SMAART

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

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Protocol authorised by

Name & Role	Date	Signature
Kathryn Maitland	**10th October 2022**	

Study Management Group Chief

Investigator: Kathryn Maitland

Co-investigators: See below

Statistician: Professor Sarah Walker

Study Management: Emmanuel Oguda

Study Coordination Centre

Study Coordination Centre: Clinical Trials Facility
Please direct all queries to the SMAART Administrator at KEMRI Wellcome Trust Programme
Phyles Maitha; PMaitha@kemri-wellcome.org Tel: +254715461761

Clinical Queries
In the first instance, all clinical queries should be passed **to Emmanuel Oguda** (EOguda@kemri-wellcome.org), Tel: +254726957045 at KEMRI Wellcome Trust Programme who will consult others members of the Clinical Management Group where necessary.

Sponsor

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

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This protocol describes the SMAART observational study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles of Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, the UK Data Protection Act 2018 and other regulatory requirements as appropriate.

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	Tel: Mobile: Email:	+254 417 525453 (switchboard) +254 726957045 EOguda@kemri-wellcome.org
Data Manager:	Christabel Mogaka	Tel: Email:	+254715811661 CMogaka@kemri-wellcome.org
KILIFI: CLINICAL GROUP			
Lead Investigator	Dr Mainga Hamaluba	Mobile: Email:	+254 795 320422 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

NAIROBI: EPIDEMIOLOGY GROUP			
Lead Investigator	Professor Robert W Snow PhD	Mobile: Email:	+254 722 523323 rsnow@kemri-wellcome.org
Coinvestigators	Dr Samuel Akech PhD MMed	Mobile: Email:	+254 721 339090 SAkech@kemri-wellcome.org

Epidemiologist	TBA	Mobile: Email:	

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.co.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:	Prof Ann Sarah Walker PhD MSc	Tel: Email:	+44 207 670 4726 rmjlasw@ucl.ac.uk
Statistician:	Dr Elizabeth George PhD MSc	Tel: Email:	+44 207 670 4931 elizabeth.george@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	Tel: Email:	+66 818 015675 arjen@tropmedres.ac
Data Manager:	Naomi Waithera, MSc	Tel: 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			
Cheif Investigator:	Prof Peter Olupot Olupot MBChB, MPH	Tel: Mobile: Fax: Email:	+256 77 2457217 +256 77 2457217 + 256 45 4435894 polupotolupot@yahoo.com
Soroti Regional Hospital, P.O Box 289, Soroti, Uganda			
Site Investigator:	Dr Florence Aloroker MBChB, MMed	Tel: Mobile: Email:	+256 45 4461382
Study Site Coordinator:	Denis Amorut	Tel: Mobile: Fax: Email:	+256 45 4461382 +256 77 4573911 +256 45 4461382 damoruts@gmail.com

Kalongo Hospital, Agago District, Northern Uganda			
Principal investigator:	Dr Okao Maurice MD, MMED Paediatrics	Tel: Email:	+ 256 779066157 maurice.okao@gmail.com
Co-investigator:	TBA	Tel: Email:	+

MOZAMBIQUE:
Manhica Health Research Centre (CISM) PO BOX 1929 Manhica,

Co Lead investigator:	Dr Pedro Aide	Tel: Email:	+258 2181 0181 pedro.aide@manhica.net
Co-Lead investigator::	Professor Quique Bassat	Tel: Email:	 quique.bassat@isglobal.org

GHANA:			
School of Medical Sciences (SMS), Department of Child Health, Kwame Nkrumah University of Science and Technology, Kumasi			
Principal investigator:	Professor Daniel Ansong	Tel: Email:	+233 208 168767 dansong@kathhsp.org
Co-investigator:	Prof Tsiri Agbenyega	Tel: Email:	+233 208 113848 tsiri@ghana.com
Co-investigator	Dr Justice Sylverken	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 Nchelenge Hospital, Luapula Province, Zambia			
Principal Investigator:	Dr Mike Chaponda	Tel: Email:	+260 212 620737 mikechaponda@yahoo.com
Co-investigator:	Dr Sam Miti	Tel: Email:	+260 212 620737 drsammiti@gmail.com
Co-investigator	Dr Luc Kambale Kamavu	Tel: Email:	nespluckam@yahoo.fr

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GLOSSARY OF ABBREVIATIONS

ACT	Antimalarial Combination Therapy
AQUAMAT	Artesunate versus Quinine in the treatment of severe falciparum malaria in African children Trial
CI	Confidence interval
CRP	C-reactive protein
FEAST	Fluid Expansion as A supportive Therapy
MRC	Medical Research Council
pfHRP2	*Plasmodium falciparum* histidine-rich protein2
PCT	Procalcitonin
POC	Point-of-care
RDT	Rapid Diagnostic Test
SMAC	Severe Malaria in African Children
SMAART	Severe Malaria in African Children A Research and Trials Consortium
SMG	Study Management Group
TRACT	TRansfusion and Treatment strategies of severe Anaemia in African children Trial
WHO	World Health Organization

KEYWORDS
Severe malaria, child, Africa, epidemiology

STUDY SUMMARY

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

DESIGN Prospective observational study

AIMS The primary aim is to characterise the contemporary epidemiology (including features at presentation, diagnostic and treatment pathway) of severe malaria presenting to hospital for admission in children in Africa, through conducting a prospective multicentre observational study across at least 6 sites in 5 countries enrolling two cohorts (i) hospitalised children with severe malaria (cases): 300 per site and (ii) time-matched hospitalised children with non-severe malaria (controls): 100 per site. Both cohorts will be followed over 6 months from admission. In addition, basic observation and in-hospital outcome data will be collected from all other children admitted with non-severe malaria ('background').

Secondary aims are to

- Compare baseline characteristics of admitted children with severe and non-severe malaria
- Characterise time from presentation to the hospital 'gateway' to ward admission and time to first dose of parenteral artesunate to assess whether delays in definitive treatment may underpin malaria severity
- Estimate the incidence of significant post-discharge events to day-180 including readmission
- Evaluate (in years 2 and 3) a point-of-care *quantitativ*e plasma *Plasmodium falciparum* histidine-rich protein2 (pfHRP2) test for estimating total body parasite burden, which could be used to swiftly identify those at greatest risk of poor outcomes.

OUTCOME MEASURES The primary research question relates to characterisation of severe malaria at hospital admission. Main longitudinal outcome measures in severe malaria cases and non-severe admitted malaria controls, whose rates will be estimated and key prognostic factors identified, are

- Mortality: in-hospital or subsequently through 6 months post-discharge (all-cause)
- Re-admission to hospital in 6 months, all-cause and with a positive malaria rapid diagnostic test (RDT)
- New episodes of potential malaria, defined by self-reported anti-malarial use, self-reported positive RDT, and self-reported febrile illnesses at follow up.

POPULATION

Inclusion criteria for admitted severe malaria cases, admitted non-severe malarial controls and admitted non-severe background malaria

1. Children aged 3 month to 15 years
2. Admitted to hospital with *P. falciparum* malaria defined by a positive Paracheck™ rapid diagnostic test
3. History of fever by self-report or documented abnormal temperature at screening (fever or hypothermia, axillary temperature >37.5°C or <36°C)

4. Caregiver provides written informed consent, including for 6-month follow-up for severe malaria cases and non-severe malaria controls (defined above)

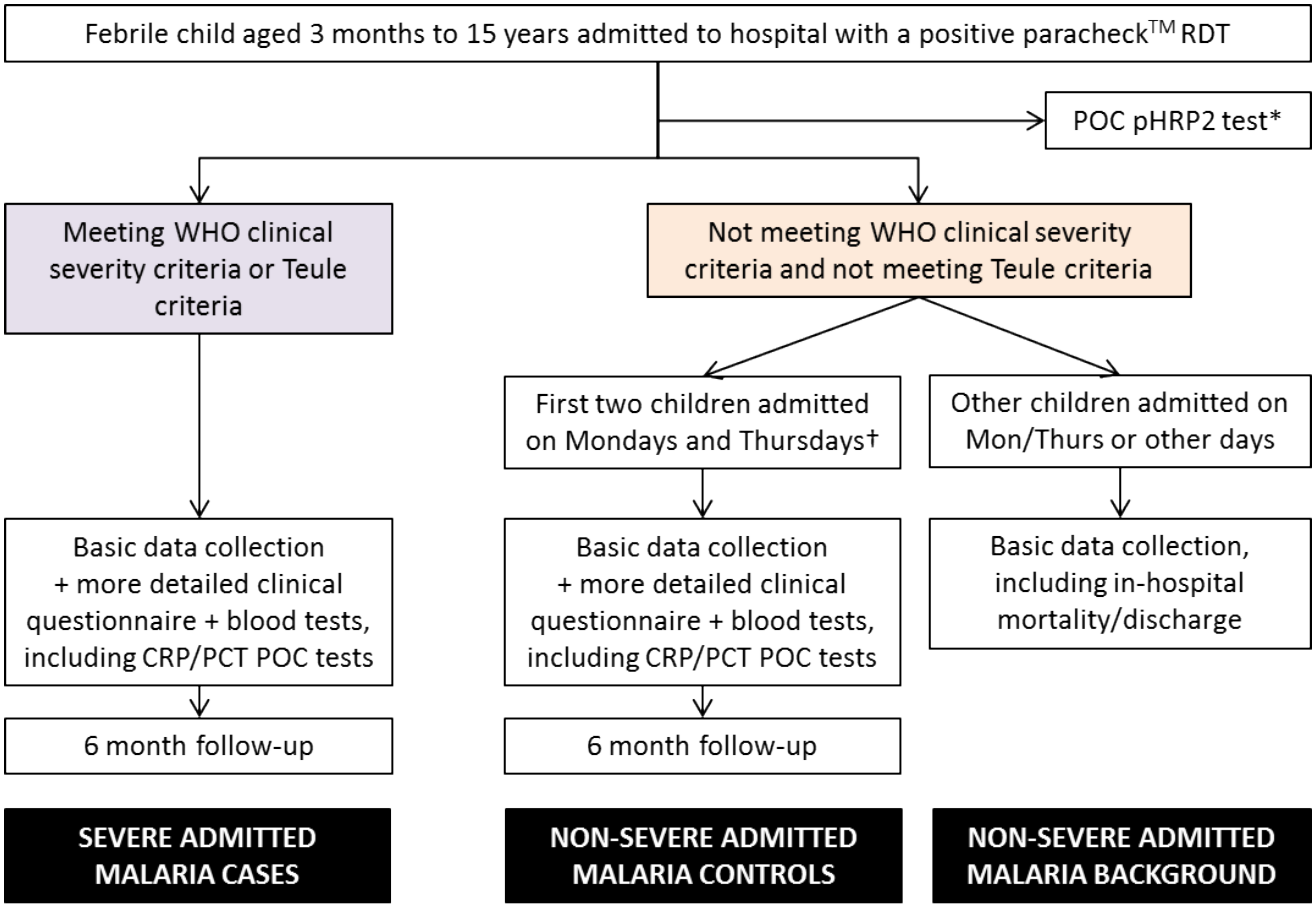
ELIGIBILITY

Cases are defined as eligible children meeting WHO Group 1 and 2 clinical severity criteria or Teule criteria including additional laboratory criteria (haemoglobin <5g/dl or identified HIV).

Controls are children meeting inclusion criteria who are admitted to hospital but have none of the clinical or laboratory severity features (consented for post-discharge follow-up) as are non-severe background (in-hospital data only).

DURATION 3 years

REFERENCE DIAGRAM



* Initially qualitative: in the second year (or as soon as this is available) the POC PfHRP2 test will be quantitative in order to refine malaria severity assessment

† Goal is to recruit 1:3 non-severe to severe admitted cases during the time periods when severe cases are being enrolled , so numbers may be fewer at some times

Note: CRP: C-reactive protein, PCT: procalcitonin; POC: Point of Care, RDT: Rapid Diagnostic Test.

NOTE This is the multisite observational study protocol for SMAART detailing the study, which will be termed the 'international protocol'. As there are centre/site-specific formatting requirements and/or local additional elements to the study eg such as age range considered for paediatric ward admission; blood sample draw volume or storage of blood samples, these will be included an site-specific addendums which mirror the main protocol and include any additional elements.

1. INTRODUCTION

1.1 BACKGROUND

Malaria control: current status

Over the last decade there has been an unprecedented rise in funding for malaria control activities, including the scale-up of long-lasting insecticide-treated bed-nets and the widespread introduction of and improved access to effective artemisinin-combination treatments (ACT). This has resulted in the disease retreating from large parts of the world. Nevertheless, malaria remains stubbornly unyielding in sub-Saharan Africa and in some parts of Asia. Today, 57% of Africans live in areas with moderate to high malaria transmission, with ten countries accounting for 87% of people exposed to the highest malaria transmission intensities globally[1]. The emergence and spread in many parts of Africa of mosquito resistance to all classes of insecticides threatens the effectiveness of these control measures, particularly because there are currently no readily available alternatives to insecticides. The emergence of artemisinin-resistance in Southeast Asia, emanating from the border areas between Thailand and Cambodia, is a major global concern[2]. Finally, a highly effective malaria vaccine remains a long way off. Early optimism that the most promising malaria vaccine candidate developed to date (RTS,S) would reduce the burden of severe and fatal malaria has proved premature, with the most recent publication of long term follow up data (to 48 months) reporting waning vaccine efficacy and showing increased risk of severe malaria from 20 months following vaccination[3].

Malaria in African children

In much of sub-Saharan Africa malaria remains the commonest cause of hospital admission and continues to play a substantial role in under 5-year mortality[4, 5]. 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 [6, 7]. 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[8-11]. Despite implementation of fast-acting and currently effective ACTs, in-patient mortality for severe malaria (excluding children who have incidental hyperparasitaemia without other features) remains unacceptably high (~10%), and is unlikely to improve without wider implementation of pre-referral artemisinin[12] and better supportive treatments[13-15]. Clinical trials investigating the safety and efficacy of adjuvant supportive therapies could close existing gaps in the severe malaria treatment algorithm and substantially improve outcomes. Yet, the current research model has severely limited the speed of advances in supportive management of severe malaria[15].

The need for a new severe malaria network

There is **no current platform** that brings together, across Africa, the expertise and resources to address the challenge of severe malaria within a distinct network. Previous work in this area relied predominantly on single-centre, investigator-led research, targeting specific subgroups of patients, enrolling small numbers and/or investigating mono-therapies [13, 14]. Only three large multicentre Phase III trials have assessed mortality as

the primary endpoint, including trials exclusively enrolling children with severe malaria investigating parenteral antimalarials (AQUAMAT[16]) and trials including large subgroups with malaria investigating supportive treatments (FEAST[17] and TRACT[18, 19]), testing fluid resuscitation and transfusion strategies respectively). The NIH-funded Severe Malaria in African Children (SMAC) consortium (AI-45955) ran from 1999 to 2011 in 5 sites, and focused largely on standardising data collection and describing prognostic features. SMAC conducted only one Phase III trial, with 24-hour parasite clearance as the primary outcome[20] . Research activities and networks in HIV in Africa have led to dramatically improved outcomes for HIV-infected children; in contrast, early investment in severe malaria in the 1990s has not been sustained. Thus, progress in understanding the pathogenesis of severe malaria and developing evidence-based treatment for its complications has evolved very slowly. The SMAART consortium, funded by a Wellcome Collaborative Grant in Science brings together a multidisciplinary group of scientists encompassing decades of clinical and academic experience, with track records of successful high quality research in low-income settings in severe malaria, from three Wellcome Trust major overseas programmes (KEMRI Wellcome Trust Programme, Kenya; 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, Zambia and Ghana).

Changing severe malaria epidemiology?

At the inception meeting of the consortium we reviewed epidemiological data on severe malaria and emerging summary data from each African site and from clinical trials (including AQUAMAT, FEAST). It became clear that the current understanding of the clinical spectrum of severe disease, largely based on work from the early 1990s, urgently needs updating. There has been a change in the clinical spectrum of severe malaria: children now present at an older age than 10 years ago[8, 11], have more ‘adult-type’ complications (e.g. acute kidney injury)[21], and blackwater fever has emerged as an important complication[22]. In addition, for children presenting to health facilities with severe and complicated malaria, there were indications of delays at triage resulting in a prolonged time to receiving a definitive parenteral antimalarial. Pre-referral use of artemisinin (recommended by WHO) does not appear to be happening in practice.

Development of Artesunate Resistance

In 2009 artemisinin resistance in falciparum malaria, characterized by a slower parasites clearance, was first identified on the Thai-Cambodian border and since then has spread throughout Southeast-Asia[23]. Artemisinin resistance facilitated the selection of partner drug resistance, resulting in high failure rates of ACTs.[24] Recently, artemisinin resistance emerged independently in sub-Saharan Africa, which harbours over 95% of the world’s falciparum malaria.[25-28]. The independent emergence of artemisinin resistance in Uganda and Rwanda, has major consequences for ACT efficacy, as yet unquantified, in the short reports. As artemisinins are the current first line treatment for severe malaria, dues to their rapid action on clearing all-stages of *Plasmodium falciparum. It is unknown at present whether* any delays in parasite clearence leads to a worse outcome in severe malaria treated with artesunate. Answering this question is crucial as even a small

reduction in treatment efficacy could increase malaria attributable mortality and morbidity significantly

Clinical Identification

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. For example, WHO definitions of severe malaria are very broad, incorporating high parasitaemia as a single criterion, and are thus applicable to a large proportion of paediatric admissions in such regions, with a relatively overall low case fatality (1-2%)[20]. Existing or novel supportive treatments could be targeted, and/or clinical trial entry criteria improved, by refining these criteria so that high risk groups (rather than all children) can be identified.

Teule Criteria

This is one good example of criteria to identify children at high risk of bacterial co-infection[29] A study conducted in Teule hospital, Tanzania investigated whether clinical criteria could identify the children with severe malaria and invasive bacterial infection. Those meeting '**Teule' criteria**[30], that is, with malaria (positive blood film or ParacheckTM rapid diagnostic test (RDT)), temperature > 38^0C or < 36^0C and ≥1 of prostration, respiratory distress, haemoglobin <5g/dl or HIV had 85% of the bacterial co-infections that were identified from microbiological testing, and had a 3-fold higher mortality than children admitted with malaria without these criteria.

Finally, children recovering from severe malaria, particularly severe malarial anaemia [18] and blackwater fever, frequently relapse, are readmitted or die in the 6 months following admission. The burden and public health implications of these observations across the entire diagnostic and treatment pathway remains largely undocumented and therefore overlooked as potential modifiable factors contributing to unsatisfactory immediate and long-term outcomes. Pre- and peri-referral (triage) care may crucially impact on immediate outcomes, whereas targeting the most vulnerable children with preventive measures or supportive care represents a pragmatic strategy to avert post-discharge morbidity and mortality.

Identifying high risk groups

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:

i) A quantitative plasma *Plasmodium falciparum* histidine-rich protein2 (pfHRP2) test, which estimates total body parasite burden, might accurately identify children with, or at risk of progressing to, severe malaria from those with incidental parasitaemia [31]

ii) Existing POC lactate tests might be able to identify those with microcirculatory dysfunction secondary to sequestration which may be amenable to targeted adjunctive therapies.

iii) C-reactive protein (CRP) and procalcitonin POC tests might identify severe malaria and bacterial co-infection[29], a critically important subgroup in terms of both outcomes and tailoring antibiotic treatment to reduce the potential for antimicrobial resistance.

Current management recommendations

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[14]. Of critical importance is 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[32]. The lack of clinical trial data are stark; even at times when over a million African children were dying annually from malaria (before year 2000), only 33 clinical trials of adjunctive (supportive) were conducted in children globally since 1980 [33] with none showing benefit [14]. Over 60% 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[34] and fluid boluses for shock[17].

A search of the clinical trial registration sites Trials.gov and ISCTRN for planned or on-going trials in severe malaria (November 2018) identified only one Phase III trial - a multicentre trial of blood transfusion strategies for severe anaemia (TRACT: ISRCTN 84086586)[35] involving several SMAART consortium members which has just reported in 2019 [19, 20]. We concluded that there was little prospect for further reducing the substantial mortality burden from severe malaria within the foreseeable future based on currently ongoing research.

Assessment of key targets for future trials

The investigators also considered both high priority risk factors (Table 1) and missed opportunities to improve short and long-term outcomes. The group identified several high-priority interventions which could be tested in 'proof-of-principle' Phase II trials, covering healthcare systems, targeted treatment and complications with high mortality, with primary endpoints based on mechanisms of action. However, major gaps in our knowledge of the spectrum still remain and observational research, as proposed in this protocol, will inform the design of these future Phase II trials.

Separate protocols will be submitted for these Phase II trials, which will be conducted in 2-3 years' time; of note, four of these proposed trials will require initial Phase I trials (also submitted as separate protocols) to inform safety and/or dosages (sevuparin, paracetamol and azithromycin) or to operationalise a protocol (the use of a non-invasive respiratory support in cerebral malaria) in some of the same sites as recruiting into this observational study.

Table 1 High priority risk admission features and complications of malaria, and their consequences

Admission feature or complication	**Frequency**	**AQUAMAT in-hospital Mortality* (Artesunate-arm)**	
Coma	32-35%	18%	
Metabolic acidosis (base excess<-8 or lactate>5mmol/L)	43-44%	15%	
Renal impairment (Urea/BUN > 20 mmol/L)	24%	22%	
Hypoglycaemia (blood glucose <3 mmol/L)	10%	15% (DOI 10.1186/1471-2334-10-334)	
Convulsions	30-32%	14%	
Invasive bacterial co-infection	5.5%	24% (DOI: 10.1186/1741-7015-12-31)	
Blackwater Fever (region specific)	14-21%	Day-28 mortality 12% (DOI:10.1093/cid/cix003)	
Recent or ongoing trials	**Frequency**	**Mortality**	**Trial:** results expected
Shock (mortality = no-bolus arm)	12%	8.5%	**FEAST:** 10.1056/NEJMoa1101549
Severe anaemia	29-30%	10%	**TRACT:** July 2018 ISRCTN84086586
Hypoxaemia (<90%)	15%-17%	14%-30%	**COAST:** Late 2020 ISRCTN15622505

* Data from AQUAMAT unless indicated where mortality figures are for quinine-treated children

RATIONALE FOR CURRENT OBSERVATIONAL STUDY

Admissions to hospitals serve as secular, temporal and spatial barometers of disease burden among populations they serve. Our current understanding of the spectrum and burden of severe malaria in children across the African continent is poor, so there is a clear need for updated epidemiological data in order to provide more accurate estimates of the contemporary spectrum of severe malaria across the enormously diverse malaria ecologies that characterise Africa and whether this has changed over time. To understand the current severe malaria burden and phenotypes, the SMAART consortium will conduct a multicentre observational study with the aim of recruiting all children admitted with severe malaria over up to three seasons in 6 sites in 5 countries (300 severe malaria cases per site), together with a representative group of time-matched non-severe malaria controls also admitted to hospital. This new platform will facilitate faster multi-site clinical investigation, epidemiological modelling and investigate the overlap with putative sepsis and other severe diseases that co-exist with malaria. These will help inform and focus the design of future Phase II and Phase III clinical trials.

Main research Question

What is the epidemiology (including features at presentation and the diagnostic and treatment pathway) of severe malaria presenting to hospital for admission in children in Africa today?

We hypothesize that there will be differences in the severity spectrum at the 6 sites across 5 countries, that the median age of presentation of paediatric severe malaria is older than historic descriptions and that children will more frequently present with complications that are more typical of the adult form of severe malaria due to the decline in malaria transmission intensity over the last 2 decades.

2. STUDY CENTRES

6 hospitals in 5 countries will participate:

- **Uganda:** Soroti Regional Referral Hospital/ and Kalongo Hospital, Agago District
- **Kenya:** Kilifi County Hospital/KEMRI Wellcome Trust Research Programme
- **Mozambique :** Manhica Health Research Centre (CISM),
- **Ghana** Kwame Nkrumah University Hospital, Kumasi/ School of Medical Sciences (SMS)
- **Zambia** Nchelenge Hospital, Luapula Province, Zambia/ Tropical Diseases Research (TDR) Centre, Ndola

3. STUDY OBJECTIVES

Primary Objective

To characterise the contemporary epidemiology (including features at presentation and the diagnostic and treatment pathway) of severe malaria presenting to hospital for admission in children in Africa, through conducting a prospective multicentre observational study across at least 6 sites in 5 countries, enrolling two cohorts of hospitalised children (i.e. stratified) with severe and non-severe malaria (Figure 1)

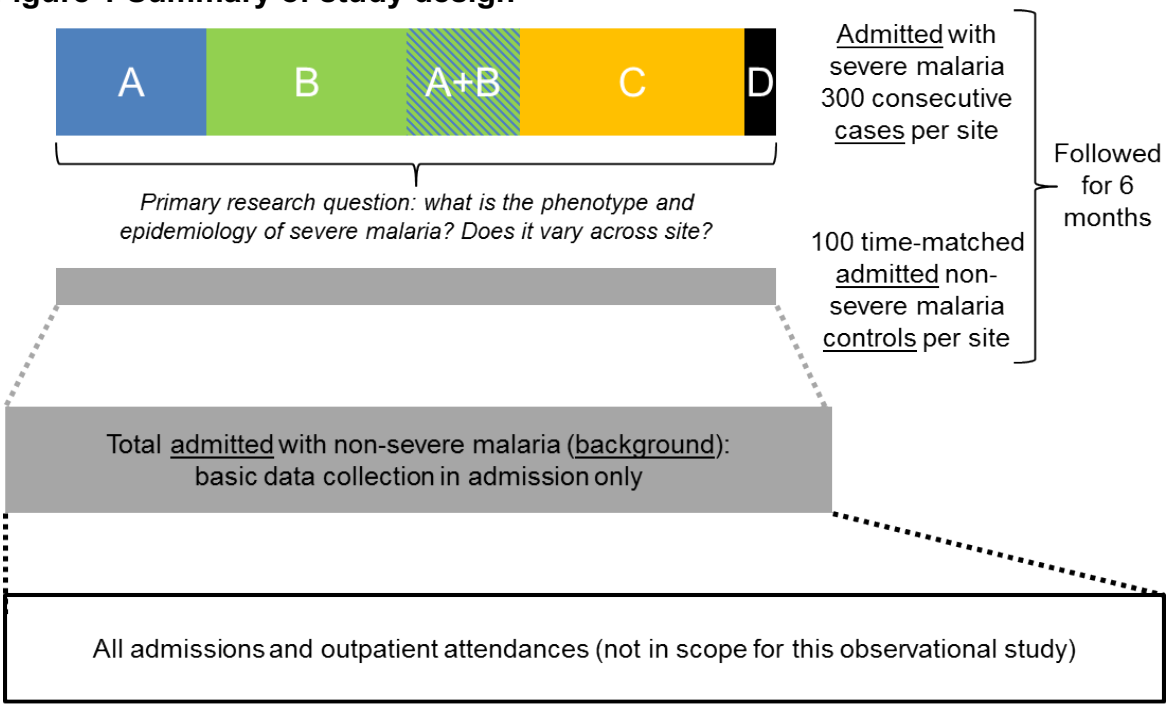
For this study, severe malaria will be defined as children meeting WHO criteria or Teule criteria [25], see section 4 below. For severe malaria, we will characterise the proportions presenting with different severe complications (denoted 'A', 'B', etc in Figure 1 below), or combination of any of or all of these, and compare these proportions across sites.

Secondary Objectives

i. To compare baseline characteristics of admitted children with severe and non-severe malaria.
ii. To document time from presentation to the hospital 'gateway' (e.g. outpatients or emergency/triage centre) to ward admission and time to first dose of parenteral artesunate to assess whether delays in initiating definitive antimalarial treatment could contribute to malaria severity.
iii. To estimate the incidence of significant post-discharge events to day-180 including readmission (all-cause and for malaria (i.e. relapse)) and all-cause mortality in severe and non-severe malaria.
iv. To develop (year 1) and evaluate (years 2 and 3) a point-of-care *quantitativ*e plasma *Plasmodium falciparum* histidine-rich protein2 (pfHRP2) test for estimating total body parasite burden, which could be used to swiftly identify those at greatest risk of poor outcomes.

The multisite observational study will become the platform for future Phase II trials.

Figure 1 Summary of study design



Note: A, B, C, D etc represent the different complications of severe malaria, e.g. cerebral malaria, blackwater fever, bacterial co-infection etc

4. STUDY DESIGN

A prospective multicentre observational study in each of 6 sites over 2-3 years recruiting the first 300 children per site admitted to hospital meeting WHO clinical signs of severe malaria and/or Teule criteria (severe malaria cases) and 100 time-matched children per site admitted to hospital with malaria without signs of severity (non-severe malaria controls). The aim is to recruit one-third the number of non-severe malaria controls to severe malaria cases over periods in the year when children are presenting with severe malaria (to account for seasonality). For practicality, and to reduce potential bias, we would focus recruitment of controls on Mondays and Thursdays, see below). These cases and controls would be followed for 6 months from first admission and recruitment into the cohort. Recruitment would stop in each site once the 300 severe cases had been enrolled.

These epidemiological data will provide multi-site prevalence estimates of different presentations of severe malaria (Figure 1), to assess the relative importance of the different potential interventions tested in future Phase II trials, and of current standard-of-care relating to use of antibiotics and other medications in severe malaria. They will also provide a quantitative assessment of differences in delays in presentation to triage and use of pre-referral artesunate in admitted children with severe versus non-severe malaria, hence the potential for interventions targeting these two components to improve outcomes.

In addition to cases and controls, we will collect basic in-hospital data on other non-severe malaria cases admitted to hospital on different days of the week (i.e. not Monday and Thursday). These children would have limited data collected on presenting characteristics (non-severe malaria 'background'), with no follow-up data collection. See

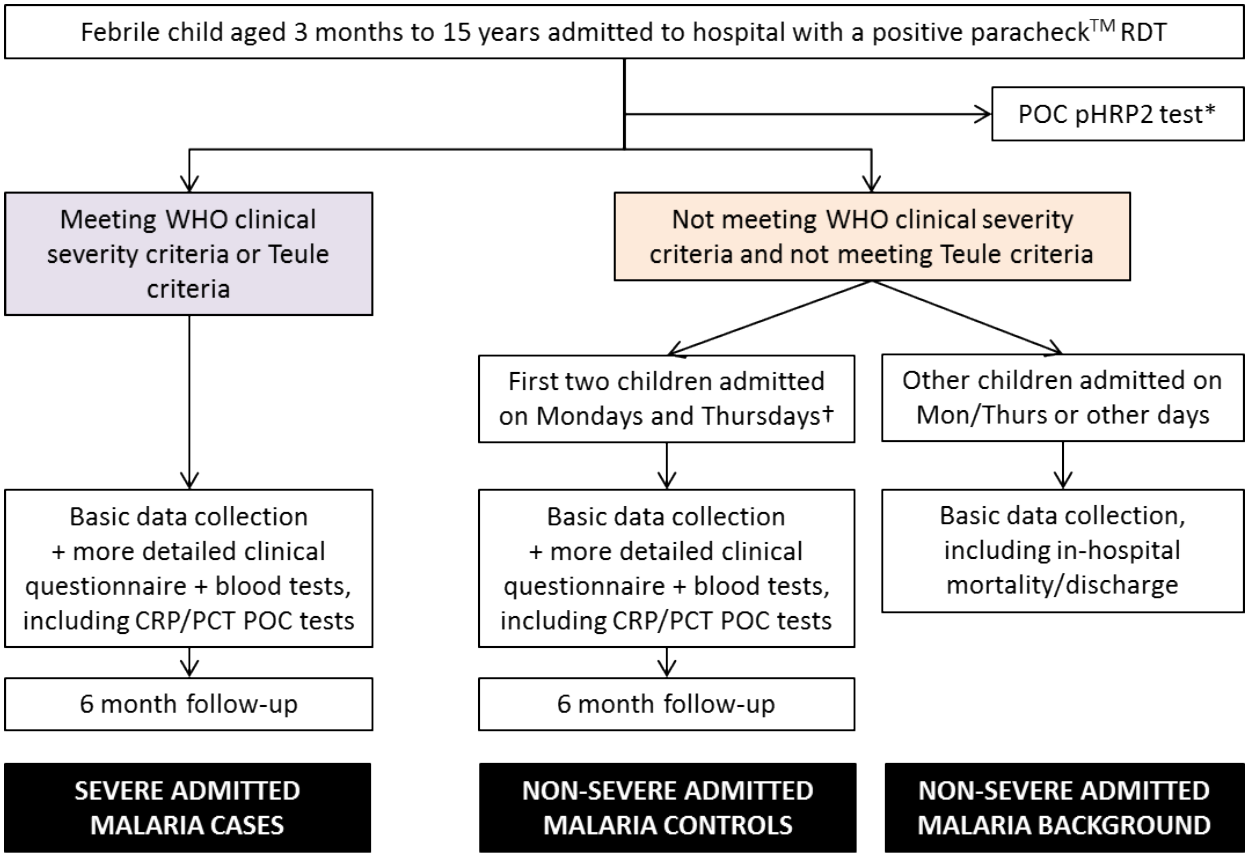
Figure 1 and Figure 2. In some centres collection of this basic in-hospital data is covered by general active surveillance activities; so may not need a dedicated consent to collect basic data including RDT.

4.1 STUDY OUTCOME MEASURES (CASES AND CONTROLS)

The primary research question relates to characterisation of severe malaria at hospital admission. Main longitudinal outcome measures in severe malaria cases and non-severe admitted malaria controls, whose rates will be estimated and key prognostic factors identified, are

- Mortality: in-hospital or subsequently through 6 months post-discharge (all-cause)
- Re-admission to hospital in 6 months, all-cause and with a positive malaria RDT
- New episodes of potential malaria, defined by self-reported anti-malarial use, self-reported positive RDT, and self-reported febrile illnesses at follow up.\

Figure 2 Study flow diagram



* Initially qualitative: in the second year (or as soon as this is available) the POC PfHRP2 test will be quantitative in order to refine malaria severity assessment

† Goal is to recruit 1:3 non-severe to severe admitted cases during the time periods when severe cases are being enrolled , so numbers may be fewer at some times

Note: CRP: C-reactive protein, PCT: procalcitonin; POC: Point of Care, RDT: Rapid Diagnostic Test.

5. PARTICIPANT ENTRY

5.1 INCLUSION CRITERIA

i) Children aged between 3 months and up to 15 years
ii) Admitted to the paediatric hospital ward with *P. falciparum* malaria defined by a positive Paracheck™ rapid diagnostic test
iii) History of fever by self-report or documented abnormal temperature at screening (fever or hypothermia (axillary temperature >37.5°C or <36°C)
iv) Caregiver provides written informed consent, including for 6-month follow-up for severe malaria cases and non-severe malaria controls (defined below)

The target population is children who are admitted to the paediatric ward of the participating hospital. Inclusion criteria allow for children up to 15 years of age to be included because the age for admission to the paediatric wards varies from site to site. Children only given antimalarials at the outpatient department are a group of less unwell patients whose specific characteristics will depend strongly on the local context, particularly number and location of lower level health centres in the area. Including this outpatient group in this observational study would therefore create an unquantifiable degree of dilution bias, and therefore they are not eligible following the criteria above and will not be included. In contrast, children who

are sick enough to be admitted to hospital are a defined population which is more generalizable across different hospitals and in whom future interventional trials could provide improvements in patient management.

Eligible children will be recruited into three cohorts, with different amounts of baseline and follow-up data collection (see section 6).

1. **Severe (admitted) malaria cases** who meet current WHO clinical severity criteria or laboratory severity criteria (where these tests are done routinely) (Group 1 and 2 from the recent reclassification of severe malaria (Table 2) (page 10 from reference [32]) and/or Teule criteria at admission, specifically (in a child with a positive *P. falciparum* malaria test)

   - **WHO clinical criteria, consisting of one or more of**
     - Impaired consciousness: prostration (also Teule criteria) or coma
     - 2 or more convulsions within the last 24 hours
     - Respiratory distress (also Teule criteria)
     - 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 (in a child with a positive *P. falciparum* malaria on RDT)
     - Dark or cola coloured urine (blackwater fever)
   - **WHO laboratory criteria**, consisting of
     - Haemoglobin <5g/dl (also Teule criteria) (if routinely done)
   - **Teule criteria:** consisting of one or more of
     - HIV (standard test for all hospitalised children)
     - Impaired consciousness: prostration or coma (also WHO clinical criteria)
     - Respiratory distress (also WHO clinical criteria)
     - Haemoglobin <5g/dl (if routinely done) (also WHO clinical criteria)

   Teule criteria formally require a temperature >38°C OR <36°C in addition to ≥1 of the clinical signs marked above; however as these clinical criteria alone define WHO severe malaria, for simplicity of enrolment, and given that the prevalence of HIV infection is expected to be <5%, **this temperature criterion will not be required in severe malaria cases for this observational study**. These Teule criteria have previously been shown to identify 85% of children with malaria and bacterial co-infections[30]. The reason for requiring a specific set of clinical/laboratory criteria for enrolment as a severe malaria case, rather than relying on physician judgement alone, is to provide an objective standardisation of the underlying severe population across sites.

Table 2 WHO severe malaria definition

Table 2 Outline bedside clinical classification of severe malaria in children in a high transmission area

Group 1	Prostrate children (prostration is the inability to sit upright in a child normally able to do so or to drink in the case children too young to sit). Three subgroups of increasing severity should be distinguished: Prostrate but fully conscious Prostrate with impaired consciousness but not in deep coma Coma (the inability to localise a painful stimulus) Respiratory distress (acidotic breathing): Mild – sustained nasal flaring and/or mild intercostal indrawing (recession) Severe – the presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing Shock compensated or decompensated (see definition above)
Group 2	Children who, although able to be treated with oral antimalarials, require supervised management because of the ri of clinical deterioration but who show none of the features of group 1 (above)*. These include children with any c following: Haemoglobin <5 g/dl or haematocrit < 15% 2 or more convulsions within a 24-h period Haemoglobinuria (blackwater) Jaundice
Group 3	Children who require parenteral treatment because of persistent vomiting but who lack any specific clinical or labor features of groups 1 or 2 (above)

*If parasite counts are immediately available, a parasitaemia over 10% should be included in group 2.

2. **Non-severe admitted malaria controls** are eligible children who do not meet any of the severity criteria above at admission. They will be the first eligible children admitted on Mondays and Thursdays, aiming to recruit approximately one-third the number of non-severe malaria controls as severe cases throughout recruitment to provide approximate time-matching. The reason for recruiting children as non-severe admitted controls on two days only (Mondays/Thursdays) is to balance workload, given the number of controls that will be characterised in detail within this study is only 100 per site (compared with 300 severe malaria cases per site), whilst ensuring approximate representativeness.

3. **Non-severe admitted malaria background** will be **all other eligible children** admitted (other children admitted on Mondays/Thursdays and children admitted on days other than Monday and Thursday) and not meeting any of the severity criteria above. (*In some centres with active surveillance, data collection in non-severe admitted malaria is already covered by general surveillance, and additional consent/approvals are not needed*.) This group of children is essential in order to estimate the overall burden of different severe malaria phenotypes as a percentage of malaria admissions overall, not just as a percentage of severe cases, and to estimate the importance of different baseline factors to good outcomes. This will be done by relating the representative subset of admitted non-severe malaria controls to this larger group of children with non-severe malaria admitted to the paediatric ward in statistical models.

All children with severe and non-severe malaria eligible for this study will be admitted to the paediatric ward, rather than being managed only as outpatients. Children managed only as outpatients are not eligible, see section 5.1 above.

5.2 EXCLUSION CRITERIA

i. Already enrolled into a clinical trial.
ii. Previously enrolled in this observational study

Children who have previously been enrolled into this observational study should in general not be co-enrolled into other clinical trials during their period of follow up. However, this may be discussed with the Study Management Group (SMG).

Severity criteria are applied <u>at the point of admission</u>: any child who has non-severe malaria at admission (control or background) but subsequently develops severity signs will have this recorded, but <u>should not then be re-recruited as a severe case</u>.

The recruitment is non-competitive between sites i.e. once all 300 cases and 100 controls are recruited then the study will not enrol anymore children at that site.

6. ASSESSMENT AND FOLLOW-UP

This is an observational study so there will be no change to the pathway by which children presenting at the hospital 'gateway' are tested for malaria (either blood film or malaria RDT) and no changes to how they make their way to the paediatric ward. Assessment for the study starts at the timepoint that a RDT-positive child is identified when they reach the paediatric ward.

Table 3 Schedule of assessments

	Arrival at 'gateway'	Admission at ward	Dis-charge	Day-28	Day-180
All febrile children aged 3m-15y					
RDT	(X)	(X)			
RDT-positive febrile children aged 3m-15y					
Assessment of severity		X			
Relevant patient information sheet and consent		X			
Basic data collection		X	X		
POC test for quantitative pHRP2* (finger prick)		X			
Malaria slide (taken at either the outpatient department or ward)	(X)	X			
Urine (for DipStick)		X			
Severe malaria cases and non-severe malaria controls					
Extended data collection		X			
Full blood count		X			
Istat: haemoglobin, lactate, blood urea nitrogen (BUN), glucose, and base excess		X			
POC tests for CRP, procalcitonin		X			
Urine (for DipStick)		X			
Ascertainment of anti-malarials, antibiotics, anti-pyretics, transfusions received			X	X	X

Vital status			X	X	X
Weight, height, middle-upper-arm circumference, head circumference, basic observations			X	X	X
Ascertainment of readmissions, potential malaria episodes				X	X
Malaria slide and RDT				X	X
Plasma sample for PfHRP2 assessment/quality control		X			
Soroti and Kalongo Hospital Only:					
[$] Stored sample for genotyping		X			
[$]Parasite clearance and lactate clearance (finger prick)		X			
Max blood draw (see section below)		7ml (9ml)[$]			

(X) indicates following usual practice in the site.

* when available (years 2-3): separate consent will be sought for this, which may be refused.

[$] Soroti and Kalongo Hospitals only to access Artesunate resistance **(**Max blood draw 9 ml**)**

Sample Draw size and Sample Storage

The blood sample volume of 7ml (9ml in Soroti and Kalongo site) is calculated based on the samples required for this study listed in the table above. If sites also include microbiology, other routine or research samples or additional blood draw for storage then the site specific addendum submitted in tandem with this international protocol will clarify this. Individual sites may add into the addendum that plasma taken from an additional blood draw, or any left over from the protocol blood draw above, will be stored, and details of planned studies/investigations included in the patient information and parental consent/patient assent consent for storage where they have funding available to support this.

Screening (at the paediatric ward)

On arrival at the paediatric ward, the clinical team will immediately screen *P falciparum* positive (by RDT) children for clinical signs of severe malaria.

Severe admitted malaria cases

Carers of children with malaria meeting WHO clinical severity/Teule criteria above [30] would be asked for consent to collect basic clinical data (see list below) and also a more detailed assessment for other signs of severity including the grade (e.g. depth of coma) and duration of different severity criteria, and severity of blackwater fever (indicated on Hillman Colour Chart). They would also be asked to provide a blood sample to be tested for haemoglobin, full blood count (in order to differentiate children with sepsis), lactate, blood urea nitrogen (BUN), glucose, and base excess using i-stat cartridges, for CRP and PCT using a POC test [36] . They would also be asked to consent for an additional RDT test (finger prick) for the point-of-care quantitative plasma *Plasmodium falciparum* histidine-rich protein2 (pfHRP2)test (once this is available) and malaria slide (to be stored for quality control) to estimate total body parasite burden. To accurately verify HRP2 and to quality control CRP/PCT we will store a 1 ml sample of plasma for batch processing. In Soroti and Kalongo sites samples from admission will be store so that parasites can be batched genotyped for Kelch mutations, plasma PfHRP2 biomass assessed. Parasite clearance time and lactate clearence time will be monitored at 4 hourly (finger prick only) for the first 24 hours and 8 hourly thereafter until lactate levels < 2 mmols and malaria slides are

negative to allow us to track artesunate antimalarial activity. A urine sample will be taken to assess for signs of haemolysis (by Multistix). They would also be asked to consent to follow- up questionnaires and visits at discharge, day-28 and day-180 to record other outcomes (readmission and survival). There would be no blood draws post-enrolment. Given the importance of including the most acutely unwell children to accurately classify phenotypes, and the fact that the research blood test results will be available for clinical care, we will seek a provision for verbal assent from parents/guardians, with written informed consent obtained once the child is stabilised, as per previous studies (largely within 1-2 hours of study recruitment)[37]. Child written assent will be for minors aged between 12 and 15 years (country-dependent age cut off) once the child is well enough to understand the assent form.

Management and outcome data will be collected (number of transfusions, use of paracetamol, antibiotics and antimalarials, date of discharge or in-hospital death) and contact and locator data recorded so that children can be followed at day-28 and day-180 by phone or face-to-face. Follow-up would record re-admissions, new malaria episodes and mortality to capture a 'revolving door syndrome'. This system has worked very successfully in our transfusion trial (TRACT) [18] with 98% and 95% 90-day and 180-day retention respectively. Episodes of potential malaria would be identified by self-reported anti-malarial use, self-reported positive RDT, and self-reported febrile illnesses, in addition to readmissions.

Non-severe admitted malaria controls

To provide a representative comparison group of children admitted but without severe malaria as defined above, we will invite carers of the first 1-2 RDT-positive febrile children without severity criteria admitted to the paediatric ward Mondays and Thursdays (to capture any post-weekend and mid-week differences) to consent for the more detailed clinical baseline, enrolment blood draw, fingerstick for the new pHRP2 RDT test, blood slide and follow-up questionnaires/visits (discharge, day-28 and day-180 to record other outcomes) (the same data collection and follow-up schedule as severe malaria cases). 100 non-severe malaria controls would be recruited per site, aiming to recruit approximately one-third the number of non-severe malaria controls to severe malaria cases over periods when children are presenting with severe malaria. In order to maintain the balance of approximately 3:1 severe cases:non-severe admitted controls, if fewer controls are being recruited from the first 1-2 children presenting on Mondays/Thursdays, addition controls may also be recruited either on Mondays/Thursdays or on other days of the week, with the goal of completing recruitment of the 100 non-severe admitted malaria controls contemporaneously with the 300 severe (admitted) cases. Given this, recruitment of non-severe admitted malaria controls would stop around the time that 300 severe malaria cases had been recruited in a site, in order to ensure approximate time-matching (even if 100 controls have not been achieved).

Collecting this information on a representative subset of admitted non-severe malaria controls, combined with basic enumeration of the total number of children with non-severe malaria admitted to the paediatric ward (non-severe admitted malaria background, see

below), will enable us to use probability weighting to estimate the burden of different severe malaria phenotypes as a percentage of malaria admissions overall, not just as a percentage of severe cases.

Non-severe admitted malaria background

Accurately representing the percentage of eligible children who have severe disease out of all those admitted with malaria requires estimates of the total number of febrile children admitted to the paediatric ward with malaria. However, the focus of this study is on severe malaria, and it is not appropriate to take additional blood and collect extended research data on all children admitted with malaria who do not meet severity criteria above. Therefore, carers of all children admitted with RDT-positive malaria who are not enrolled as severe malaria cases or non-severe malaria controls above will be approached for consent for basic research data collection alongside of their routine clinical history and examination. They will be asked for separate consent (which can be refused whilst still contributing basic research data) to an additional RDT test (finger prick) for the point-of-care quantitative plasma *Plasmodium falciparum* histidine-rich protein2 (pfHRP2) test (once this is available) and malaria slide (to be stored for quality control) to estimate total body parasite burden. No other additional blood samples will be taken.

Basic data collection will consist of

- Date of admission
- Sex, age
- Known sickle cell disease
- Duration of fever symptoms, temperature at admission
- Haemoglobin if measured routinely at this admission
- Any prior healthcare contacts or treatment for this episode, including pre-referral artesunate, other antimalarials, antibiotics, or antipyretics
- Time and distance from home to hospital
- Time between arrival at hospital 'gateway' and the paediatric ward (see below)
- Development of severe malaria (as defined above) and any transfusions post-admission without severity criteria
- Discharge date (if admitted)
- In-hospital survival to discharge

One important potential contributor to the development of severe malaria is delays between initial presentation to hospital and assessment at the paediatric ward. To try to estimate this, we will document the time that each eligible febrile child arrives at the ward, and ask carers the time they first arrived at hospital. At minimum, depending upon sites each carer will be given, by hospital staff a slip to take to the paediatric ward (or this will be recorded in usual record) with the date and time they arrived at the hospital 'gateway'. Children who are not admitted can discard this slip when they leave hospital, but those moving to the paediatric ward can present it at triage.

Discharge and Follow up

At the point of discharge or in patients who die during admission, data will be collected on study proforma on specific outcomes, namely date of discharge, date and time of death,

whether the child developed severe malaria (controls and non-severe admitted malaria background only (see above)), and, in cases and controls only (not in non-severe admitted malaria background), treatments, blood transfusions, use of intravenous fluids, oxygen or non-routine treatments.

At the follow up visits on Day 28 and Day 180 for cases and controls, a medical history since discharge/last visit will focus on ascertaining hospital re-admissions, transfusions, malaria treatments and treatment for other febrile illness including antibiotics and antipyretics. Malaria status will be confirmed by RDT at each visit, and blood slide taken. Survival status will be recorded for those attending clinic at 28 days and 180 days and any patient lost to follow-up before 6 months without withdrawing consent will be traced for vital status.

7. STATISTICS AND DATA ANALYSIS

The null hypothesis is that there will be no differences in the severity spectrum at the 6 sites across 5 countries. A total of 300 children with severe malaria in each of 6 sites provides >80% power to detect differences in the prevalence of different severe malaria phenotypes between sites of 12% or greater. Overall including 1800 children with severe malaria will ensure that the width of the 95% CI around each prevalence estimate for the different malaria phenotypes is below 5%. Associations between different components of the phenotypes will be investigated using hierarchical clustering methods.

Continuous factors will be compared univariably between severe malaria cases (n=1800) and non-severe but admitted malaria controls (n=600) using means and standard deviations (or median and interquartile range where non-normal), and categorical factors using chi-squared or Fisher's exact tests. Comparison of 1800 severe malaria cases vs 600 non-severe but admitted malaria controls provides >80% power to detect differences in continuous factors of 0.14 times their standard deviation (SD) (e.g. for a continuous factor with a SD of 10 units (on whatever scale it is measured), there would be >80% power to detect differences between severe malaria cases and non-severe malaria controls of 0.14*10=1.4 units). It also provides >80% power to detect differences in binary factors of at least 7% in their absolute prevalence.

Time-to-event outcomes will be analysed and compared between severe malaria cases and non-severe but admitted malaria controls using Kaplan Meier and Cox proportional hazards. Incidence of readmissions and potential malaria episodes will be summarised using all events as incidence per 100 child-years, and compared formally using Poisson regression (or negative binomial regression if there is evidence of over-dispersion). Predictors of these outcomes will be identified using backwards elimination with exit p=0.1 to identify an exploratory model with adequate control of confounding: interpretation of effects will focus on those with p<0.05. We will use inverse probability weighting to estimate the burden of different severe malaria phenotypes as a percentage of malaria admissions overall, not just as a percentage of severe cases, by relating the representative subset of admitted non-severe malaria controls to the larger group of children with non-severe malaria admitted to the paediatric ward (non-severe admitted malaria background). We will use similar methods to assess the prognostic value of the different WHO/Teule criteria, and whether any important prognostic factors have been missed by these criteria, using in-hospital mortality (collected on all children, including non-severe malaria 'background') using competing risks methods to adjust for time to discharge.

Evaluation of the new RDT pHRP2 test will follow standard methods for evaluating diagnostic tests. The outcome is severe malaria; sensitivity, specificity and the area under the receiver operating curve will be estimated. Positive and negative predictive value will not be estimated because the number with the outcome (cases) and the number without (controls) is fixed by the study design. Secondary analyses will also consider the test's association with 28-day and 180-day mortality, in univariable and multivariable (i.e. adjusted for other baseline factors) models. If HRP2 deletions are important, then the test's performance will be poor and it will not be taken forward after this study.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES:

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the JRCO/ICREC and local or national ethics approval bodies.

8.2 CONSENT

In children who present as emergencies, we will seek verbal consent, with written informed consent obtained once the child is stabilised, as per previous studies, when written consent has largely been obtained within 1-2 hours of study recruitment [32]. Written consent will be sought from the parent or guardian after a full explanation has been given, an information leaflet offered or read out and time allowed for consideration. In addition to parental consent it is a national ethical requirement that children above a certain age (varying by country) are required to assent to participation in the study. This assent will be taken only once the child is stable and fully able to read and/or understand the assent form and make an informed judgment whether they are happy to remain in the study. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further management or treatment.

In some centres with active surveillance, data collection in non-severe admitted malaria background is already covered by general surveillance, and additional consent/approvals are not needed.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and fulfil transparency requirements under the General Data Protection Regulation for health and care research.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London is the main research 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.

8.6 FUNDING

Wellcome has funded this study: Grant Number 209265/Z/17/Z. A written agreement with the site principal investigator and/or the investigator's institution and Imperial College will outline the funding arrangements to sites.

Families will not incur any costs from participation in this study. All travel expenses for attending the visits will be paid, based on the cost of public transport to and from the participant's home using standard rates. At follow up visits snacks and drinks will be available.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Kilifi Study Coordination Centre. A SMAART Study Management Group (SMG) will be formed comprising the Chief Investigator; site Principal Investigators, co-investigators and will be responsible for overseeing the progress of the study. The SMG will meet approximately once a year in-person and will hold a regular teleconference at approximately monthly intervals at which sites will summarise progress and challenges.

10. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the SMG. If there are named authors, these will include at least the study' Chief Investigator, Statistician and Study Coordinator. Authorship of parallel studies initiated outside of the SMG will be according to the individuals involved in the project but must acknowledge the contribution of the SMG and the Study Coordination Centre.

Imperial College London is the custodian of the data and specimens generated from the SMAART study; study data are not the property of individual participating investigators or healthcare facilities where the data were generated but shared amongst the SMG and their respective institutions.

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