> • 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) <u>Renal domain safety outcomes:</u> • Change in ALT and AST (liver enzymes) at 72 hours (adjusted for baseline) • Adverse events (AEs) of any grade judged related to paracetamol • AEs of any grade causing a change in paracetamol administration <u>SMAART-MAP outcomes:</u> • Grade 3 or 4 AEs during admission • Day 28 and Day 90 readmissions and mortality

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Randomisation	1:1 randomisation using randomised permuted blocks, stratified by site and presence of blackwater fever
Number of Participants to be Studied	150 children, 75 per arm
Duration	24 months
Funder	Wellcome
Chief Investigator	Professor Kath Maitland

TRIAL SCHEMA

Figure 1: Trial Entry, Randomisation and Treatment



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

[b] Renal function domain inclusion criteria: Creatinine >1.5xULN and one of the WHO Severity criteria (see below). Exclusion criteria: received paracetamol within 6 hours of randomisation or between screening and randomisation; known allergy to paracetamol; severe malnutrition (mid-upper arm circumference (MUAC)<11.5cm, or weight-for-length z-score <-3 for children <6 months); known history of hepatic or renal impairment.

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)*

TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule

Assessment (timepoints from randomisation)	Admission/ screening	Random-isation	3hrs (±1hr)	6 hrs (±2hrs)	12 hrs (±3 hrs)	18 hrs (±3 hrs)	24 hrs (±3 hrs)	30hrs (±3 hrs) /36 hrs (±3 hrs) /42hrs (±3 hrs)	48 hrs (±3 hrs)	54hrs (±3 hrs)/ 60hrs (±3 hrs)/ 66 hrs (±3 hrs)	72 hrs (±3 hrs)	Discharge	28 (±7) days	90 (±14) days
Clinical assessment[1]	x		x	x	x		x		x		x[6]		x	x
Point-of-care tests (0.2-0.3mls)[2]	x		x	x			x		x		x		x	x
Weight[3]	x												x	x
Malaria RDT, and thick and thin malaria slide (if available at site) (0.2ml)	x												x	x
Point-of-care (or laboratory if necessary) creatinine (0.2-0.5mls)	x													
Informed consent process[4]														
Randomisation		x												
Administer paracetamol in paracetamol arm		x		x	x	x	x	x	x	x				
Full Blood Count[5] (1ml)		x												
Liver function tests (AST and ALT) (1ml)		x									x[7]			
Urine dipstick[6]		x												
Urine storage (if possible at site) [6]		x									x[7]			
Plasma storage for creatinine test (1ml)		x					x		x		x[7]			
Plasma storage for quantitative pfHRP2 (1ml)		x												
POC pfHRP2 test (when available) (0.2ml)		x												
Ascertainment of all treatments given during admission (anticonvulsants, anti-malarials, antibiotics and transfusions).												x		
Ascertainment of readmissions, potential malaria episodes, and neurological sequalae.													x	x
Total blood draw (mls) (10.4-11.5mls for whole study)	0.6-1.0	4.2	0.2-0.3	0.2-0.3	0	0	1.2-1.3	0	1.2-1.3	0	2.2-2.3	0	0.4	0.4

Note: grayed cells indicate assessments common to all SMAART-MAP domains from the master protocol.

[1] Clinical assessment: heart rate, oxygen saturation (pulse oximetry), respiratory rate, respiratory distress, axillary temperature, blood pressure, capillary refill time, consciousness level (as measured by the Blantyre Coma Score (BCS)).

[2] Lactate, glucose and haemoglobin as point-of-care tests (lactate and glucose only at 3 hours, haemoglobin only at 28 and 90 days).

[3] Weight: assessed at screening or as soon as possible after enrolment depending on status.

[4] This could be informed consent or emergency verbal assent followed by deferred consent dependant on the child's condition – please see section 3.7 for details.

[5] Full blood count: haemoglobin, white blood cells, platelets (and differential if available as standard at site). Values from a blood draw taken for clinical reasons (i.e. not for the trial) at any time in this admission before randomisation should be used if available, rather than re-bleeding the child, as eligibility requires all children to be within 24 hr of admission at screening.

[6] This should be taken when the first urine sample is available.

[7] If the child is discharged prior to 72 hours then these assessments should be done at discharge. However, caregivers should be encouraged to stay until 72 hours wherever possible.

LAY SUMMARY

Children with severe malaria can be very sick due to the malaria parasites in their blood. As the blood flow around the body is affected by malaria this can damage important parts of the body called vital organs. The kidneys are one vital organ and malaria can impact their normal function. Kidneys produce urine which helps to remove waste products and excess water from the body and when normal function is affected this is called kidney failure.

In other studies, researchers have found that children with severe malaria and poor kidney function are at higher risk of worse outcomes (including death and prolonged stay in hospital). It is unclear how best to treat this condition and return the kidney function in these children to normal. There has been some initial research showing that paracetamol may have some benefits for treating poor kidney function and it is a safe and low cost pill. Two small studies are looking at its use in severe malaria at individual hospitals but this study plans to include children from across several hospitals and countries. We will give some children regular doses of paracetamol (which is currently used to control fever) at a slightly higher dose than usual for three days to see if their kidney function improves. We will measure their kidney function at baseline and once a day for 3 days using a marker of kidney function called creatinine. Creatinine is found in the blood and measures how well the kidneys are working. Children who have a raised creatinine when they arrive at hospital (which means that their kidneys are not working as they should in filtering the waste from blood) will be able to join this part (domain) of the SMAART trial.

A computer programme will assign an eligible child at random (like the flip of a coin) to receive either regular doses of paracetamol every 6 hours at a slightly higher dose than usual for three days or to standard of care. All children will be closely monitored but those that receive standard care may get paracetamol at a lower standard dose to manage any high temperatures they have. Paracetamol is well tolerated with few side affects and will be given orally in a liquid to drink or through a tube direct to the child's stomach if they are unable to drink.

CONTENTS

ABBREVIATIONS

ABBREVIATION	EXPANSION
AE	Adverse event
AKI	Acute Kidney Injury
ATN	Acute Tubular Necrosis
BCS	Blantyre Coma Score
BUN	Blood Urea Nitrogen
CI	Chief Investigator
CI	Confidence interval
CRF	Case Report Form
CTF	Clinical Trial Facility
CTU	*See MRC CTU at UCL*
DMC	Data Monitoring Committee
DRC	Democratic Republic of the Congo
GCP	Good Clinical Practice
Hb	Haemoglobin
IB	Investigator Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
ISRCTN	International Standard Randomised Controlled Trial Number
KEMRI-Wellcome Trust Kilifi CTF	Kenya Medical Research Institute – Wellcome Trust Kilifi Clinical Trials Facility (also generally abbreviated to CTF)
MOP	Manual of Operations
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London (also generally abbreviated to “CTU”)
MUAC	Middle upper arm circumference
PI	Principal Investigator

ABBREVIATION	EXPANSION
PfHRP2	Plasmodium falciparum histidine rich protein 2
POC	Point-of-care
RCT	Randomised controlled trial
RDT	Rapid Diagnostic Test
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
TMT	Trial Management Team
ULN	Upper Limit of Normal
WHO	World Health Organization

1 BACKGROUND

Renal involvement complicating severe malaria in African children has received relatively little attention. In contrast, renal dysfunction in adults with severe malaria is common and is known to be a major risk factor for poor outcome (Trang, Phu et al. 1992, Day, Phu et al. 2000, Das 2008). Clinically, adults present with a mixture of pre-renal and renal failure with associated acidosis suggesting acute tubular necrosis (ATN or acute kidney injury AKI) (Day, Nguyen et al. 1997, Day, Phu et al. 2000). Clinically, urine sediment findings and histopathological findings (Nguansangiam, Day et al. 2007) indicate acute tubular damage (due to parasitized red blood cells sequestered within both glomerular and tubulo-interstitial vessels). The WHO malaria treatment guidelines considers renal failure as a plasma or serum creatinine level >265 µmol/L; but does not indicate criteria for children (World Health Organisation 2022).

Nevertheless, data are now emerging indicating that biochemical markers of renal impairment are also prominent in African children with severe malaria and have prognostic relevance. Only a few studies have investigated renal function in African children with severe malaria. One prospective study in Kenyan children showed that an elevated creatinine (>80 µmol/L) complicated 96/469 (20%) severe malaria cases at admission, and was associated with an in-hospital case fatality of 26% (Maitland, Levin et al. 2003). Four factors were independently associated with fatal outcome: deep 'acidotic' breathing, hypoxia (SaO_2<90%), hypoglycaemia (<2.5mmol/L) and creatinine >80 µmol/L (odds ratio for mortality with elevated creatinine = 5.76 (95% CI 2.3-14.3) P=0.0002).

The AQUAMAT trial (Dondorp, Fanello et al. 2010) included 5425 children with severe malaria from 11 sites across 9 countries with differing malaria endemicities and established three factors that were independent predictors of fatal outcome: acidosis, impaired consciousness (coma) and an elevated blood urea nitrogen (BUN>20mg/dL) (von Seidlein, Olaosebikan et al. 2012). The estimated mortality in children with all 3 predictors was 43%. In the FEAST trial, 444/2109 (21%) children had an elevated BUN (>20mg/dL), with marked site-to-site variation in prevalence (13-32%) (Maitland, Kiguli et al. 2011). Elevated BUN was more common in areas of highest malaria transmission intensity and in children presenting with haemoglobinuria (dark urine syndrome) (123/187; 66%) compared to other cases (140/847; 17%) (Olupot-Olupot 2015). In children with dark urine syndrome, a high BUN, on univariate analysis, was associated with increased risk of fatal outcome (OR=3.5 (2.68-4.72) P<0.0001) (George, Walker et al. 2015). In addition, in two FEAST sites in Eastern Uganda, in which malaria transmission is hyper-holoendemic, the triad of dark urine, jaundice and severe anaemia were common (Olupot-Olupot P 2015), but this combination of severity features was rarely seen in other sites, suggesting a picture more akin to adult-type severe malaria where jaundice and renal involvement are more common.

These observations suggest that renal involvement may be more common than previously anticipated in African children with severe malaria and is associated with poor outcome. How best to manage this complication in African children remains uncertain without further research into promising cheap and available interventions. Akech and colleagues in a Phase II fluid resuscitation trial of Hetastarch and Dextran in severe malaria showed that 34% (27/79) children at admission had a raised creatinine (>80 µmol/L); by 8 hours this had largely resolved in all but 4% (3/75) suggesting a substantial pre-renal component reversible by fluid challenge (Akech, Jemutai et al. 2010). Nevertheless, in a large fluid resuscitation (FEAST) trial, fluid resuscitation showed excess mortality in the fluid boluses arms (receiving 20-40mls/kg saline or albumin) compared to no-bolus (maintenance only) controls (Maitland, Kiguli et al. 2011). Fluid resuscitation is no longer recommended for children with severe malaria – meaning that it cannot be recommended for first-

line management of suspected reversible renal impairment in severe malaria. There are also emerging data about the potential nephrotoxic effects of chloride-rich resuscitation fluids (such as saline and albumin) (Prowle and Bellomo 2010, Yunos, Bellomo et al. 2012).

One potentially promising treatment is paracetamol, which attenuates nephrotoxicity of haemoproteins, red-cell free haemoglobin and myoglobin in sepsis (Boutaud, Moore et al. 2010). Pilot and dose finding Phase I studies are being undertaken in Mbale, eastern Uganda (ISRCTN 84974248) in children with haemoglobinurea and elevated creatinine, and in Kinshasa, Democratic Republic of Congo (DRC) (NCT04251351) in children with fever and elevated creatinine. However, there is still a need to evaluate paracetamol in the wider population with severe malaria to understand further the potential for early benefit of paracetamol (a widely available and cheap intervention) in children with elevated creatinine indicating possible renal impairment.

Defining kidney injury in severe malaria

The WHO guidelines for identification and management of severe malaria defines impaired renal function by creatinine >265 µmol/L. However, this is based on adult normal ranges which are much higher due to higher body mass. Whilst markers of renal function that have been used in children with severe malaria include urea and creatinine, creatinine is more useful since urea levels are affected by hydration levels. Paediatric guidelines recommend the use of the paediatric RIFLE criteria to assess renal function which have been adapted from adult criteria and subsequently evaluated. Children that are at risk of renal failure have a reduced estimated creatinine clearance of 25% (based on the calculation using the Schwartz criteria (Schwartz, Haycock et al. 1976)) which is equivalent to a creatinine 1.5 times the upper limit of normal (ULN). For simplicity (and reducing the risk of miscalculation) we will use a point-of-care (POC) creatinine level >1.5 times ULN as an entry criterion. The normal ranges in children 1 month – 4 years are 13-39 µmol/L and 5-11 years are 29-53 µmol/L (Royal College of Paediatrics and Child Health 2016).

1.1 OBJECTIVES

We hypothesize that regularly-dosed paracetamol (at a higher dose than for fever control) will reduce kidney dysfunction and improves outcome by inhibiting cell-free haem-mediated oxidative damage compared with no or minimal paracetamol given for fever reduction only.

1.1.1 PRIMARY OBJECTIVE

Our primary objective is to test whether regularly dosed paracetamol given over 66 hours (corresponding to 72 hours exposure) will reduce levels of creatinine in children at high risk of renal impairment compared to standard of care; thus determining if paracetamol can reduce the evolution of kidney injury in severe malaria.

1.1.2 SECONDARY OBJECTIVES

Secondary objectives are to assess the impact of regularly dosed paracetamol during admission in children with elevated creatinine and severe malaria on:

- mortality and readmission by 90 days.
- markers of liver function (AST and ALT).

- on Grade 3 or 4 adverse events, and adverse events of any grade related to paracetamol.

An additional objective is, where it is possible, to store urine in order to assess other markers of kidney function, such as the urine albumin creatinine ratio at 72 hours.

2 SELECTION OF SITES/CLINICIANS

The trial Sponsor has overall responsibility for site and investigator selection. The Sites included in the SMAART-MAP trial are all part of the Severe Malaria - a Research and Trials Consortium group. The site/investigator inclusion criteria and steps for approval and activation are outlined in the Master Protocol.

3 SELECTION OF PATIENTS

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

The eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this study. Patients not meeting the criteria should not join the study. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

3.1 PATIENT INCLUSION CRITERIA FOR THE 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

The restriction of time since admission to 24 hours is because all children recruited in this trial will be treated with artesunate based antimalarials, which would be expected to be effective within 24 hours if malaria were the underlying cause; later clinical manifestations may have other causes.

3.2 PATIENT EXCLUSION CRITERIA FOR THE SMAART-MAP TRIAL

1. Enrolment into the SMAART-MAP trial on a previous admission

3.3 ADDITIONAL PATIENT 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)

As described above, the normal ranges in children 1 month – 4 years are 13-39 µmol/L and 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.

3.4 ADDITIONAL PATIENT 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 or weight-for-length score <-3 for children <6 months old).
4. Known history of hepatic or renal impairment.

3.5 NUMBER OF PATIENTS

75 per arm. 150 in total.

3.6 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in **Section 4.2**.

3.7 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

On arrival at the paediatric ward, the clinical team will immediately screen for *P. falciparum* (by RDT) as part of routine clinical practice. This will also determine eligibility for the SMAART-MAP trial. In some cases, positivity will be determined by a slide (also part of routine clinical practice).

Potentially eligible children (RDT/slide positive) will be identified by the nurse and clinician on duty and registered in the eligibility screening log. A member of the trial team will then perform a rapid structured assessment (comprising only clinical parameters routinely assessed at admission) of heart rate, oxygen saturation (pulse oximetry), respiratory rate, axillary temperature, blood pressure, markers of shock (capillary refill time, pulse volume and assessment of lower limb temperature) and confirm whether the child has had any seizures in this illness. Weight will be measured as standard of care and in preparation for any weight-based dosing of medications. Additionalassessments as part of routine care and as recommended by the WHO malaria treatment guidelines may involve taking finger pricks of blood, for example for haemoglobin, lactate, glucose and creatinine tests with a point-of-care analyser or at the laboratory. Details of those fulfilling the entry criteria including severity and the results of routine assessments will be entered onto a screening form, while reasons for non-eligibility will be added to the eligibility screening log.

Children who are eligible for more than one domain will only be enrolled into one domain. Enrolment into one domain over another for a child eligible for both will be directed by the Trial Management Team (TMT) following predicted and actual recruitment rates into each domain.

INFORMED CONSENT

Prospective written, informed consent will be sought from parents or guardians of children who are considered to be sufficiently stable. Parents or guardians will be given an information sheet in their usual language containing details of the trial. The sheet will be read aloud to those who are unable to read. Parents and guardians will be encouraged to ask questions about the trial prior to signing the consent form. It must be made completely and unambiguously clear that the parent or guardian of the child is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of their child. The right of the parent or guardian to refuse to participate without giving reasons must be respected. Older children should give assent to trial participation, if applicable and at an age determined by the country of enrolment. This will be recorded on a signed assent form.

EMERGENCY VERBAL ASSENT FOLLOWED BY DEFERRED CONSENT

A number of children will present as emergencies where delay in study enrolment, and thus treatment, through a consent procedure would be unacceptable. For the FEAST trial we developed and received ethical approval to use a two stage consent process in this circumstance (Maitland, Molyneux et al. 2011). Verbal assent will be sought from parents or guardians by the admitting medical team, if it is considered that the full consent process would significantly delay treatment allocation, and consequently could be detrimental to the child's health. Full consent will be sought once the child's clinical condition has been stabilized. Caregivers will be provided with a brief verbal description of the trial and will be given the opportunity to "opt out" of clinical research. The clinician will later sign the verbal assent form which will be filed with the consent form. If written consent is not provided following verbal consent, the child will be excluded from analyses from the time consent is refused. If the child dies before written consent is obtained, written consent will not be sought to avoid distress to the parents/guardians, but the child will be included in the analysis to ensure this important clinical outcome is recorded.

Signed consent forms (and signed assent forms where applicable) must be kept by the investigator and documented in the CRF and a copy given to the family.

4 REGISTRATION & RANDOMISATION

4.1 RANDOMISATION PRACTICALITIES

Randomisation lists, using variable block sizes, stratified by site and whether the child has blackwater fever or not, will be generated and hosted on an online randomisation system accessed by approved site staff. To facilitate protocol adherence, a maximum enrolled per day per site will be agreed upon (for example up to 2 children per day). This approach was very successful with respect to protocol adherence and the quality of data generated in the TRACT trial.

4.2 CO-ENROLMENT GUIDELINES AND REPORTING

Patients will not ordinarily be permitted to participate in any other clinical intervention trial or research protocol for adjunctive therapy while in the SMAART-MAP trial. Participation in other studies that do not involve an adjunctive therapy intervention such as observational studies may be acceptable, but should be discussed with the SMAART-MAP Trial Management Group (TMG). Enrolment within the SMAART-MAP trial is restricted to one domain.

5 TREATMENT OF PATIENTS

5.1 INTRODUCTION

All trial patients will receive standard of care including antibiotics (IV or oral) and anti-malarial drugs following national guidelines, based on WHO syndromic patient management (World Health Organisation 2013). All children enrolled in the trial should remain admitted to the ward until after the 72 hour clinical assessment and tests have been conducted wherever possible.

5.2 HIGH DOSE PARACETAMOL ARM

Children randomised to this arm will receive 15mg/kg paracetamol every 6 hours for 66 hours (i.e. giving 72 hours exposure) given orally or via nasogastric tube. If this is difficult due to the clinical status of the child and/or local practice, then sites can give rectal doses where this formulation is available.

5.2.1 TREATMENT SCHEDULE

Once a child has been randomised to the paracetamol arm, then they should receive their first dose of paracetamol at 15mg/kg as soon as possible after randomisation. The paracetamol will be given as dispersible tablets, following the instructions to be made into a liquid to be given orally (or via a nasogastric tube) or rectally if this is the standard practice at the site if a child is unable to take oral medication. Subsequently, doses will be given at 15mg/kg at 6 hourly intervals until the last dose at 66 hours from randomisation.

5.2.2 DISPENSING & STORAGE

Open-label paracetamol for use in the trial will be stored in the site pharmacy and dispensed to study staff.

5.2.3 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

If a child vomits the dose then it will be repeated only if vomiting occurs within 30 mins of a dose. For sites using rectal paracetamol, if this is expelled within 30 mins of the dose, then the dose will be repeated. Following standard clinical practice, the treating clinician can request extra blood tests as needed according to the child's clinical status; as paracetamol is an adjunctive therapy, the paracetamol dose can be reduced at their discretion or stopped and this will not be considered a protocol deviation (see Section 5.4).

5.2.3.A Stopping Drug Early

If a new rash appears or the child experiences itchiness then consider an allergic reaction and stop treatment with paracetamol. Other discontinuation criteria are considered in **Section 5.4.**

5.2.4 ACCOUNTABILITY & UNUSED DRUGS/DEVICES

Accountability must be maintained for all paracetamol dispensed to participants. Any diluted product that has been dispensed from pharmacy must be destroyed if not used for the treatment of a trial participant. Expired products should be quarantined prior to destruction according to local procedures and recorded in the appropriate trial-specific log. Logs may be collected centrally for monitoring purposes. More information on accountability and pharmacy procedures, including destruction procedures, can be found in the trial manual of operations (MOP).

5.2.5 COMPLIANCE & ADHERENCE

Data on compliance with administration of paracetamol by study staff at site at the dose and times indicated above will be collected on a treatment CRF. Other measures of adherence are not needed as the intervention is given by study staff rather than parents or children.

5.3 NO OR MINIMAL PARACETAMOL

Children randomised to this arm will not receive regularly dosed paracetamol. Paracetamol may be given to children at standard doses for fever control.

5.3.1 TREATMENT SCHEDULE

Temperature will be taken regularly as part of the clinical observations outlined in **Table 1** and additional assessments can be made if clinically indicated. If the child has a temperature >38.5°C, then they may receive up to 10mg/kg paracetamol given orally or via nasogastric tube (or rectally where available) no more frequently than every 8 hours at the discretion of the treating clinician. They can also receive fanning and tepid sponging to help reduce their temperature.

5.3.2 DISPENSING & STORAGE

The pharmacy will ensure there are sufficient stocks of paracetamol for fever control and the staff will collect if needed following the protocol indication above.

5.3.3 COMPLIANCE & ADHERENCE

Data on all systemic medications given to children in the trial will be recorded on a relevant CRF.

5.4 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, parents or guardians of children are consenting to trial treatment, trial follow-up and data collection. However, a child may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- Any change in the child's condition that justifies the discontinuation of treatment in the clinician's opinion
- Withdrawal of consent for treatment by the parent or guardian of the child

As the child's participation in the trial is entirely voluntary, their parent or guardian may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled, and this will not be considered a protocol deviation. Although the parent or guardian is not required to give a reason for discontinuing trial treatment, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

Early cessation of paracetamol treatment should be recorded on the relevant trial CRF(s) and flagged within the trial database, along with any accompanying information as appropriate.

Children for which paracetamol treatment is stopped early should be encouraged to continue follow-up as per the trial assessment schedule, unless the parent or guardian expressly withdraws their consent to be followed up or to provide any further data. If this occurs, see **Section 6.4** for further details.

5.5 COMPLIANCE & ADHERENCE

All children entering this trial will be severely ill and medical personnel will be responsible for administering the interventions. Site staff compliance will be regularly checked from CRF and data entry by trial staff.

5.6 TREATMENT DATA COLLECTION

Data will be collected on the dose and timing of all paracetamol given during the trial on an appropriate CRF. Detail will include whether all the liquid was consumed to estimate whether the full dose was received.

5.7 NON-TRIAL TREATMENT

All non-trial systemic treatment given in the course of the admission will be recorded on a CRF. Such concomitant medication would include anti-malarials, anti-epileptic medication, and antibiotics, following national guidelines. Any fluids, including blood transfusions, given during the admission would also be recorded. If required, maintenance fluids will be run at 3-4mls/kg per hour irrespective of age until the child can drink and retain oral fluids. Anticonvulsants and treatment for hypoglycaemia will be administered according to nationally agreed protocols.

Patients who receive non-trial treatment will remain on trial, following the same visit schedule where possible, for the purposes of follow-up and data collection (unless they withdraw their consent from all stages of the trial).

5.7.1 TREATMENT AFTER TRIAL EVENT

Treatment will be at the discretion of the responsible clinician and following national guidelines and protocols.

6 ASSESSMENTS & FOLLOW-UP

Children will be intensively monitored on the day of admission by the clinical team, and then reviewed daily by the study team until discharge (**Table 1**). Children should remain in hospital until 72 hours wherever possible, but if discharged earlier then the 72 hour clinical assessment including collection of blood samples should be conducted at discharge. Locator maps and contact numbers will be obtained as soon as possible after admission, and at a minimum on discharge to facilitate follow-up. All participants will then be seen at 4 weeks (28 days) and 3 months (90 days) from the date of randomisation, at outpatient clinics attached to each centre for evaluation of morbidity, and toxicity. During the 90 day study period, if a child does not attend a scheduled visit, then attempts should be made to contact the parents or guardians via phone (if available) and to follow-up with home visits, if at all possible.

6.1 TRIAL ASSESSMENT SCHEDULE

The trial assessment schedule is outlined in **Table 1**.

6.2 DOMAIN-SPECIFIC PROCEDURES FOR ASSESSING EFFICACY

Creatinine will be assayed retrospectively on stored plasma samples taken at baseline, 24, 48 and 72 hours from randomisation. These measures will be used to calculate the area under the curve for creatinine levels (the primary outcome).

6.3 DOMAIN-SPECIFIC PROCEDURES FOR ASSESSING SAFETY

Liver function will be assessed at 72 hours using AST and ALT. The paediatric RIFLE score (Akcan-Arikan, Zappitelli et al. 2007) will also be calculated from information recorded at 24, 48 and 72 hours. AEs judged by the investigator as being related to paracetamol (any grade) should be recorded on the appropriate CRF, in addition to safety reporting applicable to all domains (grade 3/4 AEs and SAEs, see Master protocol).

6.4 EARLY STOPPING OF FOLLOW-UP

As the child's participation in the trial is entirely voluntary, their parent or guardian may choose to discontinue trial follow-up at any time without penalty or loss of benefits to which they are otherwise entitled. As detailed in **Section 5.4**, if a parent or guardian chooses to discontinue their child's treatment in the trial, they should always be encouraged to continue with follow-up as per the trial assessment schedule. It should be made clear to the parent or guardian that continuing to provide follow-up data is important for the success of the trial. However, regardless of their decisions around their child's treatment, if the parent or guardian does not wish their child to remain on trial follow-up, their decision must be respected, and this will not be considered a protocol deviation.

It should be clear to the parent or guardian and recorded in the child's notes exactly which aspect(s) of the trial that the parent or guardian is discontinuing their participation for. These could include:

- Withdrawal from further treatment (as addressed in **Section 5.4**)
- Withdrawal from further collections of trial samples
- Withdrawal from further trial follow-up assessments or visits

Information on the specific level of the child's discontinuation should be recorded on the relevant trial Case Report Form(s) and flagged within the trial database, along with any accompanying information as appropriate (and this will not be considered a protocol deviation). Although the parent or guardian is not required to give a reason for discontinuing trial follow-up, a reasonable effort should be made to establish this reason while fully respecting the child's rights.

To ensure that important trial outcomes are compared in the population randomised and hence balanced by design (the principle of "intention-to-treat"), previously collected and de-identified data from children who stop follow-up early (i.e data collected before the point of withdrawal) will be kept and included in analysis, in line with the General Data Protection Regulation (GDPR) exemption which states that the 'right to erasure' of data does not apply where data processing is necessary for the performance of a task in the public interest in the area of public health, with the appropriate safeguards in place.

Parents or guardians may change their minds about stopping trial follow-up for their child at any time and re-consent to participation in the trial.

Children who stop trial follow-up early will not be replaced because the primary endpoint is calculated over the first 72 hours when losses to follow-up are expected to be very small.

6.5 LOSS TO FOLLOW-UP

Any child lost to follow-up before 3 months will be traced for vital status. In order to minimise losses to follow-up, locator data (maps and identifiable landmark) and mobile phone numbers will be taken as soon as possible after admission, and at a minimum on discharge and verified at every review. During the 90 day study period, if a child does not attend a scheduled visit, then attempts should be made to contact the parents or guardians via phone (if available) and to follow-up with home visits, if at all possible.

6.6 COMPLETION OF PROTOCOL FOLLOW UP

The protocol follow up will end after the last scheduled follow-up visit of the last randomised participant. Sites will be closed once data cleaning is completed and the database undergone its final lock; the regulatory authorities and ethics committee will be informed of the trial closure as required by local regulations.

7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are the same across all domains of the SMAART-MAP trial and are described in the Safety Reporting section of the Master protocol. Sites will follow national reporting guidelines for notification requirements to national ethics and regulatory bodies.

8 QUALITY ASSURANCE & CONTROL

Details regarding the risk assessment, central monitoring, on-site or remote monitoring, source data and protocol deviations are outlined in the Master protocol.

9 STATISTICAL CONSIDERATIONS

This domain of the SMAART-MAP trial is a parallel arm design comparing outcomes in children that have elevated creatinine and received regularly dosed paracetamol at 15 mg/kg over 72 hours of exposure (last dose at 66 hrs) to those that receive no paracetamol unless they have a temperature >38.5°C in which case they may receive lower dose paracetamol at 10 mg/kg for fever control.

9.1 METHOD OF RANDOMISATION

Randomisation will be stratified by site and presence of blackwater fever. Randomisation lists, using permuted blocks of variable sizes, will be generated and 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.

9.2 OUTCOME MEASURES

9.2.1 EFFICACY OUTCOMES

Primary outcome:

Area under the curve for creatinine levels calculated from measures taken from baseline, 24 hours, 48 hours and 72 hours. If any measurement is missed, e.g. through failure to store a plasma sample then missing data methods will be used (such as multiple imputation). Children who die will have their last value carried forwards. See **Section 9.6** for more detail.

Secondary outcomes:

Renal function domain outcomes:

- 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

SMAART-MAP outcomes:

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

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

Other outcomes:

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.

9.3 SAMPLE SIZE

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.

9.4 ESTIMANDS

The primary estimand for area under the curve for creatinine levels by 72 hours is described in Table 4 below.

Table 4: Estimand

Estimand attribute	Definition
Population	Children with severe malaria and raised creatinine levels that 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 in mean area under the curve from baseline to 72 hours between arms 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

9.5 INTERIM CHECKING & ANALYSES

During the SMAART-MAP trial an independent Data Monitoring Committee would 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. 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.

9.6 ANALYSIS PLAN (BRIEF)

The analyses are described fully in the Statistical Analysis Plan. In brief, the primary analysis for the trial will describe baseline parameters and compare primary and secondary endpoints by trial arm, adjusted for stratification factors. The primary analysis will follow the Estimand described above.

The primary outcome will be analysed using normal linear regression, adjusted for baseline and stratification factors. Analysis of mortality will use time-to-event methods through to day 28 and 90. Readmissions will be analysed using competing risk methods counting death as a competing risk. Changes in AST, ALT and creatinine at each time point will be analysed using normal linear regression, adjusting for baseline and stratification factors. The secondary outcome of children meeting the Risk, Injury and Failure categories from the paediatric RIFLE classification will be analysed using ordered logistic regression. Imputation methods will be used for missing data including imputing the last observation carried forwards for those that have missing creatinine due to death; or using multiple imputation by chained equations at other timepoints for those that have missing values due to issues with samples or abscondment. Measures of creatinine that are not within the window around the 72 hour clinical assessment (+/-3 hours) will be incorporated into sensitivity analyses to account for children discharged prior to 72 hours.

A secondary analysis will be carried out using Bayesian principles given the small sample size, using ACCEPT analyses (Clements, White et al. 2022). This will enable estimation of the probability that one arm is superior to the other, based on a continuous range of efficacy thresholds, and is more powerful than frequentist approaches when sample sizes are small due to the use of priors giving additional information.

10 ANCILLARY STUDIES

There are no planned ancillary studies.

11 REGULATORY & ETHICAL ISSUES

11.1 ETHICAL CONSIDERATIONS

Additional risks to those outlined in the Master protocol.

The trial is being performed in children who may potentially benefit from treatment. No more than 1ml/kg of blood will be drawn for research at any one time (including for plasma storage for creatinine and blood samples for liver function tests). Other blood tests used to determine eligibility of children is the creatinine point-of-care test (I-Stat machine with a CREA or CHEM8+ cartridge) or laboratory test and either only need a pinprick of blood, as does the POC pfHRP2 test for severe malaria which we propose to validate within this trial.

Paracetamol will be given orally in a liquid or through a nasogastric tube. Children may feel some discomfort from the nasogastric tube if they have it inserted, but any tube will be removed when the child is able to drink from a cup.

Paracetamol is a frequently used and common treatment and side effects are very few. It is currently being used in higher doses than standard of care (but at the same doses as proposed in this domain) in a trial in DRC and the independent data safety monitoring committee has had no safety concerns and the trial is continuing (personal correspondence, A Dondorp). Thus, risks from paracetamol at the higher doses are minimal.

Benefits to children in this domain are outlined in the Master protocol

All further detail on regulatory and ethical issues are found in the Master protocol including compliance, other ethical considerations including compensation, competent authority and other approvals and end of trial and comparison closure.

12 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies, which apply to this study. There will be additional site-specific insurance where required.

13 FINANCE

The trial is supported by grant funding from Wellcome, UK (Grant Number 209265/Z/17/Z). The trial will be coordinated by Imperial College. A written agreement with the site principal investigator and/or the investigator's institution and Imperial College will outline the funding arrangements to sites. The TSC will meet and review the financial aspects of the trial at least 12-monthly and report to the sponsor. Terms of reference will be developed for this activity.

14 OVERSIGHT & TRIAL COMMITTEES

All oversight and trial committees will oversee all domains of the SMAART-MAP trial. These committees and the relationship between them are described in detail in the Master Protocol.

15 PUBLICATION AND DISSEMINATION OF RESULTS

Details on publication and dissemination of results can be found in the Master protocol as these will be the same across all domains of the SMAART-MAP trial.

16 DATA AND/OR SAMPLE SHARING

Details on data sharing are outlined in the SMAART-MAP Master protocol.

17 PROTOCOL AMENDMENTS

Protocol	Date	Amendments to protocol
1.01	11th January 2024	Added ISRCTN number and updated investigator details
1.02	9th February 2024	Updated investigator details
1.1	22nd April 2024	• Correction of doses in Section 5.2 • Addition of SMAART-MAP exclusion criteria of prior enrolment • Addition of weight-for-height z-score for children between 3-6 months for exclusion due to severe malnutrition • Co-enrolment restricted to observational studies only (section 4.2) • Addition of a sentence in Section 7 to highlight reporting to ethics and regulatory bodies to follow guidelines. • Addition of POC haemoglobin test and malaria RDT at day 28 and day 90 visits.
1.2	8th May 2024	• Further correction of doses • Addition of total blood draw across the whole study in schedule of assessment table • Addition of consent process into schedule of assessment table • Addition of further detail about analysing creatinine from those discharged prior to 72 hrs • Further detail on clinical stopping criteria given in Section 5.
1.3	5th June 2024	• Further correction of doses • Addition of exclusion criteria for known history of hepatic or renal impairment

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