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H-PRIME: A clinical trial with three separate randomisations aimed at investigating the benefits of hydroxyurea, used pragmatically with only clinically-based monitoring, antimalarial prophylaxis with dihydroartemisinin-piperaquine and antibacterial prophylaxis with cotrimoxazole as potential improvements in the standard care of children living in Africa with sickle cell disease

Submission date 13/02/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol
Registration date 25/02/2020	**Overall study status** Ongoing	[X] Statistical analysis plan [_] Results
Last Edited 23/06/2025	**Condition category** Circulatory System	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Sickle cell disease is a common but neglected genetic disease that has its greatest burden in sub-Saharan Africa. Without early diagnosis and appropriate treatment, aimed primarily at preventing the common causes of ill-health and death (which include bacterial diseases and malaria) the disease is associated with high mortality during childhood. Although implementation of early life screening and the prevention of infections with vaccines, penicillin and drugs for malaria, can lead to greatly improved survival, other complications of sickle cell disease can still lead to a reduced quality of life. The overarching aim of this study will be to investigate whether several alternative treatments, delivered pragmatically by non-specialist staff in, could improve survival and quality of life for children with sickle cell disease living in resource-poor environments within sub-Saharan Africa.

Who can participate?
Children aged 1-10 years inclusive with confirmed Sickle Cell Disease (SCD).

What does the study involve?
Participants will be randomly allocated to receive one of three different treatments and will be followed up over a maximum of 48 months. The first randomisation will be to hydroxyurea,

prescribed pragmatically through a weight-band-based dosing strategy aimed at delivering either a higher dose (25 +/-5mg/kg/day), with clinically based monitoring only, versus a lower dose (10 mg/kg +/-4 mg/kg/day). The second and third randomisations will be to the standard of care prophylaxis for malaria using suphadoxine-pyramethamine given monthly or alternative prophylaxis with dihydroartemisinin-piperoquine given weekly and standard of care prophylaxis for bacterial infections with penicillin V given twice daily until the age of 5years or alternative prophylaxis with cotrimoxazole given once daily throughout childhood.

What are the possible benefits and risks of participating?
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).
The direct benefits to the participating centres will 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
Benefits For the health personnel involved
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
BENEFITS TO WIDER SOCIETY
Wider society will benefit from all of the above factors and the study will also act as a focal point for a greater appreciation and understanding of sickle cell disease within the region.
RISKS OF PARTICIPATING
It is anticipated that all study participants will be at lower risk of morbid and mortal events than they would be if not recruited to the study and that one or more of the interventions will improve their lives even further. We assess the risk benefit ratio to be extremely favourable

Where is the study run from?
Mbale Clinical Research Institute (Uganda) and KEMRI-Wellcome Trust Research Programme (Kenya)

When is the study starting and how long is it expected to run for?
January 2021 to December 2032

Who is funding the study?
The Joint Global Health Trials Scheme of the Department for International Development, UK (DFID), the Wellcome Trust and the Medical Research Council (MRC UK)

Who is the main contact?
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Contact information

Type(s)

Public

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
V2.0

Study information

Scientific Title
H-PRIME: Hydroxyurea – Pragmatic Reduction in Mortality and Economic burden: A multi-centre Phase III trial to investigate the efficacy of hydroxyurea in children with sickle cell anaemia when administered in a pragmatic fashion.

Acronym
H-PRIME

Study objectives
Current hypothesis as of 07/08/2023:
1. 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
2. Enhanced antimalarial prophylaxis with a highly-effective antimalarial drug - dihydroartemisinin-piperaquine given weekly - will reduce malaria-associated hospitalisations in comparison to normal Ugandan standard of care - sulphadoxine-pyrimethamine given monthly
3. Antimicrobial prophylaxis with co-trimoxazole given daily throughout childhood will reduce all-cause hospitalisations in comparison to standard of care prophylaxis with penicillin V, given twice daily until the age of 5 years

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Previous hypothesis:
1. Daily oral dosing with hydroxyurea, with clinically-driven rather than routine laboratory monitoring will reduce all-cause mortality compared with placebo
2. Enhanced antimalarial prophylaxis with a highly-effective antimalarial drug - dihydroartemisinin-piperaquine given weekly - will reduce malaria-associated hospitalisations in comparison to normal Ugandan standard of care- sulphadoxine-pyrimethamine given monthly
3. Antimicrobial prophylaxis with co-trimoxazole given daily throughout childhood will reduce all-cause hospitalisations in comparison to standard of care prophylaxis with penicillin V, given twice daily until the age of 5 years

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 17/09/2019, Imperial College Research Ethics Committee (Imperial College Research Ethics Committee, Imperial College London, Room 221 Medical School Building, St Marys Campus,
London, W2 1PG, UK; +44 (0)207 594 1872; researchethicscommittee@imperial.ac.uk), ref: 19IC5453
2. Approved 24/04/2023, Mbale Regional Referral Hospital Research Ethics Committee (accredited by the Uganda National Council for Science and Technology, P.O Box 921, Mbale, Uganda; +256 (0)39 3289584; mrrhrec@gmail.com), ref: UG-REC-011

Study design
2x2x2 factorial randomized open-label trial

Primary study design
Interventional

Secondary study design
Factorial design

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Sickle cell disease

Interventions
Current interventions as of 27/02/2024:
H-PRIME will recruit children between the ages of 1-10 years and follow them over a maximum period of 48 months. Children in different randomisations will be followed for the same period.

Group 1: High-dose (daily) versus low-dose (thrice weekly) oral hydroxyurea (Novartis) with clinically-driven, as opposed to routine laboratory, monitoring
Group 2: Enhanced antimalarial prophylaxis with dihydroartemisinin-piperoquine (DHA-PQP), given weekly versus Uganda standard of care (sulphadoxine-pyrimethamine given monthly)
Group 3: Antimicrobial prophylaxis with cotrimoxazole (given once daily throughout childhood) versus standard of care (penicillin V given twice daily until the age of 5 years)

Randomisation in each part of the factorial will be stratified by centre, hydroxyurea initial dose (to ensure balance across the specific doses proposed) and the other randomisations in the factorial. Randomisation will be done by the Mbale data centre 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 and 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.

Previous interventions:
H-PRIME will recruit children between the ages of 1-10 years and follow them over a maximum period of 48 months. Children in different randomisations will be followed for the same period.

Group 1: Daily oral hydroxyurea (Siklos, addmedica) with clinically-driven, as opposed to routine laboratory, monitoring versus placebo
Group 2: Enhanced antimalarial prophylaxis with dihydroartemisinin-piperoquine (DHA-PQP), given weekly versus Uganda standard of care (sulphadoxine-pyrimethamine given monthly)
Group 3: Antimicrobial prophylaxis with cotrimoxazole (given once daily throughout childhood) versus standard of care (penicillin V given twice daily until the age of 5 years)

Randomisation in each part of the factorial will be stratified by centre, hydroxyurea/placebo initial dose (since this will determine drug supply) and the other randomisations in the factorial. 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. Randomisation cards will be prepared at the KEMRI-Wellcome Trust Research Programme (KWTRP) Clinical Trial Facility (CTF) before the trial starts by staff who will not be involved in its conduct, and placed in sealed packs together with case record forms labelled with the associated trial number. A separate set of consecutively-numbered envelopes will be generated, each linked to a trial number/randomised allocation. At enrolment, the next consecutively-numbered envelope will be opened which will direct the clinician to a pack number which will always be in the next 16 packs but will not necessarily be the next one. Only when the pack is opened will the randomised allocation to interventions R1, R2 and R3 be visible on the randomisation card. The link between pack number and trial number (and hence randomised allocation) will also be randomised within blocks.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response

Phase
Phase III

Drug/device/biological/vaccine name(s)
Hydroxyurea (Novartis), dihydroartemisinin-piperaquine, sulphadoxine-pyrimethamine, co-trimoxazole, penicillin V

Primary outcome measure
Determined either at the time they occur, via direct communication from participants to the study team, or at each of the 3 monthly followup appointments:
Group 1: Mortality
Group 2: Malaria-associated hospitalisations (diagnosed by rapid diagnostic test (RDT) and confirmed by microscopy and/or PCR)
Group 3: Hospitalisations for any reason

Secondary outcome measures
Determined either at the time they occur, via direct communication from participants to the study team, or at each of the 3 monthly followup appointments:
1. Mortality (for both randomisations in which mortality is not the primary outcome - G2 and G3)
2. Malaria-associated hospitalisations (where not the primary outcome - G1 and G3)
3. All-cause hospitalisations (where not the primary outcome - G1 and G2)
4. 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.

Overall study start date
22/07/2017

Completion date
15/01/2028

Eligibility

Key inclusion criteria
1. Aged 1-10 years inclusive
2. Confirmed Sickle Cell Disease (SCD) (diagnosed either by HPLC or IEF at a qualified laboratory)
3. Have received conjugate pneumococcal vaccination against Hib and S. pneumoniae (otherwise eligible but unvaccinated children will be vaccinated through the study)
4. 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

Participant type(s)
Other

Age group
Child

Lower age limit
1 Years

Upper age limit
10 Years

Sex
Both

Target number of participants
1,800

Key exclusion criteria
1. Already meet criteria for starting hydroxyurea under Uganda National Guidelines 2026 (frequent crises (>5/year), abnormal transcranial Doppler ultrasound velocities, stroke or acute chest syndrome)
2. Already receiving hydroxyurea
3. 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)
4. Known cancer
5. A clinical history of previous or existing liver or renal diseases unrelated to sickle cell disease
6. Known cardiac ventricular dysfunction or failure or a previous history of cardiac arrhythmias
7. 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))
8. Current participation in any other clinical trial of an investigational medicinal product
9. 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

Date of first enrolment
16/01/2024

Date of final enrolment
15/06/2025

Locations

Countries of recruitment
Uganda

Study participating centre
Mbale Clinical Research Institute
Mbale Regional Referral & Teaching Hospital Complex
Pallisa Road Plot 29-33
Mbale
Uganda
PO Box 921

Study participating centre
Soroti Regional Hospital
Soroti Regional Referral Hospital
Soroti
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P.O Box 289

Study participating centre
Atutur District Hospital
Kumi District
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Study participating centre
Ngora District Hospital
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-

Sponsor information

Organisation
Imperial College London

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+44 (0)20 7594 1188
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Sponsor type
University/education

Website
https://www.imperial.ac.uk

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
The Joint Global Health Trials Scheme of the Department for International Development, UK (DFID), the Wellcome Trust and the Medical Research Council (MRC UK)

Funder Name
Department for International Development, UK Government

Alternative Name(s)
Department for International Development, UK, DFID

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal. 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.

Intention to publish date
31/12/2033

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. 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.

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).

The controlled access approach 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.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other publications	baseline characteristics	07/07/2020	21/08/2020	Yes	No
Protocol file	version 4.0.1	18/09/2023	16/05/2024	No	No
Statistical Analysis Plan	version 1.0	16/05/2024	21/05/2024	No	No
Protocol (preprint)		16/05/2025	23/06/2025	No	No
Protocol file	version 5.0	18/12/2024	23/06/2025	No	No
Statistical Analysis Plan	version 2.0	16/06/2025	23/06/2025	No	No