PARIST study protocol: a phase I/II randomised, controlled clinical trial to assess the feasibility, safety and effectiveness of paracetamol in resolving acute kidney injury in children with severe malaria

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ABSTRACT

Background Acute kidney injury (AKI) has in the past been considered a rare complication of malaria in children living in high-transmission settings. More recently, however, a growing number of paediatric case series of AKI in severe malaria studies in African children have been published (Artesunate vs Quinine in the Treatment of Severe P. falciparum Malaria in African children and Fluids Expansion as Supportive Therapy trials). The Paracetamol for Acute Renal Injury in Severe Malaria Trial (PARIST) therefore, aims to assess feasibility, safety and determine the effective dose of paracetamol, which attenuates nephrotoxicity of haemoproteins, red-cell free haemoglobin and myoglobin in children with haemoglobinuric severe malaria.

Methods PARIST is a phase I/II unblinded randomised controlled trial of 40 children aged >6 months and <12 years admitted with confirmed haemoglobinuric severe malaria (blackwater fever), a positive blood smear for P. falciparum malaria and either serum creatinine (Cr) increase by ≥0.3 mg/dL within 48 hours or to ≥1.5 times baseline and elevated blood urea nitrogen (BUN) >20 mg/dL. Children will be randomly allocated on a 1:1 basis to paracetamol intervention dose arm (20 mg/kg orally 6-hourly for 48 hours) or to a control arm to receive standard of care for temperature control (ie, tepid sponging for 30 min if fever persists give rescue treatment). Primary outcome is renal recovery at 48 hours as indicated by stoppage of progression and decrease of Cr level below baseline, BUN (<20 mg/dL). Data analysis will be on the intention-to-treat principle and a per-protocol basis.

Results from this phase I/II clinical trial will provide preliminary effectiveness data of this highly potential treatment for AKI in paediatric malaria (in particular for haemoglobinuric severe malaria) for a larger phase III trial.

INTRODUCTION

Renal involvement in severe malaria is common in adult non-immune cases in South and South East Asia (25%–50% in various series) and can progress to acute kidney injury (AKI) with anuric or oliguric renal failure.1 Classically renal
involvement in paediatric African cases of severe malaria had been thought to be minimal, but recent data suggest this problem has been under-recognised. Adult malaria associated renal failure is characterised by acute tubular injury and may require dialysis. However, the aetiology of kidney injury in the paediatric kidney is unknown and may reflect multiple insults in severe malaria, including dehydration (pre-renal failure), direct tubular or glomerular injury. The few studies that have investigated more specific measures of renal function in African children with severe malaria indicate a significant degree of abnormal renal function in children, which varies according to site. The AQUAMAT (Artesunate vs Quinine in the Treatment of Severe P. falciparum Malaria in African children) trial, involving 5425 children with severe malaria from 11 centres across 9 countries confirmed the independent significance of raised blood urea nitrogen (BUN; >20 mg/dL) and acidosis as poor prognostic signs in severe malaria in African children. BUN and pH are measures of dehydration but also reflect renal function. The Fluids Expansion as Supportive Therapy (FEAST) trial (including 67% participants with severe malaria),3 BUN>20 mg/dL was present in 316/1196 (26.4%) of Ugandan children compared with rates of ~13%–15% in Kenya and Tanzania. In addition, 17% had hyperkalaemia (raised blood K+ >5 mmol/L)—a direct sign of renal injury. A BUN>20 mg/dL was more common in two sites in Eastern Uganda (15%–22%) than in other sites with lower background malaria endemicity and found a syndrome of blackwater fever (BWF). Correspondingly, this increase in AKI recognition in childhood severe malaria has coincided with increased reports of BWF in African children, particularly in Eastern Uganda and the Democratic Republic of Congo. In these settings, BWF has been highlighted as a risk factor for in-hospital mortality especially if complicated with AKI, causes prolonged hospitalisation, hospital readmission and postdischarge mortality in African children. BWF is a complication of severe malaria in which haemolysis predominates. The intravascular haemolysis results in an accumulation of hemoproteins that can overwhelm the capacity of endogenous hemoprotein scavengers (eg, haptoglobin, haemopexin). The kidney proximal tubular epithelium is the primary route of hemoprotein clearance when endogenous scavenger systems are saturated. Exposure of renal proximal tubular cells to excess cell-free haemoglobin and heme can lead to direct cellular injury and AKI through increased oxidative stress, tubulointerstitial inflammation and endothelial activation. This calls for an increased awareness of AKI among children with severe malaria especially in the setting of BWF given the associated high mortality and morbidity. Therefore, there is a need to explore potential treatments to reduce disease progression in this high-risk group of children.

**Evidence before this study**

We systematically searched PubMed for original research articles reporting severe malaria and acute kidney or renal failure in children in sub-Saharan Africa using the following search terms (((malaria OR plasmod* ) AND (“acute kidney injury” OR “acute renal injury”)) AND ((Sub Saharan Africa OR SSA OR Africa OR africa south of the sahara OR africa, central OR africa, southern OR africa, eastern OR africa, western OR Angola OR benin OR botswana OR burkina faso OR burundi OR cabo verde OR Cape Verde OR cameroon OR central african republic OR chad OR democratic republic of the congo OR congo Brazzaville OR Côte d’Ivoire OR Ivory Coast OR equatorial guinea OR eritrea OR ethiopia OR gabon OR gambia OR ghana OR guinea OR guinea bissau OR kenya OR lesotho OR liberia OR Madagascar OR malawi OR mali OR mauritania OR Mauritius OR morocco OR mozambique OR namibia OR niger OR nigeria OR rwanda OR Sao Tome and Principe OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR south sudan OR sudan OR Swaziland OR tanzania OR togo OR tunisia OR uganda OR zambia OR Zimbabwe)())) AND (children)). We identified 65 articles (11 explicitly included AKI and BWF in African children). Several large clinical studies have confirmed the independent significance of raised BUN (>20 mg/dL) as a poor prognostic signs in severe malaria in African children.

The AQUAMAT trial, involving 5425 children with severe malaria from 11 centres across 9 countries, with differing malaria endemicities, established three factors that were independent predictors of fatal outcome: acidosis, impaired consciousness (coma) and an elevated blood urea (BUN; >20 mg/dL). The estimated mortality in children with all three predictors was 43%. A prospective study in Kenyan children, showed that an elevated creatinine (Cr) (>80 μmol/L) complicated 96/469 (20%) cases at admission, which was associated with a case fatality of 26%. In this study, four factors were independently associated with fatal outcome (deep ‘acidotic’ breathing; hypoxia (SaO2<90%), hypoglycaemia is (<2.5 mmol/L) and Cr >80 μmol/L (OR for mortality with elevated Cr was 5.76 (95% CI 2.3 to 14.3, p=0.0002). Children receiving rehydration, including fluid boluses, with malaria associated AKI commonly develop polyuria (with inappropriately high urinary potassium loss) argues for an intrinsic defect in tubular concentration ability caused by malaria, which may contribute to central volume depletion and poor outcome. The extent and safe management of this complication needs to be established in future studies.

The FEAST trial in children with febrile severe illness (severe malaria 67%),5 BUN>20 mg/dL was seen in 316/1196 (26.4%) of Ugandan children compared with rates of ~13%–15% in Kenya and Tanzania. In addition, 17% had hyperkalaemia (raised blood K+ >5 mmol/L)—a direct sign of renal injury. A BUN>20 mg/dL was more common in two sites in Eastern Uganda (15%–22%), together with clinical jaundice, than in sites with lower background endemicities of malaria (Kenya and Tanzania). This is apposite because another complication of severe malaria and renal dysfunction in Uganda noted above was the syndrome of ‘dark urine’ (a triad of haemoglobinuria, severe anaemia and jaundice). Adult malaria associated renal failure is characterised by acute tubular
injury and may require dialysis. However, the aetiology of kidney injury in the paediatric kidney is unknown and may reflect multiple insults in severe malaria, including dehydration (pre-renal failure), direct tubular or glomerular injury. WHO malaria treatment guidelines consider renal failure as a serum Cr level is serum Cr >3 mg/dL (>265 μmol/L); but do not indicate criteria for children. Guidelines for the diagnosis and treatment of renal involvement are needed, as is rational integrated fluid management and other supportive treatment in paediatric malaria, which do not currently exist.

Batte and colleagues from Mulago hospital in May 2021, while reviewing malaria-associated AKI in African children: prevalence, pathophysiology, impact and management challenges, noted that AKI is emerging as a complication of increasing clinical importance associated with substantial morbidity and mortality in African children with severe malaria. Using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define AKI, an estimated 24%–39% of African children with severe malaria have AKI with most AKI community-acquired. AKI is a risk factor for mortality in paediatric severe malaria with a stepwise increase in mortality across AKI stages.

Odiit in 2017 in Mulago hospital, while describing common childhood kidney diseases in Uganda and their prevention, cited that of 2055 children presenting to hospital in Uganda with either: severe acute gastroenteritis, severe pneumonia or severe malaria, 13.5% had AKI.

Hickson and colleagues in 2019 in Mulago hospital indicated that AKI was present in 33.2% of children with cerebral malaria or severe malarial anaemia at baseline.

Conroy and colleagues while evaluating AKI and renal recovery in Ugandan children with severe malaria indicated that the prevalence of AKI was 45.3% and was more common in Jinja (57.5%) compared with Kampala (35.5%) (p<0.0001). AKI was more common in children who reported use of herbal medications (OR 3.64, 95% CI 1.52 to 8.75, p=0.004), but was not associated with reported use of antimalarial medications, antibotics or non-steroidal anti-inflammatory medications prior to admission (p>0.05 for all). Clinically, children with AKI were more likely to present with coma, retinal haemorrhages, jaundice, haemoglobinuria, respiratory distress and a history of vomiting (p<0.05 for all). AKI was associated with a significant increase in in-hospital mortality (OR 7.98, 95% CI 3.14 to 20.32, p<0.0001), neurological deficits at discharge in survivors (OR 1.83, 95% CI 1.06 to 3.15, p=0.031) and a higher incidence of subsequent hospitalisation (incidence rate ratio 1.26, 95% CI 1.02 to 1.56, p=0.031) adjusting for child age, sex, level of consciousness, presence of severe anaemia and study site. At 1-month follow-up, 60 children (13.0%) had acute kidney disease (AKD) while 34 (7.4%) had hyperfiltration, defined as an estimated glomerular filtration rate >185 mL/min/1.73 m². There were distinct differences in the pattern of kidney injury over follow-up by site with hyperfiltration occurring in 12.4% of children from Kampala versus 1.8% of children from Jinja while AKD occurred in 1.2% of children from Kampala compared with 26.0% of children from Jinja. The presence of AKD at 1-month follow-up was associated with 4.74-fold increased odds of postdischarge mortality (95% CI 1.33 to 16.98) adjusting for age, sex and site.

Conroy et al in a prospective observational cohort study conducted to evaluate the association between BWF and AKI in children hospitalised with an acute febrile illness at Jinja regional referral hospital in Eastern Uganda noted that BWF is associated with severe AKI in children with febrile illness and results in poor outcomes. Using the KDIGO criteria to define AKI, of the 999 enrolled, 8.2% of children had a history of BWF of these 49.5% had AKI and 11.1% had severe AKI. A history of BWF was independently associated with 2.18-fold increased odds of AKI (95% CI 1.15 to 4.16) and the presence of severe AKI, not BWF, was associated with increased risk of in-hospital death (RR 2.17, 95% CI 1.01 to 4.64) adjusting for age, sex and disease severity.

Aloni et al in a retrospective review of data for 56 children <13 years old, admitted into paediatric intensive care and Nephrology Units of University Hospital of Kinshasa between January 2000 and December 2007 in the Western part of the DRC, reported BWF was the leading cause of AKI (42.8%).

Bodi et al in a case–control study conducted in four hospitals located in Kinshasa, Democratic Republic of Congo from January 2010 to December 2011. A total of 129 children, 43 with haemoglobinuria and 86 with uncomplicated malaria were recruited into the study. Among the haemoglobinuria patients, 7 (16.2%) developed AKI.

Ajetunmobi et al in a prospective case–control study carried out to determine the incidence of haemoglobinuria as confirmed by dipstick urinalysis, microscopy and spectrophotometric measurement, among children with severe malaria reported renal failure in 3/48 children with haemoglobinuria and in none of the 203 without.

Kunuanumua et al in a prospective cohort study conducted from January 2008 to December 2008 in children admitted to emergency units of five hospitals in Kinshasa for severe malaria reported acute renal failure in 89 children (23.6%) and 87 of them had BWF.

Implications of this available evidence
The essential elements that arise from these studies highlight both the importance of the emergence of AKI and BWF among African children as a significant cause of mortality and morbidity. BWF has been reported to be rare and not recognised in the recent WHO severe malaria guidelines (2014) as a treatment or research priority and furthermore the WHO guidelines are primarily addressing treatment of AKI in adults with severe malaria. Therefore, guidelines for the treatment of AKI in children with severe malaria are therefore, urgently needed.
Rationale for the research proposed

The research question was identified through robust evidence for existing gaps including an extensive literature review all of which have recognised a growing number of AKI recognition among African children with poor outcomes particularly mortality. Yet, there are no guidelines for management of AKI due to severe malaria. Therefore, there is a need to explore potential treatments for children with severe malaria and renal impairment. Using a phase I/II clinical trial, we will answer the research question: what is the effective dose of paracetamol, which attenuates nephrotoxicity of haemoproteins, red-cell free haemoglobin and myoglobin in haemoglobinuric severe malaria?

Therapeutic gap

These data emphasise the need to accurately establish the potential treatment options for severe malaria associated kidney disease in children in Africa. We propose therefore to conduct Paracetamol for Acute Renal Injury in Severe Malaria Trial (PARIST) to assess feasibility, safety and preliminary effectiveness data of this highly potential treatment for AKI in paediatric haemoglobinuric severe malaria.

Rationale for choice of adjunctive therapy

Paracetamol is a potent inhibitor of cell haemoprotein mediated lipid peroxidation since it reduces the ferryl heme to its less toxic ferric state.23 Heme-protein induced oxidation, and production of the isoprostanes and isofurans is also blocked by therapeutic concentrations of paracetamol and has shown promising effect in sepsis.23 Therefore, paracetamol offers a promising treatment for attenuating nephrotoxicity of haemoproteins, red-cell free haemoglobin and myoglobin due to severe malaria. The impact of proving the benefit of paracetamol would be tangible especially since it is widely available and cheap intervention.

Choice of comparator

Tepid sponging is one of the most common physical methods for cooling that is recommended for treating fever in children.24 Tepid sponging allows the body to lose heat through conduction, convection or evaporation. Conduction occurs when heat is exchanged between two objects in contact with one another. Convection occurs when warm air in contact with an object moves away and is replaced by cooler air in a continuous cycle.25 Children who are sponged to treat fever lose heat by all three mechanisms. Reports indicate that tepid sponging is effective and safe.26 27 In addition, it is cheap and readily available and widely used by caregivers and doctors to treat children with fever. Tepid sponging is an appropriate method for use in low-income and middle-income countries in that it can be taught easily to parents and, therefore, does not divert nursing staff from other duties. This justifies the use of this physical cooling method as a comparator in this trial. However, tepid sponging has been reported to cause chills, shivering and constriction of the skin blood vessels (which is known to cause heat conservation within the body),28 which are mild and mostly self-limiting.

Purpose

This is a phase I/II clinical trial on feasibility, safety and preliminary data on effectiveness of paracetamol. Paracetamol is already available, cheap and safe drug and we are exploring its new application for preventing cell-free haemoglobin renal toxicity and ameliorating AKI in children with severe malaria. This drug is already being used for similar purposes in pilot studies at Mahidol Oxford Research Unit (NCT01641289)29 and to prevent AKI due to free haemoglobin and myoglobin in other trials in sepsis. Our aim is to target children with BWF (haemoglobinuric severe malaria), who have a poor in-hospital and day-28 outcomes in the communities in Eastern Uganda. The data from our study will inform the design of a large phase III study on use of paracetamol for treatment of AKI in severe malaria.

Objectives

This study has three major aims

1. To conduct pharmacokinetic (PK) studies of paracetamol in patients with AKI in severe malaria.
2. To assess the feasibility of use of paracetamol in ameliorating AKI in severe malaria in Eastern Uganda.
3. To conduct safety and preliminary effectiveness study for use of paracetamol in ameliorating AKI in severe malaria.

METHODS AND MATERIALS

This clinical trial conforms to the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.30 The detailed trial registration data set can be accessed at ISRCTN: Use of paracetamol in resolving acute kidney injury in severe malaria.

Study area and site

The study site and general population have been described previously.31–35 Briefly, Mbale Regional Referral Hospital (MRRH) located in Eastern Uganda serves Tororo District 30km south of Mbale District where a recent entomological inoculation rate of 125 (95% CI 72.2 to 183.0) in 2013,34 but the earlier rate in 2006 was 397.35 These findings suggest that malaria transmission in this region is stable, intense and perennial. This region similarly has a high prevalence of BWF.10

Study population

Children aged >6 months and <12 years were admitted to the paediatric wards with confirmed haemoglobinuric malaria.

These patients will be identified on the following criteria: recorded fever or a history of fever in the current illness, plus passing of dark and confirmed as a case of
severe malaria if their peripheral blood smear is positive for asexual forms of *P. falciparum* on blood smear.

**Study design**

PARIST is a single centre prospective phase I/II randomised, controlled, parallel-group, open-label clinical trial.

**Sample size**

In this phase I/II study, we estimate that we will screen at least 450 children with severe malaria from whom 40 children with haemoglobinuric severe malaria (defined by malaria positive slide and dark urine with Hillmen urine colour chart grade >5.36 see figure 1) will be recruited at hospital admission. Using the KDIGO criteria to define AKI; Cr increase of ≥0.3 mg/dL within 48 hours or to ≥1.5 times baseline which is known or presumed to have occurred within the last 7 days and a BUN >20 mg/dL with inclusion and exclusion criteria, the 40 children will be recruited. BUN and Cr will be assessed using i-STAT.

Our sample size was informed by a number of considerations. First, the principles of clinical trials sample size guidelines for phase I trials that usually have less than 20 people while phase II trials are usually between 30 and 60.37

Sample sizes for single-stage phase II clinical trials in the literature are often based on exact (binomial) tests with levels of significance (alpha (α) <5% and power >80%).37

This study, being phase I/II, has a sample size of 40 consistent with the standard definition of sample size for the phase I/II trials. Primarily, using the A’Hern table of sample size determination (with the assumption of P0=10%, P1=25%, alpha (α)=4.19, power (d)=81.80), we arrived at the sample size n=40 with an estimated response rate r=8.37

**Eligibility criteria**

**Participant inclusion criteria**

(a) Children aged >6 months to <12 years; (b) positive RDT for *P. falciparum* malaria at admission; (c) one of the following features of severe malaria confirmed haemoglobinuria, impaired consciousness and/or severe respiratory distress; (d) guardian or parent willing and able to provide consent.

**Participant exclusion criteria**

(a) Surgery; (b) acute trauma or burns; (c) known allergy to paracetamol; (d) impaired liver function tests (LFTs); (e) known chronic renal failure or suspected non-malarial causes of renal impairment; (f) refusal to consent.

The aim of the study is to generate safety and efficacy data as well as PK profiling on the use of paracetamol in children with haemoglobinuric AKI. The numbers required to address the trial objectives are therefore balanced against the exposure of children to a therapeutic intervention for which there are limited data. We will randomise 40 children who meet the inclusion criteria (figure 2). A total of 40 (20 arm A and 20 arm B) will randomly be allocated to the PK sampling (see figure 2).

**Study interventions**

Children will be randomly allocated on a 1:1 basis to:

1. Paracetamol intervention dose arm: research nurses will administer paracetamol 20 mg/kg orally 6-hourly for 48 hours. Patients unable to swallow will receive paracetamol by nasogastric tube. If the patient vomits within 30 min of paracetamol administration, a further dose will be given.

2. Control arm: patients in the control arm will receive standard of care for temperature control. That is, fever of 37.5 °C–39.4 °C will be tepid sponged and fanned for 30 min. After 30 min, the temperature will be taken again and in case the fever persist, they will be given rescue treatment (standard of care—paracetamol 10 mg/kg). As stated in the standard of care in the Uganda Clinical Guidelines 2016.38

**Methodology for objective 1**

1. To conduct PK studies of paracetamol in patients with AKI in severe malaria. Forty eligible patients will be randomised to two arms of paracetamol and will be sampled for plasma paracetamol levels assessed from a 250 μL EDTA plasma sample. Arm A, 20 study participants receiving 20 mg of paracetamol, will further be randomised on A1 or A2 on 1:1 ratio to different sampling schedules as follows; A1 (N=10), will be sampled in the control arm will receive standard of care for temperature control. That is, fever of 37.5 °C–39.4 °C will be tepid sponged and fanned for 30 min. After 30 min, the temperature will be taken again and in case the fever persist, they will be given rescue treatment (standard of care—paracetamol 10 mg/kg). As stated in the standard of care in the Uganda Clinical Guidelines 2016.38

will continue once every 6 hours for 24 as summarised in table 1.

Methodology for objective 2
To assess the feasibility of use of paracetamol in ameliorating AKI in severe malaria in Eastern Uganda. This is a phase I/II clinical trial on a promising treatment with paracetamol in children with AKI; all of which are common in severe malaria. Screening and subsequent monitoring until resolution of AKI of appropriate number of eligible participants for elevated Cr and/BUN using I-STAT machine R1-Analyzer will be done. Adherence to PK sampling, administration of paracetamol and followed up at D28, 90 and 180, respectively will be closely monitored. In addition, we will use a survey tool to assess access, availability and use of paracetamol (Panadol) at household level and among inpatients in Eastern Uganda. These will be captured in the data collection tools, entered into a database and analysed.

Figure 2  Paracetamol for Acute Renal Injury in Severe Malaria Trial study schema and sampling. AKI, acute kidney injury; BUN, blood urea nitrogen; Cr, creatinine; LFT, liver function test.
Children will be followed up at day 28. If they still have clinical and laboratory features of kidney impairment, they will be followed up at 90 and 180 (clinical and serial measures of Cr and /BUN) and urine dipstick; children with abnormal findings will have further repeated investigations of renal function until normal results are obtained.

Methodology for objective 3
To conduct safety and preliminary effectiveness study for use of paracetamol in ameliorating AKI in severe malaria with haemoglobinuria.

Paracetamol oral dose of 20mg/kg will be administered 6-hourly for up to 48 hours. For safety, we will conduct admission LFTs and renal function tests (RFTs).

All adverse events (AEs) and severe adverse events (SAEs) will be collected and reported to research ethics committee, National Drug Authority (NDA) in Uganda and Sponsor appropriately.

For preliminary effectiveness; renal recovery at 48 hours will be indicated by stoppage of progression and decrease of Cr level below baseline, BUN (<20mg/dL) , and resolution of AKI at day 28.

Endpoints
Primary outcome measure
Correction of AKI at 48 hours, as indicated by BUN (<20mmol/L), Cr level (<80mmol/L), normal glomerular filtration index (based on Schwartz criteria), plasma Cr, BUN, urinary-plasma Cr ratio, serum urea-Cr ratio, urinary osmolality, urinary-plasma osmolality ratio and urine microscopy.

Secondary outcome measures
(a) Survival measured using mortality outcome at 48 hours and day 28; (b) resolution of AKI measured using BUN (<20mmol/L), Cr level (<80mmol/L) at day 28, 90 and 180.

Procedures
The timing of the study procedures is summarised in table 2.

Table 1 Pharmacokinetic sampling

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Screening procedure
Dedicated trial clinicians plus four nurses will be employed to conduct the study. Eligible children will be identified by the nurse and clinician on duty and registered in the eligibility-screening log. A member of the trial team will then perform a rapid structured assessment; conscious level, vital signs (heart rate, oxygen saturation, respiratory rate, axillary temperature and blood pressure) and history of haemoglobinuria in the current illness. Children who are potentially eligible with suspected AKI will have a rapid test using iSTAT to determine Cr levels and/ BUN levels and eligibility. Details of those fulfilling the entry criteria will be entered onto a screening form, while reasons for non-eligibility will be added to the eligibility-screening log. It is anticipated that this process will take approximately 20min.

Laboratory investigations
Following consent and randomisation, admission blood samples are taken for the following investigations: full blood count (FBC), urine dipstick, biochemistry (including Cr, BUN), serum electrolytes, lactate, glucose, malaria test, G6PD deficiency, HIV, Hb and CFHb at baseline and subsequently selected tests done at different time points during the admission period as spelt out in table 2, timing of study procedures. During follow-up on day 28, FBC, urine dipstick and malaria test are done and FBC and urine dipstick are done on day 90 and 180.

Allocation and masking
Randomisation process
After screening, the patients that qualify will be assigned study numbers, which correspond to those assigned in envelopes, which are arranged consecutively in sealed opaque envelopes, each assigned across the seal.

These numbers are randomly assigned prior to the start of the study by a statistician using the ‘randomizerR’ package of the statistical software R, which allows simple randomisation and adaptive assignment through minimisation procedure. Minimisation allocates patients to best maintain balance in the treatment group by calculating an imbalance score at each randomisation. It then assigns with higher probability each patient to the treatment that will reduce the imbalance. The allocation will be on 1:1 ratio to paracetamol (A) and no paracetamol (B).

Those on paracetamol (A) are further randomised in the ratio of 1:1 to A1 or A2 according to different PK sampling schedules.

A1 will be those sampled at time intervals 1, 2, 4, 6, 12, 18 and 24 hours while the A2 will be sampled at time intervals 0.5, 1.5, 2.5, 5, 12, 18 and 24 hours.

During enrolment, the study staff will pick the envelopes consecutively and open them. Each envelope will have a card that shows which arm the participant is in (A or B).

Arm B (N=20), those not receiving paracetamol immediately, but if temperature is ≥39.5°C will receive 10mg/kg; will further be randomised on B1 or B2 on 1:1 ratio to

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<td>Receive antipyretic if fever persists</td>
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<td>No paracetamol</td>
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<td>Demographics</td>
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<td>Daily till discharge, then on follow-up</td>
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<td>Medical history and physical examination</td>
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<td>Daily till discharge</td>
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<td>Urine output and fluid intake monitoring</td>
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<td>AE reporting</td>
<td>AE reporting is done throughout the study period</td>
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<td>Urine dip stick</td>
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<td>Biochemistry (including: Creatinine, BUN)</td>
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<td>Serum electrolytes</td>
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<td>Glucose</td>
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<td>HIV</td>
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different sampling schedules as follows; B1 (N=10), will be sampled at 1, 2, 4, 6 hours postrandomisation. Thereafter, sampling will continue once every 6 hours for 24 hours. B2 (N=10) will be sampled at 0.5, 1.5, 2.5, 5 hours postrandomisation. Thereafter, sampling will continue once every 6 hours for 24. Study participants randomised to PK sampling will have an extra card which indicates which PK sampling scheduling the participant will follow (A1 vs A2 or B1 vs B2). For the PK sampling on day 0, an intravenous catheter will remain in place for 24 hours. Full aseptic techniques will be used when taking blood to minimise the infection risk.

**Masking**

Due to the nature of the intervention, neither participants nor staff can be blinded to allocation, but are sturdily instructed not to disclose the allocation status of the participant at the follow-up assessments. Data entrants outside the research team will enter data into the computer in separate datasheets so that the researchers can analyse data without having access to information about the allocation.

**Clinical monitoring and further assessments**

All children will be reassessed clinically at 1, 4, 8, 24 and then every 24 hours up to day 5. At selected time points during this period the vital signs (heart rate, oxygen saturation, respiratory rate, axillary temperature, blood pressure), urine output and fluid intake, daily body weight measurement and examining for AEs will be recorded (emesis, right upper quadrant pain, tachycardia and hypotension will be monitored as per table 2.

**Further management**

All standard management protocol of cases will be adhered to except use of paracetamol intervention dose since this is a study drug. Standard Case Management in-hospital is done at the paediatric acute care unit (PACU) following the ETAT (emergency triage and treatment) guidelines, which will be followed in triaging all sick children on arrival into those with emergency signs, with priority signs or non-urgent cases. In addition, ETAT guidelines will be used to steer immediate emergency and life support treatment as the first step and means of stabilising patients. Once the emergency and priority cases are stable, underlying severe malaria will be treated using artesunate as spelt in the Uganda National Treatment Guidelines 2016. In addition patients deserving other medications including, but not exclusive to: antibiotic treatment for bacterial diseases will be given them. Furthermore, hypoglycaemic patients (blood glucose <2.2 mmol/L) will be given 2 mL of 25% dextrose per kg body weight. Dehydration will be corrected appropriately. Anticonvulsants will be administered according to nationally agreed protocols except for severe malaria.

**Protection against sources of bias**

While the randomisations are open, protection against bias is principally provided by use of entirely objective
primary endpoint (laboratory indices of AKI). Any child lost to follow-up before day-28 will be traced for vital status (and permission for this will be requested in the initial consent). A placebo-controlled design would be more complex (and costly) for a small phase II trial and requires strict control of the use of paracetamol across all participants. In the proposed design, while the protocol would recommend non-paracetamol-based antipyretic usage in the non-intervention arm, it will be possible to capture their usage (in the control arm) and thus generate important data for any future phase III trial.

Study duration
The clinical trial is expected to last 18 months from September 2021 to March 2023.

Product(s) to be tested and product supply
Paracetamol and the dosage proposed is not considered as an investigational product. However, the trial will comply with Good Manufacturing Practice regulations and ensure that the product has an accompanying certificate of analysis and is labelled for the trial to comply with Good Clinical Practice (GCP) guidelines.

Trial site selection
This is a single centre phase I/II trial to be conducted at Mbarara Regional Referral Hospital (MRRH). Each year MRRH in the Eastern region of Uganda registers between 800 and 1200 children with this dark urine syndrome, which has associated high mortality and long hospital stay.40

Recruitment and retention
In this study, we will conduct paediatric admissions ward surveillance study for severe malaria using WHO 2010 updated criteria. The surveillance for severe malaria will be done on our existing patient triage platform, which is now part and parcel of the hospital and our research unit system. This will enable sustained surveillance once we procure the data collection tools as well as point-of-care tests. Data will be collected on all children with features suggestive of severe malaria presenting to acute care unit during the 8-hour day service shift of 08:00 to 17:00 for a 5-year period 30 March 2017 to 28th February 2022.

However, for the clinical trial, we will have a dedicated study team comprised six trained clinicians, who will work alongside the rest of the hospital and research team at the site for 24 months.

As a key indicator of our success in research, our studies conducted at MRRH have delivered high-quality data within projected timeframe and within budget. We have a very good working relationship with the community and effective communication strategies as a result we enjoy high consent approval for our studies (>90%) and for our most recent trials 97% and 95% completeness of follow-up for 28-day and 6-month endpoints. We have complementary operational collaborative arrangements with the hospital, the Joint Clinical Research Centre and Busitema University. Furthermore, there is a fully functional Mbale Hospital Institutional Ethics Review Committee, which provides review and monitoring of research and ethics at MRRH. This review committee was established after we won an EDCTP grant on IRBs (CB.2011.41302.016). This strengthened the IRB at Mbale Hospital through establishment of the standard operations procedures, the Institutional review committee, communication systems (internet and phone lines), furniture, equipment and establishment of office space.

Trial subject safety
The safety of trial participants will be guaranteed at various stages. First, the patients will be managed at a public facility with all the standard of care available. Second, the study protocol will be submitted for Research Ethics Committee (REC)/Institutional Review Board (IRB) in the region. The following ethical considerations have been put into thought in the design of this study:

1. Safety assurance: the balance between any risk and benefit will be kept under constant review throughout the study and if any event occurs, it will promptly be reported to the institutional review committee, the Uganda National Counsel for Science and Technology (UNCST) and NDA.
2. Risks: at case identification, the screening form is very brief and will not waste any patient-care time because this is integrated in the triage process, we have used this before in two clinical trials with success. No studies have cited dangers of using screening forms. In addition, some of the procedures such as detection of malaria parasitaemia, Hb estimation, lactate estimation, random blood sugar, LFTs and RFTs are routine tests done in all children with critical sickness. Other than minimal pain at a time of taking the sample, no life threatening events have been reported in our setting associated with these procedures.
3. Benefits to study participants: benefits are explained to our study participants at each time we encounter them for a procedure. None of these benefits are put forward as enticement to participate. Some of the benefits arising from this study include clinical assessments by trained clinicians, education messages on the disease condition and counselling that go as a package for this study.
4. Confidentiality: will be ensured by data protection and data management procedures. On admission/enrolment, participants are issued with a unique identifying number. All clinical data will be held confidentially and personal identifiers will be removed before analysis and presentation of the results.
5. Privacy: this will be ensured by carrying data collection procedures including consenting in a quiet and private place.
6. Informed consent (IC): prospective written, IC will be sought from parents or guardians of children who are considered to be sufficiently stable. Parents or guardians will be given an information sheet in their usual language containing details of this 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.

7. We have structured IC that reflects the research activities in the research protocol. The IC will ensure confidentiality, privacy and autonomy. It will not include routinely done patient care related tests but will be for all research procedures. HIV testing is currently routinely done. Our study will access and share this routine data from the records.

8. Paracetamol is a drug already in human use in clinical settings and so we will not be doing experimentation for discovery of a new drug, but advancing knowledge on how else this drug can be used. The study will avoid all unnecessary physical and mental suffering, and injury should be avoided. The degree of risk to the study participants will not exceed that already documented in studies with paracetamol and manufacturer’s warning because we will use the recommended doses.

9. We will minimise all risks to the study participants through proper preparations as spelt in our work packages.

10. Qualified investigators and research team will conduct our study. The study participants will be at liberty to withdraw from the study at any time without any further questions and will continue to receive standard of care available without discrimination. Investigators must be ready to end the study at any stage if there is cause to believe that continuing the study is likely to result in injury, disability or death to the subject.

The study only started recruiting at the site when the ethical approvals were in place. The principal investigator (PI) is responsible for the scheduled reports to the ethics regulatory and monitoring authorities. Our external monitors will ensure that adherence to the protocol, consent process, data quality, level of training of our clinical research teams is up to date and in accordance with the GCP and International Council for Harmonisation (ICH) guidelines.

In general, this trial site in Eastern Uganda has considerable experience with this population and this will serve to minimise the risks to the patients and the trial.

Roles of the named committees

**Trial Steering Committee**

There is a steering committee of three independent members who report to the governance of the PARIST trial with a goal of proper scientific oversight of the PARIST study project.

**Data monitoring Committee**

This has been established. The Data monitoring Committee (DMC) is independent of the study organisers. During the period of recruitment to the study, interim analyses will be supplied, in strict confidence, to the DMC, together with any other analyses that the committee may request.

**Data Safety Management Board**

There is a Data Safety Management Board (DSMB) comprising three members experienced in phase two clinical trials. The focus of the DSMB is the overall integrity of the study, and its continued relevance and ability to answer the primary objective. Interim unblinded analyses will be conducted by the DSMB annually or more frequently at the discretion of the chair. A recommendation to the sponsor to discontinue recruitment, in all patients or in selected subgroups, may be made by the Trial Steering Committee (TSC) on advice from the DSMB if the data provide proof beyond reasonable doubt that one of the treatment arms is better in terms of the primary outcome or safety guided by the Haybittle-Peto criteria.41 42 A local safety monitor will be appointed to provide independent consultation on clinical care.

**Endpoint Review Committee**

An independent committee of at least three experienced clinicians and serve as reviewers of every SAEs in the trial.

**Clinical trial sponsor**

MCRI (www.mcri.ac.ug), a legal entity in Uganda is the sponsor of this trial. It is a well-established research and capacity-building institute with support from the Wellcome Trust, UK and other development agencies.

**Trial monitoring**

Independent monitoring is provided for the trial from the Clinical Trials Facility, KEMRI Wellcome Trust Programme, Kilifi, Kenya. This is done quarterly. Through these trial-monitoring sessions, there is hands-on skills transfer to the study team as well.

DATA MANAGEMENT

**Data collection**

Study clinicians are responsible for collecting data collected at enrolment, daily clinical review during the hospital stay, at follow-up visits and at re-admission. Data capture is primarily via a paper Case Report Form (CRF). These data are subsequently transferred to a secure electronic database for analysis.

**Data storage**

All clinical and laboratory data are recorded in the CRF and stored with a unique serial number identifier. Data is entered into Redcap database at the MCRI. All data is anonymised prior to the presentation or publication of any results. All data is kept confidential with access restricted on password-protected computers. The Redcap database at the MCRI has regular secure backup with both local and offsite storage. The data management system generates automated queries based on pre-programmed rules and the data manager generates manual queries using a statistical package. All queries are dealt with by the lead

site clinicians and clarified by the investigators and field staff with clear documentation. The Redcap system maintains an audit trail. Other paper source documents are still used to capture data for the screening visits, scheduled visits, unscheduled clinic visits, lab and other investigational results.

The investigators permit trial-related monitoring, audits, IRB/REC review, and regulatory inspections by providing direct access to CRFs, source data and documents. The PI is responsible for receiving, entering, cleaning, querying, analysing and storing all data that accrues from the study. Responsibility for this is delegated to the study data management team.

Data handling and retention
Data is handled according to guidelines by the UNCST and Uganda law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) are archived at trial sites for 5 years. The clean trial database file will be anonymised and maintained for 5 years.

Patient and public involvement
Patients and public were not involved in any of the phases of this clinical trial.

Intellectual property
The study has contracts between Busitema University and EDCTP the funder. The proposed research is not likely to lead to commercially exploitable outcomes. Patients will not be involved in the arrangements on intellectual property.

Insurance
MCRI has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. The study clinicians who are involved with trial procedures have professional indemnity insurance.

Safety reporting
We are using the CTCAE criteria for safety assessment in the study. Every SAE related to the studied treatment or not, expected or unexpected, must be reported within 24 hours by the investigator to the sponsor on a ‘SAE’ form on which will be indicated the date of occurrence, criterion of severity, intensity, relationship with the treatment (or the study) evaluated and the outcome. The period in which SAEs should be reported begins from the day of the written IC to the end of the follow-up (48 hours). Whenever an SAE persists at the end of the study, the investigator must follow the patient until the event is considered resolved. In addition, SAEs will be submitted to the DSMC.

Statistical analysis
Statistical analysis will be performed on all randomised and evaluated patients (intention-to-treat analysis). This will be performed using the statistical software R. A first overall descriptive analysis and analysis by group will be performed. This consists of separate estimates, numbers and percentages for qualitative variables, means, SE, medians and interquartile intervals for quantitative variables. Student’s t-test or Mann-Whitney U test, if necessary, will be used to compare quantitative variables, and χ² test or Fisher’s exact test, if necessary, will be used to compare qualitative variables between two groups at inclusion. The primary end point (renal recovery at 48 hours) will be compared between the two groups with the χ² test. One interim analyses after inclusion of a half of the patients, and one final analysis are planned.

Primary safety analyses will compare the proportion of children with a prespecified significant AE at 48 hours and 28 days in the intervention arm A or B using an unadjusted χ² test. Secondary analyses of efficacy will use Kaplan-Meier and log-rank tests to compare time to renal recovery at 48 hours (as indicated by stoppage of progression and decrease of Cr level below baseline, BUN (<20 mg/dL)). χ² tests will compare differences in serum Cr between the intervention and control group. Data on all measures of hepatic function will be assessed for normality, and means (and SD) or medians (and IQRs) presented as appropriate.

For the PK study, analysis will use NONMEM non-linear PK modelling software to determine the peak level for the two different PK sampling schedules.

Stopping guidelines: an interim-analysis will be performed on the primary endpoint when 50% of patients have been randomised and have completed the 180 days of follow-up. The interim-analysis is performed by an independent statistician, blinded for the treatment allocation. The statistician will report to the independent DSMC. The DSMC will have unblinded access to all data and will discuss the results of the interim-analysis with the steering committee in a joint meeting. The steering committee decides on the continuation of the trial and will report to the central ethics committee. The Haybittle-Peto criteria for early stopping of a trial is used: the trial will be ended using symmetric stopping boundaries at p<0.001.31 42. The trial will not be stopped in case of futility, unless the DSMC during the course of safety monitoring advises otherwise. In this case, DSMC will discuss potential stopping for futility with the TSC. A p value <0.05 will be considered as statistically significant for all analyses.

Missing values
Missing data will not be replaced. Mixed models can be used in the analysis of repeated data to avoid deleting subjects with any missing values.

ETHICS AND DISSEMINATION
Ethical and regulatory approvals
Ethical and regulatory approval has been granted by Mbale Hospital Institutional Ethics Review Committee (MRRH-REC OUT 002/2019), which provides review
and monitoring of research and ethics at MRRH. In addition, the UNCST (HS965ES) and NDA (CTC 0166/2021) also provided approval before commencement of the study. PARIST study has been registered on ISRCTN. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials 2010 guidelines.43

Consent
Trained research clinicians and nurses will introduce the trial to parents/legal guardians of children (identified as eligible at screening) who will be explained the main aspects of the trial including receiving patients information sheets. They will then be able to have an informed discussion with the participating research staff. Research clinicians/nurses will obtain written consent from parents/legal guardians of the children willing to participate in the trial. Information sheets and consent forms are provided for all parents/legal guardians of children involved in the trial. For children 8 years and above a child assent will be issued in addition.

A number of children will present as emergencies, where delay in study enrolment, and thus treatment, will not be practical or indeed ethical. We have received ethical approval to use a modified form of deferred consent; also recently used in the FEAST trial for which the deferred consent process was developed. It proposes to use a ‘two-stage’ consent process in this circumstance.44 45 Verbal assent will be sought from parents or guardians by the admitting medical team, if it is considered that the full consent process would significantly delay treatment allocation, and consequently could be detrimental to the child’s health. Full consent will be sought once the child’s clinical condition has been stabilised. Caregivers will be provided with a brief verbal description of the trial and will be given the opportunity to ‘opt out’ of clinical research. The clinician will later sign the verbal assent form, which will be filed with the consent form. If consent is withdrawn later no data from the subject will be used. Social science study of the consent processes used in FEAST found this to be acceptable to parents and healthcare workers. As in the FEAST trial, if following an assent process a child died prior to full written consent, full consent would not be sought. This process of emergency consent was approved by multiple ethics research committees for FEAST and has been subsequently approved for use in a transfusion trial in Uganda and Blantyre.46

Modification of the protocol
Any modifications to the protocol, which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed on by DSMB, chief PI and coinvestigators, and approved by the ethics committee/IRB bodies prior to implementation in accordance with local regulations.

Publication plan
Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the PI. The coauthors of the report and the publications will be the investigators and clinicians involved, on a proportionate basis of their contribution to the study, as well as the biostatistician and associated researchers. Rules on publication will follow international recommendations.49

Implementation of the trial protocol
There were two main challenges faced when operationalising this trial. The first was related to the strict eligibility criteria owing to the exclusion criteria of prior use of paracetamol within the last 24 hours to 48 hours before enrolment. This limited the number of eligible participants for enrolment into the study because this is a cheap over the counter drug with wide spread non-prescription use especially for most febrile illness before seeking medical attention at the health facilities.

In order to address this challenge, we revised the study eligibility criteria to a less strict exclusion by limiting the duration of prior paracetamol use to 24 hours before enrolment. Training for the dedicated study teams was delivered on multiple occasions and retraining conducted if there were any questions or points of confusion. We revisited the screening forms to simplify these and minimise room for error.

Second, and predictably, the COVID-19 national lockdown measures to stop the spread of the pandemic especially the second lockdown in July 2021 spanning through to the end of the year, limited recruitment rates to this study. A protracted lockdown period with a number of restrictions that limited patient access to health facilities for much of the second half of the year in 2021. As a result, numbers presenting to hospitals fell significantly, despite the fact that the paediatric ward at MRRH remained open to admissions. To increase the recruitment rate, the study team reached to the peripheral units clinicians and nurses within the MRRH catchment area, trained them on the basic eligibility of the study in order to refer potential eligible patients for enrolment.

Trial status
Enrolment to the trial started at the PACU in Mbale in September 2021 and is currently ongoing. There have been episodes of slow recruitment because of national COVID-19 restrictions (lockdown measures). By 1 August 2022, seven children had been enrolled at the study site in Mbale.

Protocol version changes
Version 1.0 was the original protocol submitted for ethical approval to MRRH-REC and was approved on 08 January 2019.
Version 2.0 detailed minor grammatical changes requested by MRRH-REC: an additional sentence in the consent form explaining the difference between the two arms and clarification of sample storage procedures. Version 2.1 changed the exclusion criteria of prior use of paracetamol from 24 to 48 hours to a lesser strict duration of 24 hours only as requested to NDA on 14 March 2022.

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Contributors All authors have made substantive intellectual contributions to the development of this protocol manuscript. PO-0 conceptualised the clinical trial and provided general guidance to the research team. All authors are involved in the implementation of this protocol. GA and CN designed the database. PO, EEE, DA, CN, WO and MO are involved in data collection. RM initially developed the laboratory implementation of this protocol. GA and CN designed the database. PO, EEIE, DA, VV and DM are involved in the design, or conduct, or reporting, or dissemination plans of this research. GP initiated the first draft of the manuscript, which was then followed by numerous iterations with substantial input and appraisal from all of the authors. All authors approve the final version of the manuscript. CN* - Carolyne Ndilla, CN - Cate Namayanja

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