KEMRI | Wellcome Trust

FLACSAM
First Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

UNIVERSITY OF OXFORD

CLINICAL TRIAL PROTOCOL

Trial title:	**First Line Antimicrobials in Children with Complicated Severe Acute Malnutrition**
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1 GENERAL INFORMATION

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**Curriculum Vitae of non-KEMRI investigators, see appendix C*

Compliance Statement

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (Note for Guidance on GCP) and applicable national regulations.

Confidentiality Statement

The information contained herein is privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you, which is indicated as privileged or confidential. This confidentiality statement also applies to data generated during the course of the study.

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2 GLOSSARY OF TERMS AND ABBREVIATIONS

AE	Adverse event
BMI	Body Mass Index
CGMR-C	Centre for Geographic Medicine Research – Coast, Kilifi, Kenya
CMR	KEMRI Centre for Microbiology Research, Nairobi
CRF	Case Report Form
CSC	Centre Scientific Committee
DSMC	Data & Safety Monitoring Committee
ESBL	Extended spectrum beta-lactamase
GCP	Good Clinical Practice
GMP	Good manufacturing practice
ICF	Information and consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IP	Investigational product(s)
IV	Intravenous
KDHS	Kenya Demographic and Health Survey
KEMRI	Kenya Medical Research Institute
KHDSS	Kilifi Demographic & Health Surveillance System
KWTRP	KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya
LSM	Local Safety Monitor
MUAC	Mid-upper arm circumference
MRRH-REC	Mbagathi Regional Referral Hospital and Research Ethics Committee
OxTREC	Oxford Tropical Research Ethics Committee
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PK	Pharmacokinetic
PPB	Pharmacy & Poisons Board, Kenya
PO	Per os (by mouth)
RCT	Randomized controlled trial
SAE	Serious adverse event
SAM	Severe acute malnutrition
SERU	KEMRI Scientific and Ethics Review Unit, Nairobi
SMS	Short message service
SOP	Standard of operating procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
TSC	Trial Steering Committee
UNCST	Uganda National Council for Science and Technology
VA	Verbal autopsy
WHO	World Health Organisation

3 LAY SUMMARY

Formal Title

First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

Lay Title

A study to compare antibiotics used to treat children with severe acute malnutrition.

What is the problem?

Children with severe malnutrition who are admitted sick to hospitals have a high mortality, usually because of infection. All children with severe malnutrition admitted to hospitals are treated with antibiotics. However, we are not sure that the current antibiotics are the most effective. It is possible that the antibiotics that are currently used as second-line should be used first. No studies have been carried out to determine if the current antibiotics used for treating malnourished children are the most appropriate. We will therefore carry out this large trial comparing different antibiotics to find out this.

What questions are we trying to answer?

We want to find out if a revised antibiotic regime for children with complicated severe acute malnutrition is safe, reduces the risk of death and improves nutritional recovery. We also want to find out how often children carry bacteria that are resistant to antibiotics in their intestines and the effects of different antibiotics on the ability for bacteria to resist antibiotic treatment and the costs to hospitals and to families of treating malnourished (SAM) and without SAM children with the different antibiotics.

Where is the study taking place, how many people does it involve and how are they selected?

We will carry out the study in Kilifi County Hospital, Coast General Hospital in Mombasa, and Mbagathi hospital in Nairobi, Kenya and Mbale Regional Referral Hospital, Uganda. We will enrol 2,000 children with severe malnutrition admitted to hospital. We will ask parents and guardians of all children between the ages of 2 months to 13 years who are admitted to hospital with severe malnutrition and would normally be treated with antibiotics according to current guideline to participate and enrol an equal number of children at each site who are admitted without SAM to examine faecal samples for bacteria that may be resistant to antibiotics.

What does the study involve for those who are in it?

After informed consent, a study clinician will examine the child and prescribe antibiotics that have been randomly allocated. A small volume of blood and a faecal sample will be taken for this research in addition to the routine tests for care at admission before antibiotic administration, and again at discharge. The children will be reviewed daily by the study team, working together with the hospital staff to provide the best care available in the hospital. Children will be followed up for 90 days from enrolment with 3 scheduled follow up visits involving a health questionnaire, anthropometry and the collection of a faecal sample at two of the visits. The levels of the antibiotics being used will be checked in the blood of 120 participants at Kenyan sites whilst in hospital. Parents and carers of approximately 650 children in both SAM and without SAM across all sites may also be interviewed about any costs they have met as a result of the child needing healthcare. If a child requires readmission to hospital, a small volume of blood will be drawn to try and determine the cause. Results of blood tests will be fed back to the clinical team to assist in care. For non-severely malnourished children, a rectal swab will be taken at admission and discharge, and information collected during admission, but we will do no additional samples or further follow up.

What are the benefits and risks/costs of the study for those involved?

Training will be enhanced for all paediatric ward staff on treatment of sick and malnourished children and assisting with control of infections within the hospitals. Drawing a blood sample carries the risks of discomfort and damage to the vein or infection; careful procedures including cleaning the skin will help prevent these. Rectal swabs and faeces collection have minimal risk. Travel costs and lost earnings associated with scheduled follow up visits will be reimbursed, based on national guidelines.

How will the study benefit society?

Knowing how better to use antibiotics in malnourished children when they are admitted to hospital will help decision-making to improve their health and survival. The findings from this research will directly inform policy and program management decisions related to the care of the sick child.

When does the study start and finish?

The study aims to start as soon as scientific and ethical approval is granted, follow up for participants is expected to continue for about 3 years and the overall study for about 5 years.

4 ABSTRACT

Children with complicated severe acute malnutrition (SAM) admitted to hospital in sub-Saharan Africa have a case fatality between 12% and more than 20%. Because children with SAM may not exhibit the usual signs of infection, WHO guidelines recommend routine antibiotics. However, this is based on "low quality evidence". There is evidence from CGMR-C, Kilifi and from other centres in Africa that bacterial resistance to the currently recommended first-line antibiotics (gentamicin plus ampicillin or penicillin) may be less effective than potential alternatives. Some hospitals in Africa are already increasing use of ceftriaxone as a first-line treatment. However, this is not based on any data that ceftriaxone actually improves outcomes. Of concern is that ceftriaxone use may also lead to increased antimicrobial resistance, including inducing extended spectrum beta-lactamase (ESBL) and other classes of resistance. We are currently undertaking a study to assess the prevalence of carriage of bacteria expressing ESBL (KEMRI/SERU/CGMR-C/023/3161; OxTREC 47-15).

A further area where evidence for policy is lacking is the use of metronidazole in severely malnourished children. The WHO guidelines recommend *"Metronidazole 7.5 mg/kg every 8 h for 7 days may be given in addition to broad-spectrum antibiotics; however, the efficacy of this treatment has not been established in clinical trials.*" Metronidazole is effective against anaerobic bacteria, small bowel bacterial overgrowth, *Clostridium difficile* colitis and also Giardia, which is common amongst children with SAM. Small cohort studies of metronidazole usage suggest there may be benefits for nutritional recovery in malnourished children. However, metronidazole can cause nausea and anorexia, potentially impairing recovery from malnutrition and may also rarely cause liver and neurological toxicity.

This multicentre clinical trial will assess the efficacy of two interventions, ceftriaxone and metronidazole, on mortality and nutritional recovery in sick, severely malnourished children in a 2x2 factorial design. There will also be an analysis of antimicrobial resistance and an economic analysis. To extend our understanding of metronidazole and ceftriaxone pharmacokinetics from protocol KEMRI/SERU/CGMR-C/023/3161; OxTREC 47-15', additional pharmacokinetic data for the dosing schedule used in the trial will be collected from 120 participants. The trial will be conducted at Kilifi County Hospital, Coast General Hospital, Mbagathi Hospital in Kenya and Mbale Regional Referral Hospital in Uganda. The trial will assess antimicrobial resistance that is carried by children in their intestines and in invasive bacterial isolates. The relative costs of care for children with SAM and without SAM for health facilities and for families, including antimicrobial usage will also be assessed. Clear data on the benefits, risks and costs of these antimicrobials will influence policy on case management and antimicrobial stewardship in this vulnerable population.

5 INTRODUCTION

Undernutrition is estimated to cause 3.1 million deaths in children each year, [1] approximately 1 million of which are due to severe acute malnutrition (SAM). Under current WHO guidelines, children are admitted to hospital with SAM only when they have complications, which usually involve infection. In many cases, SAM is only detected during clinical assessment for another severe illness.

At hospitals in Africa, typically between 15% and 18% of paediatric patients have SAM. Children with complicated SAM admitted to hospital in sub-Saharan Africa have a case fatality of between 12 and more than 20%.[2-4] Deaths mostly occur in combination with severe infection within the first 2 weeks. HIV infection is present in 15-29% of children admitted with SAM in sub-Saharan Africa and HIV is associated with a 3 fold increased risk of inpatient mortality.[3, 5] Overall, children with SAM who are admitted to hospital have a much higher mortality than non-severely malnourished children with serious infections including 'very severe pneumonia', or presumed sepsis. This risk is evident both during and after hospitalization, despite implementation of existing treatment guidelines. Mortality after discharge from hospital, while often not evident to health care providers may equal or even exceed inpatient mortality in many resource-poor settings. For example, in Kenya, hospitalized children were nearly 8 times more likely to die in the year following discharge than community peers who had not been admitted, with young age and undernutrition appearing to be the main risk factors for post-discharge mortality. [6]

The treatment of SAM involves correcting metabolic and electrolyte imbalances, treating infections and therapeutic feeding in order to prevent short-term mortality and to achieve catch-up growth. SAM with infectious complications is usually treated in hospital whilst uncomplicated SAM is treated in the community.

WHO guidelines recommend empiric IV antibiotics for all children with SAM who are admitted with infectious complications because children with SAM may not exhibit the usual signs of infection: intravenous penicillin (or ampicillin) plus gentamicin until they are medically stable, then oral amoxicillin to complete 7 days treatment.[7] However, despite recognised high mortality, empiric antibiotics for children admitted to hospital with complicated SAM have never been evaluated in a clinical trial and thus there is concern that current strategies may not be optimal.

There are few studies reporting antimicrobial sensitivity of invasive bacteria among children with SAM, and none that include clinical outcomes. At CGMR-C, Kilifi, we have run a programme of systematic surveillance of invasive bacterial infections in children since 1998 [8]. Overall, 12.9% of children admitted with SAM had bacteraemia detected. In the last 10 years, there has been a consistent trend ($P<0.001$) in the proportion of invasive isolates from children admitted with SAM that, *in vitro,* are not sensitive to ampicillin or gentamicin, to at least 38%. The proportion of isolates not susceptible to 3rd generation cephalosporins is stable at less than 14%. This is compatible with data from a recent review of data from paediatric admissions (mostly without SAM): in 26 studies (409,215 isolates) from 13 African countries, there was a prevalence of extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae from blood or urine cultures of less than 15%.[9] The prevalence of ESBL ranged from 0.7% in Malawi to 76% in tertiary centre intensive care patients in Egypt.

In Uganda, 22% of children admitted with SAM were reported to be bacteraemic.[10] Few organisms were susceptible to ampicillin (23%) and gentamicin (33%) *in vitro*, but all isolates were sensitive to ceftriaxone. In Ghana amongst all paediatric hospital admissions, 39% of blood culture isolates (excluding contaminants)

were sensitive *in vitro* to gentamicin, almost none to ampicillin and 79% were sensitive to 3rd generation cephalosporins [11]. Amongst all children admitted to hospital in Tanzania, 14% were bacteraemic,[12] of whom 33% died. For community-acquired *Enterobacteriaceae* isolates, only two-thirds were sensitive to gentamicin (20% were sensitive to ampicillin). Significant risk factors for death were antimicrobial resistance, HIV infection, other underlying infectious diseases and malnutrition. However, in most other published reports, it is not clear that *in vitro* resistance profiles among either carriage or invasive bacterial isolates actually relate to outcomes.

Ceftriaxone

Ceftriaxone is currently recommended as a second line treatment in sick children with SAM. However, some centres in Africa are already changing their local practice to use it first-line in the absence of data on susceptibility or treatment outcomes.[13] Ceftriaxone is active against a broad spectrum of Gram positive and Gram negative bacteria, including intracellular bacteria (e.g. Salmonellae, Staphylococci). Ceftriaxone is usually given once rather than four times daily, potentially saving considerable nursing time and improving the likelihood that doses will be missed in crowded and understaffed wards. Since coming off-patent in 2005, the price of ceftriaxone given once daily has become lower than penicillin or ampicillin plus gentamicin.

A significant concern regarding empiric ceftriaxone use as a first-line agent is the potential for inducing extended spectrum beta lactamase (ESBL) resistance, linked with resistance to multiple classes of antibiotics, thus threatening our ability to treat serious infections. In addition to ESBLs, Enterobacteriaceae can acquire plasmid-encoded AmpC genes as an important resistance mechanism against ß-lactams. For example, in Niger, 30% of children with SAM had ESBL detected at admission on rectal swabs (no comparison was made with non-SAM children). Of those without ESBL 94% children with SAM treated with ceftriaxone acquired faecal carriage of ESBL-encoding genes.[14] However, the clinical significance of this is unknown since outcomes were not assessed, carriage may not be reflected in disease and may disappear over time. Cephalosporin is also known to be linked to acquisition of *Clostridium difficile* infection, which is an important cause of chronic diarrhoea amongst individuals with debilitating and chronic illness, and frequent healthcare attendance.[15]

Overall, the use of ceftriaxone as a first-line antibiotic could save lives. However, potential benefits and risks in terms of mortality, costs, compliance and antimicrobial resistance are unknown. Thus, there are no data to support decision-making.

Metronidazole

The WHO guidelines recommend “Metronidazole 7.5 mg/kg every 8 h for 7 days may be given in addition to broad-spectrum antibiotics; however, the efficacy of this treatment has not been established in clinical trials.” [7]Metronidazole is commonly used in Kenya and is effective against anaerobic bacterial infections, small bowel bacterial overgrowth, *Clostridium difficile* colitis and Giardia. In a recent trial treating enteropathy in SAM in a Nairobi slum,[16] >30% of children had Giardia on microscopy. In Rwanda, amongst malnourished children, Giardia prevalence was 20% by microscopy and 60% by PCR.[17] Its antimicrobial effect is dependent on its peak concentration, and there is a significant ‘post antibiotic’ killing effect. Small cohort studies suggest metronidazole is beneficial for nutritional recovery among children with SAM. It improved appetite and reduced stool frequency associated with small bowel anaerobic

bacterial overgrowth. Breath hydrogen normalised after 5 days of oral metronidazole.[18] However, metronidazole can cause nausea and anorexia, potentially impairing recovery from malnutrition.

The proposed clinical trial will assess the efficacy of ceftriaxone versus penicillin plus gentamicin, and metronidazole versus placebo on mortality and nutritional recovery in sick, severely malnourished children in a 2x2 factorial design. The trial will be undertaken at Kilifi County Hospital, Coast General Hospital and Mbagathi Hospital in Kenya, and Mbale Regional Referral Hospital in Uganda. In order to assess antimicrobial resistance that is brought into hospital and that which is acquired on the ward, the antimicrobial susceptibility profile will be determined as a sub-study for invasive isolates and for carriage in rectal swabs in trial participants and in children without SAM being treated on the same wards. This will enable determination of the effect of carriage of antimicrobial resistance on mortality and treatment outcomes.

Currently, there are no comprehensive cost estimates for treating children with SAM and without SAM. Antimicrobial resistance may influence costs by increasing the use of more expensive antibiotics, more diagnostic investigations or a longer hospital stay. Costs of care to the health system and to families will be examined, the cost-effectiveness of different antimicrobial strategies and potential future costs including consideration of evolving antimicrobial resistance will be modelled. In the economics sub-study costing data of children without SAM will also be collected from the non-trial bacterial faecal carriage sub-study and compared with children with SAM. Clear data on the benefits and risks of these antimicrobials will influence policy on case management and antimicrobial stewardship in this vulnerable population.

6 INVESTIGATIONAL PRODUCTS

All investigational product(s) will be supplied to the trials sites by the Clinical Trials Pharmacy at the KEMRI CGMR,C Kilifi.

6.1 Ceftriaxone

A high quality commercial ceftriaxone product will be purchased and tested for quality and used in an open label fashion. The dose and frequency of administration to be used has been determined by a pre-trial pharmacokinetic study in 80 severely malnourished children in Kenya (KEMRI/SERU/CGMR-C/023/3161; OxTREC 47-15). Ceftriaxone is licensed for use in children in Kenya and Uganda.

6.2 Penicillin & Gentamicin

High quality commercial benzyl penicillin and gentamicin products will be purchased and used at standard recommended doses in an open label fashion. Benzyl penicillin and gentamicin are licensed for use in children in Kenya and Uganda.

6.3 Metronidazole & Placebo

Metronidazole and its matching placebo will be sourced from a licensed manufacturer in Kenya, who will produce it according to GMP standards. Samples will be tested by the study team in order to select the metronidazole and its placebo that look, taste and smell similar prior to production. The active drug will be tested for quality and content. The dose and frequency of administration have been determined in a pre-trial pharmacokinetic study in 80 severely malnourished children in Kenya (KEMRI/SERU/ CGMR-C/023/3161; OxTREC 47-15). Metronidazole is licensed for use in children in Kenya and Uganda.

7 JUSTIFICATION

Sick children with SAM admitted to hospital continue to have a high mortality in hospital and post-discharge. The optimum antibiotic choice and dosage are not clear. This trial will assess whether broader spectrum antibiotics can reduce mortality, improve growth and recovery compared to current WHO and national guidelines in order to inform future policy in the face of increasing antimicrobial resistance.

8 OBJECTIVES

8.1 Null hypotheses

- Mortality amongst children admitted to hospital with complicated SAM is not altered by administration of intravenous ceftriaxone or metronidazole as first line agents compared to penicillin plus gentamicin.

8.2 Primary objective

Amongst children with complicated SAM, to establish whether:

- Mortality is reduced during 90 days when treated with broader spectrum first-line antibiotics (ceftriaxone or metronidazole), compared to the currently recommended narrower spectrum antibiotics (penicillin and gentamicin).

8.3 Secondary objectives

To evaluate in trial participants:

- Suspected grade 4 toxicity and serious adverse events
- Mortality in hospital and after discharge
- Duration of hospitalisation and antimicrobial administration
- Frequency and causes of readmission to hospital during follow up
- Recovery of nutritional status during follow up
- Aetiology of infections occurring during the study and faecal carriage of bacteria expressing Extended Spectrum Beta Lactamase (ESBL), at admission, discharge and follow up

8.4 Sub-studies

- Faecal carriage of bacteria expressing Extended Spectrum Beta Lactamase (ESBL), at admission, discharge and antimicrobial prescribing among non-malnourished children admitted to the same wards who are not participating in the trial; and environmental swabbing within study hospitals.
- Detection of pathogens, antimicrobial resistance and biomarkers of infection and inflammation by ELISA, mass spectrometry and molecular methods using the faecal samples, swabs and blood samples stored during the study.
- Collection of further data on the pharmacokinetics of antibiotics in malnourished children within the trial using the trial dosing regimens.
- Estimation of provider and household costs of treatment for children with SAM and without SAM. incremental costs of the interventions within the trial period, within each episode of illness and within the cohort life time; and incremental cost per disability adjusted life year (DALY) averted by

the intervention. Creating models of future costs based on antimicrobial usage and potential trends in antimicrobial resistance.

9 TRIAL DESIGN

The trial will investigate two separate antimicrobial interventions in a 2x2 factorial design randomised controlled clinical trial. A factorial design allows more than one intervention to be tested and is useful in assessing a potential package of care. Two randomisations will be made. The two interventions will be analysed separately. Ceftriaxone and metronidazole is an effective and commonly used antibiotic combination, hence major interactions that interfere with efficacy are unlikely. However, evidence for interaction between the two interventions will be tested.

Table 1: Factorial randomisation scheme

Randomisation 1			
Ceftriaxone		Penicillin plus Gentamicin	
Randomisation 2		Randomisation 2	
Metronidazole	Placebo	Metronidazole	Placebo

10 SELECTION OF STUDY PARTICIPANTS

10.1 Description of the population to be studied

10.1.1 Screening

We will enrol children admitted at Kilifi County Hospital, Coast General Hospital and Mbagathi Hospital in Kenya and Mbale Hospital in Uganda. The screening process will be based on the standard WHO criteria for severe acute malnutrition using MUAC, weight-for-length and the presence of kwashiorkor, which is part of the normal hospital admission procedure for all children, as specified in WHO/national guidelines. A screening log will document all potentially eligible children.

10.1.2 Inclusion criteria – clinical trial participants (SAM)

- Age 2 months to 13 years inclusive
- Severe malnutrition defined as:
    - kwashiorkor at any age; or
    - for children between 6 to 59 months: MUAC <11.5cm or weight-for length Z score <-3
    - for children aged 2 to 5 months: MUAC <11cm or weight-for length Z score <-3
    - for children aged 5 to 13 years: BMI-for-age Z score <-3 or MUAC <11.5cm
- Admitted to hospital and eligible for intravenous antibiotics according to WHO guidelines
- Planning to remain within the hospital catchment area and willing to come for specified visits during the 90 day follow up period
- Informed consent provided by the parents/guardian

10.1.3 Exclusion criteria – clinical trial participants (SAM)

- Known allergy or contraindication to penicillin, gentamicin, ceftriaxone or metronidazole
- A specific and documented clinical indication for another class of antibiotic
- Previously enrolled in this study

10.1.4 Inclusion criteria - antimicrobial pharmacokinetics (SAM)

- A convenience sample of the children with SAM enrolled in the trial during normal working hours

10.1.5 Inclusion criteria – non-trial participants for faecal carriage of resistance (without SAM)

- Age 2 months to 13 years inclusive
- Without SAM (as defined above) and admitted during normal working hours
- Admitted to hospital and eligible for intravenous antibiotics according to WHO guidelines
- Informed consent provided by the parents/guardian

10.1.6 Exclusion criteria – non-trial participants for faecal carriage of resistance (without SAM)

- Previously enrolled in this study

10.2 Enrolment

Enrolment will occur at the time of admission. Details of the study will be communicated to the parents/guardians. Parents/guardians of potential participants will be approached, given information about the trial in their local language and an opportunity to ask questions, and then written consent will be sought.

11 WITHDRAWAL OR LOSS TO FOLLOW UP OF STUDY PARTICIPANTS

Subjects may be withdrawn from the study:

- By withdrawal of voluntary consent for continued participation at any time
- Loss to follow up (a subject who consistently does not return for protocol study visits, is not reachable by telephone or any other means of communication and/ is not able to be located)

The reason for withdrawal will be recorded in the case report form (CRF).

12 TREATMENT OF STUDY PARTICIPANTS

12.1 Investigational Products

Randomisation 1:

- IV ceftriaxone
- IV benzyl penicillin plus gentamicin (usual care)

Randomisation 2:

- PO metronidazole
- PO placebo identical to metronidazole

12.1.1 Storage

Study drugs will be stored as per manufacturers recommendations in the clinical trials pharmacy at Kilifi, Kenya and at the study sites.

12.1.2 Dosing

Intervention 1:

- Ceftriaxone 80 mg/kg given once a day
  or
- Benzyl penicillin (50 000 U/kg IM or IV every 6 h) plus Gentamicin (7.5 mg/kg IM or IV) once a day.

In the ceftriaxone arm, IV ceftriaxone will be given for a minimum of 48 hours and a usual maximum of 7 days. If a child receiving IV ceftriaxone is feeding well and no longer has any signs of infection or complications after 2 days and before 7 days, they will be prescribed standard care for uncomplicated SAM with oral amoxicillin (40mg/kg every 12h) to complete a total of 7 days of antibiotics, as per WHO guidance. If a child has a specific and documented indication to continue ceftriaxone beyond 7 days (e.g. proven bacterial meningitis), ceftriaxone will be continued beyond 7 days.

In the usual care arm, as per WHO guidelines, IV benzyl penicillin plus gentamicin will be given for a minimum of 2 days and a maximum of 7 days. If a child receiving IV penicillin and gentamicin is feeding well and no longer has any signs of infection or complications after 2 days and before 7 days, they will be prescribed standard care for uncomplicated SAM with oral amoxicillin (40mg/kg every 12h) to complete a total of 7 days of antibiotics, as per WHO guidance.

Children discharged before 7 days will be prescribed oral amoxicillin to take home to complete a total of 7 days of antimicrobial therapy, as per WHO guidance.

First line antimicrobial treatment in hospital may be changed on the basis of confirmed antimicrobial susceptibility results from an admission blood culture, this will be recorded in the CRF, along with the reason.

Children with specific and documented clinical indications for second or third line antimicrobials, deterioration after at least 48 hours may change antimicrobials for clinical care according to study SOPs aimed at ensuring optimum care. This will be recorded in the CRF, along with the reason.

Intervention 2:

- Oral Metronidazole 20 to 32 mg in two divided doses for 7 days
  or
- Oral Placebo for 7 days.

Metronidazole/placebo will be administered according to weight bands as shown in the table below

Weight (Kg) From	Weight (Kg) To	Dose ml	Dose mg	Upper range mg/kg/day	Lower range mg/kg/day
1.50	1.99	0.5	20	26.7	21.2
2.00	2.49	0.7	28	30	25
2.50	3.99	1	40	32	20.5
4.00	5.99	1.5	60	30	20.3
6.00	7.99	2	80	26.7	20.3
8.00	11.99	3	120	30	20.2
12.00	14.99	4	160	29.1	21.5
15.00	20.00	5	200	26.7	20

Any early discontinuation of metronidazole or placebo will be recorded in the CRF, along with the reason. Children discharged before 7 days will be prescribed oral metronidazole or placebo to complete a total of 7 days of therapy.

12.1.3 Dispensing Procedures

Each site will designate a pharmacist or other suitably qualified and trained employees (designees) to dispense trial drugs.

12.1.4 Dose Administration

Dose administration will be by trained study nurses with additional training to all ward staff.

12.1.5 Accountability

The lead pharmacist/designee and trial coordinator will maintain accurate records with sufficient information to provide a full audit trail from the receipt of the study products to their removal from site or destruction.

12.1.6 Un-blinding

Randomisation codes linking allocation to study number will be held by the trial statistician. The local safety monitor can request for them in case of an emergency or serious safety concern where it will benefit patient care. In an emergency, the PI may request the allocation if the LSM is unavailable.

12.1.7 Treatment Compliance

All antimicrobials, including trial drugs, administered in hospital will be recorded daily. Empty vials and drug bottles will be retained after drug administration. Missed doses will be logged in study CRFs.

12.2 Randomisation and Blinding

Sequential study numbers will be generated for each site according to a blocked randomisation list of random block sizes before the study begins. Randomisation codes linking allocation to study number will be held by the statistician until the database is unlocked. The local safety monitor and chair of the DSMC can request for randomisation codes from the statistician in case of an individual safety concern. Children will be allocated study numbers sequentially at each site, thus randomly allocating the intervention.

Allocation for metronidazole will remain unknown to participants and trial staff, including the coordinator and principal investigator. Metronidazole and its placebo will be masked. Drug packs will be labelled with sequential study numbers according to a prepared blocked randomisation list before the trial begins.

12.3 Clinical care

Children will be managed to the best standard available in each facility, in line with National and WHO recommendations. HIV testing by rapid antibody test is routinely offered by the hospitals involved in the trial at admission to all severely malnourished children through ‘provider initiated testing’ according to the current national guidelines for HIV testing and counselling - and appropriate follow up tests and referral for care are undertaken according to the results.

12.4 Collection of data & samples

At enrolment, baseline data of prognostic importance will be collected, including demographic and clinical characteristics.

A blood sample for determination of molecular biomarkers of infection and pathogen detection at the end of the study will be collected at enrolment (2.5ml), together with routine admission blood tests which may

include a full blood count, glucose, biochemistry and blood culture. Results of these tests will be fed back to the clinical team for care. At discharge, a further set of the same study blood samples will be drawn (2.5ml). For 120 participants, additional blood samples of 1ml for PK will be collected at enrolment and two further time points during the first 24h of admission to be analysed with their enrolment sample.

Should a child be readmitted during the study period, a further blood sample for this research (2.5ml) will be collected. There will be no further blood samples taken or used for research after discharge from hospital.

Two rectal swabs and whole stool (if passed) will be collected at admission, discharge and during follow up, to assess carriage of antimicrobial resistance and to detect pathogens by molecular methods. The sampling timetable is detailed in Table 2 below. Remaining samples will also be stored for up to 10 years for future research in line with the intentions of this protocol, subject to scientific and ethical approval.

Table 2: Study course, data collection and sample collection for children admitted to hospital

	SCREENING & ELIGIBILTY	ENROLMENT	DAILY INPATIENT REVIEW	DISCHARGE	Day 14	Day 45	Day 90	READMISSION TO HOSPITAL
Standard case management	X	X	X	X				X
Routine clinical investigations (haematology, biochemistry, blood culture, HIV and malaria)		X						X
Give study information	X	X	X	X	X	X	X	X
Informed consent		X						
Anthropometry	X	X	X	X	X	X	X	X
Data collection		X	X	X	X	X	X	X
Rectal swab x2 for antimicrobial resistance & pathogen detection		X		X		X	X	X
Whole stool for faecal inflammatory markers				X		X		
Plasma and whole blood sample for pathogen detection and biomarkers of infection (2.5ml)		X		X				X
Pharmacokinetics sampling (1ml) in a subset of participants	Enrolment & 2 further samples within 24 hours of starting antibiotics							
Rectal swab x2 for antimicrobial resistance & pathogen detection (non-trial participants without SAM)		X		X				

Environmental swabbing for ESBL and MRSA within the study hospital wards (sinks, taps, walls, beds, equipment, staff hands (anonymised)) has been added. This will be conducted together with the infection control teams and Infection Prevention Committees in the hospitals to improve infection control by providing laboratory microbiological training, sharing the data and helping implement infection control measures.

12.5 Follow up

12.5.1 During admission,

Admitted children will be reviewed daily and clinical features, progress and treatment received recorded on a structured case report form. In the event of clinical deterioration, SAE or suspected toxicity, additional tests will be performed for clinical management (for example, blood culture, blood gases, renal and liver function), will be undertaken and results made available to the child's clinical care team. At discharge, anthropometry, a clinical assessment, a blood sample and rectal swabs will be taken, and children enrolled in outpatient therapeutic feeding programmes as per WHO guidelines.

12.5.2 Pharmacokinetics

A convenience sample of 120 children admitted during working hours enrolled in the trial will have an additional 1ml of blood drawn for pharmacokinetics of ceftriaxone, metronidazole, penicillin and gentamicin at two time points during the first 24 hours after receiving these antibiotics.

12.5.3 Economics

A costing tool will be administered on a sub-set of approximately 650 patients (approximately 450 with SAM and 200 without SAM) to ascertain household incurred costs (including direct costs such as transportation and indirect costs from productivity losses associated with an episode of illness). Costs and healthcare resource utilisation will be estimated from these participant interviews and CRFs.

12.5.4 Scheduled follow up

Follow up will scheduled at 14, 45 and 90 days after enrolment, to the nearest working day. Participants will be invited to attend the follow-up clinic with reminders issued by SMS or phone call and defaulters traced at home. Some participants may still be in hospital at follow up. A health questionnaire will be administered detailing health service utilisation and mortality. Children judged to have significant illness at a follow up visit will be referred to the ward, outpatient clinic or hospital nutritionist. Faecal or rectal swab samples will be collected at these follow up visits, as per Table 2. No study-related blood samples will be taken during follow up except for investigation of illness requiring readmission.

12.5.5 Unscheduled visits

Caregivers will be asked to contact the study team and come to the study hospital if the child requires readmission. Study participants who are re-admitted to hospital will undergo standardized clinical assessment including history, examination, blood culture, malaria test and blood samples as described above and in Table 2, and other investigations, such as cultures from normally sterile sites, will be performed as clinically indicated. Participants who are admitted to hospitals other than a study site will have their medical notes for the relevant admission reviewed and data extracted on a standardized hospital re-admission form. Re-admission will be recorded as an SAE.

12.5.6 Deaths in the community

For deaths occurring outside hospital, a verbal autopsy (VA) using an internationally validated tool will be completed after an appropriate grieving period depending on individual circumstances to determine cause of death. This will be done by staff trained and experienced in obtaining verbal consent from parents, and conducting interviews sensitively using the VA tool. Verbal consent for VA will be done as per WHO recommendations, as is usual practice in surveys and previous studies.

12.5.7 Non-trial participants without SAM

Children without SAM who are admitted to the ward and meet inclusion criteria will have rectal swabs performed at admission and discharge only, without any further sampling or follow up for study purposes. Reason for admission, demographic and clinical data, outcome and antimicrobials received in hospital and costs incurred will be recorded.

13 ASSESSMENT OF SAFETY

13.1 Toxicity, Serious Adverse Events and Unexpected Events

Safety oversight will be the responsibility of the investigators and the Data Safety Monitoring Committee (DSMC) that will be convened.

13.1.1 Suspected Toxicity

Ceftriaxone and metronidazole are licensed drugs with a known profile of adverse reactions. Assessment of safety will therefore focus on severe, and causally related events. Clinical or laboratory toxicity will be reported if they are grade 4 according to the: Division of AIDS (DAIDS) Table for Grading the Severity of Adverse Events: http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf

Table 3: Pre-defined Grade 4 suspected toxicity events

New episodes of:

Allergic and Cutaneous reactions one or more of:	• Anaphylaxis • Bronchospasm requiring treatment • Exfoliative dermatitis		
Severe anaemia **Neutropenia** **Thrombocytopenia**	• Severe anaemia • Neutrophil count • Platelets	Hb	<4g/dl <0.4 x 10^9 /L <25 x 10^9 /L
Encephalopathy & Neurological one or more of:	• Impaired consciousness: • Convulsions • New focal neurological signs	AVPU	P or U
	• >3.5 x upper limit of normal:	Creatinine	>138 µmol/L
Abnormal liver function one or more of:	• >10 x upper limit of normal:	ALT AST ALP	>450 IU/L >620 IU/L >4,060 IU/L
	• >5 x upper limit of normal:	Bilirubin	>63 µmol/L

13.1.2 Serious Adverse Events (SAE)

An adverse event (whether or not considered related to the investigational product) resulting in any of the following outcomes is defined as an SAE:

- Death (from any cause at any time)
- Life-threatening event (i.e., the subject was, in the view of the investigator, at immediate risk of death from the event that occurred).
- Persistent or significant disability or incapacity (i.e., substantial disruption of ability to carry out normal life functions).
- Hospitalisation or an important medical event requiring medical or surgical intervention to prevent one of the outcomes listed above. Examples include severe adverse drug reactions such as severe allergic reaction or blood dyscrasias requiring intensive treatment.

13.1.3 Suspected and Unexpected Serious Adverse Reaction (SUSAR)

These are the reactions that are serious (as defined above) but not expected AND considered to be related to the investigational product. This definition captures the important events that are attributed to the product but do not follow known pattern of response to study product.

13.1.4 Serious Adverse Events, Assessment of Causality

An assessment of the relationship of the event to the study drug will be undertaken by the senior clinical investigators. This interpretation will be based on the type of event, the relationship of the event to the time of administration, and the known biology of the intervention (Table 4). The following are guidelines for assessing the relationship of administration of the product to the event.

Table 4: Guidelines for assessing the relationship of drug administration to an adverse event

0	No Relationship	No temporal relationship to drug ***and*** alternate aetiology (clinical state, environmental or other interventions); ***and*** does not follow known pattern of response to study product
1	Unlikely	Unlikely temporal relationship to drug ***and*** *a*lternate aetiology likely (clinical state, environmental or other interventions) ***and*** *d*oes not follow known typical or plausible pattern of response to drug.
2	Possible	Reasonable temporal relationship to drug; ***or*** event not readily produced by clinical state, environmental or other interventions; ***or s***imilar pattern of response to that seen with other drugs
3	Probable	Reasonable temporal relationship to drug; ***and*** event not readily produced by clinical state, environment, or other interventions ***or*** known pattern of response seen with other drugs
4	Definite	Reasonable temporal relationship to drug; ***and*** event not readily produced by clinical state, environment, or other interventions; ***and*** known pattern of response seen with other drugs

13.1.5 Emergency Procedures

In the event of an abnormal clinical or laboratory finding by the study clinician, children will receive appropriate treatment according to WHO guidelines, including admission for assessment and/or treatment where appropriate. Usual clinical practice for suspected reactions to study drugs will be followed. Where necessary for patient safety, this may include un-blinding of the randomised allocation by the local safety monitor, PI or delegate if this would alter the management of the child.

13.1.6 Follow up of adverse events

Serious Adverse Events will be followed up by the investigator until their resolution or stabilisation or until causality is determined to be unrelated to trial interventions. The outcome will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal

13.1.7 Assessment of Causes of Death

An endpoint review committee, comprising two individuals experienced in paediatric care in sub-Saharan Africa, will review all clinical and laboratory information for children who die during the trial to determine the causes of death that will be used in the final analysis. The endpoint review committee will remain blinded to the randomised allocations.

13.2 Reporting of Toxicity, SAEs & SUSARS

Because the study population is known to have a high rate of mortality, deterioration and readmission, a high background rate of SAEs is expected. A summary of all SAEs and suspected toxicity events will be reported every 3 months. The report will include the site; study number; date of event; subject details (initials, sex and age); nature of event; relevant history; outcome and a judgement of causality. The summary report of all SAEs will be sent the LSM, DSMC, the national ethics and regulatory committees and sponsor. SAEs that are deemed definitely causally related to the study drug and SUSARs will be initially reported to the sponsor, DSMC and regulatory bodies within 7 days of the investigators becoming aware of the event with a follow up report being provided within a further eight calendar days. The DSMC will conduct unblinded analyses of the main study outcome and rates of SAEs and inform the TSC in the event of conclusive data on harms or benefits of any of the trial allocations.

14 PROTOCOL DEVIATIONS

The investigator will conduct the trial in compliance with the protocol agreed to by the sponsor, the University of Oxford, and which was given approval by the ethics committees. The investigator will sign the protocol to confirm agreement. The investigator will not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval from ethics of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involve only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)). The investigator, or person designated by the investigator, will document and explain any deviation from the approved protocol in the protocol deviation file. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior ethics approval. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment(s) should be submitted: for ethical review and approval.

15 QUALITY CONTROL AND QUALITY ASSURANCE

The chief investigator will ensure that staff involved with the trial are:

- properly qualified to assume responsibility for conduct of the study
- willing to comply with GCP and applicable regulations
- be prepared for audits and monitoring
- able to recruit in sufficient numbers and on time
- well informed about the protocol, the investigational products, and their study responsibilities

The principal investigator will ensure that each site has:

- Sufficient time to complete the study
- Adequate number of qualified staff and adequate facilities to complete the study
- Staff who are well informed about the protocol, the IP, and their study responsibilities

The study will be monitored by the KEMRI/Wellcome Clinical Trials Facility Monitoring Team, who will develop risk-based monitoring plan for the study. Monitoring at Mbale, Uganda will be done by the KEMRI/Wellcome Clinical Trials Facility Monitoring Team jointly with the Mbale Clinical Research Institute Quality Control Officer and Monitoring Team. The monitoring teams comprise of trial coordinators and trial managers from the various trials currently running within the units. To achieve independence during the monitoring, the monitors for this study will be trial coordinators/managers working on another trial.

A comprehensive study initiation visit will be done at which all staff will be trained in protocol specific procedure, and check that all trial logistics are in place. Routine monitoring will be conducted every three months or more frequently if required. A close-out visit will be performed at the end of the trial. Its goal is to make sure that the sites have all the documents necessary for archiving. The monitors role is part of the quality system that will ensure that all participants have duly completed informed consent, entries relating to eligibility, consent and that staff on the study are following their SOP's in accordance to protocol.

16 DATA MANAGEMENT

16.1 Data collection

16.1.1 Participant data

Study clinicians will be responsible for collecting data collected at enrolment, daily clinical review including recording all antimicrobials during the hospital stay, at follow up visits and at re-admission. Data capture will be primarily via a paper CRF. These data will be subsequently transferred to a secure electronic database for analysis.

16.1.2 Provider and household cost data

We will estimate the unit costs of each health service event from a provider and household perspective. Provider costs will be estimated for both the intervention and control groups for both interventions. They will include both the costs at the site level and costs incurred outside the study sites (e.g. nutritional rehabilitation products). We will estimate costs using a micro-costing approach. The treatment of those with SAM will first be mapped to identify all possible health service usage and the inputs involved through interviews with health care providers and study staff. Inputs are likely to include staff time spent on care for children with SAM, drug administration, feed preparation and administration. The quantities of these inputs will be measured using a combination of hospital data (e.g. lengths of stay), study patient level records (e.g. medicines prescribed) and interviews/ timesheets and observations of staff (to estimate time spent on SAM).

Patient incurred costs will be collected as described above, through interviews conducted with approximately 650 participants across all sites (approximately 450 with SAM and 200 without SAM) during discharge and follow-up. Costs incurred by participant's families for hospitalisation and attending outpatient nutritional therapeutic care in the community, associated transport lost earnings whilst attending care will be determined.

To estimate the costs of the study cohort within the trial period, healthcare resource utilisation (such as days in hospital, antimicrobial usage and clinic attendances) will be estimated from the individual participant's follow-up interviews and daily CRF records.

16.2 Data storage

Data will be stored on the secure OpenClinica® database. All data will be kept confidential with access restricted on password protected computers. The OpenClinica system in Kilifi has regular secure backup with both local and offsite (i.e. in the KWTRP server room in Nairobi) storage. The data management system will generate automated queries based on pre-programmed rules and the data manager will generate manual queries using a statistical package. All queries will be dealt with by the lead site clinicians and clarified by the investigators and field staff with clear documentation. The OpenClinica system maintains an audit trail. Other

paper source documents may still be used to capture data for the screening visits, scheduled visits, unscheduled clinic visits, lab and other investigational results.

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

17 STATISTICAL CONSIDERATIONS

17.1 Determination of sample size

Sample size for mortality is based on our surveillance of inpatient mortality amongst paediatric admissions with SAM at the proposed sites of a minimum of 16% (range 12-19%). The targeted effect size of a hazard ratio of 0.67 to 0.72 for the primary outcome of mortality is informed by a small trial in Sudan comparing 2 days of IM ceftriaxone vs. amoxicillin,[19] with an effect size of 0.52 (95% CI 0.29-0.90), and is aimed at detecting a degree of mortality reduction that would be clinically relevant.

Loss to follow up is assumed to be 6% up to 90 days. This is conservatively based on our recent antimicrobial prophylaxis trial [20] in which loss to follow up plus voluntary withdrawal is 2.5% at 3 months and 6% at 12 months. Calculated using the *Analysis Resources for Trials* macro for STATA (version 1.0.4, MRC Clinical Trials Unit), a sample size of 1000 per arm gives >90% power (2 sided at 5% significance) for hazard ratios of up to 0.67 and power of >80% for hazard ratios up to 0.72, which would be regarded as clinically important.

For nutritional recovery, the effect size for recovery from SAM is based on data at 90 days in our recent RCT (randomized controlled trial) of antimicrobial prophylaxis.[20] At baseline, mean MUAC was 10.6cm (sd 1.06) and at 90 days, 12.2cm (sd 1.35); a mean change of 1.6cm (sd 1.1). A sample size of 1,000 per arm, allowing for the estimates mortality and loss to follow up described above, gives >90% power to detect a change in MUAC of 1.9cm (sd 1.3) from 1.6cm (sd 1.1) for a t-test with unequal variances.

17.2 Planned statistical methods

Analysis of the two interventions will be conducted separately, as if two separate trials, with an additional analysis of interaction between the two interventions, as is usual for factorial design trials. Primary and secondary analyses will be performed on an intention to treat basis. A statistical analysis plan will be developed and approved by the TSC and DSMC prior to unblinding and locking of the study database. The criterion for statistical significance at the final analysis will be $P<0.05$.

17.2.1 Enrolment & follow up

Screening, enrolment, reasons for non-enrolment, randomisation and loss to follow up will be detailed in a CONSORT diagram. The rate of loss to follow up and total observation time in days will be calculated.

17.2.2 Baseline characteristics

Baseline demographic, clinical and anthropometric characteristics of expected prognostic importance will be described overall and for each of the randomised groups. The bacterial aetiology and antimicrobial susceptibility of bacteraemia identified at the admission blood culture will be described. Faecal carriage of bacteria expressing ESBL will be determined at the index admission to hospital.

17.2.3 Safety

Suspected grade 4 toxicity events and SAEs during administration of investigational products will be described along with the proportion of participants affected and compared between randomised groups by calculating incidence rate ratio.

17.2.4 Assessment of primary outcomes

Mortality will be assessed using a Kaplan-Meier plot and the hazard ratio (95% CI) for death up to 90 days calculated using Cox proportional hazards regression unadjusted, and adjusted for site.

17.2.5 Assessment of secondary outcomes, the following will be assessed for both interventions:

- Suspected grade 4 toxicity events during receipt of study first-line ceftriaxone, metronidazole/placebo, penicillin or gentamicin.
- SAEs occurring between enrolment and study completion.
- Mortality within the first 48 hours, by day 7 and until discharge from the index hospitalisation.
- Mortality occurring after discharge from the index hospital admission during follow up.
- Causes of death, as determined by an endpoint review committee.
- Duration in days of the index hospitalisation from admission to discharge.
- Incidence of re-admission, defined as at least one overnight stay in a hospital or health facility.
- Causes of re-admission, as determined by the admitting study clinician, during the trial.
- Total duration in days spent admitted in hospital during the trial.
- Duration in days of 1st, 2nd and 3rd line antimicrobial administration during the index admission.
- Total duration in days of inpatient 1st, 2nd and 3rd line antimicrobial administration during the trial during any period spent admitted in hospital.
- Bacterial aetiology and antimicrobial susceptibility of invasive infections at the time of index admission and during follow up identified by blood, cerebrospinal fluid, urine or sterile site culture.
- Change in MUAC; weight-for-length; weight-for-age and length-for-age from baseline to 14, 45 and 90 days, calculated using WHO 2006 growth standards.
- Faecal carriage of bacteria expressing Extended Spectrum Beta Lactamase (ESBL) at discharge from the index hospital admission, day 45 and day 90 and compared between trial allocation groups. Effect modification of the two interventions on mortality by the presence of ESBL in baseline and discharge rectal swab samples and antimicrobial resistance detected in blood cultures will be determined.

17.2.6 Assessment of sub-study outcomes

- Pathogens and antimicrobial resistance in blood and faecal samples will be detected by molecular methods using TaqMan PCR array cards and allele-specific PCR, 16s rRNA amplification, whole genome and shotgun sequencing or bacterial toxin detection (*C. difficile*) and compared between trial allocation groups, with children without SAM (not in the trial) who have been assessed for faecal carriage of ESBL, and with isolates from environmental swabs taken in the study hospitals. Pathogens isolated from blood or faecal culture will be sub-cultured, identified and sequenced to detect and further detect and characterise antimicrobial resistance genes contributing to antimicrobial resistance phenotypes. Expertise and collaboration in high-throughput sequencing is need to build and maintain capacity in Kenya for this fast-moving field. These analyses will be undertaken in Kilifi, Kenya or, for high-throughput sequencing, at other sites in Kenya, or at the University of Oxford, UK, under appropriate MTAs, as required. Data and extracted DNA will be

returned to the KWTRP to link to conventional microbiological culture work, resistance testing and participant outcomes. There is evidence that antimicrobial resistance defined by genotype may predict treatment outcomes better than by conventional culture. Therefore, we aim to continue this through the main trial, which will be able to assess outcomes to inform policy. Biomarkers of invasive infection, and gut and systemic inflammation will be assessed by mass spectrometry, ELISA, Taqman, multiplex Luminex® bead array and similar methods in Kilifi.

- Pharmacokinetics data for the dosing schedule used in the trial 120 participants will include 60 who are receiving each of the four trial drugs. Data will be modelled together with the data from the existing pharmacokinetics study (KEMRI/SERU/CGMR-C/023/3161; OxTREC 47-15) for ceftriaxone and metronidazole, and an existing neonatal PK platform http://www.tdmx.eu/Launch-TDMx/ for penicillin and gentamicin. These samples will be analysed in Kenya and in the UK. Analysis will use NONMEM® non-linear PK modelling software to determine the peak level and time above the minimum inhibitory concentration for common bacteria causing invasive infection.
- **Economics** outcomes will be assessed using a combination of 'within trial' analysis of the trial cohort and modelling to estimate incremental costs and outcomes over longer time periods (over the course of an episode of illness and over a life time). For the within trial analysis, unit costs will be combined with health care utilisation at the individual level to assess the probability that the intervention is cost-effective. We will use descriptive analysis in assessing costs incurred for participants with and without SAM. Decision analytical modelling will be used to estimate incremental cost-effectiveness over the longer periods, which will incorporate the estimation of disability adjusted life years and potential future costs (cost savings) when considering for potential antibiotic resistance. Confidence intervals will also be calculated for the incremental cost-effectiveness ratios. Sensitivity analyses will be carried out in order to factor in uncertainty due to assumptions on cost data and the choice of model.

18 INTELLECTUAL PROPERTY

Any intellectual property rights that arise from the work will be safeguarded according to the current KEMRI guidelines and the Industrial Property Act of 2001, sections 32, 58 and 80. The scientific and intellectual contributions of all persons involved in the research will be appropriately acknowledged in all publications and presentations arising from the work.

19 TIME FRAME/DURATION OF THE TRIAL

The trial enrolment and follow up will be conducted during a period of 3 years. A further 2 years will be required for analysis, dissemination and to complete the secondary laboratory analyses.

	2016		2017				2018				2019				2020				2021			
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Scientific & ethical approval		X	X																			
PPB approval		X	X																			
IP testing & manufacture		X	X																			
Database set up		X	X																			
Training		X	X																			
Trial initiation			X																			
Recruitment & follow up			X	X	X	X	X	X	X	X	X	X	X	X								
Trial close out														X								
Analysis															X	X						
Secondary data & lab analyses															X	X	X	X	X	X	X	X
Engagement & Dissemination	X	X	X				X				X			X	X				X	X		

20 ETHICAL CONSIDERATIONS

The proposal will be subject to ethical approval from the KEMRI Scientific and Ethical Review Unit (SERU), Nairobi; Mbale Regional Referral Hospital Research and Ethics Committee (MRRH-REC), Uganda National Council for Science and Technology (UNCST), Uganda; and the Oxford Tropical Research Ethics Committee (OxTREC), University of Oxford, UK. The study will be registered on an independent study registry www.clinicaltrials.gov. The study will be conducted according to ICH GCP guidelines and the Declaration of Helsinki. Findings from other studies with implications for the on-going running of the trial will be discussed by the trial investigators with the TSC and DSMC to support best practices throughout the study.

20.1 Human Subjects

First do no harm

20.1.1 Risks

The investigational drugs that will be used in this trial are already registered for use in children in Kenya and Uganda. The most common side effects include; skin rash, abdominal discomfort, headache, loss of appetite, nausea and vomiting. Penicillins and cephalosporins can cause an anaphylactic reaction in those who are allergic. We will therefore inquire about any history of drug allergies prior to enrolment.

The risks of blood drawing include pain, infection at the site of the cannula and thrombophlebitis. These will be minimised by careful technique according to a standard SOP, cannula site inspection and replacement or removal where necessary. No more than 1ml/kg of blood will be drawn for research at any one time. The risks of rectal swabbing are small and will be minimised by training and adherence to a standardised SOP.

20.1.2 Benefits to the Patients and Community as a whole

Children will have close observation whilst admitted. We will ensure referral to appropriate nutritional care and clinical care services for all participants at discharge from hospital or for problems identified at follow up visits. Additional clinical staff will be recruited and will undertake study duties and assist in care, adding to the staff available for clinical care on the wards. Training will be given at the study sites on managing severely ill children, antimicrobial usage and infection control.

For children with SAM who are clinical trial participants, the study will provide second line antibiotics according to the study SOP free of charge if they are indicated by culture and antimicrobial susceptibility testing of invasive bacterial isolates or prescribed by a senior study clinician. Costs of inpatient care, consultations and investigations that are available within the study hospital will be paid for by the study for readmissions. The study contributes to knowledge informing the appropriate use of antimicrobials, thus benefitting the whole community.

20.1.3 Confidentiality

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.

20.1.4 Informed Consent

Consent will be required for all data and samples taken for research purposes. Consenting will be done in a separate area to ensure privacy and the opportunity to ask questions and discuss concerns. This will be done in the paediatric ward, high dependency unit or in casualty once the decision to admit has been made. Parents or legal guardians will be able to consent separately for participation in the study, storage of data and samples for future research, and export of samples for investigations that cannot currently be conducted in Kenya.

Clinical officers, nurses and field workers and will be trained in providing information and administering the consent procedure, following a standard operating procedure in the local language of participants using didactic learning and role plays.

20.1.5 Compensation

A small reimbursement allowance to cover travel costs and out of pocket expenses associated with participation will be provided at each scheduled visit, based on local norms and guidelines (approximately 350 to 650 KSH, 3.5 to 6.5 USD, dependent on location and length of travel). A meal will also be provided to the participant during scheduled study visits.

20.2 Community Engagement

Community engagement will be through regular meetings with the community involving KEMRI-Community Representatives and County Health and hospital management teams. At these meetings, information and feedback will be given and received.

20.3 Stakeholder information giving

We will engage key patient informants, including nurses, clinical staff and domestic staff. We will expand ongoing communication activities about research to include this study in order to support mothers receiving information on the study before being asked for consent. Care will be taken to ensure that the

alternative first line antibiotic combination being used is not promoted as the treatment of choice, but as an alternative strategy that is awaiting a formal clinical trial to inform policy.

21 DATA SHARING

Data sharing will be considered by applying to the Data Governance Committee at CGMR,C Kilifi who will manage the process and ensure that appropriate ethical approval is in place and consent has been obtained for uses outside those given in this protocol. Explanation of this eventuality will be included in the participant information and consent form. We intend to share anonymised data with the CHAIN network cohort study (KEMRI/SERU/CGMR-C /054/3318, OxTREC 34-16) which consists of institutions doing studies in malnourished children in Africa and South Asia; to upload anonymised bacterial and resistance sequences on recognised international repositories; and share anonymised bacterial sequence data relating to bacterial resistance with groups working an antimicrobial resistance in Kenya and UK.

22 ARCHIVING AND RECORD RETENTION

The investigator will keep all trial documents for at least 5 years after the completion or discontinuation of the trial. Source documents will be retained for a minimum of 2 years from the end of the study in the institution's archive. CRFs will be retained for at least 10 years.

23 FINANCING AND INSURANCE

23.1 Budget

	KSH	USD
(a) Personnel, salaries and other disbursements		
Medical and clinical officers	61,784,444	617,844
Research nurses	7,500,000	75,000
Fieldworkers	16,453,519	164,535
Data manager/data supervisors	5,000,000	50,000
Laboratory coordinator	4,000,000	40,000
%FTE Prof Sam Kariuki	1,730,556	17,306
Lab technologists CGMR,C x 2 and CMR x 2	5,075,093	50,751
(b) Patient costs, travel, food and/or supplies		
Reimbursement of travel and time for follow up	3,703,704	37,037
(c) Equipment		
Computers/accessories/software x 8	394,815	3,948
Minus 80°C freezers & fridges	2,407,407	24,074
Cool boxes, ice packs & transport thermometers	26,667	267
Anthropometry equipment	605,185	6,052
(d) Supplies		
Study drugs	7,222,222	72,222
Laboratory work: Microbiology (CGMR,C and CMR) & PK	12,805,556	128,056
Clinical consumables - gloves, needles syringes etc	4,892,315	48,923
Other drugs, scan and patient care	8,379,630	83,796
(e) Travel and accommodation		
Setting up (meeting costs, staff training, workshops)	4,901,111	49,011
Site supervision (PI, coordinator and monitoring visits)	927,963	9,280
Community & stakeholder engagement, feedback meetings	1,842,593	18,426

Travel, workshops & international/local conferences	4,777,778	47,778
(f) Transportation, vehicle repairs, insurance etc		
Participant tracing	222,222	2,222
Courier costs	3,041,667	30,417
(g) Operating expenses postage, printing etc		
Telephone/internet/communications	600,000	6,000
Printing & stationery – files, SOPs, CRFs	1,795,648	17,956
Office furniture & refurbishment	925,926	9,259
(h) Animals acquisition, food, cages etc N/A		
(i) Consultancy fees N/A		
(j) Contingency 15%	24,152,403	241,524
(k) Indirect costs 8% to the grant receiving institution	14,813,474	148,135
Total	**199,981,895**	**1,999,819**

23.2 Justification of the Budget

The budget covers the cost of setting up a study team, infrastructure and equipment in the four hospitals for the study, based on experience of previous trials. Clinical, nursing and fieldworker support covers the extra work involved in accurate and timely drug administration and taking research samples. Lab costs include molecular assays, culture and antimicrobial susceptibility testing for enteric bacteria.

23.3 Insurance

The University of Oxford has a specialist insurance policy in place – Newline Underwriting Management Ltd, at Lloyd's of London – 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.

24 TRIAL MANAGEMENT

24.1 Sponsor

The trial sponsor is the University of Oxford. The sponsor will be responsible for ensuring appropriate arrangements are in place for the initiation, management and financing of the trial, the trial is conducted to a high scientific quality and the rights of participants are protected.

24.2 Trial steering and safety monitoring committees

A trial steering committee (TSC) will be appointed to oversee the running of the trial, chaired by Prof Diana Gibb at the MRC Clinical Trials Unit, London. Independent members are Prof Grace Irimu and Prof Mike Sharland.

A data safety and monitoring committee (DSMC) will be convened, chaired by Prof Tim Peto at the University of Oxford. Members are Prof Greg Fegan and Dr Charles Opondo.

The focus of the DSMC is safety, 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 DSMC 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 TSC on advice from the DSMC 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.[21, 22] A local safety monitor (LSM) will be appointed to provide independent consultation on clinical care, management of clinical cases.

25 TRAINING AND SETTING UP

At each site an initial period will be spent training staff in anthropometry and management of severe malnutrition in order that children will be managed in line with WHO recommendations to the best standard available at each hospital. This will be followed by study-specific training. Staff at all sites will be trained on the background to the trial; scientific and ethical aspects of clinical research and trials; ICH GCP; anthropometry; data collection; communication and consenting procedures; infection control and management of sick and malnourished children.

26 REPORTING, DISSEMINATION AND NOTIFICATION OF RESULTS

This study will be undertaken with the medical and nursing unit staff and the hospital consultants, who have been involved in its design and will be essential in its implementation. Information arising from the study will be fed back through hospital-wide meetings. Individual subjects will remain blinded to their study allocation at their last follow up visit. Results of the study will be fed back to the study community through the KEMRI community representatives, public meetings, district nutritionists of the districts involved and the follow up clinics in each site. Results will be shared nationally through presentation at the Kenya Paediatric Association annual scientific meeting and international scientific meetings. The results will be published in a peer reviewed journal.

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28 APPENDICES

28.1 Role of each investigator

	Study design and development	Community engagement	Pharmaceutical Oversight & PK	Training	Data Management	Clinical care	Data and sample collection	Microbiology & Resistance Analysis	Trial & Data Analysis	Economic Analysis	Report writing
Prof James Berkley	⊙			⊙				⊙	⊙		⊙
Dr Caroline Ogwang	⊙	⊙		⊙		⊙	⊙		⊙		⊙
Dr Neema Mturi	⊙	⊙				⊙	⊙				⊙
Mr Isaiah Njagi		⊙		⊙			⊙				⊙
Ms Sheila Murunga	⊙	⊙		⊙	⊙	⊙	⊙		⊙		⊙
Mr Johnstone Thitiri	⊙	⊙		⊙	⊙	⊙	⊙				⊙
Mr Joseph Waichungo	⊙			⊙				⊙	⊙		⊙
Mrs Laura Mwalekwa	⊙	⊙		⊙		⊙	⊙		⊙		⊙
Mrs Molline Timbwa	⊙	⊙		⊙		⊙	⊙		⊙		⊙
Mr Shalton Mwaringa	⊙	⊙		⊙		⊙	⊙		⊙		⊙
Mrs Grace Dena	⊙	⊙				⊙	⊙				⊙
Dr Jimmy Shangala	⊙		⊙						⊙		⊙
Mrs Fauzat Hamid	⊙	⊙				⊙	⊙				⊙
Mr John Odhiambo	⊙	⊙				⊙	⊙				⊙
Mr Joshua Wambua	⊙	⊙				⊙	⊙				⊙
Mrs Mwanamvua Boga	⊙	⊙				⊙	⊙				⊙
Ms Rehema Ali	⊙	⊙				⊙	⊙				⊙
Dr Julie Jemutai	⊙						⊙			⊙	⊙
Ms Rebecca Gathoni							⊙			⊙	⊙
Prof Kathryn Maitland	⊙					⊙	⊙				⊙
Dr Victor Bandika	⊙	⊙				⊙	⊙				⊙
Dr Jones Makori Obonyo	⊙		⊙						⊙		⊙
Dr Christine Manyasi	⊙	⊙				⊙	⊙				⊙
Dr Peter Olupot-Olupot	⊙	⊙		⊙		⊙	⊙				⊙
Prof Samuel Kariuki	⊙							⊙	⊙		⊙
Dr Anna Vassall	⊙			⊙						⊙	⊙
Dr Gabriela Gomez				⊙						⊙	⊙
Prof Greg Fegan	⊙				⊙				⊙		⊙
Dr Joseph Standing	⊙		⊙					⊙	⊙		⊙

28.2 Patient Information Sheets and Informed Consent Forms

KEMRI Wellcome Trust Research Programme: Patient Information and Consent Form

First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

(Trial participant)

Institution	Investigators
Kenya Medical Research Institute, Kilifi, Kenya	Caroline Ogwang, Neema Mturi, Isaiah Njagi, Shalton Mwaringa, Grace Dena, Rehema Ali, Sheila Murunga, Kathryn Maitland, Johnstone Thitiri, Joseph Waichungo, Jimmy Shangala, Mwanamvua Boga, Samuel Kariuki, James Berkley, Julie Jemutai, Rebecca Gathoni
Coast General Hospital, Mombasa, Kenya	Victor Bandika, Jones Makori Obonyo, Laura Mwalekwa, John Odhiambo, Fauzat Hamid
Mbagathi Hospital & University of Nairobi, Kenya	Christine Manyasi, Molline Timbwa, Joshua Wambua
Mbale Hospital, Uganda	Peter Olupot-Olupot, Kathryn Maitland
London School of Hygiene & Tropical Medicine, UK	Anna Vassall, Gabriela Gomez
Swansea Medical School, UK	Greg Fegan
University College London, UK	Joseph Standing

LAY TITLE: A study to compare antibiotics used to treat children with severe malnutrition.

Introduction

Your child is being admitted to hospital because they are sick. He or she has been examined by the study team and also found to have malnutrition. Your child will have a blood test done to check their general health, and will be given antibiotics to treat infections that are common in children with malnutrition. These tests and treatment are part of the normal care for a child with malnutrition.

Who is carrying out this study?

This study is being carried out by KEMRI in Kenya and Mbale Hospital in Uganda in collaboration with University of Oxford, UK. KEMRI is a Kenyan government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit.

What is this study about?

In this study we want to find out which antibiotics that are given to treat infections in children admitted with malnutrition are most effective. We will be looking at two different types of antibiotics that are used: i) those that are given by injection and ii) an antibiotic that is given orally. Children who are enrolled in this study will participate in investigation of both the injectable and the oral antibiotics.

All children with severe malnutrition who are admitted to hospital are treated with antibiotics by injection because they often have serious infections. In this study, children will receive one of two different types of antibiotic treatment by injection.

- The usual current treatment that uses two drugs: penicillin and gentamicin
- An alternative treatment that uses one drug: ceftriaxone

Children with severe malnutrition are also sometime treated with an oral antibiotic to clear gut infections, but we are not sure if it is helpful, and some hospitals use it and some don't. In this study, children will also receive one of the following:

- Metronidazole (often known as Flagyl)
- A similar liquid that does not contain an antibiotic.

All of the antibiotic drugs being used in this study are widely used and already licenced for use in children in Kenya and Uganda *[sites to delete as appropriate].*

In this study we will ask 2000 children admitted with severe malnutrition to participate. The decision on which child gets which drugs will be decided by a system based on chance, without any preference. All participants will have the same chance of receiving any of the treatment arms.

We will find out if there is any difference between the treatment groups by closely watching the progress of everyone in the study. To make sure that the findings of this study are as accurate as possible it is important that no one knows which child is receiving which oral medication until the end of research. We are asking your permission for your child to participate in this study.

What will it involve for me/my child if I agree?
If you agree for your child to participate, we will first assess their clinical status by taking body measurements, asking you questions about their health and factors that might contribute to their illness, as well as examining them. Some of the questions that you will be asked by the study team concerning the household and family are detailed.

In addition to the blood tests taken as part of the normal admission procedures, we will take an additional small amount of blood from the child's arm at the same time that samples are taken as part of your child's normal treatment. The extra amount taken for research will be half a teaspoon (2.5 ml). The same volume of blood will be taken should a child be readmitted before the end of the study period. We will also take two small faecal samples using a soft cotton wool swab for research. Other samples to be taken after the initiation of treatment are as follows:

Number of days after enrolment	**Sample to be collected**
At admission	2 small faecal samples taken using a soft cotton wool swab & half a teaspoon (2.5ml) of blood
At discharge	2 small faecal samples taken using a soft cotton wool swab & one sample of whole faeces & half a teaspoon (2.5ml) of blood
45 days	2 small faecal samples taken using a soft cotton wool swab & one sample of whole faeces
90 days	2 small faecal samples taken using a soft cotton wool swab
Readmission to hospital	Half a teaspoon of blood (2.5ml) taken at admission in addition to the usual investigations undertaken to help treat your child & 2 small fecal samples taken using a soft cotton wool swab

There will be scheduled study visits following the initiation of treatment; on days 14, 45 and 90 after today. At these scheduled visits the following will be done: body measurements (weight, circumference of the arm and height); clinical assessment; and collection of information on their health progress. Collection of the small faecal sample using a soft cotton wool swab will not hurt your child.

Whilst your child is in hospital and at the scheduled follow up visits we may also ask you questions about the costs that you and your family have encountered as a result of the hospitalisation and any outpatient care that your child receives. If your child does not attend the follow up visits, we will contact you by phone and may need to visit your home to find out about your child.

Are there any risks or disadvantages to me/my child of taking part?
Our priority for every participant is their well-being. The antibiotics that will be given in the study are already regularly used routinely in hospitals. Some of the side effects that have been associated with them include: loss of appetite, abdominal discomfort, diarrhoea, vomiting, skin rash and very rarely an allergic reaction.

The amount of blood taken is too small to affect your child's health. Taking blood from the arm causes a small amount of pain, bruising, swelling, discomfort and a very small chance of infection. If this happens, we will provide treatment. We will use a careful procedure to help prevent these. If your child needs further blood tests as part of their care, these will be done at the same time. Use of a swab to collect faecal samples poses very low risk to your child. If your child has diarrhoea and their stools need to be tested to inform treatment, we will do that separately.

An independent committee will monitor this research continuously to ensure participants safety and rights are respected at all times. If for any reason the doctors looking after your child think they would benefit from leaving this trial, they will recommend this and ensure that you receive the normal treatment given to people who are not in the trial.

You will be asked to bring your child back for follow up at the clinic on specific days, and we will pay for the costs of your transport, but only for these scheduled study visits. You will be reimbursed for transport costs incurred during study visits based on actual amount spent. This will include transport costs if you will need to collect a faecal/stool sample at home and bring it later to the clinic. The participant will also be provided with a meal and compensated for study related out of pocket expenses at the rate of Ksh 350 for Kilifi participants and Ksh 650 for Mombasa and Nairobi participants [delete as appropriate] for each study visit you attend.

This research is supported by University of Oxford who will pay for any treatment or compensation in the unlikely event of any injury resulting from participation in this study.

Are there any advantages to my child of taking part?
Your child will be reviewed daily by one of our study clinicians, together with the regular hospital staff. The study is supporting additional training and staffing for the children's ward for this hospital. We will provide alternative antibiotics at no cost (according to recommended antibiotic guidelines) if they are needed and ensure that your child is referred to nutrition clinic and other clinical services on discharge, as needed. We will pay the costs of your child's re-admission to this hospital. We will also pay for any consultations and investigations that are available in this hospital. There is no other direct benefit to you in participating, but you will also be helping us to improve care for children who have malnutrition in the future.

What happens if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want your child to take part. Your child will still receive the recommended standard of care if they do not take part. No blood samples for research will be taken, but the clinicians may still wish to test your child's blood in the usual way for their care. If you do agree you can change your mind at any time and withdraw your child from the research. This will not affect your child's care now or in the future.

What happens to the samples?
All the information and samples collected will be held confidentially. Individual names are removed from all samples and replaced by codes, so that samples can only be linked to the children by people closely concerned with the research. Most of the research tests that will be done on the blood and faecal samples will be done in Kilifi or Nairobi. However, some tests to better identify any bacteria found cannot be done in Kenya, so part of the samples will be sent to the University of Oxford or the London School of Hygiene and Tropical Medicine, UK. After the research, a small portion of the blood and stool samples will be stored. We would like to store them for up to ten years. In this time, new research about children's health relating to the objectives of this study may be done on these samples. This is expected to involve using new ways of looking for infection. All such research must first be approved by a national independent expert committee to ensure your safety, rights and privacy are respected.

Who will have access to information about me/my child in this research?
All our research records are stored securely in locked cabinets and password protected computers. Only a few people who are closely concerned with the research will be able to view information from participants.

In future, information collected or generated during this study may be used to support new research by other researchers in Kenya and other countries. In all cases, we will only share information with other researchers in ways that do not reveal individual participants' identities. For example, we will remove information that could identify people, such as their names and where they live, and replace this information with number codes. Any future research using information from this study must first be approved by a local or national expert committee to make sure that the interests of participants and their communities are protected.

Who has approved this research?
All research at KEMRI has to be approved before it begins. An independent national committee, an international committee and a committee in Kilifi have looked carefully at this work and agreed that the research is important, that it will be conducted properly and your safety and rights have been respected.

What if I have any questions?
You are free to ask questions of any staff at any time. You can also contact the research team using these contacts:

Dr Caroline Ogwang, KEMRI Wellcome Trust Research Programme, P.O. Box 230, Kilifi. Telephone: 0729 950260 or 0722 203417, 041 7522063

If you want to ask someone independent about this research please contact:
Community Liaison Manager, KEMRI Wellcome Trust Research Programme, P.O. Box 230, Kilifi. Telephone: 041 7522 063, Mobile 0723 342 780 or 0705 154 386
and
The Secretary - KEMRI/Scientific and Ethics Review Unit, P. O. BOX 54840-00200, Nairobi, Tel number: 020 272 2541 Mobile: 0722 205 901 or 0733 400 003 email: seru@kemri.org

KEMRI Wellcome Trust Research Programme consent form

First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

Trial participants

I, [being a parent/guardian of _____ (name of child),] have had the research explained to me. I have understood all that has been read/explained and had my questions answered satisfactorily.

Please insert the boxes below or add others where relevant

☐ Yes *please tick* I agree to participate/allow my child to take part in this research

☐ Yes *please tick* I agree to samples being stored for future research that is in line with this study.

☐ Yes *please tick* I agree to samples being exported to the UK for tests that cannot be done in Kenya.

(Details of sample storage, future use and export are contained in the participant information sheet)

I understand that I can change my mind at any stage and it will not affect to me/my child in any way.

Parent/guardian's signature: _____ **Date** _____

Parent/guardian's name: _____ **Time** _____
(Please print name)

_____

Where parent/guardian cannot read, ensure a witness* observes consent process and signs below:

I attest that the information concerning this research was accurately explained to and apparently understood by the subject/parent/guardian and that informed consent was freely given by the subject/parent/guardian.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____

**A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.*

Thumbprint of the parent as named above if they cannot write:

I have followed the study SOP to obtain consent from the [participant/guardian]. S/he apparently understood the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Designee/investigator's signature: _____ **Date** _____

Designee/investigator's name: _____**Time** _____
(Please print name)

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

KEMRI Wellcome Trust Research Programme: Patient Information and Consent Form

First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

(Non-SAM Participant)

Institution	Investigators
Kenya Medical Research Institute, Kilifi, Kenya	Caroline Ogwang, Neema Mturi, Isaiah Njagi, Shalton Mwaringa, Grace Dena, Rehema Ali, Sheila Murunga, Kathryn Maitland, Johnstone Thitiri, Joseph Waichungo, Jimmy Shangala, Mwanamvua Boga, Samuel Kariuki, James Berkley, Julie Jemutai, Rebecca Gathoni
Coast General Hospital, Mombasa, Kenya	Victor Bandika, Jones Makori Obonyo, Laura Mwalekwa, John Odhiambo, Fauzat Hamid
Mbagathi Hospital & University of Nairobi, Kenya	Christine Manyasi, Molline Timbwa, Joshua Wambua
Mbale Hospital, Uganda	Peter Olupot-Olupot, Kathryn Maitland
London School of Hygiene & Tropical Medicine, UK	Anna Vassall, Gabriela Gomez
Swansea Medical School, UK	Greg Fegan
University College London, UK	Joseph Standing

LAY TITLE: A study of antibiotics used to treat children with malnutrition.

Your child is being admitted to hospital because they are sick. Your child will have a blood test done to check their general health, and will be given medicines. These tests and treatment are the normal care for a child who is admitted to hospital.

What is KEMRI and what is this study about?

KEMRI in Kenya and Mbale Hospital in Uganda in collaboration with University of Oxford, UK. KEMRI is a Kenyan government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit.

Children admitted to hospitals are often treated with antibiotics, especially those with malnutrition. However, some bacteria can resist antibiotics and it is possible that the antibiotics that are currently recommended should be changed. Your child does not have severe malnutrition, but could still help us with this research. We want to find out whether children carry bacteria that can resist antibiotics in their bowel, and if there are differences between well-nourished and malnourished children.

The study is important because the types of antibiotics needed to fight infection may be different in malnourished children. We are therefore asking your permission to be a part of understanding these problems.

What will it involve for me and my child if I agree?

We are asking:

1. To take a sample of faeces at admission (now) and again when you child is discharged from hospital using a soft swab. This will not hurt your child.
2. To use the information about your child's condition at admission and discharge, and which antibiotic drugs they are given in hospital.
3. Whilst your child is in hospital, we may also ask you questions about the costs that you and your family have encountered as a result of the hospitalisation and any outpatient care that your child receives. Some of the questions that you will be asked by the study team concerning the household and family are detailed.

Everything else that is done during your stay in hospital will be part of normal tests and treatment requested by doctors. If there are any other research activities that KEMRI staff would like you/your child to be involved in, staff shall explain and ask you first.

Are there any risks or disadvantages to me taking part?
KEMRI's priority for every patient is her care. The study will not involve any additional needles and the swab is very low risk.

Are there any benefits to me/my child of taking part?
Your child will be reviewed daily by one of our study clinicians, together with the regular hospital staff. There is no other direct benefit to you in participating, but you will also be helping us to improve care for children in the future. If your child has diarrhoea and a faecal sample needs to be examined, this will be done separately.

What happens if I refuse to participate?
It is up to you if you want to be a part of the research. You will have the same care whether you take part or not. If you do agree now, you can change your mind at any time and not take part in the research. This will not affect your care now or in the future.

What happens to the samples?
All the information and samples collected will be held confidentially. Individual names are removed from all samples and replaced by codes, so that samples can only be linked to the children by people closely concerned with the research. Most of the research tests that will be done on the blood and faecal samples will be done in Kilifi or Nairobi. However, some tests to better identify any bacteria found cannot be done in Kenya, so part of the samples will be sent to the University of Oxford or the London School of Hygiene and Tropical Medicine, UK. After the research, a small portion of the blood and stool samples will be stored. We would like to store them for up to ten years. In this time, new research about children's health relating to the objectives of this study may be done on these samples. This is expected to involve using new ways of looking for infection. All such research must first be approved by a national independent expert committee to ensure your safety, rights and privacy are respected.

Who will have access to information about me/my child in this research?
All our research records are stored securely in locked cabinets and password protected computers. Only a few people who are closely concerned with the research will be able to view information from mothers.

Who has allowed this research to take place?
An independent national committee and a committee in Kilifi have looked carefully at this work and agreed that the research is important, that it will be conducted properly and your safety and rights have been respected.

What if I have any questions?
You may ask any of our staff questions at any time. You can also contact those who are responsible for the care of you and your child and this research:

Dr. Caroline Ogwang KEMRI- Wellcome Trust [Kilifi County Hospital] P.O.Box. 230, Kenya.
Telephone: 0729 950260 7522063

If you want to ask someone independent about this research please contact:
Community Liaison Manager, KEMRI Wellcome Trust Research Programme, P.O. Box 230, Kilifi. Telephone: 0723 342 780 or 041 7522 063

The Secretary, Scientific and Ethics Review Unit (SERU), P. O. BOX 54840-00200, Nairobi, Tel number: 020 272 2541 Mobile: 0722 205 901 or 0733 400 003

Joint KEMRI/MoH research on antibiotics used to treat children with malnutrition.

Non-SAM participant (rectal swabs only)

I being the parent/guardian of, _____ (child's name), have had the research explained to me. I have understood all that has been read and had my questions answered satisfactorily.

Please insert the boxes below where relevant:

☐ Yes *please tick* I agree to participate/allow my child to take part in this research

☐ Yes *please tick* I agree to samples being stored for future research that is in line with this study.

☐ Yes *please tick* I agree to samples being exported to the UK for tests that cannot be done in Kenya.

(Details of sample storage, future use and export are contained in the participant information sheet)

I understand that I can change my mind at any stage and it will not affect me or my baby in any way.

Parent's/guardian's signature: _____ **Date** _____

Parent's/guardian's name: _____**Time** _____

(Please print name)

I certify that I have followed the study SOP to obtain consent from the [participant]. She/he apparently understood the nature and the purpose of the study and consents to participation in the study. She has been given opportunity to ask questions which have been answered satisfactorily.

Designee/investigator's signature: _____ **Date** _____

Designee/investigator's name: _____ **Time** _____

(Please print name)

Only necessary if the participant cannot read:

I *attest that the information concerning this research was accurately explained to and apparently understood by the subject and that informed consent was freely given by the participant.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____

(Please print name)

***A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.**

Thumbprint of the subject as named above if they cannot write:

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

KEMRI Wellcome Trust Research Programme: Patient Information and Consent Form

First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

(*Pharmacokinetics SAM Participant)*

Institution	Investigators
Kenya Medical Research Institute, Kilifi, Kenya	Caroline Ogwang, Neema Mturi, Isaiah Njagi, Shalton Mwaringa, Grace Dena, Rehema Ali, Sheila Murunga, Kathryn Maitland, Johnstone Thitiri, Joseph Waichungo, Jimmy Shangala, Mwanamvua Boga, Samuel Kariuki, James Berkley, Julie Jemutai, Rebecca Gathoni
Coast General Hospital, Mombasa, Kenya	Victor Bandika, Jones Makori Obonyo, Laura Mwalekwa, John Odhiambo, Fauzat Hamid
Mbagathi Hospital & University of Nairobi, Kenya	Christine Manyasi, Molline Timbwa, Joshua Wambua
Mbale Hospital, Uganda	Peter Olupot-Olupot, Kathryn Maitland
London School of Hygiene & Tropical Medicine, UK	Anna Vassall, Gabriela Gomez
Swansea Medical School, UK	Greg Fegan
University College London, UK	Joseph Standing

LAY TITLE: A study to compare antibiotics used to treat children with severe malnutrition.

Introduction

Your child is being admitted to hospital because they are sick. He or she has been examined by the study team and found to have malnutrition. Your child will have a blood test done to check their general health, and will be given antibiotics to treat infections that are common in children with malnutrition. These tests and treatment are part of the normal care for a child with malnutrition.

Who is carrying out this study?

This study is being carried out by KEMRI in Kenya and Mbale Hospital in Uganda in collaboration with University of Oxford, UK. KEMRI is a Kenyan government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit.

What is this study about?

In this study we want to find out which antibiotics that are given to treat infections in children admitted with malnutrition are most effective. We will be looking at two different types of antibiotics that are used: i) those that are given by injection and ii) an antibiotic that is given orally. Children who are enrolled in this study will participate in investigation of both the injectable and the oral antibiotics.

All children with severe malnutrition who are admitted to hospital are treated with antibiotics by injection because they often have serious infections. In this study, children will receive one of two different types of antibiotic treatment by injection.

- The usual current treatment that uses two drugs: penicillin and gentamicin
- An alternative treatment that uses one drug: ceftriaxone

Children with severe malnutrition are also sometime treated with an oral antibiotic to clear gut infections, but we are not sure if it is helpful, and some hospitals use it and some don't. In this study, children will also receive one of the following:

- Metronidazole (often known as Flagyl)
- A similar liquid that does not contain an antibiotic.

All of the antibiotic drugs being used in this study are widely used and already licenced for use in children in Kenya and Uganda *[sites to delete as appropriate].* However, we would like to check that the doses of the antibiotics are alright for malnourished children by taking 2 small blood samples (1/4 teaspoon) during the first 24 hours after your child has received these drugs.

In this study we will ask 2000 children admitted with severe malnutrition to participate. The decision on which child gets which drugs will be decided by a system based on chance, without any preference. All participants will have the same chance of receiving any of the treatment arms.

We will find out if there is any difference between the treatment groups by closely watching the progress of everyone in the study. To make sure that the findings of this study are as accurate as possible it is important that no one knows which child is receiving which oral medication until the end of research. We are asking your permission for your child to participate in this study.

What will it involve for me/my child if I agree?
If you agree for your child to participate, we will first assess their clinical status by taking body measurements, asking you questions about their health and factors that might contribute to their illness, as well as examining them. Some of the questions that you will be asked by the study team concerning the household and family are detailed.

In addition to the blood tests taken as part of the normal admission procedures, we will take an additional small amount of blood from the child's arm at the same time that samples are taken as part of your child's normal treatment. The extra amount taken for research will be half a teaspoon (3.5 ml). The same volume of blood will be taken should a child be readmitted before the end of the study period. We will also take two small faecal samples using a soft cotton wool swab for research. Other samples to be taken after the initiation of treatment are as follows:

Number of days after enrolment	**Sample to be collected**
At admission	2 small faecal samples taken using a soft cotton wool swab & half a teaspoon (3.5ml) of blood
During the first 24h hours	2 blood samples, each about a quarter of a teaspoon (1ml) during the first 24 hours after receiving these drugs.
At discharge	2 small faecal samples taken using a soft cotton wool swab & one sample of whole faeces & half a teaspoon (2.5ml) of blood
45 days	2 small faecal samples taken using a soft cotton wool swab & one sample of whole faeces
90 days	2 small faecal samples taken using a soft cotton wool swab
Readmission to hospital	Half a teaspoon of blood (2.5ml) taken at admission in addition to the usual investigations undertaken to help treat your child & 2 small fecal samples taken using a soft cotton wool swab

There will be scheduled study visits following the initiation of treatment; on days 14, 45 and 90 after today. At these scheduled visits the following will be done: body measurements (weight, circumference of the arm and height); clinical assessment; and collection of information on their health progress. Collection of the small faecal sample using a soft cotton wool swab will not hurt your child.

Whilst your child is in hospital and at the scheduled follow up visits we may also ask you questions about the costs that you and your family have encountered as a result of the hospitalisation and any outpatient

care that your child receives. If your child does not attend the follow up visits, we will contact you by phone and may need to visit your home to find out about your child.

Are there any risks or disadvantages to me/my child of taking part?
Our priority for every participant is their well-being. The antibiotics that will be given in the study are already regularly used routinely in hospitals. Some of the side effects that have been associated with them include: loss of appetite, abdominal discomfort, diarrhoea, vomiting, skin rash and very rarely an allergic reaction.

The amount of blood taken is too small to affect your child's health. Taking blood from the arm causes a small amount of pain, bruising, swelling, discomfort and a very small chance of infection. If this happens, we will provide treatment. We will use a careful procedure to help prevent these. If your child needs further blood tests as part of their care, these will be done at the same time. Use of a swab to collect faecal samples poses very low risk to your child. If your child has diarrhoea and their stools need to be tested to inform treatment, we will do that separately.

An independent committee will monitor this research continuously to ensure participants safety and rights are respected at all times. If for any reason the doctors looking after your child think they would benefit from leaving this trial, they will recommend this and ensure that you receive the normal treatment given to people who are not in the trial.

You will be asked to bring your child back for follow up at the clinic on specific days, and we will pay for the costs of your transport, but only for these scheduled study visits. You will be reimbursed for transport costs incurred during study visits based on actual amount spent. This will include transport costs if you will need to collect a faecal/stool sample at home and bring it later to the clinic. The participant will also be provided with a meal and compensated for study related out of pocket expenses at the rate of Ksh 350 for Kilifi participants and Ksh 650 for Mombasa and Nairobi participants [delete as appropriate] for each study visit you attend.

This research is supported by University of Oxford who will pay for any treatment or compensation in the unlikely event of any injury resulting from participation in this study.

Are there any advantages to my child of taking part?
Your child will be reviewed daily by one of our study clinicians, together with the regular hospital staff. The study is supporting additional training and staffing for the children's ward for this hospital. We will provide alternative antibiotics at no cost (according to recommended antibiotic guidelines) if they are needed and ensure that your child is referred to nutrition clinic and other clinical services on discharge, as needed. We will pay the costs of your child's re-admission to this hospital. We will also pay for any consultations and investigations that are available in this hospital. There is no other direct benefit to you in participating, but you will also be helping us to improve care for children who have malnutrition in the future.

What happens if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want your child to take part. Your child will still receive the recommended standard of care if they do not take part. No blood samples for research will be taken, but the clinicians may still wish to test your child's blood in the usual way for their

care. If you do agree you can change your mind at any time and withdraw your child from the research. This will not affect your child's care now or in the future.

What happens to the samples?
All the information and samples collected will be held confidentially. Individual names are removed from all samples and replaced by codes, so that samples can only be linked to the children by people closely concerned with the research. Most of the research tests that will be done on the blood and faecal samples will be done in Kilifi or Nairobi. However, some tests to better identify any bacteria found cannot be done in Kenya, so part of the samples will be sent to the University of Oxford or the London school of Hygiene and Tropical Medicine, UK. After the research, a small portion of the blood and stool samples will be stored. We would like to store them for up to ten years. In this time, new research about children's health relating to the objectives of this study may be done on these samples. This is expected to involve using new ways of looking for infection. All such research must first be approved by a national independent expert committee to ensure your safety, rights and privacy are respected.

Who will have access to information about me/my child in this research?
All our research records are stored securely in locked cabinets and password protected computers. Only a few people who are closely concerned with the research will be able to view information from participants.

In future, information collected or generated during this study may be used to support new research by other researchers in Kenya and other countries. In all cases, we will only share information with other researchers in ways that do not reveal individual participants' identities. For example, we will remove information that could identify people, such as their names and where they live, and replace this information with number codes. Any future research using information from this study must first be approved by a local or national expert committee to make sure that the interests of participants and their communities are protected.

Who has approved this research?
All research at KEMRI has to be approved before it begins. An independent national committee, an international committee and a committee in Kilifi have looked carefully at this work and agreed that the research is important, that it will be conducted properly and your safety and rights have been respected.

What if I have any questions?
You are free to ask questions of any staff at any time. You can also contact the research team using these contacts:
Dr Caroline Ogwang, KEMRI Wellcome Trust Research Programme, P.O. Box 230, Kilifi. Telephone: 0729 950260 or 0722 203417, 041 7522063

If you want to ask someone independent about this research please contact:
Community Liaison Manager, KEMRI Wellcome Trust Research Programme, P.O. Box 230, Kilifi. Telephone: 041 7522 063, Mobile 0723 342 780 or 0705 154 386; and
The Secretary - KEMRI/Scientific and Ethics Review Unit, P. O. BOX 54840-00200, Nairobi, Tel number: 020 272 2541 Mobile: 0722 205 901 or 0733 400 003 email: seru@kemri.org

KEMRI Wellcome Trust Research Programme consent form

First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

Pharmacokinetics participant

I, [being a parent/guardian of _____ (name of child),] have had the research explained to me. I have understood all that has been read/explained and had my questions answered satisfactorily.

Please insert the boxes below or add others where relevant

☐ Yes *please tick* I agree to participate/allow my child to take part in this research

☐ Yes *please tick* I agree to samples being stored for future research that is in line with this study.

☐ Yes *please tick* I agree to samples being exported to the UK for tests that cannot be done in Kenya.

(Details of sample storage, future use and export are contained in the participant information sheet)

I understand that I can change my mind at any stage and it will not affect to me/my child in any way.

Parent/guardian's signature: _____ **Date** _____

Parent/guardian's name: _____ **Time** _____
(Please print name)

_____

Where parent/guardian cannot read, ensure a witness* observes consent process and signs below:

I attest that the information concerning this research was accurately explained to and apparently understood by the subject/parent/guardian and that informed consent was freely given by the subject/parent/guardian.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____

**A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.*

Thumbprint of the parent as named above if they cannot write:

I have followed the study SOP to obtain consent from the [participant/guardian]. S/he apparently understood the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Designee/investigator's signature: _____ **Date** _____

Designee/investigator's name : _____**Time** _____
(Please print name)

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

Mbale Regional Referral Hospital Clinical Research Unit: Patient Information and Consent Form

First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

(Trial participant)

Institution	Investigators
Mbale Hospital, Uganda	Peter Olupot-Olupot, Kathryn Maitland
Kenya Medical Research Institute, Kilifi, Kenya	Caroline Ogwang, Neema Mturi, Isaiah Njagi, Shalton Mwaringa, Sheila Murunga, Grace Dena, Rehema Ali, Kathryn Maitland, Johnstone Thitiri, Joseph Waichungo, Jimmy Shangala, Mwanamvua Boga, Samuel Kariuki, James Berkley, Julie Jemutai, Rebecca Gathoni
Coast General Hospital, Mombasa, Kenya	Victor Bandika, Jones Makori Obonyo, Laura Mwalekwa, John Odhiambo, Fauzat Hamid
Mbagathi Hospital & University of Nairobi, Kenya	Christine Manyasi, Molline Timbwa, Joshua Wambua
London School of Hygiene & Tropical Medicine, UK	Anna Vassall, Gabriela Gomez
Swansea Medical School, UK	Greg Fegan
University College London, UK	Joseph Standing

LAY TITLE: A study to compare antibiotics used to treat children with severe malnutrition.

Introduction

Your child is being admitted to hospital because they are sick. He or she has been examined by the study team and also found to have malnutrition. Your child will have a blood test done to check their general health, and will be given antibiotics to treat infections that are common in children with malnutrition. These tests and treatment are part of the normal care for a child with malnutrition.

Who is carrying out this study?

This study is being carried out by Mbale Hospital in collaboration with KEMRI in Kenya and the University of Oxford, UK. KEMRI is a Kenyan government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit.

What is this study about?

In this study we want to find out which antibiotics that are given to treat infections in children admitted with malnutrition are most effective. We will be looking at two different types of antibiotics that are used: i) those that are given by injection and ii) an antibiotic that is given orally. Children who are enrolled in this study will participate in investigation of both the injectable and the oral antibiotics.

All children with severe malnutrition who are admitted to hospital are treated with antibiotics by injection because they often have serious infections. In this study, children will receive one of two different types of antibiotic treatment by injection.

- The usual current treatment that uses two drugs: penicillin and gentamicin
- An alternative treatment that uses one drug: ceftriaxone

Children with severe malnutrition are also sometime treated with an oral antibiotic to clear gut infections, but we are not sure if it is helpful, and some hospitals use it and some don't. In this study, children will also receive one of the following:

- Metronidazole (often known as Flagyl)
- A similar liquid that does not contain an antibiotic.

All of the antibiotic drugs being used in this study are widely used and already licenced for use in children in Kenya and Uganda *[sites to delete as appropriate].*

In this study we will ask 2000 children admitted with severe malnutrition to participate. The decision on which child gets which drugs will be decided by a system based on chance, without any preference. All participants will have the same chance of receiving any of the treatment arms.

We will find out if there is any difference between the treatment groups by closely watching the progress of everyone in the study. To make sure that the findings of this study are as accurate as possible it is important that no one knows which child is receiving which oral medication until the end of research. We are asking your permission for your child to participate in this study.

What will it involve for me/my child if I agree?
If you agree for your child to participate, we will first assess their clinical status by taking body measurements, asking you questions about their health and factors that might contribute to their illness, as well as examining them. Some of the questions that you will be asked by the study team concerning the household and family are detailed.

In addition to the blood tests taken as part of the normal admission procedures, we will take an additional small amount of blood from the child's arm at the same time that samples are taken as part of your child's normal treatment. The extra amount taken for research will be half a teaspoon (2.5 ml). The same volume of blood will be taken should a child be readmitted before the end of the study period. We will also take two small faecal samples using a soft cotton wool swab for research. Other samples to be taken after the initiation of treatment are as follows:

Number of days after enrolment	**Sample to be collected**
At admission	2 small faecal samples taken using a soft cotton wool swab & half a teaspoon (2.5ml) of blood
At discharge	2 small faecal samples taken using a soft cotton wool swab & one sample of whole faeces & half a teaspoon (2.5ml) of blood
45 days	2 small faecal samples taken using a soft cotton wool swab & one sample of whole faeces
90 days	2 small faecal samples taken using a soft cotton wool swab
Readmission to hospital	Half a teaspoon of blood (2.5ml) taken at admission in addition to the usual investigations undertaken to help treat your child & 2 small faecal samples taken using a soft cotton wool swab.

There will be scheduled study visits following the initiation of treatment; on days 14, 45 and 90 after today. At these scheduled visits the following will be done: body measurements (weight, circumference of the arm and height); clinical assessment; and collection of information on their health progress. Collection of the small faecal sample using a soft cotton wool swab will not hurt your child.

Whilst your child is in hospital and at the scheduled follow up visits we may also ask you questions about the costs that you and your family have encountered as a result of the hospitalisation and any outpatient care that your child receives. If your child does not attend the follow up visits, we will contact you by phone and may need to visit your home to find out about your child.

Are there any risks or disadvantages to me/my child of taking part?
Our priority for every participant is their well-being. The antibiotics that will be given in the study are already regularly used routinely in hospitals. Some of the side effects that have been associated with them include: loss of appetite, abdominal discomfort, diarrhoea, vomiting, skin rash and very rarely an allergic reaction.

The amount of blood taken is too small to affect your child's health. Taking blood from the arm causes a small amount of pain, bruising, swelling, discomfort and a very small chance of infection. If this happens, we will provide treatment. We will use a careful procedure to help prevent these. If your child needs further blood tests as part of their care, these will be done at the same time. Use of a swab to collect faecal samples poses very low risk to your child. If your child has diarrhoea and their stools need to be tested to inform treatment, we will do that separately.

An independent committee will monitor this research continuously to ensure participants safety and rights are respected at all times. If for any reason the doctors looking after your child think they would benefit from leaving this trial, they will recommend this and ensure that you receive the normal treatment given to people who are not in the trial.

You will be asked to bring your child back for follow up at the clinic on specific days, and we will pay for the costs of your transport, but only for these scheduled study visits. You will be reimbursed for transport costs incurred during study visits based on actual amount spent. This will include transport costs if you will need to collect a faecal/stool sample at home and bring it later to the clinic. The participant will also be provided with a meal and compensated for study related out of pocket expenses at the rate of Ksh 350 for Kilifi participants and Ksh 650 for Mombasa and Nairobi participants [delete as appropriate] for each study visit you attend.

This research is supported by University of Oxford who will pay for any treatment or compensation in the unlikely event of any injury resulting from participation in this study.

Are there any advantages to my child of taking part?
Your child will be reviewed daily by one of our study clinicians, together with the regular hospital staff. The study is supporting additional training and staffing for the children's ward for this hospital. We will provide alternative antibiotics at no cost (according to recommended antibiotic guidelines) if they are needed and ensure that your child is referred to nutrition clinic and other clinical services on discharge, as needed. We will pay the costs of your child's re-admission to this hospital. We will also pay for any consultations and investigations that are available in this hospital. There is no other direct benefit to you in participating, but you will also be helping us to improve care for children who have malnutrition in the future.

What happens if I refuse to participate?
All participation in research is voluntary. You are free to decide if you want your child to take part. Your child will still receive the recommended standard of care if they do not take part. No blood samples for research will be taken, but the clinicians may still wish to test your child's blood in the usual way for their care. If you do agree you can change your mind at any time and withdraw your child from the research. This will not affect your child's care now or in the future.

What happens to the samples?
All the information and samples collected will be held confidentially. Individual names are removed from all samples and replaced by codes, so that samples can only be linked to the children by people closely concerned with the research. Most of the research tests that will be done on the blood and faecal samples will be done in Kilifi or Nairobi. However, some tests to better identify any bacteria found cannot be done in Kenya, so part of the samples will be sent to the University of Oxford or the London School of Hygiene and Tropical Medicine, UK. After the research, a small portion of the blood and stool samples will be stored. We would like to store them for up to ten years. In this time, new research about children's health relating to the objectives of this study may be done on these samples. This is expected to involve using new ways of looking for infection. All such research must first be approved by a national independent expert committee to ensure your safety, rights and privacy are respected.

Who will have access to information about me/my child in this research?
All our research records are stored securely in locked cabinets and password protected computers. Only a few people who are closely concerned with the research will be able to view information from participants.

In future, information collected or generated during this study may be used to support new research by other researchers in Kenya and other countries. In all cases, we will only share information with other researchers in ways that do not reveal individual participants' identities. For example, we will remove information that could identify people, such as their names and where they live, and replace this information with number codes. Any future research using information from this study must first be approved by a local or national expert committee to make sure that the interests of participants and their communities are protected.

Who has approved this research?
All research at KEMRI has to be approved before it begins. An independent national committee, an international committee and a committee in Kilifi have looked carefully at this work and agreed that the research is important, that it will be conducted properly and your safety and rights have been respected.

What if I have any questions?
You are free to ask questions of any staff at any time. You can also contact the research team using these contacts:

Dr. Peter Olupot-Olupot, Mbale Regional Referral Hospital Clinical Research Unit, P.O. Box 1966, Mbale, Uganda. Telephone 0772 457 217.

If you want to ask someone independent about this research please contact:
The Chairman, Mbale Regional Referral Hospital Research & Ethics Committee (MRRH-REC), Dr. John Stephen Obbo Olwenyi, P.O. Box 921, Mbale, Uganda. Telephone 0772 437 407.

Mbale Regional Referral Hospital Clinical Research Unit consent form

First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

I, ……[being a parent/guardian of _____ (name of child),] have read about or had the research explained to me. I have understood all that I have read / has been explained to me and had my questions answered satisfactorily.

☐ Yes (*please tick)* I agree to participate/allow my child to take part in this research
☐ Yes (*please tick)* I agree to samples being stored for future research that is in line with this study.
☐ Yes (*please tick)* I agree to samples being exported to Kenya and the UK for tests that cannot be done in Uganda.
(Details of sample storage, future use and export are contained in the participant information sheet)

I understand that I can change my mind at any stage and it will not affect to me/my child in any way.

Parent/guardian's signature: _____ **Date** _____

Parent/guardian's name: _____ **Time** _____
(Please print name)

_____

Where parent/guardian cannot read, ensure a witness* observes consent process and signs below:

I attest that the information concerning this research was accurately explained to and apparently understood by the subject/parent/guardian and that informed consent was freely given by the subject/parent/guardian.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____

**A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.*

Thumbprint of the parent as named above if they cannot write:

I have followed the study SOP to obtain consent from the [participant/guardian]. S/he apparently understood the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Designee/investigator's signature: _____ **Date** _____

Designee/investigator's name : _____**Time** _____
(Please print name)

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

Mbale Regional Referral Hospital Clinical Research Unit: Patient Information and Consent Form
First-Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

(Non-SAM Participant)

Institution	Investigators
Mbale Hospital, Uganda	Peter Olupot-Olupot, Kathryn Maitland
Kenya Medical Research Institute, Kilifi, Kenya	Caroline Ogwang, Neema Mturi, Isaiah Njagi, Shalton Mwaringa, Sheila Murunga, Grace Dena, Rehema Ali, Kathryn Maitland, Johnstone Thitiri, Joseph Waichungo, Jimmy Shangala, Mwanamvua Boga, Samuel Kariuki, James Berkley, Julie Jemutai, Rebecca Gathoni
Coast General Hospital, Mombasa, Kenya	Victor Bandika, Jones Makori Obonyo, Laura Mwalekwa, John Odhiambo, Fauzat Hamid
Mbagathi Hospital & University of Nairobi, Kenya	Christine Manyasi, Molline Timbwa, Joshua Wambua
London School of Hygiene & Tropical Medicine, UK	Anna Vassall, Gabriela Gomez
Swansea Medical School, UK	Greg Fegan
University College London, UK	Joseph Standing

LAY TITLE: A study of antibiotics used to treat children with malnutrition.

Your child is being admitted to hospital because they are sick. Your child will have a blood test done to check their general health, and will be given medicines. These tests and treatment are the normal care for a child who is admitted to hospital.

Who is carrying out this study?

This study is being carried out by Mbale Hospital in collaboration with KEMRI in Kenya and the University of Oxford, UK. KEMRI is a Kenyan government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit.

What is this study about?

Mbale Hospital in Uganda and KEMRI in Kenya, in collaboration with University of Oxford, UK. KEMRI is a Kenyan government organization that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit.

Children admitted to hospitals are often treated with antibiotics, especially those with malnutrition. However, some bacteria can resist antibiotics and it is possible that the antibiotics that are currently recommended should be changed. Your child does not have severe malnutrition, but could still help us with this research. We want to find out whether children carry bacteria that can resist antibiotics in their bowel, and if there are differences between well-nourished and malnourished children. The study is important because the types of antibiotics needed to fight infection may be different in malnourished children. We are therefore asking your permission to be a part of understanding these problems.

What will it involve for me and my child if I agree?

We are asking:

1. To take a sample of faeces at admission (now) and again when you child is discharged from hospital using a soft swab. This will not hurt your child.
2. To use the information about your child' condition at admission and discharge, and which antibiotic drugs they are given in hospital.
3. Whilst your child is in hospital and at the scheduled follow up visits we may also ask you questions about the costs that you and your family have encountered as a result of the hospitalisation and any outpatient care that your child receives. Some of the questions that you will be asked by the study team concerning the household and family are detailed.

Everything else that is done during your stay in hospital will be part of normal tests and treatment requested by doctors. If there are any other research activities that our staff would like you/your child to be involved in, staff shall explain and ask you first.

Are there any risks or disadvantages to me taking part?
KEMRI's priority for every patient is her care. The study will not involve any additional needles and the swab is very low risk.

Are there any benefits to me/my child of taking part?
Your child will be reviewed daily by one of our study clinicians, together with the regular hospital staff. There is no other direct benefit to you in participating, but you will also be helping us to improve care for children in the future. If your child has diarrhoea and a faecal sample needs to be examined, this will be done separately.

What happens if I refuse to participate?
It is up to you if you want to be a part of the research. You will have the same care whether you take part or not. If you do agree now, you can change your mind at any time and not take part in the research. This will not affect your care now or in the future.

What happens to the samples?
All the information and samples collected will be held confidentially. Individual names are removed from all samples and replaced by codes, so that samples can only be linked to the children by people closely concerned with the research. Most of the research tests that will be done on the blood and faecal samples will be done in Kilifi or Nairobi, Kenya. However, some tests to better identify any bacteria found cannot be done in Uganda or Kenya, so part of the samples will be sent to the University of Oxford or the London school of Hygiene and Tropical Medicine, UK. After the research, a small portion of the blood and stool samples will be stored. We would like to store them for up to ten years. In this time, new research about children's health relating to the objectives of this study may be done on these samples. This is expected to involve using new ways of looking for infection. All such research must first be approved by a national independent expert committee to ensure your safety, rights and privacy are respected.

Who will have access to information about me/my child in this research?
All our research records are stored securely in locked cabinets and password protected computers. Only a few people who are closely concerned with the research will be able to view information from mothers.

Who has allowed this research to take place?
An independent national committee and a committee in Kilifi have looked carefully at this work and agreed that the research is important, that it will be conducted properly and your safety and rights have been respected.

What if I have any questions?
You may ask any of our staff questions at any time. You can also contact those who are responsible for the care of you and your child and this research:
Dr. Peter Olupot-Olupot, Mbale Regional Referral Hospital Clinical Research Unit, P.O. Box 1966, Mbale, Uganda. Telephone 0772 457 217.

If you want to ask someone independent about this research, please contact:
The Chairman, Mbale Regional Referral Hospital Research & Ethics Committee (MRRH-REC), Dr. John Stephen Obbo Olwenyi, P.O. Box 921, Mbale, Uganda. Telephone 0772 437 407.

Joint KEMRI/MoH research on antibiotics used to treat children with malnutrition.

Non-SAM participant (rectal swabs only)

I being the parent/guardian of, _____ (child's name), have had the research explained to me. I have understood all that has been read and had my questions answered satisfactorily.

Please insert the boxes below where relevant:

☐ Yes *please tick* I agree to participate/allow my child to take part in this research

☐ Yes *please tick* I agree to samples being stored for future research that is in line with this study.

☐ Yes *please tick* I agree to samples being exported to Kenya and the UK for tests that cannot be done in Kenya.

(Details of sample storage, future use and export are contained in the participant information sheet)

I understand that I can change my mind at any stage and it will not affect me or my baby in any way.

Parent's/guardian's signature: _____ **Date** _____

Parent's/guardian's name: _____**Time** _____

(Please print name)

I certify that I have followed the study SOP to obtain consent from the [participant]. She/he apparently understood the nature and the purpose of the study and consents to participation in the study. She has been given opportunity to ask questions which have been answered satisfactorily.

Designee/investigator's signature: _____ **Date** _____

Designee/investigator's name: _____ **Time** _____

(Please print name)

Only necessary if the participant cannot read:

I *attest that the information concerning this research was accurately explained to and apparently understood by the subject and that informed consent was freely given by the participant.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____

(Please print name)

***A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.**

Thumbprint of the subject as named above if they cannot write:

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

28.3 Curriculum Vitae of non-KEMRI investigators