Funders:

H-PRIME
Hydroxyurea - Pragmatic Reduction In Mortality and Economic burden

Version:	**5.0**
Date:	**18th December 2024**
ISRCTN:	**ISRCTN15724013**
ICREC no:	**19IC5453**

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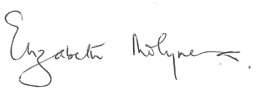
Signature:	
Date:	**18th December 2024**

GENERAL INFORMATION

This protocol describes the H-PRIME trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the trial coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the principles of the UK Data Protection Act and other regulatory requirements as appropriate.

TRIAL ADMINISTRATION

Trial Coordination Centre: Mbale Clinical Research Institute, Mbale, Uganda. Please direct all queries to the H-PRIME Trial Administrator (to be named; telephone and e-mail to be advised).

CLINICAL QUERIES

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SPONSOR

Imperial College London is the main research Sponsor for this trial. For further information regarding the sponsorship conditions please contact the Head of Regulatory Compliance at:

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FUNDER

H-PRIME is funded by the Joint Global Health Trials Scheme of the Department for International Development, UK (DFID), the Wellcome Trust and the Medical Research Council (MRC UK) (grant number MR/S004904/1).

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ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AR	Adverse reaction
ARC	Absolute Reticulocyte Count
ARROW	Anti-retroviral research for watoto (trial)
CAB	Community Advisory Board
CEA	Cost-effectiveness analyses
CHPL	Central Public Health Laboratory
CI	Chief Investigator
COAST	Children's oxygen administration strategy trial
CRF	Case record form
CRP	C-reactive protein
CTCAE	Common Toxicity Criteria for Adverse Events
CTF	Clinical Trials facility
CTU	Clinical Trials Unit
CTX	Cotrimoxazole
CY	Child-years
DALY	Disability-adjusted life-year
DART	Development of antiretroviral therapy in Africa (trial)
DBS	Dried blood spots
DFID	Department for International Development
DHA-PQP	Dihydroartemisinin-piperaquine
DNA	Deoxy-ribo-nucleic acid
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ERC	Endpoint Review Committee
EU	European Union
FEAST	Fluid expansion as a supportive treatment trial
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
Hb	Haemoglobin
HbF	Fetal haemoglobin
HPLC	High performance liquid chromatography

HR	Hazard ratio
ICH	International Committee on Harmonisation
IDA	Iron deficiency anaemia
IEF	Isoelectric focusing
IMP	Investigational Medicinal Product
IPT	Intermittent preventative treatment
IRB	Institutional Review Board
IV	Intravenous
KEMRI	Kenya Medical Research Institute
KWTRP	KEMRI-Wellcome Trust Research Programme
LPS	Lipopolysaccharide
MCRI	Mbale Clinical Research Institute
MOP	Manual of operations
MRC	Medical Research Council
MTD	Maximum tolerated dose
MUAC	Middle upper arm circumference
NOHARM	Novel use of hydroxyurea in an African region with malaria
NTS	Non-Typhoidal Salmonellae
PK	Pharmacokinetics
PI	Principal Investigator
PIS	Patient information sheet
PMC	PubMed Central
QA	Quality Assurance
QALY	Quality-adjusted life-year
QC	Quality Control
QMP	Quality Management Plan
QoL	Quality of Life
PCR	Polymerase chain reaction
R1	Randomisation 1
R2	Randomisation 2
R3	Randomisation 3
REACH	Realising effectiveness across continents of hydroxyrea
RCT	Randomised controlled trial
RDT	Rapid diagnostic test (for malaria)
REC	Research Ethics Committee

SAE	Serious adverse events
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SCD	Sickle cell disease
SDGs	Sustainable development goals
SOC	Standard of care
SOP	Standard Operating Procedure
SNP	Single Nucleotide Polymorphism
SP	Sulphadoxine-pyrimethamine
SPC	Summary of product characteristics
SSC	Study Site coordinator
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
TRACT	Transfusions in African Children Trial
UAE	Unexpected adverse reaction
U&E	Urea and Electrolytes
UCL	University College London
WHO	World Health Organisation

GLOSSARY OF TERMS

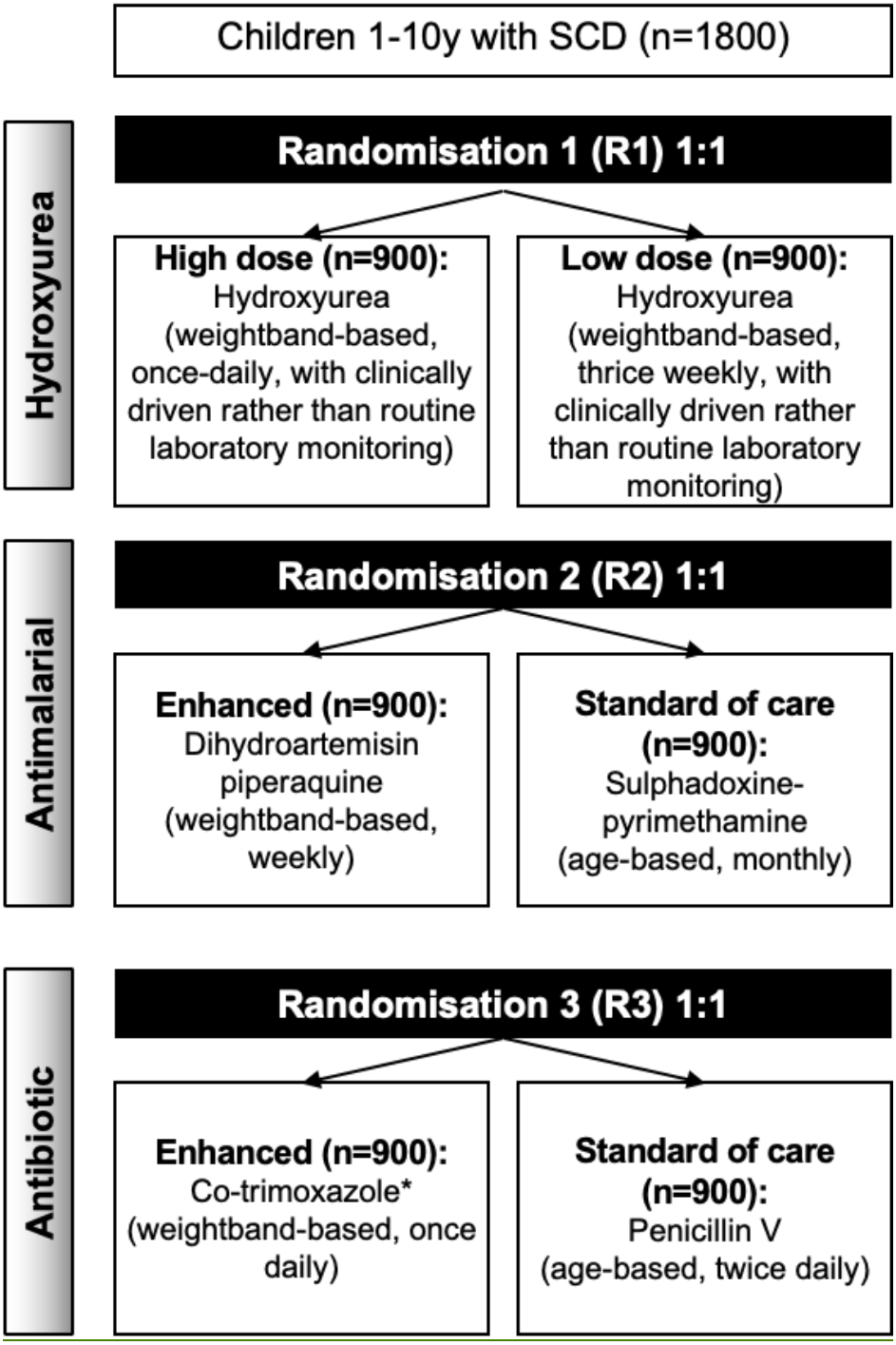
Impaired consciousness	Prostration or coma
Prostration	Inability to sit unsupported
Respiratory distress	Deep breathing or increased work of breathing
Profound anaemia	Haemoglobin < 4g/dl
Severe anaemia	Haemoglobin < 6g/dl
Severe and complicated anaemia	Severe anaemia with jaundice AND/OR respiratory distress AND/OR impaired consciousness AND/OR haemoglobinuria/dark urine
Severe illness	Children with impaired consciousness or respiratory distress

TRIAL SUMMARY

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
ACRONYM (or Short Title of Trial)	H-PRIME
Long Title of Trial	Hydroxyurea - Pragmatic Reduction In Mortality and Economic burden
Version	5.0
Date	18th December 2024
ISRCTN #	ISRCTN – ISRCTN15724013
Trial Design	A 2x2x2 factorial randomised open-label trial, conducted in four centres in Eastern Uganda
Type of Participants to be Studied	Children aged 1 to 10 years inclusive with a laboratory confirmed diagnosis of sickle cell disease (SCD)
Interventions to be Compared	The trial will have 3 intervention strategies aimed at reducing mortality and morbidity in children with SCD ▪ **R1:** high-dose (daily) versus low-dose (thrice weekly) oral hydroxyurea dosing based on standard weight-bands and and given with clinically driven (based on clinical signs/symptoms) rather than routine, scheduled laboratory monitoring ▪ **R2:** enhanced antimalarial prophylaxis with weekly dihydroartemisinin-piperaquine (DHA-PQP) vs standard of care (SOC) (monthly sulphadoxine-pyrimethamine, SP) (open-label) ▪ **R3:** antimicrobial prophylaxis with daily co-trimoxazole (CTX) throughout childhood/adolescence vs SOC (twice-daily penicillin V until the age of 5 years) (open-label)
Trial Hypotheses	▪ **R1:** oral high-dose (daily) hydroxyurea with clinically driven rather than routine laboratory monitoring will reduce all-cause mortality compared with oral low-dose (thrice-weekly) hydroxyurea ▪ **R2:** enhanced antimalarial prophylaxis will reduce malaria-associated hospitalisations vs SOC ▪ **R3:** CTX antimicrobial prophylaxis will reduce all-cause hospitalisations vs SOC
Primary Outcome Measure(s)	▪ **R1:** mortality ▪ **R2:** malaria-associated hospitalisations (diagnosed by EITHER rapid diagnostic test (RDT) OR microscopy OR PCR) ▪ **R3:** hospitalisations for any reason All endpoints will be included from enrolment to the common trial follow-up end-date 48 months after the first randomisation.
Secondary Outcome Measure(s)	▪ Mortality (for randomisations in which mortality is not the primary outcome) ▪ Malaria-associated hospitalisations (where not the primary outcome) ▪ All-cause hospitalisations (where not the primary outcome) ▪ Any of the following specific SCD-specific complications requiring medical intervention (Grade 2 or above): painful crisis, hand-foot syndrome, splenic sequestration, acute chest syndrome or stroke

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	▪ Number and volume of blood transfusions received ▪ Haemoglobin and fetal haemoglobin (HbF) values ▪ Grade 3 or 4 renal (creatinine) or liver function test (AST/ALT) results ▪ Febrile events that are treated with intravenous antibiotics ▪ Specific bacterial bloodstream infections confirmed by blood culture or molecular typing ▪ Serious adverse events (SAEs)
Other Outcome Measure(s)	▪ Hospitalisations lasting 7 days or longer ▪ Total duration of hospitalisations ▪ Febrile events reported at follow up visits or detected during hospitalisation ▪ Grade 3 and 4 adverse events (AEs), further categorised according to whether or not they are potentially related to SCD ▪ Grade 3 and 4 adverse events (AEs) considered possibly, probably or definitely related to hydroxyurea, or malaria/bacterial prophylaxis (for each specific randomisation) ▪ Measures of nutritional status (including Z-scores for weight, height and mid upper-arm circumference (MUAC)) ▪ Quality of life (QoL) ▪ Costs and cost-effectiveness
Randomisation	All randomisations will be 1:1 using a factorial design, ie each randomisation will be balanced by design for allocation to other interventions or not.
Number of Participants to be Studied	1800 HbSS children.
Duration	Participants will be randomised over 2 years, and will be followed until the common end of follow-up date 48 months after the first randomisation. The overall trial duration is therefore 4 years.
Ancillary Studies/Substudies	▪ Economics and cost-effectiveness ▪ Cardio-safety and pharmacokinetics ▪ Molecular diagnostics and malaria resistance
Sponsor	Imperial College, London
Funder	Department for International Development, UK (DFID), the Wellcome Trust and the Medical Research Council (MRC) UK through the Joint Global Health Trials Scheme
Chief Investigator	Professor Thomas N Williams

TRIAL SCHEMA



*Note: Because co-trimoxazole (CTX) and sulphadoxine-pyrimethamine (SP) should provide similar anti-malarial cover (see details below) and because both contain a sulphonamide component which, with its long half-life, increases the risk of overdosing if both are co-administered, pragmatically, children randomised to both CTX prophylaxis and SOC anti-malarials (suphadoxine-pyrimethamine, SP) will receive CTX alone without additional SP (with the further benefit of reducing pill count).

TRIAL ASSESSMENT SCHEDULE

	Screening (mth -3)	Month in trial 0	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	Key solicited events*
Patient information and consent for screening and SCD testing	X																			
Whole blood sample for SCD testing and plasma storage [1]	X																			
Informed consent (including for sample storage and genetic tests)		X																		
History & physical examination (medical officer) [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug dispensing (until next scheduled visit)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Symptom check list and EQ-5D-Youth (nurse)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adherence assessment [3]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PedsQL [4]		X					X				X				X				X	
Haematology [5] (2ml)	X	X		X	X		X		X		X		X		X		X		X	
Renal and Liver function tests (2ml) [6]	X	X		X	X		X		X		X		X		X		X		X	
Urine pregnancy test if female and reached menarche [7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rapid diagnostic test (RDT) AND blood slide for malaria [8]																				X
Blood draw for storage:		X																		
- Plasma storage [9]		X					X				X				X				X	
- Whole blood for human genetics [10]		X																		
- Whole blood filter paper x2 for PCR/pharmacokinetic studies [11]																				X
TOTAL Blood draw (all children) in ml (non-substudies)	4ml	4	0	4	4	0	4	0	4	0	4	0	4	0	4	0	4	0	4	1
Substudy (n=200)																				
Electrocardiography		X	X		X		X				X				X				X	
Whole blood filter paper x2 for pharmacokinetics (1ml)			X		X		X				X				X				X	X

* Febrile events (potential malaria) or any cardiac adverse event, including rhythm problems.

[1] Using the EDTA sample collected for haematology.
[2] Including weight, height, MUAC, adverse events, resource utilisation. The physician/medical officer will prescribe medication to the next visit and make decisions on any modifications of therapy as necessary, including requesting results of standard full blood count as needed based on clinical signs/symptoms.
[3] Pill count and nurse administered questionnaire throughout; at months 6, 12 and then annually a longer adherence/acceptability questionnaire will elicit both understanding of drug dosing regimens and reasons for non-adherence, and participant opinions about the different regimens, particularly with regard to pill burden and complexity.
[4] PedsQL and PedsQL sickle cell disease module: self-reported if 5 years and older, carer proxy if <5 years.
[5] Haematology: Hb, HbF, MCV, WBC, lymphocytes, neutrophils, platelets, reticulocytes. Results will not be routinely returned to physicians; results of standard full blood count (not HbF) may be requested if needed for clinical management based on clinical signs/symptoms. Do not repeat at screening if values available in the preceding 3 months.
[6] Creatinine, ALT and AST
[7] If screening pregnancy test is positive then participant will not be recruited. See Section 6.4 for management of a positive pregnancy test at other visits.
[8] Prepared from EDTA sample collected for haematology.
[9] From tube collected for haematology.
[10] Remaining from [9].
[11] From finger stick or from [9].

Note: screening visit should take place at least 1 week and not more than 4 months before randomisation. Children who are not already established within routine clinic follow-up must attend two follow-up visits before randomisation to ensure that they are able and willing to comply with the trial assessment schedule.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 BACKGROUND

The term sickle cell disease (SCD) describes a group of conditions in which the main form of haemoglobin produced is Haemoglobin S (HbS) and which are characterised by chronic anaemia, intermittent crises and progressive multi-organ deterioration.[1] HbS is produced as the result of a single base change mutation (A>T: rs334 – the β^s mutation) in codon 6 in *HBB* (HbSS). It is inherently more unstable than normal adult haemoglobin (HbA) and polymerizes at low oxygen tensions to result in abnormal and misshapen "sickled" red blood cells. A number of different forms of SCD can occur, but the most common are caused by the homozygous inheritance of the β^s mutation (HbSS), the co-inheritance of β^s with β–thalassaemia (HbS/β-thalassaemia) or the co-inheritance of β^s with mutations of which the most common is HbC (HbSC disease).[1] Without specific treatment, SCD results in high rates of both disability and early mortality.[1]

Heterozygous carriers of the β^s mutation (who have sickle cell trait; HbAS) enjoy preferential survival in areas affected by *P. falciparum* malaria.[2] As a result, this mutation has been selected to high population frequencies in tropical regions of Africa and India, where the vast majority of children with SCD are therefore born.[3] Most children born with SCD in high-income countries are diagnosed early and treated by specialists. As a result, almost all now survive to adulthood,[4] largely because of a small number of simple interventions that target common causes of early mortality such as splenic sequestration and bacterial infections.[5-7] Nevertheless, wherever they are born, all children with SCD suffer from greater or lesser degrees of chronic ill health, including delayed growth and development, splenic dysfunction, chronic pain, nocturnal hypoxaemia, neurocognitive delay, poor school performance, cerebrovascular and parenchymal brain damage, glomerular hyperfiltration, microalbuminuria and early pulmonary hypertension.[8] As such, analogous to other childhood medical conditions like juvenile diabetes, cystic fibrosis or haemophilia, SCD in children and adolescents should be considered a chronic disorder in need of long-term therapy.[8] Given this, a growing number of treatments are increasingly being used to manage patients in high-income countries, including chronic transfusion therapy, stem-cell transplantation, gene-therapy or editing and a large number of potentially promising new drugs.[9,10]

The global distribution of the β^s allele means that the majority of children with SCD (>250,000 births annually) are born in sub-Saharan Africa: >75% of all SCD births worldwide.[11] In marked contrast to high-income countries, new-born screening is rare within this region, the majority of cases are never diagnosed and 50-90% of affected children die before their fifth birthday.[12] As a result, SCD is a major cause of morbidity throughout most of sub-Saharan Africa, and currently accounts for 5-16% of under-5 mortality overall.[13,14] Despite these facts, SCD is widely neglected within the region and many countries have no policies for its routine diagnosis or treatment.[15] Of the commonly available disease-modifying treatments, all are considered either too complex or too expensive to be realistic options for sub-Saharan Africa within the foreseeable future with only one exception - hydroxyurea – the primary focus of this protocol.

Uganda has the fifth highest burden of SCD globally (10-15,000 annual births),[7,16] wherein the Eastern Region is among the worst affected.[16] This area typifies SCD-affected populations throughout much of sub-Saharan Africa, where country boundaries are arbitrary in comparison to the allele prevalence. Clinical resources within the region are severely constrained, malaria remains hyper-endemic (and recalcitrant to interventions) and under-5 mortality remains high (~80/1000; national census 2016). Recently, SCD has become a priority issue for the Ugandan Ministry of Health and an opportunistic national new-born screening programme is currently being launched on the back of an

existing screening programme for mother-to-child transmission of HIV.[16] Nevertheless, most clinics within Uganda still offer little but folic acid and infection prophylaxis, when available. They also do not have the capacity to monitor hydroxyurea with frequent clinical follow up and laboratory tests as is routinely undertaken in high-income settings and in current clinical trials evaluating safety of hydroxyurea in the African region.[17,18]

Few data have been published on the epidemiology of childhood SCD within sub-Saharan Africa. In recent years, we have shown that mortality is extremely high in undiagnosed and untreated children (50-90% by 5 years),[12] but that it is considerably lower in children who attend clinics and receive even the most simple of treatments. For example, in 122 children recruited aged 3-12 months in Kilifi, Kenya, none of whom received hydroxyurea treatment, under-5 mortality was 29 (5.8 (95% CI 4.0-8.6) deaths/100 child-years (CY)),[19] yet it was significantly lower (2.9; 1.5-5.9/100CY) among those receiving a package of basic care that included education, anti-bacterial prophylaxis with penicillin V and regular follow-up at a specialist clinic. Despite these reductions in overall mortality, the disease burden remained substantial with an overall incidence of hospital admission of 20.9 (17.3-25.2)/100CY and rates for severe anaemia, stroke, and invasive bacterial infections of 4.8 (3.2-7.1), 0.7 (0.2-2.8) and 3.0 (2.0-4.7)/100CY respectively.[19]

1.2 HYDROXYUREA

Hydroxyurea is orally administered once daily and has a well-established safety and efficacy profile when used to treat SCD in high-income countries with resources to undertake regular monitoring. It is one of only two disease-modifying agents that are currently licensed for the treatment of SCD worldwide,[8] and is also included for the treatment of SCD on the WHO list of essential medicines for children.[20] Hydroxyurea increases levels of both fetal (HbF) and total haemoglobin, and reduces both inflammation and haemolysis.[8] These therapeutic effects lead to wide-ranging benefits that include better growth, lower levels of end-organ damage, fewer strokes and painful crises and reduced mortality.[8]

Generic tablet and capsule formulations of hydroxyurea are manufactured and distributed in Africa by several companies, although all are used off-licence in the treatment of SCD. While a growing number of patients within the continent are now beginning to use hydroxyurea, several factors, including a higher prevalence of nutritional deficiencies and infectious comorbidities, make it unclear whether hydroxyurea will be as safe and effective there as it is in high-income settings.[21] Of note, in high-income countries, the standard approach to hydroxyurea therapy involves individually escalating the dose while closely monitoring haematological parameters to a point approaching toxicity - the maximum tolerated dose (MTD) - in the belief that this will bring the greatest benefits.[8] **The need for frequent visits to clinics that are staffed by clinicians with expertise in the use of hydroxyurea and who have access to expensive laboratory monitoring (which is not routinely available in most hospitals within the public sector), together with the need for a range of different strength formulations to achieve an accurate MTD, mean that this individualised, dose-escalation approach, is unreachable for the majority of patients who live in low-income countries in sub-Saharan Africa.** Furthermore, until very recently, the only formulations of hydroxyurea that been widely available in Uganda have been capsules of 500 or 200mg strength, that do not provide the flexibility to provide for sufficiently accurate dosing to achieve the desired MTD dosing range.

For these reasons further trials exploring more pragmatic public health approaches to dosing, that can be used safely without the need for extensive routine laboratory monitoring, have increasingly been identified as major research priorities.[21-24] **Current recommendations for hydroxyurea treatment under the Uganda Clinical Guidelines - frequent crises (>5/year), abnormal transcranial Doppler ultrasound velocities (which are not routinely measured within the country), stroke and**

acute chest syndrome[25] - are highly conservative, meaning that many of the potential benefits of early and universal implementation are likely to be missed.

1.2.1 RELEVANT CLINICAL TRIALS

A recent Cochrane Systematic review of use of hydroxyurea in the treatment of SCD concluded that "there is still insufficient evidence on the long-term benefits of hydroxyurea, particularly in preventing chronic complications of SCD, recommending a standard dose or dose escalation to maximum tolerated dose" and that "future studies should be designed to address such uncertainties".[26] That review, however, included no data from Africa, where most children with undiagnosed and untreated SCD live.

Two small trials conducted in India (n=60 randomised to hydroxyurea vs placebo[27] and n=144 single group receiving hydroxyurea[28]), found that low dose hydroxyurea (10mg/kg/day) was both safe and effective, in terms of HbF responses; however, baseline levels of HbF are higher in Indian than African patients,[26] meaning that these results are not necessarily generalisable to Africa. To date, only one placebo-controlled (n=208 (NO-HARM[17])), one single-arm, open-label trial (n=635 (REACH[18])) and one low versus high dose trial (n=220 (SPRING[29])) of hydroxyurea have been published from Africa, while a further single-arm, open-label trial (n=29[30,31]) is currently in progress. None have been powered for mortality and all have included levels of follow-up and routine laboratory monitoring that would be unrealistic for wider implementation in low-income settings. Several H-PRIME investigators are involved in the REACH trial, through which we have already shown that hydroxyurea is both safe and effective against a broad range of clinical outcomes that include malaria episodes and death.[18] However, REACH includes individualised dose escalation of hydroxyurea to the MTD that requires intense levels of laboratory monitoring to titrate dosages, approaches that are not feasible, and owing to high costs of the laboratory tests are currently not available, for widespread rollout in low-income settings. In addition, four different formulation strengths are used to achieve the precise MTD dosing that is a key feature of the trial. As a result, it cannot be assumed that hydroxyurea would be equally safe or effective if introduced widely and at lower-level health centres, using standardised, and inevitably on average lower, doses without similar intensive routine laboratory monitoring.

1.2.2 REAL WORLD IMPLEMENTATION

Where hydroxyurea is available in Africa, most often, it is being used informally and with little of the laboratory monitoring that is standard in treatment recommendations globally. Moreover, it is generally being reserved for children with multiple complications of SCD and is not widely being recommended as standard of care for all. While the REACH[18], NOHARM[32] and SPRING trials[29] have all suggested that hydroxyurea is both safe and effective in Africa when used in the general population of children with SCD, rather than those with multiple complications, all three trials involved levels of clinical and laboratory monitoring that were similar to those used in high-income settings, leaving major questions over what might happen if hydroxyurea therapy was to be implemented under real world conditions. For this reason, some experts have suggested that hydroxyurea should be prescribed at moderate doses (10-20mg/kg/day) that can be safely used with minimal monitoring[27,28,33,34]. Conversely, others have proposed that higher doses should be used to maximize benefit[8], although it cannot be taken for granted that this will not be associated with an increased risk of harm from toxicity if implemented under real-world conditions. A major aim of H-PRIME will therefore be to address this question through an open-label randomised trial of high dose (25 mg/kg/day, range 15-30 mg/kg/day) versus low dose (10 mg/kg, range 6-13 mg/kg/day) hydroxyurea, delivered pragmatically through a weight-band based approach.

1.3 PROPHYLAXIS AGAINST OTHER INFECTIONS

Malaria and bacterial infections are widely considered to be the commonest causes of early mortality among children with SCD in sub-Saharan Africa.[35] Previous work from H-PRIME investigators suggests that although the absolute risk of malaria may not be increased, it more often results in catastrophic anaemia and subsequent death.[36,37] Moreover, we have recently estimated that the risk of bacteraemia is exceptionally high, at approximately 5% per year.[38,39] Although *S. pneumoniae* was the most important organism in those studies, almost half of all infections were caused by Gram negative bacteria, including non-typhoidal salmonellae (NTS) (18%), *H. influenzae* type b (12%), *E. coli* (6%) and *Acinetobacter sp* (6%).[38,39]

Several drugs are commonly used for malaria prophylaxis in different parts of Africa, including chloroquine, proguanil and sulphadoxine-pyrimethamine (SP), which has recently been recommended as standard of care (SOC) in Uganda.[40] However, given current rates of resistance, all these drugs are now sub-optimal.[37] Similarly, although twice daily penicillin V prophylaxis and the introduction of newer vaccines will almost certainly reduce the rates of infections caused by both *S. pneumoniae* and *H. influenzae* type b, it is possible that greater benefits would accrue with protection against a broader range of infections, the most important of which are outlined above. A recent major systematic review of antibiotics and antimalarials[41] in SCD identified few studies, most too small to make definitive conclusions.

Multi-drug resistant *P. falciparum* malaria is now common throughout much of sub-Saharan Africa and is a particular concern in Uganda,[42] where efficacy of the standard preventive regimen for children with SCD (monthly SP [40]) is now <10%.[42] We hypothesise that an alternative regimen, weekly DHA-PQP, may be more effective. Intermittent preventive treatment (IPT) with DHA-PQP is both highly effective and very well tolerated in infants, children, adults and pregnant women.[43,44] Although DHA-PQP has been associated with QT prolongation, in a recent major review of over 200,000 individuals, the WHO found no evidence for a raised incidence of sudden cardiac death.[45] While various dosing strategies have been used, a weekly approach has predicted benefits over other regimes, in particular higher efficacy and reduced concerns about compliance and safety, because of lower peak levels from a lower dose taken every week compared with a higher dose taken once a month.[46] Nevertheless, recognising that DHA-PQP might behave differently in children with SCD or in those on hydroxyurea we will also conduct a sub-study to monitor for both cardiotoxicity and pharmacokinetic and pharmacodynamics (PK/PD) in subsets of trial participants. We will also monitor for the possibility of emerging malaria resistance through a collaboration with the SpotMalaria project.[47]

In terms of antimicrobial prophylaxis, a range of potential agents have activity against a broader range of Gram-positive and negative organisms than penicillin V, including azithromycin, amoxicillin, co-amoxiclav and the cephalosporins. However, all pose risks in terms of side effects and the development of wider antimicrobial resistance in commensal microflora. On balance, cotrimoxazole (CTX) strikes a good balance between risk - including the development of antimicrobial resistance - and potential benefit. Moreover, unlike many of the other options, CTX is not normally used in the treatment of serious and life-threatening infections. CTX is cheap, readily available and is widely used as prophylaxis in both HIV-exposed uninfected and infected children, where it has been found to be both extremely safe and strongly protective against all-cause mortality despite high background levels of microbial drug-resistance.[48-50] Finally, its once daily dosing (as opposed to twice daily for penicillin) is attractive for compliance. Together, these characteristics mean that using CTX rather than penicillin V could be easily implemented both quickly and at scale. Further the sustained increase in the risk of infections beyond the age of 5 years[51-53] means that use throughout the whole of childhood could be a valuable alternative strategy for bacterial prophylaxis, compared with restricting antibiotic prophylaxis to those under 5 years as recommended in current guidelines.[25] The

main agent targeted by penicillin V is *Streptococcus pneumoniae*: however, widespread pneumococcal vaccination (in particular in all children enrolled in H-PRIME) now make this a less important pathogen to target with antimicrobial prophylaxis.

1.4 RATIONALE FOR CURRENT TRIAL

SCD is a major cause of mortality and morbidity during childhood throughout much of sub-Saharan Africa. The main triggers relate to the pathophysiological consequences of the disease itself and to bacterial and malarial infections. **The overarching questions that we wish to address is whether the long-term survival and quality of life among children living with SCD in sub-Saharan Africa could be improved through the pragmatic delivery of simple and affordable interventions?**

A large pragmatic mortality-endpoint trial in SCD is needed now for several compelling reasons. Previous trials investigating hydroxyurea have not been designed and powered to investigate the survival of children with SCD living in malaria-endemic regions of sub-Saharan Africa.[17,18] Moreover, strategies for delivery based on uniform weight-band based dosing were not investigated in the two most definitive trials conducted in Africa to date[17,18] which, further, did not involve clinically driven, pragmatic, laboratory monitoring approaches that could be generalisable across sub-Saharan Africa where, in the main, there is a lack of specialist laboratory services. Existing trials, therefore, have not provided the evidence that is needed to influence policy regarding the safety and efficacy of wider drug uptake in regions where quality-controlled routine and frequent laboratory monitoring is not available. However, failing to tackle SCD survival because of infrastructure constraints could mean that many countries within the region will miss their Sustainable Development Goals (SDGs) both in terms of deaths averted and their promise that "no one must be left behind".[54] Second, with demographic transition[55] an increasing number of children with SCD will inevitably survive to require medical attention, and to become chronically unwell, develop long term complications including strokes, and place a disproportionate burden on medical and blood transfusion services.[7] Finally, SCD is at last being recognised as a key health challenge by international agencies[56,57] and by African governments, including Uganda.[16] This is manifest by the recent introduction of selective early life screening in Uganda during recent years[16] and their plans for universal screening in the near future. Without trials like H-PRIME, it will be impossible to develop regionally appropriate policies that could genuinely impact on morbidity and mortality. Specifically, **while hydroxyurea is now increasingly being used, it is not known whether it will be either well-tolerated or effective in the informal way in which it is most commonly being taken.**

The most important outstanding questions are therefore:

- Would hydroxyurea therapy, commenced early in life for all children diagnosed with SCD, be both well-tolerated and effective in reducing mortality and morbidity in sub-Saharan Africa if used at fixed weight-band based doses with minimal clinically driven (rather than regular and pre-planned routine) laboratory monitoring?
- Can further reductions in mortality and/or morbidity be achieved through better approaches to preventing malaria and bacterial infections?

Combining investigation of the different interventions into one trial not only allows us to evaluate the role of hydroxyurea against different backgrounds of interventions that may be used in the next decade, but also allows us to answer the most relevant management questions efficiently in a single trial.

1.4.1 RISKS

Hydroxyurea, DHA-PQP and CTX prophylaxis have been widely used in children with minimal risk, as have the comparators SP and penicillin V. However, all medications confer potential additional risks from their administration: the trial will directly evaluate whether these potential risks are

outweighed by improved survival and reduced hospitalisations. Blood samples will be required from all trial children. However, the volumes of blood required would be minimised as much as possible and be kept well within the maximum locally agreed volumes. Children will have to attend regular clinic visits for monitoring.

1.4.2 BENEFITS

Extra clinical personnel, regular clinical assessment of participants and basic equipment for patient monitoring will be available during the trial so that if SCD complications were to arise they will be detected and treated more often. Pre-trial training will include sign recognition for these complications and training on treatment. Both these will be covered in detail in the trial Manual of Operations (MOP).

1.4.3 FOR THE CHILD

The direct benefits to the child and/or family (outlined in the patient information sheet (PIS)) include:

- Closer observation during the trial, which, as a result, allows doctors and nurses to make important changes to the child's management.
- The dependable supply of standard of care medicines that could otherwise be subject to stockouts, free of charge to parents.
- Additional education about their condition.
- The parents or guardians for the children will be asked to return for follow up at the H-PRIME clinic every three months for 2-4 years.

1.4.4 FOR THE CENTRES

The direct benefits to the participating centres include:

- Support, capacity development and training in the management of SCD in childhood and the use of hydroxyurea therapy.
- Establishing or further developing SCD clinics.

1.4.5 FOR HEALTH PERSONNEL

The direct benefits to health personnel are mainly professional development of the members of the trial teams and clinical teams for the purposes of running the trial – including training in clinical trials, good clinical and laboratory practice, and research ethics. However, as above, they will also receive standardised training in the identification and treatment of SCD and relevant adverse events.

2 SELECTION OF CENTRES AND CLINICIANS

Four health facilities in Eastern Uganda will participate:

- Mbale Regional Referral Hospital, Mbale (lead site providing laboratory support for patient monitoring and sample storage and local data and trial management)
- Soroti Regional Referral Hospital, Soroti
- Atutur District Hospital
- Ngora Health Centre IV

Together, these hospitals provide care to 23 districts with a combined population of >7.2 million people (Uganda national census 2014). This region is characterised by high levels of malaria transmission with an estimated entomological inoculation rate of >100 infective bites/year.[58,59] These centres all run large SCD clinics that together manage a heavy patient load: even without widespread screening, they already serve >3000 SCD children <10 years of age. Nevertheless, they have relatively limited resources in terms of staff and laboratory facilities, reflecting the clinical situation throughout much of sub-Saharan Africa. Soroti, Ngora and Atutur have not previously used hydroxyurea and the drug is not used routinely in Mbale beyond the REACH clinical trial. These centres have been chosen as trial sites on the basis of criteria below.

2.1 CENTRE/INVESTIGATOR INCLUSION CRITERIA

To participate in the trial, investigators and clinical centres must fulfil a set of basic criteria defined below.

2.1.1 CENTRE PI'S QUALIFICATIONS & AGREEMENTS

1. The centre PI should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their centre and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the institutional review board (IRB), and/or the regulatory authority(ies).

2. The centre PI should be aware of, and should comply with, the principles of ICH GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators at the centre.

3. The centre PI should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority(ies).

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

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

2.1.2 ADEQUATE RESOURCES

1. The centre PI should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

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

3. The centre PI should have available or appoint an adequate number of qualified staff for the duration of the trial to conduct the trial properly and safely.

4. The centre PI 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.

2.1.3 CENTRE ASSESSMENT

Each selected trial centre must provide a completed Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Investigator Statement verifies that the centre is willing, and able to comply with the requirements of the trial. This will be signed by the Principal Investigator at the centre. In addition, and in compliance with the principles of ICH GCP, all centre staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the Mbale Clinical Research Institute (MCRI). The MCRI 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 Trial Master File (TMF) at the centre and also at the MCRI.

2.2 APPROVAL AND ACTIVATION

On receipt of the above documents at the MCRI, written confirmation will be sent to the PI.

1. The centre should conduct the trial in compliance with the protocol as agreed by the Sponsor and, if required, by the regulatory authority(ies), and approved by the REC and/or IRB.

2. The centre PI or delegate should document and explain any deviation from the approved protocol, and communicate this with the trial team at the MCRI.

A list of activated centres may be obtained from the Trial Administrator.

3 TRIAL OBJECTIVES AND DESIGN

3.1 TRIAL OBJECTIVES

The primary objective of the trial is to identify pragmatic, effective, safe and acceptable interventions to reduce short and longer-term mortality and morbidity in children with SCD in sub-Saharan Africa. There are three hypotheses being tested

1. [Randomisation, **R1**] Oral hydroxyurea at a fixed weight-band based high dose given daily with clinically driven (rather than routine scheduled) laboratory monitoring, without titrating doses to the MTD, will reduce all-cause mortality compared fixed weight-band based low dose given three times a week with clinically driven (rather than routine scheduled) laboratory monitoring
2. [**R2**] Enhanced antimalarial prophylaxis will reduce malaria-associated hospitalisation vs standard of care (SOC) (open-label)
3. [**R3**] Enhanced antimicrobial prophylaxis will reduce all-cause hospitalisation vs SOC (open-label)

Secondary objectives include

- To determine the efficacy of the strategies above on other measures of morbidity
- To determine the safety and tolerability of the strategies above
- To identify the most cost-effective interventions to reduce mortality and morbidity, and assess their budget impact
- To investigate the cardiac safety of DHA-PQP in children with sickle cell disease

To investigate the resistance patterns of malaria parasites acquired by children on different forms of malaria prophylaxis

3.2 TRIAL DESIGN

H-PRIME is a multi-centre 2x2x2 factorial randomised controlled trial of a total of 1800 HbSS children aged 1 to 10 years inclusive. Children will be enrolled over 2 years from four centres in Uganda and followed for 2-4 years, until 4 years after the first child was randomised. The trial will simultaneously evaluate three ways to reduce morbidity and mortality associated with SCD as described above.

1800 children will be randomised 1:1 factorially to each of the following comparisons:

1. **[R1] daily oral high dose hydroxyurea vs thrice weekly oral low dose hydroxyurea (n=900 in each group)**
2. **[R2] weekly DHA-PQP vs monthly SP (SOC) (open-label) (n=900 in each group)**
3. **[R3] once daily CTX given throughout childhood, vs penicillin V given twice daily until 5 years of age (SOC) (open-label) (n=900 in each group)**

Both SOC groups are as defined in the Uganda Clinical Guidelines 2023.[25] Because CTX and SP should provide similar anti-malarial cover and to avoid overdosing with sulphonamide compounds, pragmatically children randomised to CTX prophylaxis under the antibiotic randomisation and to SOC anti-malarials under the anti-malarial randomisation will receive CTX alone without additional SP (with the further benefit of reducing pill burden). Thus, R2 and R3 together compare four pragmatic strategies for improving anti-malarial and anti-bacterial cover:

a) SP (all ages) + penicillin V if <5 years (SOC)
b) DHA-PQP (all ages) + penicillin V if <5 years (improved anti-malarials, equivalent antibiotic cover)
c) CTX (improved anti-bacterial cover whilst maintaining equivalent anti-malarial cover)

d) DHA-PQP+CTX (improved anti-malarial and anti-bacterial cover)

3.3 TRIAL OUTCOME MEASURES

3.3.1 PRIMARY OUTCOME

- **R1:** mortality (all-cause)
- **R2:** malaria-associated hospitalisations (diagnosed by rapid diagnostic test (RDT) OR microscopy OR PCR)
- **R3:** hospitalisation for any reason

All endpoints will be included from enrolment to the common trial follow-up end-date 48 months after the first randomisation.

All-cause mortality has been selected as the primary endpoint for the hydroxyurea comparison because of the challenges in ascertaining cause-specific mortality in the low-income settings where this trial will be conducted; it is arguably the most relevant endpoint both to patients and African Ministries of Health from the perspective of resource allocation.

3.3.2 SECONDARY OUTCOMES

- Mortality (where mortality is not the primary outcome for that randomisation)
- Malaria-associated hospitalisations (where not the primary outcome)
- All-cause hospitalisations (where not the primary outcome)
- Any of the following SCD-specific complications requiring medical intervention (Grade 2 or above): painful crisis, hand-foot syndrome, splenic sequestration, acute chest syndrome or stroke
- Number of blood transfusions and volume of blood transfused
- Haemoglobin (Hb) and fetal haemoglobin (HbF) concentrations
- Grade 3 or 4 renal (creatinine) or liver function test (AST/ALT) result
- Febrile events treated with intravenous antibiotics
- Specific bacterial bloodstream infections confirmed by blood culture or molecular typing
- Serious adverse events (SAEs)

3.3.3 OTHER OUTCOMES

- The total number of hospitalisations lasting 7 days or longer
- The total duration of all hospitalisations
- Febrile events reported at follow up visits or detected during hospitalisation
- Grade 3 and 4 adverse events (AEs), further categorised according to whether or not they potentially related to SCD (see **Table 1** below)
- Grade 3 and 4 adverse events (AEs) considered possibly, probably or definitely related to hydroxyurea, or to malaria/bacterial prophylaxis (for each specific randomisation)
- Measures of nutritional status (including Z-scores for weight, height and mid upper-arm circumference (MUAC))
- Quality of life (QoL)
- Costs and cost-effectiveness

Table 1. Recognised complications of SCD

Acute chest syndrome	Empyema	Pain, long bone
Adeno-tonsillar disease	Hand-foot syndrome/dactylitis	Pain, severe abdominal
Albuminuria	Headache	Pain, sternal or rib
Amenorrhoea	Haematuria	Priapism
Anaemia (severe)	Hemiplegia	Proteinuria
Aplastic crisis	Haemolysis	Pneumonia
Arthralgia	Hepatic sequestration	Pulmonary embolism
Avascular necrosis of hip/shoulder	Hepatomegaly	Pulmonary hypertension
Bacteraemia	Hospitalisation >24 hours	Pulmonary infiltrate on chest x-ray
Bone infarction	Hyperbilirubinaemia	Pyelonephritis
Cardiac arrhythmia	Hypersplenism	Renal failure
Cardiomegaly	Hypertension	Renal insufficiency
Cerebrovascular accident	Hypocalcaemia	Renal papillary necrosis
Cholecystitis	Hyposthenuria	Reticulocytopaenia
Cholelithiasis	Hypotension	Reticulocytosis
Cognitive dysfunction	Hypoxaemia (PO_2 <65mm Hg)	Retinopathy
Constipation	Ileus	Retinal haemorrhage
Cranial nerve palsy	Infection, bacterial	Rhabdomyolysis
Death	Infection, pneumococcal	Seizure
Decreased renal function	Infection, line	Septicaemia
Decreased lung function	Infection, viral	Silent organ infarction
Delayed growth/puberty	Jaundice	Skin ulcer
Depression	Leukocytosis	Splenic sequestration
Dizziness	Meningitis	Splenomegaly
Electrolyte imbalance	Nephropathy	Stroke
Elevated urinary urobilinogen	Osteomyelitis	Transient Ischemic Attack (TIA)
Elevated serum transaminases	Pain, back	Tonsillar enlargement or infection
Elevated TCD velocities	Pain, chest	Transfusion, unanticipated
Fever	Pain, joint	Vaso-occlusive pain

Note: List of expected and potentially serious adverse events associated with sickle cell anaemia. Table 1 may not be all-inclusive. Investigators should use clinical judgment along with consensus knowledge about SCD in determining event expectedness, see **Section 7.2.1.C**.

3.3.4 PROTECTION AGAINST BIAS

The clinically-driven laboratory monitoring approach that will be used in H-PRIME (see **Section 5.2.2** for details) will reduce the risk of bias with regard to compliance with the continuation of the hydroxyurea randomisation due to physician behaviour (and hence patient management).

The first randomisation to high vs low dose hydroxyurea will be open label because blinding a dose randomisation is extremely challenging due to the need to provide both placebo and active drug to the lower dose group, and then ensure that children receive the correct placebo/active drug at different dosing intervals. Practically, given that the number of doses that can be achieved even with a scored tablet remains relatively limited, the most pragmatic way to achieve a lower dose is to give drug thrice weekly. However, blinding this would require different drugs for different days of the week, which would carry a very large risk that children would not receive the right placebo/active drug on the right days, thus invalidating the randomisation. For this reason, the randomisation to

high vs low dose will be open label. The second and third randomisations will be open-label because they have active comparators, for anti-malarials which are also given at different frequencies (DHA-PQP weekly vs SP monthly), so that blinding would require a complex and high-pill burden "double-dummy" approach. This additional pill burden over 2-4 years is also difficult to justify. In addition, the active comparators mean that case management by physicians is less likely to be affected by their knowledge of which form of prophylaxis is being received. Furthermore, one intention of this pragmatic strategy trial is to assess the likely impact of medication non-compliance in these additional interventions on outcomes, which would not be possible with blinding.

Additional protection against bias is provided by our selection of trial endpoints: all are as objective as possible, particularly death from all causes and laboratory test results at scheduled visits. Hospital admissions are clinically significant events, and it is reasonable to assume, therefore, that they will be approximately ascertained without bias. Any child lost to follow-up will be traced for vital status based on location and mobile phone data that will be verified at each trial visit. Finally, to further protect from bias an independent Endpoint Review Committee will adjudicate on the causes of death and hospitalisation and whether (without knowledge of actual randomisation) events were unlikely, possibly/probably, or uncertainly to have been related to each intervention, were those affected to have received them.

4 PARTICIPANT ENTRY

4.1 SCREENING

4.1.1 SCREENING PROCEDURE

Eligible children will be screened for potential recruitment into the trial from several sources.

- Those currently under active follow-up for SCD at hospitals where the trial centres are located (where >3000 eligible children are already registered)
- Children admitted to paediatric wards of the same hospitals who have SCD diagnosed as part of targeted screening
- Children identified through the national SCD early life screening programme (which is currently being developed)

Children who are not already registered at one of the SCD clinics at participating centres will undergo a minimum 3-month pre-treatment screening and observation period to allow diagnostic confirmation of SCD status and to ensure that the families are able and willing to return to clinic for regular follow-up. Following informed consent for screening, 4mls of blood will be collected - 2 mls into EDTA for confirmatory SCD testing, a full blood count and plasma storage, and 2 mls into a serum separator tube for renal and liver function tests. Testing for SCD will be by use of a rapid diagnostic test (either the Gazelle™ mini-electrophoresis or other validated method) followed by confirmatory testing by either high performance liquid chromatography (HPLC) at the Mbale Clinical Research Institute (MCRI) or by isoelectric focusing (IEF) at the Uganda Central Public Health Laboratory. Screening consent will be taken explicitly for this sample, which will determine whether or not children are eligible for the trial. Children screening positive for HbSS will be established on SOC following the Uganda Clinical Guidelines 2023.[25] This includes folic acid (5mg daily) and malaria (SP) and antimicrobial prophylaxis (penicillin V if aged <5 years) as described below. Care will be further standardised by ensuring that all children have received all vaccines within the WHO Expanded Programme on Immunisation schedule, receive anti-helminthic drugs where appropriate (every 3 months in children <5 years) and have been issued an insecticide-impregnated bed-net to help prevent malaria. Before randomisation, children must have attended at least two clinic visits, either following screening if newly attending the clinic or through previous follow-up at the local clinic.

All children formally screened for recruitment will have a screening case record form (CRF) completed and will be registered in the trial register. Consent will also be taken for the storage of screening blood samples and for their use for diagnostic testing by molecular methods.

4.2 ELIGIBILITY FOR RANDOMISATION

The eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this trial. Patients not meeting the criteria should not join the trial. For the safety of the patients, as well as to ensure that the results of this trial 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.

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

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

4.2.1 INCLUSION CRITERIA

- Aged 1-10 years inclusive
- SCD diagnosed by rapid test and confirmed using either HPLC or IEF at a qualified laboratory
- Have received conjugate pneumococcal vaccination against Hib and *S. pneumoniae* (otherwise eligible but unvaccinated children will be vaccinated through the study as above)
- Carer willing/able to provide consent and to bring the child for follow-up visits, as demonstrated by either regular attendance at SCD clinics to date, or attending two visits (one of which may be the screening visit) before randomisation

This age range is based on the mortality risks with SCD, the practicality of weight-band-based dosing and the ability of children to swallow divided tablets.

4.2.2 EXCLUSION CRITERIA

- Weighing <8kg – exclusion pending the achievement of 8kg or more
- Already meet criteria for starting hydroxyurea in national guidelines (frequent crises (>5/year), known abnormal transcranial Doppler ultrasound velocities, stroke or acute chest syndrome)
- Already receiving hydroxyurea, defined as having been prescribed hydroxyurea at any time during the preceding 6 months, or ever having received hydroxyurea for more than 3 months
- Taking concomitant medications that are contraindicated with any of the trial medications (hydroxyurea, SP, DHA-PQP, penicillin V, cotrimoxazole) (including, but not limited to, nefazodone, verapamil, rifampicin, isoniazid, ethambutol)
- A positive pregnancy test at screening or enrolment visits
- Known allergy to any of the randomized drugs used in the trial: ie hydroxyurea, SP, DHA-PQP, penicillin V or cotrimoxazole
- Known cancer
- A clinical history of previous or existing liver or renal diseases unrelated to sickle cell disease
- Known cardiac ventricular dysfunction or failure or a previous history of cardiac arrhythmias
- Known HIV (these children should receive cotrimoxazole prophylaxis and many will be receiving antiretrovirals that are contraindicated with one or more trial medications (zidovudine, amprenavir, atazanavir, indinavir, nelfinavir, ritonavir))
- Current participation in any other clinical trial of an investigational medicinal product
- The receipt of a blood transfusion within the preceding 3 month period (this will render the diagnostic confirmation of SCD unreliable)
- Presence of acute infection on the day of screening (e.g. symptomatic *P. falciparum* malaria, pneumonia, septicaemia, meningitis, newly identified tuberculosis) – such children may be enrolled after recovery from an acute infection if they do not meet other exclusion criteria

4.3 RANDOMISATION AND ENROLMENT PROCEDURE

4.3.1 PRACTICALITIES

The randomisation visit may be scheduled at any time between 1 week and 4 months after the screening visit, providing the participant/carer feels they have had adequate time to consider trial participation and that they have attended at least two follow-up visits if the child has not previously been undergoing routine follow-up in a SCD clinic.

The child should be physically present together with a trial clinician in either the site clinic or a hospital ward at the time of randomisation. The participant's eligibility for enrolment will be confirmed. Before randomisation, the trial team should confirm the results of the confirmatory sickle test as showing HbSS. Carers and participants (where applicable) must confirm that they have read

the relevant patient information sheets. Written informed consent to enter into the trial and be randomised must then be obtained from parents/guardians of, or other person with legal responsibility (including legal authorities) for, the child, after explanation of the aims, methods, benefits, and potential hazards of the trial and BEFORE any trial-specific procedures are performed or any blood is taken for the trial. Older children should give assent to trial participation. Signed trial consent/assent forms must be kept by the investigator and documented in the CRF and a copy given to the participant or family.

It must be made completely and unambiguously clear that the participant (or parent or guardian of a 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 their treatment or that of their child.

For all children, the primary carer providing consent will be asked to nominate another one or two carers (depending upon local practice) who will be responsible for the child's welfare in the event that they are unable to continue caring for them. Whilst the carer who consented is alive, counselling of any other person who brings the child to the clinic is necessary to explain the trial, but re-consent is not needed. If the carer who originally gave consent dies, it will be necessary to obtain re-consent from the next nominated primary carer.

After consenting to trial participation (day 0), enrolment assessments will be performed as summarised in the Trial Assessment schedule. When possible, and particularly if there is doubt about the place of residence of a child and his/her family, a map should be drawn indicating the place of residence. Where mobile phone numbers are provided for contact, these should be called from the clinic. Blood will be drawn for a full blood count, plasma storage and DNA extraction (to test for other genetic modifiers including known conditions such as α-thalassaemia and G6PD-deficiency and as yet unknown modifiers by use of genome-wide and DNA sequence-based studies (2ml EDTA tube) and for renal and liver function tests (2 ml serum separator tube).

4.3.2 RANDOMISATION

Randomisation in each part of the factorial will be stratified by centre, hydroxyurea initial dose (to ensure balance across the specific doses proposed, see **Table 2** below) and the other randomisations in the factorial. Randomisation will be done by the Mbale data centre (which has reliable power and internet connectivity) using an online randomisation server. Other sites will telephone Mbale to perform randomisation. Randomisation lists will be prepared by the Trial Statistician at the MRC CTU using random permuted blocks, stratified by trial centre and initial hydroxyurea weight-band (or family, see below). The lists will be incorporated securely into the online randomisation server, ensuring allocation concealment. If there are connectivity issues, randomisation will be delayed, since this is not an emergency situation.

Those being randomised will have their initials, age in years, randomisation date and trial number recorded in the trial register. Those who refuse randomisation will have initials, age in years, and reason for refusal recorded. The register will be kept in a secure place in each clinical site, must be available for monitoring, audit and inspection, and will be the responsibility of the Principal Investigator at that site.

The clinician should complete a prescription with the participant's details and trial medications as allocated. The prescription will be for 1 month until the next scheduled clinic visit. The pharmacist or pharmacy technician should ensure that the participant knows how to take the different drugs before they leave the clinic, and that they know to contact the team or bring the child to clinic immediately if they have any problems or concerns.

4.3.3 ENROLMENT OF DIFFERENT MEMBERS OF THE SAME FAMILY/HOUSEHOLD INTO THE TRIAL

It is possible that multiple individuals from the same family/household could enter the trial. For a number of reasons, we judge that it is important that all children within the same family should receive the same allocations to all randomised interventions. First, with regard to the hydroxyurea randomisation, it could prove confusing if different family members were assigned to different arms and received different dosing frequency (some once-daily, some thrice-weekly), and with regard to the second and third randomisations, there is some risk that parents could confuse weekly DHA-PQP doses with monthly SP doses, or daily Pen V or CTX allocations within families. While this would not be necessary if recruitment was restricted to one child per family, this also runs the risk of drug pooling and dilution of any genuine treatment effects and we do not consider that it would be ethical to restrict randomisation to one child per family. In practice we anticipate that most families will not contribute more than 1 or 2 children.

With these considerations in mind, we will cater for multiple children within families as follows. Firstly, we will screen all children within families wherever any might be affected, such that randomisation of all affected children within a family can occur simultaneously (i.e. per family randomisation). We will include family randomisation as an additional stratum in the weight-band based dosing, since families will require more drug for multiple children (i.e. strata will be 3-<8kg, 8-<17kg, 17-<25kg, 25-<33kg, 33kg+, family). Finally, all participants will be counselled that they should on no account share their trial drugs with anyone who is not recruited to H-PRIME.

4.3.4 CO-ENROLMENT GUIDELINES

Participants will not ordinarily be permitted to participate in any other trial of an investigational medicinal product or other intervention while under follow-up in the H-PRIME trial. Participation in other studies that do not involve an intervention (i.e. observational studies) may be acceptable, but should be discussed with the H-PRIME Trial Management Group (TMG). The H-PRIME TMG will consider co-enrolment of H-PRIME participants onto other trials where the interventions do not conflict with the H-PRIME objectives on a case-by-case basis.

5 TREATMENTS

5.1 INTRODUCTION

All trial participants will initiate randomised open label hydroxyurea (at high (daily) or low (thrice weekly) dose, see **Table 2** below) and malarial and antimicrobial prophylaxis. The proposed interventions are all based on giving parts of tablets, reducing complexity in procurement, and facilitating sustainability. Dosing is based on simple weight- or age-band-based algorithms, aligning with WHO thresholds and doses wherever possible. All children will receive folic acid 1mg daily. All children under 5 years will receive anti-helminthic drugs every 3 months. CRFs will collect data on all administered drugs.

Body weight should be obtained by weighing children on a standardised digital weighing scale. Children should be weighed in light clothes, without shoes. Body weight reported by parents is not acceptable. Body weight should be obtained at enrolment and every subsequent visit. This weight should be used to determine the correct weight-band for the dose prescribed until the next visit. To reduce the risk of drug toxicities, doses issued until the next visit should always be based on the weight at the current visit, even though children may gain weight before the next visit. For example, a child weighing 9.9kg at their current visit should be prescribed the dose for the 6-<10kg weight-band, even though it is likely that they will increase weight before their subsequent visit.

All once-daily drugs should be taken together at a fixed time of day, either morning or evening, according to the preference of both children and carers, which may vary over time in the trial, but should not vary day by day.

5.2 HYDROXYUREA

5.2.1 PRODUCTS AND TREATMENT SCHEDULE

Children will be randomised 1:1 to hydroxyurea at fixed high dose vs hydroxyurea at fixed low dose. Both will be provided as 1000mg tablets (supplied by Novartis), scored three times into four 250mg sections. This formulation of hydroxyurea is already licensed by the National Drug Authority in Uganda.

We will deliver the drug at two different target doses: a high dose of 25 (15-30) mg/kg/day or low dose of 10 (6-13) mg/kg/day using fixed weight-band based doses as shown in **Table 2**. The high dose group will take this dose every day; the low dose group will take this dose three times a week (suggesting Monday, Wednesday, Friday) to fit with the school/working week, but can be flexible based on parents/carers preferences.

Table 2. Weight-band based dosing of hyroxyurea, cotrimoxazole and DHA-PQP

Weight band	Dose					
	High dose hydroxyurea		Cotrimoxazole	DHA-PQP		
	Tablets (1000mg)	Total mg	Total mg sulphamethoxazole /trimethoprim**	Tablets (20/160mg)	Tablets (80/640mg)	Total mg
3 - <6kg	*		100/20	1	-	20/160
6 - <8kg	*		200/40	1	-	20/160
8 - <10kg	¼	250	200/40	1½		30/240
10 - <11kg	¼	250	200/40	1½		30/240
11 - <14kg	¼	250	200/40	2***	½***	40/320
14 - <17kg	¼	250	400/80	2***	½***	40/320
17 - <20kg	½	500	400/80	3	-	60/480
20 - <25kg	½	500	400/80	3	-	60/480
25 - <33kg	¾	750	800/160		1	80/640
33 - <60 kg	1	1000	800/160		1½	120/960

Note: The low dose hydroxurea randomision will be to the same dose as the high dose randomisation but will be given on only three days / week (suggesting Monday, Wednesday and Friday) instead of every day of the week

* Children who drop below 8kg will be temporarily excluded from the hydroxyurea randomisation until they re-attain a weight of 8kg or more.

** may be taken as paediatric tablets (400/80mg) or adult tablets (800/160mg) or parts of paediatric/adult tablets

*** given EITHER with one strength tablet or the other

Table 3. Age based dosing of SP and penicillin V

Age	Dose			
	SP		Penicillin V	
	Tablets (500/25 mg)	Total mg	Tablets (250 mg)	Total mg
1-<3y	½	250/12.5	½	125
2-<3y	½	250/12.5	½	125
3-<5y	½	250/12.5	1	250
5-<10y	1	500/25	1	250
10-<15y	2	1000/50	1	250

5.2.2 DOSE MODIFICATIONS AND INTERRUPTIONS OF HYDROXYUREA

H-PRIME will test the benefits and risks of pragmatically delivering hydroxyurea using weight-band based doses and administered with only clinically driven haematological monitoring. Hydroxyurea dosing will be temporarily withheld on any participant whose weight drops below 8kg during the course of the trial until such time as they re-attain a weight of 8kg or more.

For research purposes, we will collect standard data on haematological efficacy and toxicity (full blood and reticulocyte counts, and HbF measurements) 6 monthly; however, the results of these tests will not be returned to clinicians routinely in either randomised group and will not be used for clinical management. The only exception will be if severely abnormal values are detected, as defined by Grade 4 laboratory adverse events as outlined in **Table 7**. Such results will be communicated to the site clinicians as soon as they are identified. Under all other circumstances, decisions to interrupt trial drug in both hydroxyurea randomised groups will be based on clinical grounds, supported where necessary by results of blood tests that would normally be available locally (i.e. haemoglobin only) and that will be ordered on clinical grounds only (based on signs/symptoms). Alternatively, if clinical

complications coincide with phlebotomy visits, we will release the results of these scheduled blood counts on the basis of specific clinical indications to limit the number of blood draws. However, reticulocyte counts and HbF, tests which are not routinely available or affordable at the participating centres, or more widely in Uganda beyond a limited number of research centres, will not be fed back to clinicians and should not be requested as they are not used routinely for clinical management. This type of approach was used successfully (and safely) in the large adult (DART[60]) and paediatric (ARROW[61]) trials of clinically-driven monitoring for HIV treatment and informed management guidelines in Uganda.

Clinicians will be free to conduct haemoglobin tests for suspected severe anaemia/crises or febrile illness or send blood cultures for suspected bacterial sepsis, as locally available. If such a haemoglobin test, conducted on the basis of clinical suspicion, is <5g/dl, in the first instance hydroxyurea should generally be temporarily discontinued for a minimum of 1 week, and the child carefully reviewed clinically, with additional haemoglobin tests performed as indicated. In case of persisting suspected toxicity to hydroxyurea, and 2 or more temporary discontinuations of hydroxyurea, the primary course of action should either be to restart hydroxyurea at half dose or discontinue the drug permanently. Additional management guidelines are provided in the MOP.

Toxicity will be managed in both randomised groups according to standard clinical practice.

Children randomised to low dose hydroxyurea who meet Uganda clinical guidelines for initiation of hydroxyurea during the trial (see **Section 5.2.4** below) should commence daily hydroxyurea therapy as directed in the Uganda National Guidelines[25], following the doses in **Table 2** (children randomised to high dose hydroxyurea are already receiving doses following the guidelines).

5.2.3 STOPPING DRUG EARLY

General discontinuation criteria are considered in **Section 5.88.**

5.2.4 INITIATION OF DAILY HYDROXYUREA

Participants in H-PRIME should discontinue low dose hydroxyurea and switch to daily dosing based on the Uganda Clinical Guidelines 2023[25] and shown in **Table 2** if they meet any the following criteria:

- >5 crises in one calendar year (i.e. six crises or more)
- Known abnormal transcranial Doppler ultrasound velocities
- Stroke, as evidenced by the development of unilateral weakness or paralysis persisting for more than one week with features on neurological examination consistent with this diagnosis.
- Acute chest syndrome: given the difficulties in differenting acute chest syndrome from pneumonia, and the need for access to chest X-ray facilities, this will be operationalised by 3 or more admissions for pneumonia or lower respiratory tract infections within one calendar year.

5.2.5 EXPECTED TOXICITIES OF HYDROXYUREA

Hydroxyurea is expected to lower white blood cell, red blood cell, and platelet counts. This is common and, based on results from NOHARM[17] and REACH[18] (which together included more than 800 children treated for more than 3 years) is unlikely to reach dangerous levels that cause any problems. If a child presents with clinical symptoms suggestive of such toxicities, then clinicians should request a haemoglobin or other blood tests that are routinely available, see **Section 5.2.2** above.

Other expected toxicities, according to the Summary of Product Characteristics (SPC), are summarised in **Table 4**. Many are mild and often resolve spontaneously.

Table 4. Expected adverse events on hydroxyurea from the SPC

System	Frequency	Event
Blood and lymphatic disorders	Very common	Bone marrow depression[1] including neutropenia, reticulocytopenia or macrocytosis[2]
	Common	Thrombocytopenia, anaemia[3]
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
Skin and subcutaneous tissue disorders	Common	Skin reactions (e.g. oral, ungula and cutaneous pigmentation) and oral mucositis
	Uncommon	Rash, melanonychia, alopecia
	Rare	Leg ulcers
	Very rare	Systemic and cutaneous lupus erythematous
	Not known	Cutaneous dryness
Reproductive system and breast disorders	Very common	Oligospermia, azoospermia[4]
	Not known	Amenorrhea
Hepatobiliary disorders	Rare	Elevated liver enzymes
Gastrointestinal disorders	Uncommon	Nausea
	Not known	Gastrointestinal disturbances, vomiting, gastrointestinal ulcer, severe hypomagnesemia
Infections and infestations	Not known	Parvovirus B19 infection
Vascular disorders	Not known	Bleeding
Neoplasms	Not known	Leukaemia
General disorders	Not known	Fever
Other	Not known	Weight gain[4]

[1]Haematological recovery usually occurs within two weeks of withdrawal of hydroxycarbamide.
[2]The macrocytosis caused by hydroxycarbamide is not vitamin B12 or folic acid dependent.
[3]Mainly due to an infection with Parvovirus or a splenic sequestration.
[4]Oligospermia and azoospermia are in general reversible, but have to be taken into account when fatherhood is desired (see section 5.3). These disorders are also associated with the underlying disease.
[5]Weight gain may be an effect of improved general conditions.
Note: The frequency of complications, defined as very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data), are based on the summary of product characteristics released through the European Medicine Agency.[62]

5.3 ANTIMALARIAL PROPHYLAXIS

5.3.1 PRODUCTS AND TREATMENT SCHEDULE

Children will be randomised 1:1 to enhanced antimalarial prophylaxis with weekly DHA-PQP, vs monthly SP (SOC as defined in the Uganda Clinical Guidelines 2023[25]).

Because CTX and SP should provide similar anti-malarial cover, and to avoid overdosing with sulphonamide compounds, pragmatically, children randomised to CTX prophylaxis under the antibiotic randomisation and SOC anti-malarials under the anti-malarial randomisation will receive CTX alone without additional SP (with the further advantage of reducing pill burden).

5.3.2 DHA-PQP

DHA-PQP will be given once weekly on a fixed day of the week, the day to be chosen by the primary carer (i.e. one-third of the monthly dose given once a week) following WHO-recommended doses (5-<8kg 20/160mg; 8-<11kg 30/240mg; 11-<17 kg 40/320 and ≥17 kg 60/480[43,44,46]). This regime is simpler than the standard monthly DHA-PQP schedule, which involves dosing on 3 consecutive days

once a month. Our research teams have experience in weekly dosing of children when the standard of care was weekly chloroquine tablets. Adherence during that period for children on this regimen for over 10 years was over 95% (Mbale Hospital Sickle Clinic Report).

Importantly, PK studies indicate that the once-weekly dosing regimen leads to lower peak levels[46] than the monthly dosing regimen. Although a recent meta-analysis of nearly 200,000 individuals[63] demonstrated no excess risk of sudden cardiac death with DHA-PQP, if there were any undetected excess risk, particularly in this SCD population, physiologically it would be mostly likely related to maximum concentration. Hence the weekly dosing regimen is highly likely to be safer from the point of view of potential cardiotoxicity. Further, the weekly regime results in higher trough levels, which protect against the development of parasite resistance through reducing exposure to sub-therapeutic drug levels and is also more tolerant to missing doses. We therefore consider that weekly dosing will be both better tolerated and more effective than monthly dosing; it is supported by the Medicines for Malaria Venture.

5.3.2.A Dose modifications and interruptions of DHA-PQP

Following the dosing recommendations in the Summary of Product Characteristics, parents and participants will be instructed that the weekly dose of DHA-PQP should be taken on an empty stomach, with water but without food for the 3 hours before and 3 hours after a dose. For this reason, parents will be advised to give this weekly dose at a time that fits best with their child's routine; however, the drugs should be administered at least 3 hours after children have eaten breakfast and children should then be limited to water thereafter until they receive their next meal at least 3 hours post-dose. In others, it might be more convenient to administer the dose during the evening, at least 3 hours after supper and before they retire for bed. Parents will be counselled regarding these two options and requested to follow the option they are most comfortable with for the duration of the study. As this is only a once-weekly activity it is not anticipated that this will present an unduly onerous responsibility. General discontinuation criteria for DHA-PQP are considered in **Section 5.8**. Doses should not be reduced.

5.3.3 EXPECTED TOXICITIES OF DHA-PQP

The expected toxicities of DHA-PQP, along with their frequencies among children, as based on the Summary of Product Characteristics, are summarised in **Table 5**.

Table 5. Expected adverse drug reactions that are associated with DHA-PQP in children

System	Very common	Common	Uncommon
Infections and infestations	Influenza *P. falciparum* infection	Respiratory tract infection Ear infection	
Blood and lymphatic system disorders		Anaemia Leukocytosis Leukopenia/neutropenia Thrombocytopenia	Hypochromia Lymphadenopathy Splenomegaly Thrombocytopenia
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders			Convulsion Headache
Eye disorders		Conjunctivitis	
Cardiac disorders		Heart rate irregularities QT/QTc prolonged	Cardiac murmur Cardiac conduction disorders
Respiratory, thoracic and mediastinal disorders	Cough		Epistaxis Rhinorrhoea
Gastrointestinal disorders		Abdominal pain Vomiting Diarrhoea	Nausea Stomatitis
Hepatobiliary disorders			Hepatitis Hepatomegaly Jaundice Abnormal liver function tests
Skin and subcutaneous tissue disorders		Dermatitis Rash	Pruritis Acanthosis
Musculoskeletal and connective tissue disorders			Arthralgia
General disorders and administration site conditions	Pyrexia	Asthenia	

Note: based on the SPC for Eurartesim.[64] Events are listed under system organ class, and ranked by headings of frequency, the most frequent first, using the following convention: Very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

5.3.4 SULPHADOXINE PYRIMETHAMINE (SP)

SP will be given monthly following WHO-recommended doses (1-5 years ½ tab (250/12.5mg); 5-10 years 1 tab (500/25mg); 10-15 years 2 tabs (1000/50mg)[40] (**Table 3**).

5.3.4.A Dose modifications and interruptions of SP

General discontinuation criteria for SP are considered in **Section 5.8.** Doses should not be reduced.

5.3.5 EXPECTED TOXICITIES OF SP

At recommended doses, SP is generally extremely well tolerated; however, the following events can occur rarely in individuals receiving SP:

- Skin reactions including rash, pruritis, photosensitivity and slight hair loss.
- Erythema multiforme Stevens Johnson syndrome and Lyell's syndrome.
- Hepatic reactions including a transient rise in liver enzymes and hepatitis.
- Gastrointestinal reactions including nausea and vomiting.

- Haematological changes including thrombocytopaenia, leukopenia and agranulocytosis.

5.3.6 STOPPING ANTI-MALARIAL PROPHYLAXIS EARLY

General discontinuation criteria for SP are considered in **Section 5.8.** As anti-malarial prophylaxis is recommended in the Uganda Clinical Guidelines for SCD, 2023,[25] children would generally be expected to remain on it for the duration of follow-up.

5.4 ANTIMICROBIAL PROPHYLAXIS

5.4.1 PRODUCTS AND TREATMENT SCHEDULE

Children will be randomised 1:1 to

- enhanced anti-bacterial prophylaxis with once daily CTX given throughout childhood, sto
- penicillin V given twice daily until 5 years of age (SOC as defined in the Uganda Clinical Guidelines 2023[25])

5.4.2 COTRIMOXAZOLE

Cotrimoxazole dosing will follow WHO weight-band based recommendations for prophylaxis in HIV-infected children:[65] 3-<6kg 100/20mg; 6-<14kg 200/40mg; 14–<25kg 400/80mg; 25+kg 800/160mg (**Table 2**). This may be administered as any formulation including suspension 200/40mg per 5mls, 100/20mg dispersible tablets or 400/80mg or 800/160mg tablets or parts thereof. The dispersible tablets may be taken with water or mixed with feeds. Children will take cotrimoxazole throughout their trial participation.

5.4.2.A Dose modifications and interruptions of CTX

General discontinuation criteria for CTX are as outlined in **Section 5.8**. Doses should not be reduced.

5.4.3 EXPECTED TOXICITIES OF CTX

The expected toxicities associated with CTX are similar to those described for sulphadoxine pyrimethamine above.

5.4.4 PENICILLIN V

Penicillin dosing will be based on age: <3 years 125mg; 3-5 years 250mg, both given twice daily (**Table 3**). Following the SOC in the Uganda Clinical Guidelines,[25] children randomised to penicillin will stop taking this intervention at the age of 5 years.

5.4.4.A Dose modifications and interruptions of Penicillin V

General discontinuation criteria for penicillin V are considered in **Section 5.8**. Doses should not be reduced.

5.4.5 EXPECTED TOXICITIES OF PENICILLIN V

Penicillin V is normally well tolerated at recommended doses. The most important events in children receiving penicillin V are:

- Hypersensitivity including rash, pruritis, photosensitivity and in extreme rare cases anaphylactic reactions.
- Gastrointestinal reactions including nausea, vomiting, glossitis and stomatitis.
- Blood dyscrasias including leucopoenia, thrombocytopaenia and agranulocytosis.
- Overgrowth of normal commensals including candida.

5.4.6 STOPPING ANTIMICROBIAL PROPHYLAXIS EARLY

General discontinuation criteria for both forms of antimicrobial prophylaxis are considered in **Section 5.8.** Following SOC in national guidelines for SCD,[25] children randomised to penicillin V would be expected to stop penicillin V on their fifth birthday. Children randomised to CTX will remain on it for the duration of follow-up.

5.5 DISPENSING OF ALL TRIAL MEDICATION AND ACCOUNTABILITY

For all trial drugs, the designated trial pharmacist or nurse will confirm receipt of supplies prior to the commencement of the trial. Inventories will be conducted regularly, and logs returned to the MCRI. All drugs dispensed to participants will be recorded on a dispensing log or logged online. At each site, a named person (trial pharmacist or research nurse) must maintain complete records of all medication dispensed and returned.

Carers will be provided with a full supply of drugs at each visit sufficient to last until the next scheduled clinic visit. All drugs are open-label and will therefore be prescribed in exact amounts to last until the next clinic visit. No additional pills of these other open-label drugs will be dispensed to avoid carers only returning to clinic when these drugs are finished. Carers will be requested to return all empty bottles and any unused drug to the follow-up clinic.

On no account should any drug assigned to a participant be used by anyone else. Unused trial drug must be returned to the site if a participant withdraws from treatment.

5.5.1 ACCOUNTABILITY AND UNUSED DRUGS

Procedures for drug distribution, labelling, accountability, and destruction will be detailed in the H-PRIME Pharmacy Manual of Operations (MOP). Drug accountability will be regularly monitored, and the remaining stocks checked against the amounts dispensed. At the end of the trial, all remaining investigational drugs will be destroyed. MCRI will monitor drug accountability centrally and during site visits.

5.6 COMPLIANCE AND ADHERENCE

The Ugandan national guidelines recommend use of daily penicillin V prophylaxis and folic acid, and monthly SP, in children with SCD. We therefore do not anticipate substantial compliance problems in this group with motivated carers given their child's chronic condition. The trial drugs are used relatively widely as prophylaxis in children with at most modest rates of toxicity and high acceptability. As the interventions will start immediately following randomisation, suitable patient information and fully informed consent procedures will ensure that participants understand the trial requirements. All carers will be asked questions about adherence using a standard questionnaire at clinic visits according to the flow sheet. Any non-compliance due to lack of acceptability or side-effects would also likely occur if the interventions were incorporated within clinical practice and is part of a pragmatic strategy being evaluated. The intention-to-treat comparison will therefore incorporate such "strategy non-compliance" that is anticipated in general clinical practice. Finally, in our current and recent REACH[31] and NOHARM[17] trials compliance with daily hydroxyurea therapy was universally high, reaching >95% across both trials and all trial sites (Ware, personal communication).

5.7 TRIAL MEDICATION OVERDOSE

Parents/guardians of the children participating in the trial will be counselled about the importance of taking the oral medications as prescribed. Parents/guardians should contact the H-PRIME clinic immediately if their child has been overdosed, to receive appropriate advice. Participants will then

be managed on a case-by-case basis and toxicity will be managed in all randomised groups according to standard clinical practice.

5.8 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, parents/guardians are consenting to trial treatment, trial follow-up and data collection for their child. However, an individual participant may stop any one or all of their randomised trial treatments early or it may be stopped early, either temporarily or permanently, for any of the following reasons:

- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- A fall in weight to less than 8kg
- Any change in the participant's condition that justifies the discontinuation of trial treatment in the clinician's opinion
- Inadequate compliance with the protocol treatment in the judgement of the treating physician
- Withdrawal of consent for treatment by the participant or their carer
- The onset of pregnancy in female partipants

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

Any other non-trial medication a trial participant receives should be recorded, and participants should remain in the trial for the purpose of follow-up and data analysis "on-study, off-study-treatment" (unless the participant explicitly withdraws their consent from all stages of the trial). If a participant is withdrawn from all follow-up, refer to **Section 6.6**.

5.9 TREATMENT DATA COLLECTION

Information about all medication received, including formulation, frequency, dose and reasons for change will be collected on the trial CRFs. All oral, intravenous, intramuscular, and topical treatments for any condition are considered a concomitant medication, including blood transfusion.

5.10 NON-TRIAL TREATMENT

All necessary concomitant medications are allowed. If a medication with a known drug interaction to one of the trial medications is essential for a participant's management, then, if appropriate dose adjustment is not possible, the trial medication should be stopped and the concomitant medication used.

6 ASSESSMENT AND FOLLOW-UP

6.1 SUMMARY

The Trial Assessment Schedule on p13 summarises all assessments and procedures.

All participants will be followed for a minimum of 2 years and a maximum of 4 years. Trial follow-up will finish 4 years after the first participant is randomised. All participants will be seen at clinic at screening, randomisation, 1 and 3 months later and then every 3 months. Visits will include evaluations from both physicians/medical officers/clinical officers and nurses.

Trial visit schedules will be prepared for each participant at randomisation, and participants should be followed on the same schedule even if their trial medication is discontinued. The target dates for trial visits are determined by the date of randomisation and are not affected by subsequent events. Clinics may choose to re-schedule visits to allow for public holidays or other unavoidable circumstances that affect the scheduled visit date, but the re-scheduled visit should ideally be no more than 7 days (either before or after) from the originally scheduled visit date.

Participants will be expected to attend on the scheduled day unless agreed in advance with the clinic. Participants will be given a card with the contact details for the trial research team, so they can contact them if needed to re-arrange a visit. If they are unable to attend on the day, every effort should be made to complete the visit within 7 days of the scheduled date. If a scheduled visit is missed without notice, then the clinic should endeavour to contact the participant by phone or by home visit.

If a participant is more than 7 days late for a scheduled trial visit, up to three attempts will be made to contact and trace the child. An additional visit will be performed as soon as possible, including the appropriate assessments that were specified in the trial schedule for the visit week that was missed.

The schedule defines visit dates (with windows) necessary for data collection, but the participant may be seen more frequently as needed, at the discretion of the treating clinician, for example if the participant develops drug toxicity or other clinical events. At any such unscheduled visits, routine assessments as for a standard clinician and nurse visit will be performed (as for month 3). Other laboratory tests will be performed as clinically indicated. **In particular, participants in all groups may undergo all necessary diagnostic tests that are available locally for clinical management of illness.**

The participants' carers will be encouraged to contact the trial clinicians in the event of illness. In addition, hospital wards will be regularly reviewed for trial participants and out-of-hospital mortality will be ascertained by telephone contact and community follow-up.

At each assessment (months 0, 1, 3, 6, 9, 12, 15, 18, 24, 27, 30, 33, 36, 39, 42, 45, 48), the following will be undertaken:

- Administration of a symptom checklist by a nurse or other trial staff member to detect intercurrent illness or adverse events to medication. The severity and likely relationship of any adverse events to medication will be documented by a physician/medical officer in the child's notes, and where applicable on the case record forms.
- Medical history since last visit including adverse events (including specific questions about specific complications including strokes and painful crises), signs and symptoms of SCD, inpatient and outpatient attendances, both with appropriate laboratory forms completed to document test results, blood transfusions.

- Weight, height, mid-upper arm circumference (MUAC)
- Assessment of adherence to trial medication by pill counts and nurse administered brief questionnaire (not week 0).
- EQ-5D-Youth assessment of activities of daily living by a nurse or other trial staff member
- Changes in trial drugs and other concomitant medication, and use of clinically driven laboratory monitoring to determine any changes.
- A malaria RDT, thick and thin films, and 2x filter paper whole blood samples for malaria resistance testing will be collected in children with documented fever (digital axillary temperature >=37.5^{0}C) and/or other symptoms suggestive of malaria along with a blood culture where possible. Any child with signs warranting hospital admission will be referred immediately. This will also be done at extra (non-scheduled) visits where the child presents with fever
- 2x filter paper whole blood samples for pharmacokinetic analysis will be taken at any scheduled or unscheduled visit where any cardiac problems are reported (including suspected or proven cardiac arrythmia). Any child with signs warranting hospital admission will be referred immediately.
- Money for transport will be given by the clinical coordinator or designee.
- Urine pregnancy tests will be carried out at every visit in any female who has reached menarche; any such females will be counselled against becoming pregnant.

At specific visits, the following will be undertaken:

- At months 0, 3, 6 and then 6-monthly, a full blood count will be performed together with HbF and reticulocyte count. Other haematology (or laboratory) tests may be performed if clinically indicated, but are not required by the protocol. HbF and reticulocyte counts should not be requested for clinical management.
- Annually, the PedsQL measurement model for the Pediatric Quality of Life Inventory (self-reported for children >5 years and Parent Proxy Report for younger children), which has been widely used in HIV and other trials, along with the sickle modules of the same instrument.[66]
- Annually, 4ml blood will be take for 2ml plasma storage.

In a specific sub-study (see **Section 9**), the following will be undertaken:

- Electrocardiography: enrolment (baseline), month 1 (pre and 4 hours post-dose), month 6 (pre and 4 hours post-dose), month 12 (pre and 4 hours post-dose) and then annually.
- Pharmacokinetics: in the same children at the same timepoints, blood on filter paper will be taken for retrospective analysis of DHA-PQP and SP blood levels.

6.2 PROCEDURES FOR ASSESSING EFFICACY

6.2.1 CLINICAL EVENTS (ALL PARTICIPANTS)

- Survival status will be recorded at each visit. Any participant who misses a scheduled clinic visit without withdrawing consent will be traced for vital status.
- Other serious adverse events will be reported as soon as the doctor becomes aware of them (see **Section 7**), including through ward rounds for admitted children. Given the catchment areas of the hospitals, children would generally be re-admitted to the same clinical site. The details reported will include laboratory data, and any additional clinical narrative.
- At all visits, a history of intercurrent hospital admissions and/or blood transfusion will be solicited.

6.2.2 HAEMOTOLOGICAL RECOVERY (ALL PARTICIPANTS)

- Haemoglobin, HbF and other blood count parameters will be measured every 6 months.

As described in **Section 5.2.2**, results of these blood tests will not be released to clinicians, unless clinical complications coincide with phlebotomy visits, and the clinician requests a haemoglobin test result for clinical reasons (based on signs/symptoms) in order to limit the number of blood draws. The only exception will be the detection of potentially dangerously abnormal values, as defined by Grade 4 laboratory adverse events outlined in **Table 7**, which will be automatically returned to clinicians.

6.2.3 PROCEDURES FOR ASSESSING SAFETY (ALL PARTICIPANTS)

The symptom checklist used at each visit will explicitly prompt for symptoms relating to possible drug toxicities. Additional safety blood tests or investigations that are available locally may be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

Serious, solicited and grade 3 or 4 adverse events will be reported on the case report form.

6.2.4 PROCEDURES FOR ASSESSING ADHERENCE (ALL PARTICIPANTS)

Adherence to all intervention drugs will be assessed in all participants at each visit by pill counts for tablets and a nurse-administered questionnaire to the child's carer or, where appropriate, to the child (at the discretion of the nurse or doctor depending on age).

6.3 OTHER ASSESSMENTS

6.3.1 HEALTH ECONOMICS

See **Section 9.1**.

6.4 PREGNANCY

Hydroxyurea is a Category D drug with teratogenic potential. There are no adequate and well-controlled studies in pregnant women, so precautions will be taken in the H-PRIME trial to recommend against pregnancy and to regularly monitor menstruating female participants for pregnancy. Only children under 10 years will be recruited: given the pubertal delay associated with SCD,[67] these girls will not have reached menarche. Post-randomisation, whether a girl has reached menarche will be ascertained at every visit. All girls with childbearing potential will be counselled about the potential risks associated with pregnancy whilst taking hydroxyurea and the potential risks to the infant. On reaching menarche, the girl may choose to discontinue hydroxyurea and continue to receive other trial medications and follow-up in the trial if she wishes. If she wishes to continue on hydroxyurea, she will be advised to use highly effective contraception if sexually active and to report to the study staff as soon as possible if there is a possibility of pregnancy. Pregnancy testing will be conducted at every visit in any girl who has reached menarche. If a girl is found to be pregnant, hydroxyurea will be discontinued immediately. Pregnant participants should receive counselling about their options and receive support to make decisions about continuing pregnancy. The pregnancy must be followed up to determine outcome and status of mother and child. Pregnancy complications must be reported as an AE or SAE as appropriate: pregnancy per se is not an AE or an SAE. Any SAE occurring in association with a pregnancy brought to the investigator´s attention after the participant has completed the study and considered by the investigator as possibly related to any IMP should also be reported as an SAE.

Male participants will also be counseled about the need to avoid fathering a child while taking hydroxyurea.

6.5 EARLY STOPPING OF FOLLOW-UP

A parent or guardian who chooses to discontinue trial treatment for their child should be encouraged to follow the other trial procedures and follow-up schedule. However, if they do not wish to remain on trial follow-up, their decision must be respected, and the participant will be withdrawn from the trial completely. The MCRI should be informed of this in writing using the appropriate documentation (Appendix I). Prior to transferring out of the trial, the parent or guardian will be asked to have assessments performed as appropriate for a final trial visit. They would be at liberty to refuse any or all individual components of the assessment.

If follow-up is stopped early, the medical data collected during their participation in the trial up to this point will be kept and used in the analysis, as consent cannot be withdrawn for data already collected. Similarly, samples obtained prior to this time will be processed according to the protocol, unless the parent or guardian explicitly and unprompted requests otherwise. Consent for future use of stored samples already collected can be refused when leaving the trial early (but this should follow a discussion).

Participants who have left the trial may subsequently re-consent to participation in the trial if they change their minds about participation. If they return, they will follow the same randomisations as initially allocated.

Participants who stop trial follow-up early will not be replaced (the sample size calculation includes adjustment for lost to follow-up).

6.6 PARTICIPANT TRANSFERS

If a participant moves within the region, then their follow-up may be transferred to another trial centre. They should retain their original trial number.

If a participant moves from the area, reasonable efforts should be made to continue their follow-up, e.g. by them continuing to come to clinic providing that the site has sufficient funds to cover the necessary transport refund, or for example by conducting visits over the telephone. If this is not possible (e.g. if the participant moves to a different country), then the participant should be considered as lost to follow-up. The participant may or may not choose to formally register this as a withdrawal of consent.

6.7 LOSS TO FOLLOW-UP

Any child lost to follow-up before the end of the trial 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 at screening and verified at every review. If the child misses any scheduled visit, attempts should be made to contact the participant via phone (if available) and to follow-up with home visits, if at all possible.

For operational management at participating sites, a child will be classified as “lost to follow-up” only when three scheduled visits have been missed and attempts to contact the child/carer have been unsuccessful. If an individual telephone follow-up visit is missed, the site team should continue to attempt to contact the carer via phone and/or email for all future visits. Home visits should be offered on a case-by-case basis as appropriate to minimise loss to follow-up. If it is evident that a face-to-face visit cannot be arranged during the designated time frame, every effort should be made to conduct telephone follow-up instead.

In the statistical analysis, a participant will be regarded as 'lost to follow-up' if they were not seen in clinic and vital status was not otherwise ascertained through telephone or home visits, within 3 months of the end of the trial and were not known to have died.

6.8 TRIAL CLOSURE

The trial will end after the last follow-up visit of the last randomised participant, which will be 4 years after the first randomisation. At that point, all participants will revert to standard of care pending final analysis and determination of optimal management.

Sites will be closed once data cleaning is completed and the regulatory authorities and ethics committee will be informed.

7 SAFETY REPORTING

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials.

7.1 DEFINITIONS

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

Table 6. 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. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

*** 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.

Note: Suspected Unexpected Serious Adverse Reaction (SUSAR) will not be assessed in H-PRIME as it falls outside the scope of the European Union Clinical Trial Regulations.

7.1.1 MEDICINAL PRODUCTS

An investigational medicinal product is defined as the tested investigational medicinal product (IMP) and the comparators used in the trial (EU guidance ENTR/CT 3, April 2006 revision). For H-PRIME, this includes hydroxyurea, SP, DHA-PQP, CTX and penicillin V.

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

7.1.2 ADVERSE EVENTS

Adverse Events (AEs) include:

- An exacerbation of a pre-existing illness
- 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 after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment

Adverse Events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g. elective cosmetic surgery, social admissions
- Overdose of medication without signs or symptoms

7.1.3 OTHER NOTABLE EVENTS

Pregnancy-related events do not constitute SAEs unless they result in a condition that meets the seriousness criteria defining SAEs (e.g. septic abortion, congenital abnormality). However, they are notifiable events and therefore should be reported as soon as possible to the MCRI. There are no other notable events.

7.2 INVESTIGATOR RESPONSIBILITIES

7.2.1 INVESTIGATOR ASSESSMENT

7.2.1.A Seriousness

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in **Table 6**. If the event is serious, then an SAE Form must be completed and the Chief Investigator and the Trial Coordinating Centre at MCRI must be notified within 1 working day.

7.2.1.B Severity or grading of adverse events

The severity of AEs and/or ARs (serious and non-serious) in this trial should be graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50), with the exception of specific laboratory abnormalities listed in **Table 7** below which will be graded as in the REACH trial recognising the lower normal levels in African populations and/or in individuals with sickle cell disease.

Table 7. List of laboratory exceptions to the CTCAE version 5.0 grading

Parameter	Grade 2	Grade 3	Grade 4
Haemoglobin (g/dL)	5.0 – 5.499	4.0 – 4.9	<4.0
Total white blood count (x 10^9/L)	1.0 – 1.999	0.5 – 0.999	<0.5
Neutrophils (x 10^9/L)	0.5 – 0.999	0.2 – 0.499	<0.2
Platelets (x 10^9/L)	50 – 79	20 – 49	<20
Total Bilirubin (μmols/L)	85.5 – 171	172.7 – 342	>342
AST (IU/L)	150 – 300	301 – 1000	>1000
ALT (IU/L)	150 - 300	301 – 1000	>1000
Creatinine (μmol/L)	Doubling of baseline serum AND value ≥88.4μmol/L	141.4–176.8	>176.8
ARC (x 10^9/L) (when Hb <7.0 g/dL)	50-80	10-49	<10

Any event for which no specific grading is provided for in the CTCAE should be graded as follows:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care activities of daily living.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

7.2.1.C Causality

The investigator responsible for the care of the participant must assess the causality of all serious events or reactions in relation to the trial medications using the definitions in

Table 8. Investigators should use clinical judgment, taking into account the chronological relationship between the administration of the drug and the occurrence of the adverse reaction, along with consensus knowledge about SCD in determining event causality. There are six categories: unrelated, unlikely, possible, probable, definitely related and not assessable. These follow the WHO-Uppsala Monitoring Centre criteria[68] but combine the unclassified and unclassifiable categories into one "not assessable" category, and include an unrelated category because many of the drugs used in H-PRIME have known side-effects based on many years of use. As all children are on multiple drugs in some situations it will be clear that a reaction is to one drug being taken and therefore not to others being taken. These categories have been widely used in trials conducted across the EU and previous trials in acutely sick children (including those with HIV infection) across Africa. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possibly, probably, or definitely related, then the event is classified as an SAR. If any doubt about the causality exists, the local investigator should inform the trial coordination centre who will notify the Chief Investigators. Other clinicians may be asked to advise in some cases.

Table 8. Causality assessment

Relationship	WHO	Description*
Unrelated**	-	There is no evidence of any causal relationship and there is another probable/definite explanation for the event (e.g. the participant's clinical condition, other concomitant treatment)
Unlikely	Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	Possible	There is some evidence to suggest a causal relationship (e.g. 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 (e.g. the participant's clinical condition, other concomitant treatments).
Probable	Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	Certain	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable***	Unassessable Unclassifiable Conditional Unclassified	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

** All points should be reasonably complied with.*
*** An adverse event is classified as "Unrelated" when there is no plausible time relationship to drug intake and the event can be fully explained by other factors such as underlying disease or other drugs. It includes coincidental events.*
**** The term includes Unassessable / Unclassifiable / Conditional / Unclassified events where additional data is required, or data cannot be verified.*

7.3 REPORTING PROCEDURES

At each clinical review the clinician or nurse will check for adverse events. In the event of an abnormal clinical or laboratory finding by the trial clinician, children will receive appropriate treatment according to national or WHO clinical guidelines, including admission for assessment and/or treatment where appropriate. All non-serious AEs and ARs, whether expected or not, should be recorded in the child's medical notes and, if appropriate, reported in the clinical symptoms section of the appropriate CRF and data entered within the agreed timescale. As medications used in the trial are all licenced in children, clinical or laboratory toxicity will be reported on CRFs if grade 3 or 4, serious or if they lead to modification, or temporary or permanent discontinuation, of any trial treatment. SAEs and SARs should be notified to the Trial co-ordinating centre at MCRI and the Chief Investigator within 1 working day of the trial team becoming aware of the event. The Trial co-ordinating centre will ensure that the Mbale Regional Referral Hospital Research Ethics Committee and the Uganda National Drug Authority are informed within 7 days of the investigator becoming aware of the event. The Uganda National Council for Science and Technology will be informed through regular reports.

The reporting procedures are detailed within the safety reporting SOP. Any questions concerning adverse event reporting should be directed to the trial coordination centre in the first instance via email or by telephone. SAEs will be reviewed immediately by a designated clinician (SAE reviewer). 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.

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

Local investigators should report all SAEs as required by their Local Research Ethics Committee. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Contact details for reporting SAEs
Please send SAE forms to:
hprime.sae@mcri.ac.ug
Tel: +256 774 573 911

8 STATISTICAL CONSIDERATIONS

8.1 SAMPLE SIZE

The primary outcome for the high versus low dose hydroxyurea randomisation will be all cause mortality. Data from a range of recent relevant trials[18,29] suggest that a range of mortality rates are plausible among children treated with low dose hydroxyurea in Africa. **Table 9** summarises those rates and the power to show a range of plausible mortality reductions with either 80% or 90% power within a trial recruiting 900 children to each group.

Table 9. Power calculation

Mortality rate (deaths / 100 person years) in the low dose group	Relative reduction detectable for the high dose group with 90% power	Absolute risk reduction	Relative reduction detectable with 80% power	Absolute risk reduction
2.5	51%	-1.3	45%	-1.1
3.0	48%	-1.4	42%	-1.3
3.5	45%	-1.6	39%	-1.4
4.0	42%	-1.7	37%	-1.5

We therefore anticipate that a trial involving a total of 1800 children will be well powered to show an approximate halving of mortality between the randomised hydroxyurea groups, and to show smaller differences at the upper end of plausible rates within the low dose group. Whilst the detectable relative reduction is slightly higher at lower event rates in the low dose group, the detectable absolute change in risk remains above 1 per 100 child-years, ie we would still be able to detect any benefits associated with high dose hydroxyurea given with pragmatic clinical and laboratory monitoring that still saved at least one extra child's life for every 100 children treated for one year.

The malaria/antimicrobial comparisons are not powered for mortality. The 1800 children randomised to DHA-PQP vs SP (or CTX in those randomised to CTX with standard antimalarials) will provide 86% power to detect a 36% relative reduction from 4.7 to 3.0 malaria-associated hospitalisations/100CY respectively, assuming that hydroxyurea does not directly affect either of these endpoints (no inflation factor). Allowing even as much as a 50% reduction in malarial and all-cause hospitalisations associated with hydroxyurea, our power to detect these same relative reductions associated with the anti-malarial and antibiotic randomisations drops from >85% to 76% and 79% respectively, but we retain >85% power to detect relative reductions of 40% and 22% respectively, which are still clinically meaningful.

Similarly, 1800 children randomised to CTX vs penicillin V will give 87% power to detect a 20% relative reduction from 20 to 16 all-cause hospitalisations/100CY respectively. These calculations are based on a reasonable assumption that CTX provides equivalent anti-malarial cover to SP, based on concerns about SP resistance and CTX effectiveness.[61]

Interactions will be explored in subgroup analyses. If instead R2&R3 are treated as a 4-arm comparison, assuming two-sided alpha=0.017 to allow for 3 pairwise comparisons with SOC for anti-malarials and antibiotics, 1800 children provides 80% power to detect a 51% relative reduction from

4.7 to 2.3 malaria-associated hospitalisations/100CY and a 29% relative reduction from 20 to 14.2 all-cause hospitalisations/100CY.

8.2 STATISTICAL ANALYSIS

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

Each intervention is hypothesised to be superior to standard of care, and therefore the proposed analysis is intention to treat, including all randomised participants.

The primary analysis of mortality in children randomised to high versus low dose hydroxyurea will use time-to-event methods (Kaplan-Meier, log-rank test, proportional hazards models), stratified by centre and adjusting for initial hydroxyurea dose (randomisation stratification factors). If the primary superiority hypothesis is not met (ie high dose is not shown to be superior to low dose in terms of mortality), then we will conduct secondary exploratory non-inferiority analyses to assess whether mortality is non-inferior with low dose compared to high dose hydroxyurea. This will be conducted at a one-sided significance level (as we do not expect that low dose will be superior to high dose in terms of mortality). The planned non-inferiority margin will be a 5% absolute difference in cumulative mortality at 3 years. Assuming no true difference between the arms, the expected mortality in the high dose group is 11% at 3 years; 1800 children will provide 91% power to demonstrate non-inferiority assuming 5% loss to follow up (one-sided α=0.025). If the high dose 3 year mortality is less than 7.5% (approximately 2.5/100 CY in Table 9 above) then the non-inferiority margin will be modified to 3.5% absolute difference (without reference to the accumulating comparative data) to reflect the equivalent relative differences between arms.

Analyses of hospitalisations (malaria-specific and all-cause) will use Poisson regression if there is no evidence of over-dispersion, or negative binomial models if there is evidence of over-dispersion ($p<0.01$), using the number of hospitalisations as the count and the time at risk under follow-up as the exposure. Zero-inflated models will be used if there is statistical evidence ($p<0.01$) that more children than expected do not experience the outcome. Similar methods will be used to analyse other time-to-event and count outcomes.

Pre-specified subgroup analyses will include each of the other randomised allocations (ie exploration of interactions in the factorial design), together with the other randomisation stratification factors (centre, initial hydroxyurea dose). We will also investigate a priori whether there was any evidence for a different impact of the interventions according to age, haematological indices and time in the trial (to assess for attenuation of effects over time). These will be considered both as categorical variables, splitting at terciles, and as natural cubic splines.

Continuous secondary outcome measures will be analysed using normal linear regression, adjusted for baseline values and randomisation stratification factors, with generalised estimating equations (independent working correlation) used to compare randomised groups across multiple timepoints. The frequency of hospital re-admissions and adverse events will be tabulated by body systems and by randomised groups, and the number of events experienced by each participant will be compared across randomised groups using Fisher's exact test.

For the within-trial analysis, the differential cost of the treatment interventions will be related to their differential outcomes in terms of the primary outcome. The relative cost-effectiveness of the alternative forms of management will then be assessed using standard decision rules and a full stochastic analysis will be undertaken. A cost-utility analysis will also be conducted using a standard approach. The within-trial analysis will be augmented by extrapolation beyond the trial follow-up

using decision-analytic modelling. The aim of this analysis will be to predict the implications of any difference in clinical endpoints in the trial for subsequent quality-adjusted survival duration and long-term resource costs. This will inform the question of whether any differences in drug costs between the treatment groups are offset by reduction in other treatment costs or health improvements in the long-term.

8.3 INTERIM REVIEWS

During the trial an independent Data Monitoring Committee will meet to review unblinded data for all three randomised comparisons at least annually. They will review data on enrolment, safety, adherence to randomised strategies, efficacy and safety at regular intervals and in strict confidence. The DMC will meet within 6 months of the first recruitment, and will subsequently determine the frequency of their meetings, which could be more frequent than annually if they think necessary.

A decision to discontinue recruitment, in all participants or in selected subgroups, will be made only if the results are likely to convince the general clinical community and participants in the trial. The DMC will report to the Trial Steering Committee (TSC), if, in their view, the data provide proof beyond reasonable doubt that one of the allocated strategies is better than its comparator in terms of the primary outcome. The guiding statistical criterion for “proof beyond reasonable doubt” is the Haybittle-Peto criterion of a difference of at least 3 standard deviations in an interim analysis of a major endpoint. The TSC will then decide whether to amend (including the possibility of dropping one of the transfusion strategies) or stop the trial before the end of the planned follow-up. If a decision is made to continue, the DMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates.

9 ANCILLARY STUDIES

9.1 HEALTH ECONOMICS

Little is currently known about the economic burden faced by families with children affected by SCD, particularly within sub-Saharan Africa. Policymakers require information on the costs and health effects of alternative interventions when considering how to allocate limited resources to meet the population's health needs. Most research on the economic aspects of SCD has focused on the medical costs borne by insurance or health care providers in the United States,[69] although three recent studies did originate from Africa.[70-72] Direct medical and non-medical costs as well as indirect costs of SCD for individual participants and their families such as the costs of vitamins or other medical devices, transport to facilities, lost opportunities for work, time off school and other relevant factors have rarely been evaluated. These may be substantial in the rural areas in which this trial will be conducted.

We will calculate the cost-effectiveness of the intervention using a societal perspective that will take into account the costs borne (such as the costs of all medications, blood tests used for routine clinical management, clinic visits, hospital admissions and other healthcare resources and lost opportunities for paid and unpaid employment) by all parties: the health system, the carers and the affected children themselves. Unit cost data will be obtained from basic costings, costs available in the literature and data collected in other economic analyses of management strategies for children in Uganda (e.g. FEAST,[73] TRACT[74] and COAST[75]). The association between costs, benefits and baseline characteristics will be estimated, and cost-effectiveness estimated subject to uncertainty over model parameters. Longer-term extrapolation outside the trial will be based on stochastic compartmental models. As mortality is the primary outcome, cost-effectiveness will also be estimated on the basis of lives saved. Finally, we will also study affordability by relating the distribution of cost per child to that of family income and health care expenditure per child in the area.

9.2 CARDIO-SAFETY AND PHARMACOKINETICS

Although DHA-PQP is associated with QT prolongation, a major review of over 200,000 individuals from the WHO found no evidence for a raised incidence of sudden cardiac death.[45] A weekly DHA-PQP dosing approach has predicted benefits over other regimes, including higher efficacy and reduced concerns about compliance and safety, because of lower peak levels from a lower dose taken every week compared with a higher dose taken once a month.[46,76] Support for this dosing regimen also comes from a recent interventional study in Lihir Island, Papua New Guinea,[77] that enrolled healthy individuals aged 3 to 60 years who received a standard 3-day course of DHA-PQP on 3 consecutive months. Twelve-lead electrocardiography (ECG) readings were conducted pre-dose and 4h after the final dose of each month. In 69 participants who completed all treatment courses and ECG measurements, the mean (SD) increase in QTcF from pre-dose to 4h post-dose was 19.6 (17.8) ms for the first-course and 17.1 (17.1) ms for the third-course. 3 (4%) and 2 (3%) participants had a QTcF prolongation of >60 ms from baseline after the first course and third course, respectively. No participants had QTcF intervals of >500 ms at any timepoint.

However, to assess cardiotoxicity in children with SCD, 200 children enrolled into H-PRIME at the Mbale site will enter into a cardiac and pharmacokinetic sub-study. At enrolment (before their first dose), all children will receive a fully automated 12-lead ECG reading. Any abnormal results will be confirmed through manual review of these ECGs, with a particular focus on the QT intervals and QTc (corrected QT intervals, corrected using Fridericia's correction)[78] (see Cardiac substudy MOP for details). This will be repeated at one month, 6 months then 12 months and then annually thereafter. At post-randomisation visits, children involved in this sub-study will be asked to come to clinic on the

weekday that they would usually take their DHA-PQP dose if randomised to DHA-PQP, or on the day they would take their monthly SP if randomised to the anti-malarial control. A 12-lead ECG will be recorded both pre-dose and 4h post-dose. Those in the DHA-PQP group will take their drugs on an empty stomach with water only since drug absorption is less predictable if taken with fatty foods. The primary endpoint of this substudy will be QT interval correction (QTc using Fridericia's correction (QTcF)) prolongation from baseline to 4h post-dosing 1 year post-randomisation. Secondary substudy endpoints will be this change at different timepoints, the number with QTcF prolongation of >60 ms from baseline at each subsequent visit, and the number with QTcF intervals of >500 ms at any timepoint. Endpoints based on QTcB will also be secondary outcomes, as both correction factors introduce artefactual prolongation or shortening, particularly in children who have tachycardic heart rates.[78]

Including 200 children in the substudy (expected to be equally distributed between DHA-PQP vs SP by design, and similarly all other randomisations), provides at least 90% power to detect differences of 10 ms between DHA-PQP and SP, assuming a SD of 20 ms (slightly larger than above, given the children are younger with SCD) and assuming 20% without valid readings at 1 year. Recruiting 100 children receiving DHA-PQP would provide a final 95% confidence interval around an observation of no QTcF intervals of >500 ms during the trial from 0-1.8%, ie could reliably exclude this clinically relevant outcome happening in >2% of children.

The DMC would also monitor unblinded outcome data from this cardiac substudy in their regular meetings.

In order to relate any changes in QTFc to drug levels, at the same post-randomisation timepoints we will take whole blood filter papers from the substudy children receiving DHA-PQP pre-dose (to reflect a trough level) and at 3-4 hours post-dose (to reflect a peak level). Piperaquine levels will be determined retrospectively at the Mahidol Oxford Research Unit at Bangkok.

9.3 MOLECULAR DIAGNOSTICS AND MALARIA RESISTANCE

We will collect dried blood spots (DBS) during febrile events to investigate for bacteraemia, malaria and malaria resistance profiles using molecular methods. For malaria, this will be achieved through a collaboration with SpotMalaria.[47] DBS samples will be batched and sent periodically by courier to the Wellcome Trust Sanger Institute in Hinxton, UK, where they will be amplified and sequenced to check for the development of any de-novo mutations that might be associated with the development of DHA-PQP or SP resistance. Results from this work will be fed back to the study investigators within 6 months of submission to SpotMalaria and the results of these studies will also be monitored by the DMC. Aditionally, among children on DHA-PQP, filter paper samples will be collected to test for DHA-PQP levels during any episodes of fever. This will be in addition to routine testing for malaria by use of RDTs and thick and thin blood films.

9.4 LONG-TERM STORAGE

Study samples will be stored at the Mbale Clinical Research Institute, and the majority of the assays are planned to be conducted at laboratories in Mbale and Soroti. However, if it is necessary study samples may be shipped to a laboratory outside of Uganda for testing, and participants will be informed about this and explicit consent for this obtained. Only enough of the sample will be shipped to complete the tests required. Once those tests have been done and the specific study has ended, any samples left over in that laboratory will be destroyed or returned to Uganda to go back into long term storage. Any researcher who wants to use study samples for a new study not included in this protocol must get approval from the Mbale Regional Refrerral Hospital Research and Ethics

Committee and Professor Olupot-Olupot; again participants will be informed about this and explicit consent for this obtained.

10 QUALITY ASSURANCE AND CONTROL

10.1 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 ICH 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.

10.2 MONITORING AT TRIAL COORDINATION CENTRE

Data entry into the online trial database will be done for all trial sites at MCRI. Each site will be responsible for their local trial management. The site will retain the original CRF; and scanned copies will be shared with Mbale for data entry. Any amendments to CRFs will be made on both the original and photo copy. 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 re-uploaded and entered into the database at MCRI. MCRI will also send reminders for any overdue and/or missing data with the regular inconsistency reports of errors.

10.3 MONITORING AT LOCAL CENTRES

This trial will be monitored according to a Monitoring and Quality Management Plan which will set out the frequency of visits, the degree of source document verification against the case record forms and the requirements for triggered on-site monitoring visits. This plan will also detail the procedures for review and sign-off. The monitoring will adhere to the principles of ICH GCP. It is anticipated that the monitoring will start with 100% source document verification as in the previous TRACT trial. This will be reviewed for each site once a satisfactory and sustained performance in quality assurance is established.

A detailed site initiation visit with training will be performed at each trial site by staff from either the KEMRI-Wellcome Trust Research Programme (KWTRP) Clinical Trial Facility (CTF) or the MRC CTU who will be specifically trained for this role. The site initiation visits will include training in the trial procedures, as well as practical training in expected toxicities for trial interventions, and reporting guidelines for adverse events. All staff at sites involved in the trial will receive formal training in GCP through a dedicated training programme during site initiation visit and will also be required to complete an on-line course.

The trial monitoring team will consist of the locally commissioned clinical trials monitors. The KWTRP CTF and the MRC CTU oversee standards and quality of all trials that they conduct and through their monitoring systems and SOPs are organised to ensure that all sites can be monitored with equal independence and rigor. All monitors will be appropriately qualified and trained.
At each monitoring visit monitors will:

- verify completeness of Trial Master File
- confirm adherence to protocol
- review eligibility verification and consent procedures
- look for missed clinical event reporting

- verify completeness, consistency and accuracy of data being entered on CRFs
- evaluate drug accountability
- provide additional training as needed

The monitors will require access to all patient medical records including, but not limited to, laboratory test results and prescriptions. The investigator (or delegated deputy) should work with the monitor to ensure that any problems detected are resolved.

10.3.1 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. Participants' consent for this must be obtained. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

The following data should all be verifiable from source documents:

- signed consent forms
- dates of visits including dates any trial specimens were taken and processed in the laboratory
- eligibility and baseline values for all participants
- participant clinical and laboratory data
- clinical endpoints
- serious adverse events and severe (grade 3/4) adverse events
- dates drug dispensed and (if necessary) drugs returned
- pharmacy/clinic drug logs
- concomitant medication dispensed.

Not all such information will be monitored; rather, the monitoring plan will describe a risk-based approach to monitoring based on ongoing random samples of participant clinical and laboratory data which may be increased if issues are identified.

10.3.2 CONFIDENTIALITY

We plan to follow the principles of the UK Data Protection Act 2018 regardless of the countries where the trial is being conducted. In particular, the investigator must assure that participants' anonymity will be maintained and that their identities will be protected from unauthorised parties. Participants will be assigned a trial identification number, and this will be used on CRFs; participants will not be identified by their name. The investigator will keep securely a separate participant trial register linking these identification numbers to name and age. This unique trial number will identify all laboratory specimens, case record forms, and other records and no names will be used on any trial documentation, in order to maintain confidentiality. All records will be kept in locked locations. Clinical information will not be released without written permission, except as necessary for monitoring by the trial monitors.

11 REGULATORY AND ETHICAL ISSUES

11.1 TRIAL REGISTRATION

This trial has been registered with the International Standard Randomised Clinical Trial Number Register, where it is identified as (number pending).

11.2 ETHICS APPROVAL

The Trial Coordination Centre has obtained approval from the Imperial College Research Ethics Committee (ICREC). This trial will be submitted for approval to the Mbale Regional Referral Hospital Research and Ethics Committee (MRRH-REC), Uganda National Council for Science and Technology (UNCST), and the National Drug Authority (NDA). Permission to conduct the study at the respective study sites will be sought from the respective hospital management committees.

The trial will be conducted in accordance with the recommendations on Research Involving Human Participants in Uganda (UNCST, July 2014), and the principles of Good Clinical Practice (GCP) as laid down on the NIH online Course.

Prospective written, informed consent will be sought from parents or guardians of children. Parents or guardians will be given an information sheet in their usual language containing details of the H-PRIME 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. The right of the participant to refuse to participate without giving reasons must be respected.

11.3 SPONSOR

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

11.4 INDEMNITY

The Mbale Clinical Research Institute holds indemnity for this trial under the following policy:

Insured: Mbale Clinical Research Institute.
Period: 15/08/2023 to 14/08/2028
Policy Number: 051-H0-512030-23 (4) Hydroxyurea-Pragmatic Reduction in Mortality and Economic Burden (H-PRIME)

11.5 FUNDING

The trial is supported by grant funding from the Joint Global Health Trials board (Medical Research Council (MRC UK), the Department for International Development, UK (DFID), and the Wellcome Trust). 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.

11.6 AUDITS AND INSPECTIONS

The trial may be subject to inspection and audit by Imperial College London under their remit as Sponsor and other regulatory bodies to ensure adherence to GCP.

12 TRIAL MANAGEMENT

12.1 SITE TRIAL MANAGEMENT TEAMS

A trial management team (TMT) will be formed at each site to conduct the day-to-day management of the trial at the site (Site TMTs). This will include the investigators and trial staff at the site. These groups will meet every one-to-two weeks and will be chaired by the principal investigator or co-principal investigator at the site. The group will discuss issues related to the progress of the trial at the site and ensure that the trial is running well.

12.2 TRIAL MANAGEMENT GROUP

An H-PRIME Trial Management Group (TMG) will be formed comprising the Chief Investigator, centre Principal Investigators, co-investigators, and Trial Managers, other lead investigators (clinical and non-clinical), members of the MRC CTU that will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be coordinated through the MCRI. The TMG will meet approximately once a year in-person and will hold a regular teleconference at approximately 3-monthly intervals at which sites will summarise progress and challenges and bring up for discussion any difficulties, as well as discuss and decide matters of general importance for the trial. This group will be chaired by the Chief Investigator and all decisions regarding the overall running of the trial will be made in this forum with the exception of matters of fundamental importance to the viability of the trial or that require major changes to the protocol. These will be referred to the Trial Steering Committee (TSC). The full details can be found in the TMG Charter.

12.3 TRIAL STEERING COMMITTEE

The trial will be managed by a Trial Steering Committee (TSC) with an independent chairperson (Professor Elizabeth Molyneux OBE), a majority of independent members and one Principal Investigator or key investigator from each of the sites, from Imperial College, and from MRC CTU. Prof Molyneux previously chaired the FEAST and TRACT TSCs. Full details can be found in the TSC Charter. Professor Molyneux, an internationally respected clinical investigator with extensive experience in the care of haematological conditions in Africa, will be supported by the following additional independent members:

1) Professor Grace Ndeezi, a consultant paediatrician based at Makarere University in Kampala
2) Doctor Henry Ddungu, a haematologist at the Mulago National Referral and Teaching Hospital in Kampala
3) Dr Sam Okware, Chair East Africa Consortium for Clinical Research, Kampala and Director General of Uganda National Health Research Organisation, Kampala
4) Professor William Macharia, a consultant paediatrician and Associate Dean for Research at Aga Khan University, Nairobi

Non-independent TSC members will be Williams and Ware as joint Chief-Investigators of the trial, Olupot-Olupot as Uganda country PI, and Kiyaga (Uganda National Public Health Laboratory) (majority independent members).

Each centre will either use their existing Community Advisory Board (CAB) or form a specific patient liaison group who will be responsible for liaising with their independent representatives on the TSC and feeding back concerns and questions from the community. They will also hear about the latest developments in the trial and the wider scientific community.

12.4 INDEPENDENT DATA MONITORING COMMITTEE

The independent Data Monitoring Committee (DMC) will be chaired by Professor Tim Peto (University of Oxford, UK) who has extensive experience chairing DMCs for trials in acutely sick children in Africa. Other members will be Prof Philippa Musoke, Makarere University, Uganda and Dr Jim Todd, Mwanza, Tanzania who, together with Prof Peto, acted as the DMC for previous FEAST and TRACT trials; and Dr Victor Musiime, Makarere University, Uganda who will join the DMC for this trial (4 independent members in total, 2 from Uganda). The DMC will make recommendations to the H-PRIME Trial Steering Committee as to the continuation of the trial on the basis of data from all randomised children, and the cardiac sub-study. See **Section 8.3** for details. Full details can be found in the DMC Charter.

12.5 CLINICAL REVIEW COMMITTEE

Clinical endpoints, specifically cause of death and relationship to all possible interventional drugs will be reviewed by a clinical endpoint review committee consisting of the joint Chief Investigators (Prof Williams and Prof Ware), the trial paediatrician, site Investigators and other co-opted members as deemed necessary by the Chief Investigators.

13 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. Named authors of the first publication of the trial results will include at least the trial's Chief Investigator, Centre Principal Investigators, Statistician and Trial Coordinator. 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 Trial Coordination Centre.

The H-PRIME TSC (which contains a majority of members independent of the trial team) is the custodian of the data and specimens generated from the H-PRIME trial; H-PRIME 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 abstractss 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 Lancet and from the publication policies used in other trials coordinated by the MRC CTU at UCL:

- 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 MRC policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. 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 trial, 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 trial 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 participants 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 H-PRIME Trial Steering Committee. The presentation or publication of any data collected by the participating investigators on participants 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.

13.1 DATA SHARING AND INTELLECTUAL PROPERTY

The collaborating research partners have met and have agree on the following data access and use rights before commencement of the study. First, that the ownership of the H-PRIME dataset will lie with the H-PRIME Trial Steering Committee, who will approve all requests for use of trial data before and after the trial ends, based on a controlled access approach (requests before the end of the trial also to be approved by the H-PRIME Data Monitoring Committee). No data will be shared that compromises the confidentiality of research participants or their communities. No collaborating research partner will transfer data to any third parties without the written consent of the other partners. On completion of the trial, local researchers will have unrestricted access rights to data sets collected through this collaborative research project. We will follow the funder's regulations with regard to Intellectual Property (IP). As this relates to a legal issue, IP issues will be laid out in the contract between partners.

The H-PRIME dataset will be held electronically for at least 20 years after the end of the trial in accordance with MRC policy. As above, proposals to use H-PRIME data and samples will be welcomed and supported widely where this does not conflict with existing plans within the trial team (e.g. as described in the primary and secondary objectives of the trial above).

The controlled access approach[79] is based on the following principles:

- No data should be released that would compromise an ongoing trial.
- 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.

Researchers wishing to access data should contact the Trial Management Group in the first instance.

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APPENDIX I WITHDRAWAL FORM

Please initial (or mark) box if you agree:

I/my child no longer wish to (or cannot) take H-PRIME study drugs and do not wish to (or cannot) attend further visits. I/my child agree to being contacted in the future (home visits or telephone) and to my/my child's medical records being consulted in future to obtain clinical information for H-PRIME.	

Need to set up a procedure to follow the child up through visits and medical records and report any trial outcomes on the appropriate form. Inform the child and carer that s/he may still return for follow-up visits only or for further study drugs and follow-up visits at a later date if they change their mind.

I/my child no longer wish to (or cannot) take H-PRIME study drugs and do not wish to (or cannot) attend further visits. I/my child do not agree to being contacted in the future or to my/my child's medical records being consulted in future to obtain clinical information for H-PRIME.	

Discontinue all follow up through medical records. The child and carer must sign a new consent form if s/he decides to rejoin the study at a later date.

Parent or carer's signature (or thumbprint if unable to read or write)	Print name	Date and time (day/month/year/24hr clock)

Child's signature (or thumbprint if unable to read or write) where appropriate	Print name	Date and time (day/month/year/24hr clock)

Witness's signature (if thumbprint used above)	Print name	Date (day/month/year/24hr clock)

Doctor's signature	Print name	Date (day/month/year/24hr clock)

IMPORTANT: Copy of signed original to be given to patient
Signed original to be kept on file by the researcher