Gastroenteritis: Rehydration of children with Severe Acute Malnutrition (GASTROSAM)

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

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

Abstract:

Children hospitalised with severe acute malnutrition (SAM) are frequently complicated (>50%) by diarrhoea ($\geq$3 watery stools/day) which is accompanied by poor outcomes (case fatality 21%). Rehydration guidelines for SAM are exceptionally conservative and controversial, as they rely upon expert opinion, recommending restriction of intravenous (iv) to cases with advanced shock and exclusive use of low sodium intravenous and oral rehydration solutions (ORS) for fear of fluid and/or sodium overload. Our research group have conducted previous research to show that hypotonic solutions for rehydration and shock management resulted in worse outcomes than isotonic Ringers Lactate. Also, an observational study was conducted in Mbale which incorporated detailed investigation of myocardial function and haemodynamic response to intravenous rehydration for SAM children with severe dehydration due to diarrhoea. This study showed a very high mortality of children managed in accordance to WHO SAM rehydration guidelines (80%) with echocardiographic evidence of fluid responsiveness with intravenous rehydration (i.e. that is was safe and resulted in a positive myocardial response to rehydration) but indicated children remained grossly 'under-filled', and concluded the need to assess more liberal volumes of fluid rehydration.

The proposed GASTROSAM trial is the next step in reappraising current recommendations. We aim to evaluate standard (usually used in non-SAM children) liberal strategies for both iv and oral rehydration in SAM children with diarrhoea. This Phase II trial will generate safety and data on survival to 96 hours, 7 days and 28 days of rehydration strategies incorporating two strata for management of (A) severe dehydration comparing both rates of rehydration and volume of iv replacement and (B) the composition of ORS for children with some dehydration (post iv-rehydration) designed as a partial factorial trial.

The two major questions to be addressed are

(1) In Stratum A involving SAM children with clinical signs of severe dehydration (approximately 10% loss) whether 'liberal' rehydration strategy using 100mls/kg of isotonic Ringers Lactate with either:
   (i) standard WHO Plan C for rapid rehydration over 3-5 hours (incorporating boluses for shock) versus
   (ii) slower fixed rate of intravenous rehydration over 8 hours (and no boluses) are safer and result in better outcomes versus
   (iii) current WHO SAM guidelines recommending oral rehydration with low-sodium ReSoMal and restricting iv to those with advanced shock only (15 ml/kg bolus (plus one repeat).

(2) In Stratum B in children with diarrhoea with clinical signs of 'some dehydration' and for those in Stratum A (follow on treatment post-intravenous rehydration) whether oral rehydration with (i)WHO standard oral rehydration solution (ORS) for non-SAM results in less hyponatraemia and less adverse outcomes than (ii) current recommendation advocating low sodium (ReSoMal) ORS.

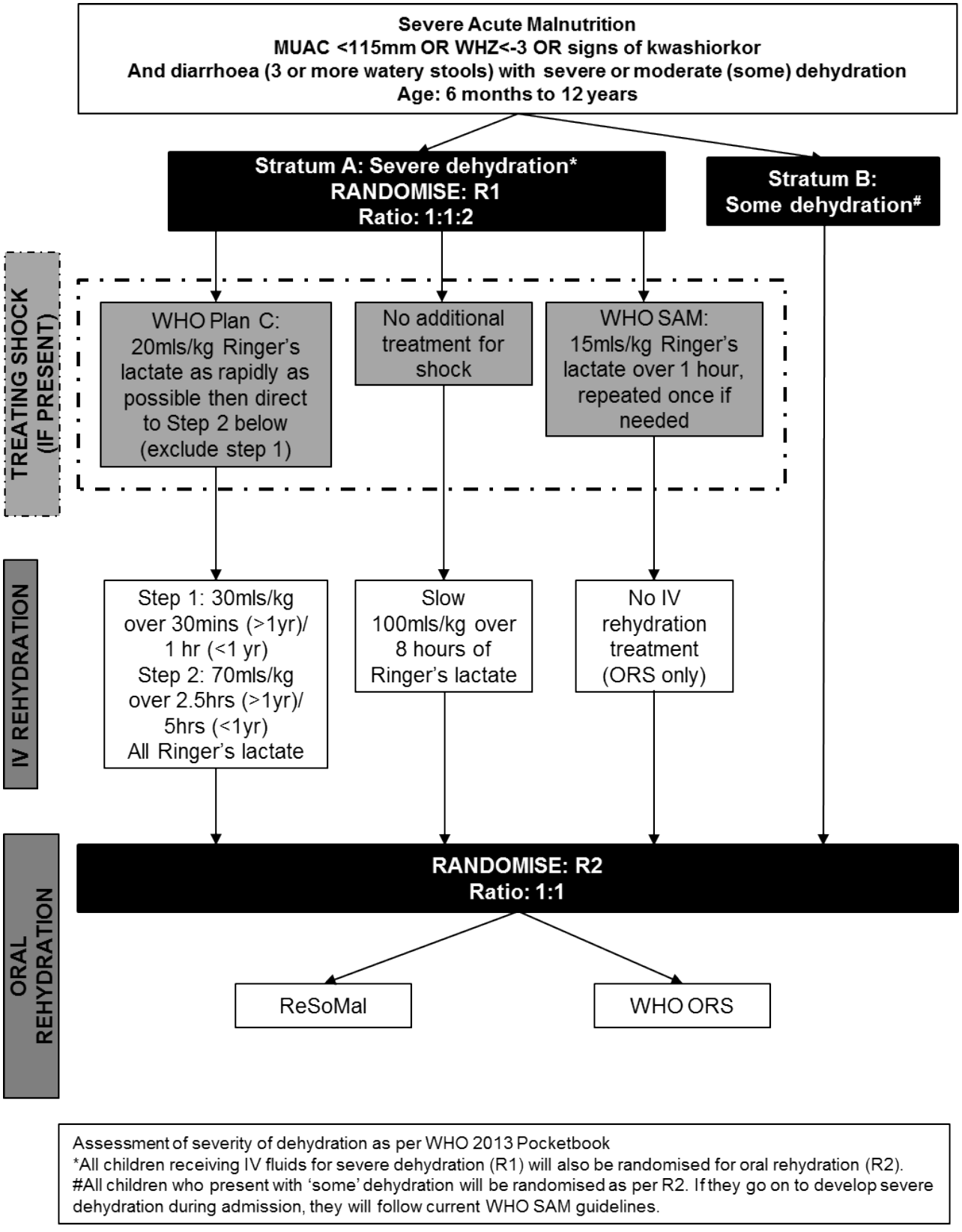
There is an urgent need to reappraise the recommendations; since they lack any relevant studies and have largely ignored published data contradicting these opinions and therefore most clinicians are fearful of use of intravenous fluids owing to the very strongly worded warnings about the potential harm. Demonstrating that intravenous rehydration is safe in children with SAM will be an important achievement. Our multidisciplinary group, including experts in child health, infectious diseases, clinical trials and critical illness, are uniquely placed to conduct this research. A number of the co-applicants were involved in the design and conduct of the largest and only controlled of fluid resuscitation, FEAST, in children with shock dueto severe febrile illness.

3. Trial Summary

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
ACRONYM	GASTROSAM
Long Title of Trial	Gastroenteritis: Rehydration of children with severe acute malnutrition
Version	3.0
Date	19th October 2022
ISRCTN #	ISRCTN76149273
ICREC	18IC4427
Study Design	Open Phase II trial with a factorial design
Type of Participants to be Studied	Children aged 6 months to 12 years with severe acute malnutrition (SAM) hospitalised gastroenteritis (> 3 loose stools/day) and signs of severe or some dehydration
Setting	Mbale and Soroti Regional Referral Hospitals, Eastern Uganda Kilifi County Hospital, Kilifi, Kenya Coast General Teaching and Referral Hospital, Mombasa Kenya Maiduguri, Nigeria Magaria, Niger Madarounfa, Niger
Interventions to be Compared	**Stratum A** (severe dehydration only) Children with be randomised (1:1:2) to compare: **i)** **WHO Plan C arm**: Rapid iv rehydration as per WHO Plan C (usually for non-SAM) children (100mls/kg Ringers Lactate (RL) over 3-6 hours according to age including boluses (20mls/kg) for those with shock) **ii)** **Slow Rehydration Arm**: A slower iv rehydration regimen (100 mls/kg RL given over 8 hours and no boluses). **iii)** **WHO SAM arm:** rehydration regime: ORS and iv boluses of RL only for shock (standard of care) **Stratum B:** all children with some or severe dehydration post iv rehydration will compare (1:1 ratio) **i)** Standard WHO ORS given for non-SAM (experimental) versus **ii)** WHO SAM-recommended low-sodium RESOMAL
Study Hypotheses	• For children with severe dehydration we hypothesize that standard intravenous regime WHO Plan C (100mls/kg over 3-5 hours) used for non-SAM gastroenteritis will result in better outcomes than current SAM rehydration recommendations. • We hypothesize that 100mls/kg over 8 hours will result in fewer fluid related adverse events than rapid WHO Plan C guideline. • We also hypothesize that standard ORS solutions may be equally as effective with fewer side effects than low salt ReSoMal.
Primary Outcome Measure(s)	**Primary outcome for Intravenous rehydration**: Mortality to 96 hours **Primary outcome for Oral rehydration strategy:** change from randomisation in sodium levels at 24 hours.

Secondary Outcome Measure(s)	Measures assessing safety (evidence of pulmonary oedema or heart failure); change in sodium at 24 hours compared to 8 hours post enrolment (ie post-iv levels) for those in Stratum A; perturbations of electrolyte abnormalities (severe hyponatraemia <125 mmols/L or hypokalaemia <2.5mol/L), weight; MUAC change to Day 3 and Day 7; and Day-28 survival.
Number of Participants	**272 childre**n in the stratum with severe dehydration and an additional **64** children with some dehydration; **overall 336 children**.
Duration	36 months
Ancillary Studies/Substudies	Myocardial function
Sponsor	**Imperial College, London**
Funder	**Medical Research Council** **Médecins Sans Frontierés**
Trial Manager	**Emmanuel Oguda**
Chief Investigator	**Kathryn Maitland**
MRC CTU at UCL Project Leader	**Elizabeth C George**

4. Trial Flow



Assessment of severity of dehydration as per WHO 2013 Pocketbook
*All children receiving IV fluids for severe dehydration (R1) will also be randomised for oral rehydration (R2).
#All children who present with 'some' dehydration will be randomised as per R2. If they go on to develop severe dehydration during admission, they will follow current WHO SAM guidelines.

5. Table of visits and assessments

Hours (h) /Days (d)	0*h	8h	24h	Day 3	96 h	7d^	28d^
Consent and information sheet	X						
Clinical examination (doctor/doctor visit)	X	X	X				(X)
Nurse observation/visit		X	X			X	(X)
Survival Status					X	X	X
Vital observations, anthropometry	X	X	X	X		(X)	(X)
Laboratory investigations							
Haematology	X		X			(X[£])	X[£]
Biochemistry (Chemistry and Osmolarity[$])	X	X	X			(X[£])	
Lactate/Glucose	X	X	(X)				
Malaria slide + /- RDT	X		(X)			(X[£])	(X[£])
Blood culture (if microbiological facilities present)	(X)						
HIV testing	X						
Urine (dipstick and save) [#]	X	(X)	(X)			(X[£])	
Cross match (for transfusion) (red top) if indicated	X						
Stored samples							
Plasma for Cardiac Biomarkers[$]	X	X	X			X	

* At Enrolment

^ Day 7 and Day 28 if child discharged and unable to return then confirmation of survivorship can be done by telephone

()[£] optional

Only for children who are catheterised

[$] Where facilities for plasma and storage possible

6. Abbreviations

AGE Acute Gastroenteritis
AVPU Alert, voice, pain, unresponsive: system of recording patient's level of consciousness
CRF Case report form
DSMB Data Safety Monitoring Board
DMC Data Monitoring Committee
ETAT Emergency triage assessment and treatment
FEAST Fluid Expansion As a Supportive Therapy
GEMS Global Enteric Multicentre study
GI Gastrointestinal
GOARN Global Outbreak Alert and Response Network
ICREC Imperial College Research Ethics Committee
KWTRP KEMRI Wellcome Trust Project
KCH Kilifi County Hospital
MRC Medical Research Council
MSF Médecins Sans Frontières
MUAC Mid-upper arm circumference
NGT Nasogastric tube
ORS Oral Rehydration Solution
ReSoMal Low sodium Rehydration Salt Solution for Malnutrition
SAM Severe acute malnutrition
SERU Scientific ethics review unit
TSC Trial Steering Committee
US Ultrasound
WHO World Health Organization

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8. Introduction

Worldwide, an estimated 2.5 billion cases of acute gastroenteritis occur annually in children under 5 years. In these children, gastroenteritis is the second biggest cause of mortality (after acute respiratory illnesses) with the vast majority occurring in low resource settings such as sub-Saharan Africa[1]. A large case-control study Global Enteric Multicentre study (GEMS) carried out in Africa and Asia showed that patients with moderate/ severe gastroenteritis are 8.5 times more likely to die than non-gastroenteritis controls[2]. A third of the fatalities occurred < 7days following hospitalisation – with baseline nutritional status an important factor in outcome. Improvements in early management may therefore be critical for improving outcome.

For children with SAM the current WHO recommendations for rehydration of children with signs of severe dehydration and diarrhoea are exceptionally conservative and very controversial. First, recommendations for intravenous (iv) rehydration is restricted only to those with advanced shock, a group we have documentedto have an exceptionally high mortality rate (82% Day 28 mortality) on current guidelines since they focusingon the exclusive use of oral rehydration using low-sodium ORS (ReSoMal)[3]. The guidelines lack relevant clinical studies, founded largely on a time-honoured and strongly held belief that the malnourished heart is at risk of failure. Moreover, guidelines indicate SAM children have an inability to cope with sodium-rich solutions (expert opinion, with no published primary data) recommending a preference hypotonic (half strength Darrow's or lactated Ringers) solutions for iv resuscitation[4]. The controversy surrounding these recommendations was reviewed by Dr Brewster in 2006 (Critical appraisal of the management of severe malnutrition) in which he states 'The World Health Organization (WHO) Manual has five pages on this issue (rehydration), which is somewhat unbalanced compared with the 11 lines on TB/HIV' [5]. This is rather paradoxical since there have been few studies to inform such recommendation and the limited number of studies and trials suggesting that standard approaches are not harmful were not included in the WHO recommendations. Subsequent updates of these recommendations have also failed to include reference to relevant research challenging these guidelines (see below).

Challenging the WHO recommendations

First, these recommendations for rehydration and shock management are not physiological, since isotonic solutions are required to expand circulating volume, with hypotonic solutions more liable to cause water overload. Secondly, there are no commercial products available, thus requiring 'reconstitution' of these half strength solution at the point of implementation (ie at the bedside) which is fraught with potential errors and risk of nosocomial infection. Furthermore, the stance that 'severe diarrhoea' is unusual and in SAM the presence of diarrhoea is usual and of trivial consequence and that signs of severe dehydration (decreased skin turgor or sunken eyes) are unreliable and reflect a lack of fat mass[6] lack a scientific published evidence-base. In two decades guidelines have not been revised (including updated 2013 guidelines)[4, 6] despite emerging evidence from Africa, challenging these premises- where both diarrhoea and signs of severe dehydration were shown to have very high mortality[7, 8]**.** These are summarised below.

Data from Africa and systematic reviews

A prospective study involving 920 Kenyan children showed that 50% of children admitted with SAM had diarrhoea (case-fatality 21% versus 9% without diarrhoea) and a further 16% developed diarrhoea during admission (case-fatality 18%)[8]. Key risk factors for death were bacteraemia and signs of severe dehydration (decreased skin turgor or sunken eyes) and severe hyponatraemia - challenging the assumption that signsof severe dehydration are 'unreliable' and diarrhoea plays a limited role in the poor outcomes.

We have recently conducted two systematic reviews summarizing the evidence underpinning the iv and oral rehydration recommendations for SAM[9, 10]. For iv rehydration we found no clinical trials providing a direct assessment of the current WHO guidelines[9]. Three small Phase II trials comparing WHO fluid recommendations to less stringent fluid resuscitation indicated that iv rehydration is safe with no evidence provided of fluid-overload or heart failure[11-13]. Children receiving the restrictive WHO regime had a very poor outcome with 48-hour and Day 28 mortality of 36% and 82% respectively[13]. The AFRIM study incorporated systematic and detailed assessment of myocardial function demonstrating evidence of fluid responsive myocardial indices and that median systematic vascular resistance index remained very high post

fluid resuscitation indicative of 'under filling' rather than overload[13]. A number of clinical studies examining myocardial function in African children also concluded that although cardiac mass is reduced (consistent with body mass) there were no significant differences in cardiac index, stroke volume index and heart rate between inpatient children with and without SAM (reviewed in Houston *et al*)[9, 14]. A trial conducted in India using rapid intravenous therapy in SAM children in cholera showed a liberal rehydration regime was safe[11], butthis was not taken into consideration in the updated 2013 SAM guidelines[4].

For the management of 'some dehydration' two small clinical trials in Asian children have compared the use of ReSoMal against other low osmolar ORS[15, 16]; both were equally effective in rehydration. However, both trials showed the development of hyponatraemia with ReSoMal in Asian children, with one child developing seizures with severe hyponatraemia. Neither reported any mortality. No trials have been conducted in Africa, where SAM mortality remains high, with a key risk factor for fatality being hyponatraemia.

Finally, relevant to a broader population hospitalised with acute diarrhoea with severe dehydration (~10% weight loss) a prospective study showed that ~ 20% temporarily fulfilled anthropometric criteria for SAM (MUAC <11.5cm) but were 'reclassified' as undernourished[17] following rehydration. Thus, the current recommendations have much wider implications as potentially 20% of non-SAM children could be inappropriately rehydrated in accordance to WHO SAM protocol. This may have contributed to the poor outcomes observed in the GEMS study[2].

GASTRO trial (ICREC, 16IC3388, initial approval: 18/08/2016; ISRCTN 67518332**)**
We have recently completed a trial of slow versus rapid rehydration (as proposed for this trial) in Kenyan and Uganda children with severe dehydration following gastroenteritis [18]. Children with severe malnutrition were excluded from this trial. We enrolled 121 children and had only 3 deaths (2.5% mortality).

	Enrolled	SAEs	Deaths
Slow Arm (Experimental)	61	2	1
WHO Plan C Arm	61	3	2
Total	122	5	3

Only 1 SAE in Uganda – Mbale but no deaths. Kilifi 4 SAEs – 3 deaths.

Whilst the trial was not powered to examine superiority of one arm over the other; it did demonstrate that the experimental arm (Slow rehydration) was safe and compared to historic controls (which showed unselected data on the outcome of gastroenteritis on current plan C management across a network of Kenya hospitals including 1211 children with severe dehydration that in-hospital mortality was 12% in those with severe dehydration)[19] both arms had substantially lower mortality.

9. Justification for the Study

The principal aim of GASTROSAM is to reappraise these recommendations and evaluate 'standard' strategies for both intravenous (iv) and oral rehydration (as they are interlinked as a 'treatment bundle'). Demonstrating that intravenous rehydration is safe in children with SAM will be an important achievement.

Outcome remains poor in children hospitalised with diarrhoea, especially those with moderate and severe malnutrition. There is an urgent need to reappraise both the rehydration guidelines for both SAM and non-SAM owing to the very poor outcomes. Although numerous studies have indicated concerns over clinical assessment of degree of dehydration a number of census statements have considered these including ESPHGAN[20] and NICE[21] guidelines indicating similar definitions for severe dehydration (with NICE indicating signs of shock to be included). Both review groups recognized that volume of 100 mls/kg for deficit replacement is probably correct for severe dehydration (~ 10% loss) but the evidence supporting rate of rehydration is very poorly informed with both rapid or ultra-rapid recommendations superseding a previous recommendation of rehydration over 24 hours. NICE indicated an urgent need for 'RCTs to provide cost

effectiveness and safety of rapid versus slow rehydration'. Our research group has been contacted by a number of agencies (ISARIC, MSF and GOARN from WHO) to advise on recommendations for the management of severe dehydration in malnourished children in both the Ebola and cholera epidemics (as SAM guidelines do not differentiate between cholera and non-cholera for iv rehydration) (personal communication). They are supportive of the research objectives and will remain engaged over the course of the trial. The overarching aim is to generate the relevant evidence for refinement of future guidelines. Potential refinements anticipated include which children benefit from intravenous rehydration, the rate of rehydration and whether children with severe malnutrition should be managed by the same guideline as other children or by a dedicated guideline.

10. Our hypotheses:

For children with SAM with severe dehydration we hypothesize that standard intravenous regime WHO Plan C (100mls/kg over 3-5 hours) used for non-SAM gastroenteritis with severe dehydration will result in better outcomes than the current very conservative SAM rehydration recommendations. In addition, we propose that the rate of rehydration may be critical and hypothesize that 100mls/kg over 8 hours in SAM children will result in fewer fluid related adverse effects than rapid WHO Plan C guideline. We also propose that standard ORS solutions may be equally as effective with fewer side effects than low salt ReSoMal.

11. General Objectives:

To compare the rate and volume of rehydration in children with signs of severe dehydration (see study population) secondary to gastroenteritis on a primary endpoint of 96-hour mortality:

(i) Current standard WHO rehydration protocol Plan C usually used in non-SAM children.
(ii) A slower rehydration regimen using the same total volume (100ml/kg of Ringers Lactate) over 8 hours, irrespective of age
(iii) The current WHO restrictive intravenous rehydration strategy for SAM children.

In children with diarrhoea complicated by moderate or 'some' dehydration (see study population) and as follow on rehydration post-intravenous rehydration in those with severe dehydration whether oral rehydration with

(i) WHO standard oral rehydration solution (ORS) for non-SAM[21] is safer and results in less hyponatraemia and better outcomes compared to
(ii) current recommendation advocating low sodium (ReSoMal) ORS[4]

12. Specific Objectives

a) To examine survival to 96 hours, Day 7 and Day 28
b) To document adverse events, particularly related to cardiovascular compromise and neurological events.
c) To examine the feasibility (and adherence to) each of the strategies proposed
d) Gather a series of clinical and biochemical data on:
    i. Initial assessment of dehydration
    ii. Response to treatment of children by IV rehydration.
e) To inform robust definitions of outcomes for a larger phase III trial

13. Design and Methodology

Study sites:

Mbale Regional Referral Hospital, Soroti Regional Referral Hospital in Uganda, Kilifi County Hospital and Coast General Hospital in Kenya, Maiduguri MSF project in Nigeria, Magaria MSF project in

Niger, Madarounfa MSF project in Niger.

Study design:

A Multicentre Open Phase II trial of efficacy and safety on survival to 96 hours, 7 days and 28 days of rehydration strategies incorporating two strata for management of (A) severe dehydration comparing both rates of rehydration and volume of iv fluid replacement and (B) the composition of ORS for children with some dehydration and for children post iv rehydration.

Study populations

Inclusion criteria:

Children hospitalised with SAM criteria (defined as any of: mid-upper arm circumference (MUAC) <11.5cm, WHZ <-3SD or kwashiorkor)[22], aged 6 months to 12 years, with gastroenteritis (> 3 loose stools/24 hours):

Severe dehydration: Stratum A

Signs of severe dehydration (as per WHO definition two or more of: unable to drink or AVPU <A, sunken eyes or reduced skin pinch (>2seconds) or an inability to take or retain oral fluids), with or without shock.Shock will be defined by the recent 2016 WHO ETAT criteria; a patient with all of the following: cold peripheries with a weak and fast pulse (rate not specified) and a capillary refill time >3 seconds[22].

Moderate/Some dehydration: Stratum B

Defined as two or more of restlessness or irritable, thirsty, sunken eyes or skin pinch goes back slowly(<=2 s).

Exclusion criteria:

Diarrhoea lasting more than 14-days
Known congenital or rheumatic heart disease
Refusal of consent

14. Sampling

Sample size determination.

In version 1.0 the GASTROSAM sample size calculations for both randomisations were based on studies conducted in children with malnutrition and diarrhoea. For the primary endpoint of urine output for the GASTROSAM A stratum this was based on two African studies have reported on urine output (a surrogate for rehydration and perfusion status) in response to intravenous rehydration. Akech *et al*[12] reported persistence of oliguria (urine output<1ml/Kg/hour) at 8 hours was more common in those receiving the WHO regimen with hypotonic solution (mean volume 30ml/Kg, with 9/22 (41%) as oliguric) vs children receiving isotonic Ringers Lactate (mean volume39ml/Kg, 3/25 (12%) as oliguric), p=0.05[12]). In the second study using RL for rehydration oliguria was present in 3/11 (27%) on WHO regime vs 2/9 (22%) standard rehydration fluid-resuscitation[13].

For Version 3.0 we reviewed the literature on mortality which was informed by an physiological observational study (AFRIM) investigating liberal rehydration versus WHO guideline[13]. Overall, mortality in the WHO arm was 9/11 (81.8%) to Day 28 and of these deaths 7/11 had occurred by 96-hours (64% mortality). We therefore considered that this was realistic primary endpoint for this current trial of intravenous rehydration strategies and complete retention in the trial to this endpoint (96 hours survivorship) is highly feasible. On the basis of the available data we estimated a slightly lower mortality of 58 % in the WHO arm (as mortality is often lower in clinical trials) a 30% relative reduction in mortality rate at 96 hours to 41% in the combined liberal arms would have a power of 80% and a 2-sided test with alpha 0.05. This would require a higher number in the intravenous rehydration group 272 (or an extra 136 children from the original sample size). The investigator group, including MSF investigators felt that this was realistic and it would be feasible to enrol ~ 12-15 children per week across 7 sites.

For oral rehydration strategies there have been two studies,both conducted in Asia, examined changes in sodium in response to oral rehydration with ReSoMal, with nofatalities in either trial. In WHO ORS group 1/64

(2%) developed severe hyponatraemia (Sodium≤120mmol/L)vs 3/62 (5%) in those receiving ReSoMal. Sodium levels were similar at baseline in but was lower at 24- and 48-hours in ReSoMal group (p<0.01 and p<0.001 respectively)[14]. A trial comparing ReSoMal vs. hypo- osmolar ORS found a greater proportion of children receiving ReSoMal developed hyponatraemia (15.4% vs.1.9%, p=0.03)[15].

Based on these data we calculated that for the Stratum A randomisation of 272 children would give 80% power (with 1:1:2 randomisation), with 68 to the rapid WHO Plan C arm, 68 to slow rehydration arm (100mls/kg over 8 hours) and 136 to the WHO SAM arm to show a 30% lower 96 hour mortality in the liberal strategies compared to the WHO SAM arm. All children in Stratum A will also be randomised to ORS strategies. In addition i**ncluding 64 children with some dehydration in Stratum B (1:1)** would give >90% power to detect a 3mmol/L difference in sodium levels (assuming mean of 132mmol/L and sd of 7) at 24 hours betweenthe ReSoMal and ORS randomisation (total n=336, 168 per arm (32 some dehydration, 136 severe dehydration).
Overall, the trial will enrol 336 children across the seven sites.

Sampling procedures

All eligible children will be admitted to designated areas consented and, if they agree to participate, randomized to fast orslow arm (treatment allocation will be using cards in opaque sealed envelopes). The following table highlights clinical and laboratory investigations for both those in stratum A and B.

Hours (h) /Days (d)	0*h	8h	24h	Day 3	96 h	7d^	28
Consent and information sheet	X						
Clinical examination (doctor/doctor visit)	X	X	X				
Nurse observation/visit		X	X			X	
Survival Status					X	X	
Vital observations, anthropometry	X	X	X	X		(X)	
Laboratory investigations							
Haematology	X		X			(X)	
Biochemistry (Chemistry and Osmolarity[$])	X	X	X			(X)	
Lactate/Glucose	X	X	(X)				
Malaria slide + /- RDT	X		(X)			(X)	
Blood culture (if microbiological facilities present)	(X)						
HIV testing	X						
Urine (dipstick and save) [#]	X	(X)	(X)			(X)	
Cross match (for transfusion) (red top) if indicated	X						
Stored samples							
Plasma for Cardiac Biomarkers[$]	X	X	X			X	

*at enrolment
(X) optional
^ Day 7 and Day 28 if child discharge and able to return confirmation of survivorship can be done by telephone
# Only for children who are catheterised
[$] only in sites where sample storage is possible

15. Study Procedures

All children admitted with an acute history of gastroenteritis will be screened for study inclusion by the paediatric triage/admission team.

Consent Process

Once eligibility has been confirmed, authorized trial staff will approach parents/guardians to invite their child to take part in the trial. An information sheet will be provided to the parent/guardian in their usual language containing details of the GASTROSAM trial. The sheet will be read aloud to those who are unable to read. The

doctor/nurse will check that the information has been fully understood and parents/guardians will be encouraged to ask questions they may have about their child's participation in GASTROSAM. Where possible, prospective written informed consent will be sought from parents/guardians who will then be asked to sign the Consent Form. If parents/guardians are unable to sign, a thumbprint will be taken in lieu of a signature. A copy of the Consent Form will be given to the parent/guardian, the original placed in the patient's medical notes, and a copy kept in the Investigator Site File.

Treatment Allocation

Following consent, children will be randomly allocated to the treatment arms. Children in Stratum A with severe dehydration will be simultaneously assigned two randomisations (one for the IV rehydration strategy in a 1:1:2 ratio) and one for the oral rehydration strategy (1:1 ratio)). Children in Stratum B will be randomised to oral rehydration strategies (1:1 ratio). See **Trial flow Figure 1.** Randomisation lists will be generated separately for each stratum and kept at the MRC CTU at UCL, London. Opaque sealed envelopes containing the randomized allocation will be prepared before the trial at the Clinical trials facility, KWTRP, Kilifi. These will contain the actual allocation visible only once opened. The cards will be numbered consecutively withineach stratum and opened in numerical order.

GASTROSAM Stratum A

Signs of severe dehydration treatment Arms 1:1:2

- **iv)** **WHO Plan C arm**: Rapid iv rehydration as per WHO Plan C (usually for non-SAM) children (100mls/kg Ringers Lactate (RL) over 3-6 hours according to age including boluses (20mls/kg) for those with shock) n=68
- **v)** **Slow Rehydration Arm**: A slower iv rehydration regimen (100 mls/kg RL given over 8 hours and no boluses).n=68
- **vi)** **WHO SAM arm:** rehydration regime: ORS and iv boluses of RL only for shock (standard of care) n=135

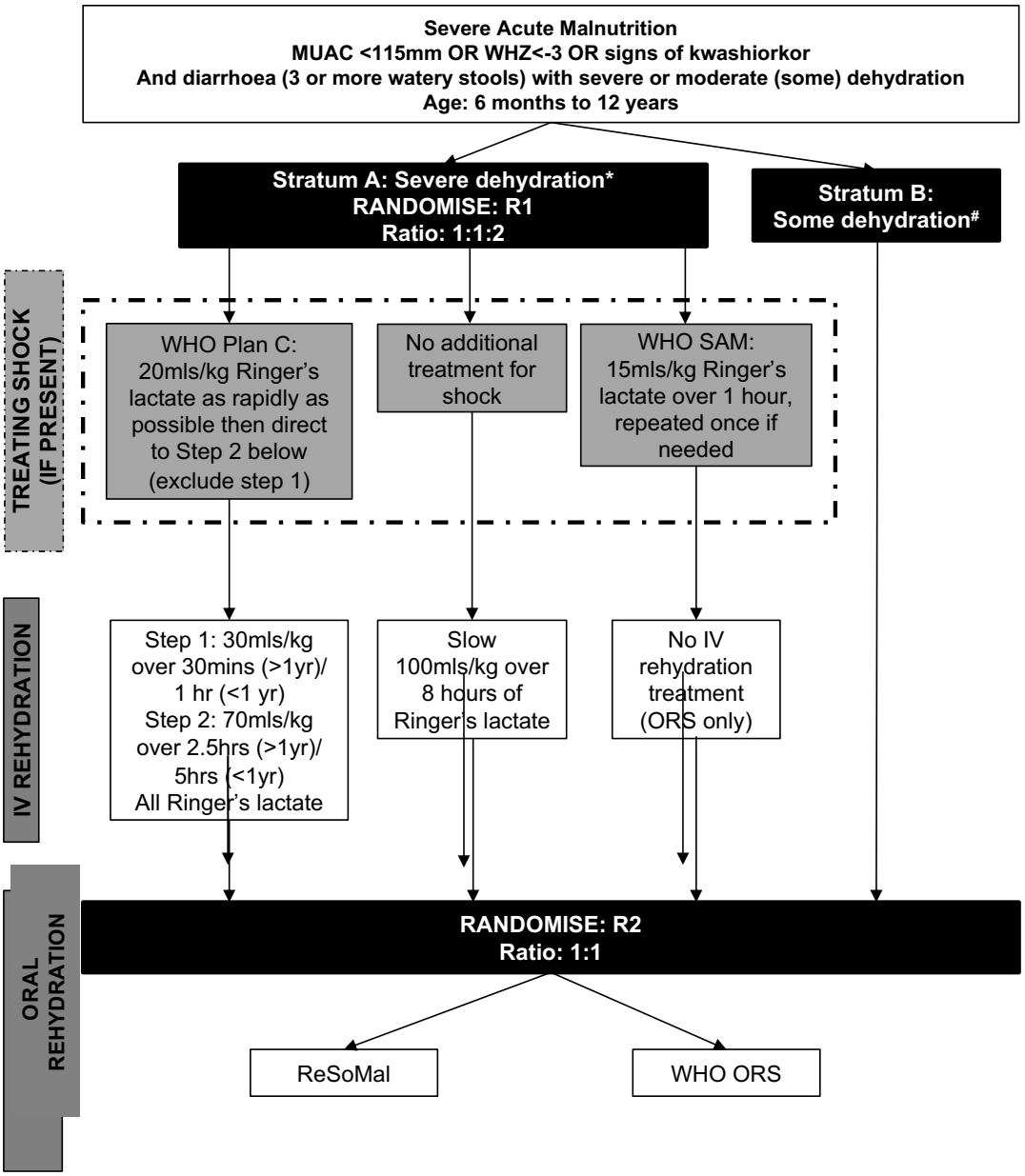
A second (simultaneous) randomisation in this stratum (for all three iv rehydration strategies) will be to one of two oral rehydration solutions for initial (some dehydration) or subsequent rehydration (see below). Children presenting with some (moderate)dehydration (defined as two of restlessness or irritable; thirsty, sunken eyes or skin pinch goes back slow willalso be randomization to one of two oral rehydration solutions (GASTROSAM Stratum B) **(ratio 1:1 for both groups)**

GASTROSAM Stratum B

- **iii)** Standard WHO ORS given for non-SAM (experimental) versus
- **iv)** WHO SAM-recommended low-sodium RESOMAL

Both oral rehydration solutions will be given in accordance with **WHO Plan B oral rehydration regime over 4 hours.** Treatment will be given according to requirements during hospitalisation (and may include continuing or restarting ORS to replace on-going loses or iv rehydration development of severe dehydration).All children can start oral ORS as soon as they are able to take and retain oral fluids, even if before IV rehydration is complete (which is replacing deficit). For children unable to take orally we will consider temporary placement of nasogastric tubes.

Figure 1 Trial Flow GASTROSAM trial protocol (STRATUM A and B)



16. Clinical Endpoints

Primary outcome for Intravenous rehydration: Mortality at 96 hours.
Primary outcome for Oral rehydration strategy: change from randomisation (=0 hours timepoint)) in plasma sodium levels at 24 hours. **Secondary outcomes** Measures assessing safety (evidence of pulmonary oedema or heart failure) during admission; change in plasma sodium levels from completion of iv rehydration (8 hours from randomisation) to 24 hours from randomisation for thosein Stratum A; perturbations of electrolyte abnormalities (severe hyponatraemia <125 mmols/L or hypokalaemia <2.5

mol/L) over 8 hours, weight and MUAC change to Day 3 and Day 7; and Day-28 survival.

If possible children should be catheterized in order to achieve accurate fluid balance calculations. For children who are catheterised we will collect samples of urine at 1 hour, 8hrs, 24hrs and on day-7 to measure urinary osmolality (where laboratory facilities permit) and electrolytes. The urinary catheter can be removed after 8 hours. Urinary catherisation and urine sampling are not mandatory i.e. where there are difficulties in collection of urine for sampling and/or parental discomfort with catheterization then urine collection/catherisation should not be pursued. All children will have a daily weight and fluid balance calculated until discharge (performed at the same time each day). Children will be followed up on Day 7 and Day 28 (after study enrolment (Day 0)) to confirm survivorship status. Where children are able to attend for clinical follow up their survival status will be confirmed by telephone or community field worker. Children attending follow up will be reviewed by a clinician, have their weight, observations recorded., a further blood sample (biochemistry, renal function and where laboratory facilities permit measurement of cardiac enzymes Day 7 only). We will also collect one further urine sample for urinary electrolytes (only for those children who were originally catheterised and samples stored).

Clinical and haemodynamic (vital signs) responses will be monitored every 30 minutes for the first 2 hours then hourly until 8 hours, and 4-8 hourly up to 24 hours and then 24 hourly until discharge, as will pre-specified SAEs of interest:

a) new onset seizures or worsening conscious level
b) signs of pulmonary oedema
c) and/or cardiac failure after the initiation of intravenous rehydration

Time to tolerate oral fluids/feeds and maintenance of normal fluid balance and time to discharge will also be collected.

Routine blood samples will be collected at admission and 24 hours. At 8 and 24 hours post enrolment an additional 2-4 mls blood sample will be collected for biochemistry (for electrolytes and renal function and where laboratory facilities permit measurement for serum and urine osmolality, and cardiac enzyme analysis). All children will have their HIV assessed routinely at hospital admission, in accordance with national guidelines.

Serious Adverse Events and interim analyses

SAEs will be reviewed immediately by a designated physician (SAE reviewer) and reported to the appropriate ethics and regulatory committees within one week. Severe adverse events will use the standardized definitions and externalreview process of these events will be carried out using the same criteria as were used in the FEAST trial. All relevant adverse events are reported in the case report form (CRF) and SAE form. The reporting procedure is captured within the safety reporting SOP. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance (Kilifi). The Chief investigator will inform the Trial Steering Committee (TSC) and Data Safety and Monitoring Board (DSMB) for review on a regular basis (as deemed necessary).

Data Safety and Monitoring Board (DSMB)

An independent DSMB will be set up to review data on enrolment, safety, adherence to the trial protocol and efficacy at regular intervals and in strict confidence. The DSMB will make recommendations to the TSC as to the continuation of the trial. The DMC will be comprised of a chair and three other independent members.

Membership of both of these committees are in the DSMB charter.

17. Clinical Management

Following correction of severe dehydration (based on a review of WHO clinical signs and observations), children will be assessed for their ability to take oral rehydration or feeds. Children who are able to take andretain oral fluids/feeds and who are in neutral or marginally positive fluid balance (both input and output willbe measured) will be considered as satisfactorily rehydrated.

All children will be offered oral rehydration fluids alongside their IV rehydration regimen, in GASTROSAM thiswill follow randomised treatment allocation. Each child will have an input-output monitoring chart i.e. including urinary catheter volumes (if catherisated) and diaper weights, to document the volumes that children in both arms are drinking and retaining as well as defining clinical end-points that will be used to guide when to stop IV fluids in future studies. For the purposes of this study, each child will aim to complete their allocated IV fluid hydration regimen.

Management of potential complications

Irrespective of which arm of the trial patients are included in, the treatment of life-threatening side effects would be assured. This would include prospective monitoring for pulmonary oedema (to be treated with oxygen and diuretics), signs of cardiac failure and signs of cerebral oedema. The development of severe hypotension in any group would be treated with a fluid bolus therapy to restore systolic blood pressure. Mechanical ventilation is not available any of the hospital which largely reflects the typical situation in mosthospitals in sub-Saharan Africa. In the case of a child who develops clinical signs and fluid overload: the management plan is to stop IV fluids; and, if there are clear signs of pulmonary oedema, to administer IV frusemide and oxygen; monitoring the child closely with hourly observations until stable and further fluid management to be administered orally (or via NGT if the child is unable to take fluids orally)

If, after the initial rehydration regimen is completed, there are ongoing significant GI fluid losses, this will bemanaged according to clinical signs preference which, if severe dehydration or shock develops may include one repeat of intravenous regime previously allocated protocol and then, after this, personalize fluidmanagement to take account of input/output.

18. Research Physiological measures

Myocardial Function

In a selection of children (in Kilifi, Kenya), we aim to study in greater depth myocardial, haemodynamic responses and microvascular perfusion to the fluid strategies using non-invasive ultrasonography and echocardiography (Vivid q N BT12 Echo Ultrasound Machine, KEMRI-WTRP). Echocardiography data collection will be standardized; 80 frames/sec in the parasternal and apical windows at admission (0 hr), 1, 4, 8 and 24 hours.Two-dimensional grayscale three-beat ECG gated loops will be obtained in the apical long axis, apical 4- chamber, apical 2-chamber, parasternal short axis (at basal, mid-papillary and apical levels) and parasternal long axis views and stored for retrospective/offline analysis of ventricular systolic and diastolic function. Standard colour Doppler imaging with pulsed and continuous waves will be used to quantify the maximal flow velocities, pressure gradients and regurgitation (if any) across the aortic, pulmonic, mitral and tricuspidvalves. Echocardiography is non-invasive and does not involve any pain or discomfort to the child. It will take approximately 15minutes.

19. Ethical Considerations

Ethical approval will be sought from Mbale Regional Hospital Research Ethics committees, Scientific Ethics Review Unit (SERU)-Kenya Medical Research Institute and from MSF-Ethical Review Board, Niger and the Comité National d'Ethique et de Recherche Scientifique from Niger, National Health

Research Ethics Committee from Nigeria, from Imperial College Research Ethics Committee(ICREC), who is the sponsor of the study.

Risks:

"First, do no harm." The study will be performed in patients who may potentially benefit from the treatment.The risks of cannula insertion and 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.

Whilst there is a concern that liberal fluid rehydration may cause heart failure, our recent publication on myocardial function in this population given rehydration did not show this resulted in heart failure. Children enrolled in GASTROSAM will be very closely monitored, with using the same systems for adverse event reporting used in the FEAST trial and the transfusion (TRACT) trial- that examined more liberal volumes of fluid and blood respectively than was currently recommended. Blinded SAEs (removing all references to intervention arm) will be independently adjudicated by an endpoint review committee.
In neither FEAST nor the TRACT trial were any concerns raised by the data monitoring committee that moreliberal volumes were causing fluid overload. GASTROSAM will be conducted in 3 of the trial sites for FEAST and TRACT and are familiar with the conduct of trials in critically sick children. All study teams will undergo detailed training and included in the manual of operations will be clear guidelines on what signs to look for and how to treat suspected fluid overload or heart failure, which were developed and implemented in the FEAST trial.

Benefits.

All patients will be closely monitored so that clinical deteriorations can be identified at the earliest opportunity and appropriate therapy initiated. In general, the trial sites in Africa have considerable experience with this population and this will serve to minimise the risks to the patients and the trial. Prior to the start, the dedicated study teams will undergo detailed training on general management of SAM and its complications and receive very detailed training on fluid management. This will be included in the manual of operations which will provide clear guidelines on what signs to look for and how to treat suspected fluid overload or heart failure, which were developed and implemented in the FEAST trial. We believe this will afford all children enrolled in the trial with a higher quality of care.

Patient Consent

Prospective written, informed consent will be sought from parents or guardians of children who are considered to be sufficiently stable. Parents or guardians will be given an information sheet in their usual language containing details of the GASTROSAM study. These will be translated into to local languages, and then back translated (to ensure details are correct) prior to piloting before the initiation of the trial. The sheetwill be read aloud to those who are unable to read. Parents and guardians will be encouraged to ask questionsabout the trial prior to signing the consent form. Consent will include permission for the collection of admission and follow-up blood samples for later aetiological investigations. The rights of the participant to refuse to participate without giving reasons must be respected.

A number of children will present as emergencies where delay in study enrolment, and thus treatment, will not be practical or indeed humane. We will use a modified form of deferred consent; used in the FEAST trial we developed and received ethical approval for. It proposes to use a 'two-stage' consent process in this circumstance [23, 24]. Verbal assent will be sought from parents or

guardians by the admitting medical team, if it is considered that the full consent process would significantlydelay treatment allocation, and consequently could be detrimental to the child's health. Full consent will be sought once the child's clinical condition has been stabilized.

Caregivers will be provided with a brief verbal description of the trial and will be given the opportunity to "opt out" of clinical research. The clinician will later sign the verbal assent form, which will be filed with the consent form. If consent is withdrawn later no data from the subject will be used. Social science study of the consent processes used in FEAST found this tobe acceptable to parents and health-care workers. As in the FEAST trial, if following an assent process a childdied prior to full written consent, full consent would not be sought. This was process of emergency consent was approved (by multiple ethics research committees for FEAST and has been subsequently approved for use in a transfusion trial in Uganda and Blantyre)

Community Engagement Strategy and feedback

Where possible community engagement will be through regular meetings with the local communities involving hospital community representatives. At these meetings, information and feedback will be given and received. Each site would either use their existing Community Advisory Board (CAB) or form a specific patient liaison group to feedback concerns and questions from the community and hear about the latest developments in the trial and the wider scientific community, where possible. Dialogue with these groups will be maintained through regular briefing meetings during the course of the trial and will be a standing item at each TSC meeting.

Public engagement: Results from this trial will be disseminated locally through community meetings and national meetings with the wider healthcare professional community. These systems have been developed for dissemination of MRC FEAST trial results, and we plan to extend these with the ongoing TRACT trial and to this proposed trial (GASTROSAM).

National policymakers: The PIs will discuss with their Ministry of Health about the proposed trial. A summaryor briefs will be produced to highlight the trial results and next steps required to inform rationale evidence-based guidelines.

International policymakers: We have already had teleconferences with members of the epidemic consortium ISSARIC and WHO GOARN (Global Outbreak Alert and Response Network), UK Rapid Response Teams and MSF International Coordinator to share the systematic reviews we undertook in preparation of the study outline proposed [9,10]. The current rehydration management guidelines for children with severe malnutrition are under intense speculation currently as a potential reason for the poor outcome in the current cholera epidemics in Africa (no report published). Through these connections will seek meetings withWHO, UNICEF and other international policy makers to discuss the results and subsequent trial plans.

Confidentiality

All clinical data will be held confidentially. Participants' identification data will be collected as part of the trial follow-up procedures. The KCTF and MRC CTU will preserve the confidentiality of participants taking part, which will comply with requirements for data protection in the countries where the research is being conducted. All data will be anonymised prior to presentation or publication of any results.

Data Sharing

After completion of the study, requests for data access from researchers outside the study team will be considered by the trial management team and clinical trials unit (Data Governance

Committee), and whereindicated, requestors will be asked to develop scientific protocols for approval of secondary analyses. The potential to share data will be included in the participant Information and Consent Form.

20. Data Management:

(a) Data Storage

All clinical and laboratory data will be recorded in the CRF and stored with a unique serial number identifier.Data will be entered onto Open Clinica. Prof Maitland's team at KCH will enable CRF and database development. All data will be regularly backed up and backup copies stored both on and off site. Paper records will be archived in locked cabinets. These cabinets will have limited access with prior authorisation.

(b) Data Management and Statistical Analysis

The data will be examined for inconsistencies during the trial by the statistician and fed back to study sites for corrections following GCP procedures.

The primary analysis for the trial will describe baseline parameters (stratified by study stratum and arm), describe time to tolerate oral fluids/feeds and maintenance of normal fluid balance and time to discharge, and compare primary and secondary endpoints by trial arm. The primary analysis will be by intention to treat.The primary endpoint of 96-hour mortality will be compared between arms with a chi-squared test assuming unequal variances between the arms, and comparing the WHO SAM arm to the other two arms (WHO Plan C and Slow rehydration arm) combined.

A secondary analysis will be pair-wise comparisons of urine output using a t-test between each arm and thestandard of care (WHO SAM arm). The primary endpoint for the oral rehydration comparison of change in sodium at 24 hours will be analysed using normal linear regression, adjusting for baseline (measured at randomisation), with appropriate transformations if necessary.

The secondary endpoint of change in sodium at 24 hours from post-iv levels for those in stratum A will also use normal linear regression, adjusting for the value measured after the end of their iv rehydration. Changes in weight, MUAC and electrolytes will be analysed using normal linear regression (potentially on log- transformed data), and generalised estimating equations to jointly model changes during admission and at day-7. Analysis of adverse events, including mortality, evidence of pulmonary oedema and heart failure, will use time to event methods through day 28 counting in hospital death as a competing risk. Adverse events will also be summarised by body system. Analysis of perturbations of electrolyte abnormalities (severe hyponatraemia (<125mmols/L) or hypokalaemia (<2.5mol/L) will use time to event methods through day 7 counting in hospital death as a competing risk.

(C) Intellectual Property

Any Intellectual property rights that arise from the work will be safeguarded according to the KEMRI IPR Policy of 2015 and the Industrial Property Act of 2001, sections 32, 58 and 80. The scientific and intellectualcontributions of all persons involved in the research will be appropriately acknowledged in all publications and presentations arising from the work.

20 Informed consent form

Patient information and consent form, including verbal assent form are attached separately.

21 Data collection tools

Please see attached Case Report Forms

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Insert Institution/hospital: **Patient Information and Consent Form**

STUDY TITLE: **Gastroenteritis Rehydration Of children with Severe Acute Malnutrition. (GASTRO-SAM)**

LAY TITLE: **Giving fluids to children admitted with Malnutrition and diarrhoea.**

Institution	**Investigators.**
Insert Institution/hospital	
Imperial college UK	Prof. Kathryn Maitland.

Introduction:

Your child has been examined by the doctor and found to have severe malnutrition plus signs of severe fluid loss (called dehydration) as a result of an illness which causes diarrhoea and vomiting called gastroenteritis. We need to admit your child to a hospital, take some blood tests and treat them to replace these losses. Currently, the country is following the World Health Organization (WHO) recommendation of giving Oral rehydration solution (ORS) and ONLY giving fluids through the veins for those with danger signs. WHO also recommends fluids through the veins if the patient cannot take oral fluids.

Who is carrying out this study?

This research is being carried out by insert institution/hospital which is a governmental or non-governmental 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 research, we aim to find out what is the best way to replace the fluid losses, whether we need to replace the fluid losses orally or through the veins either rapidly or more slowly. We also intend to find out for those with moderate dehydration (following resolution of severe dehydration), whether the currently recommended solution ReSoMal is better than standard ORS which is the solution used in those without severe malnutrition.

We aim to enroll 336 participants in 7 sites in 4 countries in Africa, 2 in Uganda, 2 in in Kenya and Medicine Sans Frontières centres in Nigeria and Niger.

What will it involve for me/my child?

Participants will be selected depending on how they present (Group A with severe dehydration, Group B for those with moderate dehydration to one of three options below:

Group A

i) Rapid fluids by a drip using 100mls/kg of a fluid called Ringers Lactate over 3-6 hours
ii) A slower rehydration by drip (100 mls/kg Ringers Lactate) given over 8 hours
iii) WHO rehydration regime: ORS and with the drip (Fluids through the vein) being used for those with danger signs. (current Standard of care)

Group B

Following resolution of severe dehydration and for those with moderate dehydration, the participants will receive one of the two options below oral fluids

i) Standard WHO ORS given for non-malnourished (experimental) versus
ii) WHO low-sodium rehydration solution called RESOMAL for children with severe acute malnutrition.

Each of the types of treatment a child is given will be decided by chance.

- All children will be closely watched to decide whether to make any changes to treatment. This monitoring will be through regular checks by the nurses. In this study, we will take a blood sample on admission and at 24 hour (one day) after admission. The sample when your child is admitted we will take 2 teaspoons? to help understand how sick your child is and how to treat them. The second sample after one day be 1/2 teaspoon will help check on whether your child is recovering
-
-
- We will take daily measurements of weight and MUAC to check on the child's progress from enrollment until discharge with more focus on 3 days measurements.
-

- Where children are unable to take fluids by mouth we will insert a tube through the nose into the stomach. This procedures will be done by well trained staff using clean equipment to minimize risk of infection.

- Where possible we will also ask you to come back to the hospital/clinic for follow up to check on your child's progress on day 7 and day 28. This will include measuring your child's weight and record other observations. If you are unable to attend these visits we will call you by phone to check on how your child is .

-

Are there any risks or disadvantages to me/my child of taking part?

- Our priority for every participant is his or her well-being.

- Giving fluids by drips is extensively used in children in insert country and other parts of the world. We will be monitoring your child very closely. If for any reason the doctor thinks that it is not in your child's best interest to be in the trial, then s/he will not be enrolled in the trial but will be given normal standard of care. There are no costs for being included in the trial.

- Taking blood from the arm causes a small amount of pain, swelling, discomfort and minimal chance of infection. If this happens, we will provide treatment. The amount taken is too small to affect your child's health.

- For children who will come back to the clinic for routine health examination so we can find out how your child is doing. We will pay for your transport to hospital and back so you can attend these visits (depending on where you come from and the amount you spend on public transport). We will also compensate you for study related out of pocket expenses while attending this clinic visit at the rate of insert amount for each follow-up visit. During the follow up visits, we will treat any illnesses we find your child has or arrange a referral to appropriate clinic or hospital if need be. These referrals will be done through the usual insert country government procedures using insert specific levels/ e.g district, county, or regional government resources e.g., ambulance and nurses. We expect the follow up visits will take approximately an hour excluding travel time.
- An independent committee will monitor this research continuously to ensure participants safety and rights are respected at all times.

Are there any advantages to me/my child for taking part?

Your child will get close observation and our usual standard treatments during the trial, and by taking part your child may help us improve the care of children who have severe dehydration and Severe Acute Malnutrition in the future.

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 your child receives the normal treatment given to children who are not in the trial.

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. 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?

Individual names will be removed from all samples and replaced by codes, to ensure that samples can only be linked to the participants by people closely concerned with the research. All the research tests that will be done on the sample will be done here in insert institution/hospital.

After the research, a small portion of the blood sample will be stored in our laboratories in insert institution/hospital.
In future, new research may be done on these samples. Future research must first be approved by the national independent ethics committee to ensure participants' rights and safety are respected

Who will have access to information about 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 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.

In order to do this study, we will share anonymized individual and summary information we collect or generate with other collaborators involved in the study in ways that do not reveal individual participants' identities.

Who has approved this research?

All research at insert institution/hospital must be approved before it begins by several national, local, and international committees who look carefully at planned work. They must agree that the research is important, relevant to insert country and follows nationally and internationally agreed research guidelines. This includes ensuring that all participants' safety and rights are respected.

What if I have any questions?

You are free to ask me or any of our staff any questions about this research. If you have any further questions about the study, you are free to contact the research team using the contacts below:

Insert contact details

If you want to ask someone independent anything about this research, please contact:

Insert contact details

And

Insert contact details

Insert Institution/hospital consent form for:

Giving fluids to children admitted with Malnutrition and diarrhoea

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. And I agree to allow my child to take part in the research.

Please initial the sentences that reflect your choices, and then sign below:

_____I do wish to be notified by investigators in the event of research findings of possible importance to my family members or myself. **Yes** □ **No** □

_____I agree that the study team use the identifier that I have provided (telephone number, country ID number, etc.) to locate me in the future if need be. **Yes** □ **No** □

I agree to my child's samples being stored and used for future research **Yes** □ **No** □

understand that I can change my mind at any stage, and it will not affect 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 parent/guardian and that informed consent was freely given by the parent/guardian.

Witness' signature:_____**Date** _____

Witness' name: _____**Time** _____

(Please print name)

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

_____

I have followed the ethical procedure to obtain consent from the parent/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