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

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Statistical Analysis Plan version 4.0

GASTROSAM Statistical Analysis Plan

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Author	**Position**	**Signature**	**Date**
Roisin Connon	Delegated Statistician, MRC CTU at UCL	DocuSigned by: Roisin Connon 1671D28A21C9468...	17-Dec-2024
Reviewed by			
Elizabeth George	Trial Statistician, MRC CTU at UCL	Signed by: Elizabeth George B9A8483524244412...	18-Dec-2024
Approved by			
Professor Kathryn Maitland	Chief Investigator, Imperial College	DocuSigned by: Kath Maitland 4FEBBA0BB1BD4CC...	17-Dec-2024

Revision history

Version	Author	Date	Reason for Revision
Draft 0.1	Roisin Connon	29Jan2020	Roisin Connon first draft
Draft 0.2	Roisin Connon	13Mar2020	Incorporated Sarah Walker's comments on first draft
Draft 0.3	Roisin Connon	31Mar2020	Incorporated Lizzie George's comments on v0.2
Version 1.0	Roisin Connon	24Apr2020	Further comments from KM and SW
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Draft 1.2	Roisin Connon	27Apr2023	Updated following comments from EG
Draft 1.3	Roisin Connon	10May2023	Updated following comments from KM
Draft 1.4	Roisin Connon	24Aug2023	Updated following review by JT (DMC statistician).
Version 2.0	Roisin Connon	6Sep2023	Accepted all changes from v1.4.
Draft 2.1	Roisin Connon	18Oct2023	Corrected typo in section 8.6, updates to sections 8.6, 8.7 and 8.8.
Draft 2.2	Roisin Connon	10Nov2023	Edits to missing data section 6.4.
Draft 2.3	Roisin Connon	17Nov2023	Update section 8.6 following comment from JT.
Version 3.0	Roisin Connon	27Nov2023	Accepted all changes from v2.3.
Draft 3.1	Roisin Connon	06Nov2024	Correction to population summary measure for estimand in section 4.1. Removed summary of grade 3/4 adverse events and added additional analyses in section 8.8.

Draft 3.2	Roisin Connon	21Nov2024	Update following comments from KM.
Draft 3.3	Roisin Connon	9Dec2024	Updated definition of dehydration is section 7.
Version 4.0	Roisin Connon	17Dec2024	Accepted all changes from draft 3.3 and upversioned.

Contents

1 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**.** A third of the fatalities occurred <7 days following hospitalisation and nutritional status is an important factor in outcome. Improvements in early management may therefore be critical for improving outcome.

The current WHO recommendations for rehydration of children with severe acute malnutrition (SAM) and signs of severe dehydration are very conservative, with intravenous (IV) rehydration restricted only to those with advanced shock. Recent systematic reviews have found no evidence of fluid overload or heart failure with less stringent fluid resuscitation.

GASTROSAM aims to reappraise these recommendations and evaluate 'standard' strategies for both IV and oral rehydration. Demonstrating that intravenous rehydration is safe in children with SAM will be an important achievement.

1 Trial objectives and hypotheses

1.1 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 is safer and results in less hyponatraemia and better outcomes compared to
(ii) current recommendation advocating low sodium (ReSoMal) ORS

1.2 Hypotheses

For children with SAM with severe dehydration we hypothesize that standard intravenous regime WHO PlanC (100mls/kg over 3-5 hours) used for non-SAM gastroenteritis with severe dehydration will result in betteroutcomes 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 willresult in fewer fluid related adverse effects than rapid WHO Plan C guideline. We also propose that standardORS solutions may be equally as effective with fewer side effects than low salt ReSoMal.

2 Trial design

2.1 Design and outline

GASTROSAM is a multicentre open Phase II trial with a partial factorial design enrolling children aged 6 months to 12 years with severe acute malnutrition (SAM) hospitalised with gastroenteritis and signs of

dehydration. There are two strata within the trial. Stratum A consists of children with severe dehydration, who are randomised to one of three IV rehydration regimens and one of two oral rehydration regimens. In Stratum B, children with moderate or 'some' dehydration are randomised to an oral rehydration regimen only. Randomisation is stratified by site. Both the IV and ORS comparisons will test for superiority.

The IV rehydration regimens are:

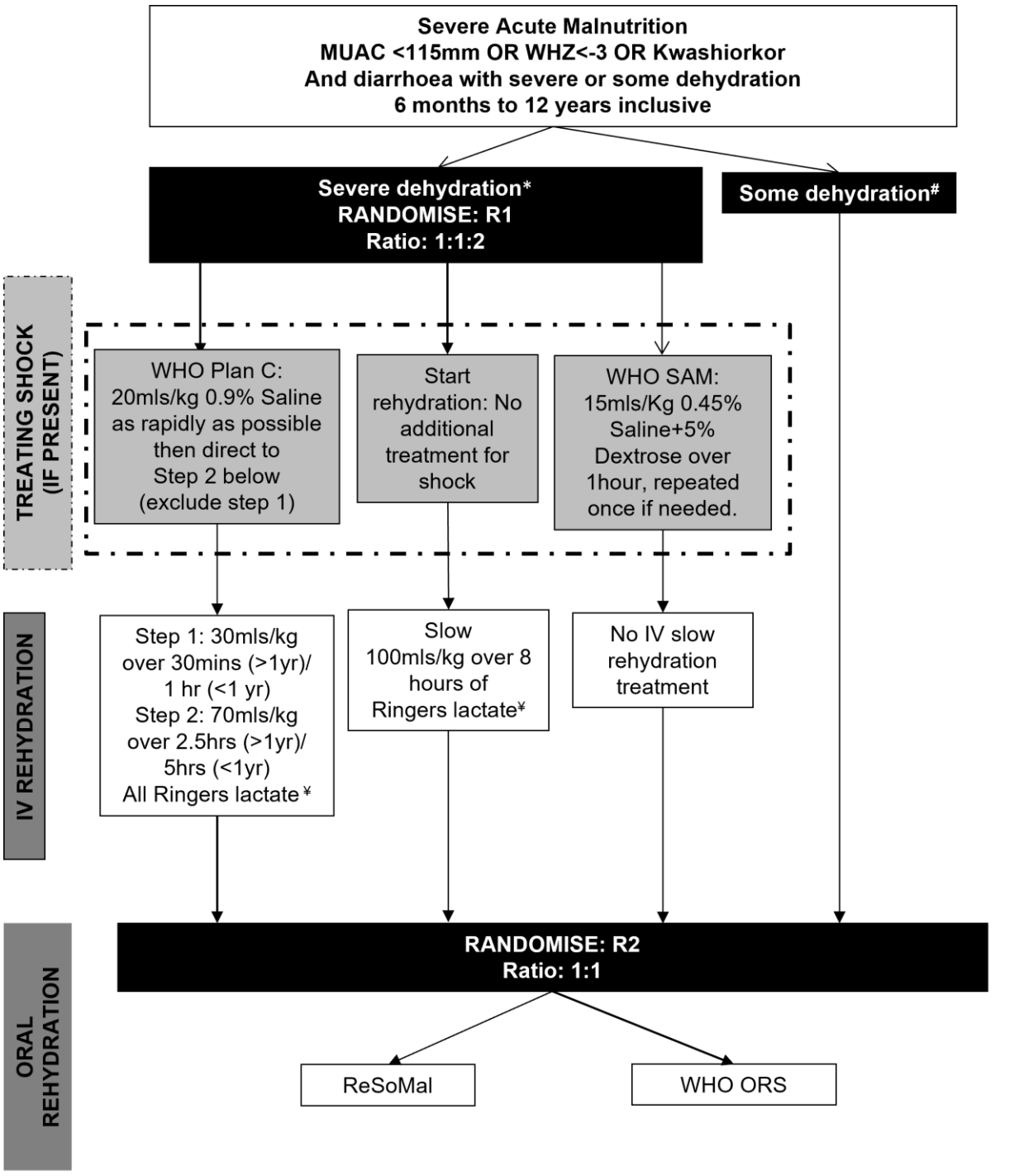
(i) **WHO Plan C**: rapid IV rehydration as per WHO Plan C (usually for non-SAM) children (100 mls/kg Ringer's Lactate (RL) over 3-6 hours according to age including boluses (20 mls/kg) for those with shock)
(ii) **Slow rehydration**: A slower IV rehydration regimen (100 mls/kg RL given over 8 hours and no boluses)
(iii) **WHO SAM**: ORS and IV boluses of RL only for shock (standard of care)

The oral rehydration regimens are:

(i) **WHO ORS:** standard oral rehydration solution (ORS) usually prescribed for non-SAM children
(ii) **ReSoMal:** current recommendation advocating low sodium

2.2 Trial schema

The trial design is summarised in the scheme below.



Assessment of severity of dehydration as per WHO 2013 Pocketbook
*All children receiving IV fluids for severe dehydration (R1) will also be randomised as per 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.
¥Ringer's lactate/5% Dextrose can be used in place of Ringer's lactate

2.3 Population

Eligibility for the trial is based on the child meeting all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

- Aged 6 months to 12 years
- SAM defined as any of:
    - Mid-upper arm circumference (MUAC) <11.5cm
    - Weight for height z-score (WHZ) <-3
    - Kwashiorkor
- Gastroenteritis (>3 loose stools per day)

Inclusion criteria for GASTROSAM A (severe dehydration):

- Signs of severe dehydration as per WHO definition, two or more of:
    - AVPU < A
    - Sunken eyes
    - Skin pinch goes back slowly (>2 seconds)
    - Unable to take or retain oral fluids

Inclusion criteria for GASTROSAM B (moderate or some dehydration):

- **Two or more of:**
    - Restless or irritable
    - Thirsty
    - Sunken eyes
    - Skin pinch goes back slowly (≤2 seconds)

Exclusion criteria:

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

3 Sample size

The sample size for version 3.0 of the protocol is 336 children in total (272 with severe dehydration and an additional 64 with some dehydration). Details of the sample size calculation are given in section 14 of the protocol.

4 Estimands

4.1 Primary estimand for IV rehydration comparison

Treatments	The primary comparison is between the WHO SAM rehydration regimen, and the Slow and WHO Plan C regimens combined. Regimens are defined in section 2.1.
Population	The population is children aged 6 months to 12 years with gastroenteritis and severe dehydration in Kenya, Uganda, Niger and Nigeria that meet the inclusion/exclusion criteria for strata A defined in section 2.3.
Endpoint	Mortality at 96 hours
Population-level summary measure	Risk ratio
Intercurrent events	
Any deviation from randomised strategy	Treatment policy

4.2 Primary estimand for ORS comparison

Treatments	The comparison is between WHO ORS and ReSoMal.
Population	The population is children aged 6 months to 12 years with gastroenteritis and severe or some dehydration in Kenya, Uganda, Niger and Nigeria that meet the inclusion/exclusion criteria for either strata A or B defined in section 2.1 and who survive up to 24 hours from randomisation.
Endpoint	Change in sodium levels from baseline to 24 hours
Population-level summary measure	Mean difference
Intercurrent events	
Any deviation from randomised strategy	Treatment policy
Death before 24 hours	Principal stratum

5 Outcome measures

5.1 Primary outcomes

The primary outcome for the intravenous rehydration comparison is mortality at 96 hours.

The primary outcome for the oral rehydration comparison is the change in sodium levels from baseline to 24 hours.

5.2 Secondary outcomes

- Pulmonary oedema or heart failure within 28 days
- Change in sodium levels from post-IV levels to 24 hours for those in Stratum A
- Change in weight from baseline to day 7
- Change in MUAC from baseline to day 7
- Day 28 survival
- Severe hyponatraemia (<125 mmol/L) or hypokalaemia (<2.5 mmol/L)
- Urine output (mls/kg/hour) from 0 to 8 hours

6 Analysis Principles

All analysis will be performed using Stata software (updated and validated).

6.1 Statistical testing

The primary analyses comparing IV rehydration strategies will compare the standard of care (WHO SAM) vs the other two intervention arms combined. Pairwise comparisons will also be performed between WHO SAM and each intervention arm individually.

All statistical tests will be two-sided with a significance level of 0.05. Estimates will be presented with 95% confidence intervals. No adjustment to p-values or confidence intervals will be made to allow for testing multiple secondary outcomes.

6.2 Analysis population

The primary analysis will be intention to treat. Children for whom assent was given but subsequent full consent refused will be excluded. Children for whom assent was given but then absconded (so full consent was not obtained) will be included.

6.3 Timing of analyses

Interim analyses will take place while the trial is ongoing, with reports reviewed by the Data Monitoring Committee (DMC). The frequency and timing of interim analyses will be determined by the DMC.

The final analysis will take place when all participants have completed their 28 day follow up visit, or are known to have died, withdrawn from the trial or been lost to follow up.

6.4 Missing data

Analysis of primary and secondary outcomes will be based on observed data only, unless the endpoint has missing data for >10% of children, in which case multiple imputation will be used to impute the missing values, separately within each randomised group in each strata.

6.5 Stopping guideline

There are no formal stopping rules for GASTROSAM is a small phase II trial and rules based on very low p-values are unlikely to be useful. The Data Monitoring Committee (DMC) will review data by arm for safety and efficacy regularly during the trial and will make their recommendations to the TSC based on all information provided to them as well as any relevant external information.

7 Derivation of data to be analysed

Time

Time will be calculated from randomisation for primary analyses.

Definition of baseline

Baseline values for all measurements will be those recorded on the screening and eligibility form, baseline assessment form or samples taken at admission on the blood test results form.

Visit windows

Analysis of outcomes at day 7 will allow values taken within the window of 5 to 10 days from randomisation, while for day 28 a window of 7 days either side will be allowed. Any values outside of these windows will be excluded from the analysis. If there are multiple measurements that fall within the window, the nearest to the expected date will be used. If there are two measurements are equally close to the timepoint, the earliest measurement will be used.

Standardisation of anthropometry

Weight and MUAC will be standardised for age and z-scores calculated using WHO Reference 2007 Charts.

The WHO charts only have reference values for weight-for-age for children up to 10 years, which does not cover the full age range of children included in the trial. Children older than 10 years will be excluded from analysis using weight-for-age z-scores.

The WHO charts have reference values for MUAC-for-age for children aged between 3 months and 5 years. For children aged above 5 years z-scores will be calculated from reference data published in Mramba 2017[1].

Definition of censoring

For time to event analyses children who have not had an event will be censored at the earlier of 28 days from randomisation or date last known alive.

Truncation of data

All weight-for-age and MUAC-for-age values during the trial will be visually inspected. Outliers four standard deviations from the mean at each time point will be set to missing, after querying with site. Values larger than the 99th percentile or smaller than the 1st percentile across all time points will be compared to other values in the child's records. Any large deviations (greater than two standard deviations of values at that timepoint) from prior or subsequent measurements will be truncated to the 99th or 1st percentile before analysis. Any truncated values will be back transformed to the original scale.

Free text

Several fields are free text for other conditions. These will be categorised based on self-evident corrections, e.g. spelling. Adverse events and hospitalisations will be coded consistently (e.g. anaemia and malaria will be equivalent to malaria and anaemia) in consultation with the Chief Investigator.

Transformation of continuous measures

Normality of all continuous measures and their change from baseline will be assessed using the Shapiro-Wilk test. Box-Cox transformations of the original absolute measurements will be used in the case of gross ($p<0.0001$) deviations.

Definition of shock

Episodes of shock will be identified based on the WHO definition: cold peripheries, weak pulse and a capillary refill time >3 seconds.

Assessment of dehydration based on weight

Children will be categorised as having 'moderate' or 'severe' dehydration by comparing the weight at randomisation to their weight at day 1 as an estimate of their pre-illness weight. 5% lower weight at baseline will be classed as moderate dehydration, and 10% as severe.

8 Analysis details

All analysis will be included in the final report, and all except for the items listed in italics will be included in reports for the DMC.

8.1 Enrolment and eligibility

- Enrolment over time: plot by calendar month and site
- Recruitment tabulated by site and strata, n (% of recruitment per site)
- Eligibility: number and reasons for any children randomised in error and excluded or ineligible children included in the analysis

8.2 CONSORT diagram

IV rehydration (Stratum A)

- Number assessed for eligibility, number and reasons for ineligibility
- Number randomised to each arm and number who received IV rehydration
- Number lost to follow up by 96 hours by arm
- Number with vital status known at 96 hours

Oral rehydration (Strata A and B)

- Number assessed for eligibility, number and reasons for ineligibility
- Number randomised to each arm
- Number who started ORS by arm
- Number died, lost to follow up by 24 hours by arm
- Number included in analysis

8.3 Baseline characteristics

The following baseline characteristics will be summarised by the specified statistics. These will be presented by strata (GASTROSAM A and B). Variables will be presented by randomisation if there is a difference between randomised groups of $p \leq 0.05$, used as a flagging device for imbalance and expected for 1 in 20 characteristics by chance, with p-values from Kruskal-Wallis tests, chi-squared tests or Fisher's exact test if cell values are small.

- Sex: n (%) male, female
- Age at admission (months): median (IQR)
- Weight (kg), weight-for-age z-score: median (IQR)
- MUAC (cm), MUAC-for-age z-score: median (IQR)
- Axillary temperature (°C), respiratory rate (bpm), oxygen saturation (%), heart rate (bpm), capillary refill time (s), systolic blood pressure (mmHg), diastolic blood pressure (mmHg): median (IQR)
- Fever (axilliary temperature >37.5°C), hypothermia (axillary temperature <35.0°C), tachypnoea (respiratory rate >40 bpm), hypoxia (oxygen saturation <90%), tachycardia (heart rate > 160

bpm at age <12 months; >120 bpm at age 12 months to 5 years), bradycardia (heart rate <80 bpm), prolonged capillary refill time (≥3 seconds), moderately severe hypotension (systolic blood pressure 50-75 in children aged <12 months; 60-75 if aged 1-5 years; 70-85 if aged >5 years): n (%) yes, no

- Temperature gradient, weak pulse, cold peripheries, WHO-defined shock: n (%) yes, no
- Consciousness level: n (%) alert, prostrate, coma
- Severity of dehydration based on weight: n (%) moderate, severe

Severity criteria

- AVPU, n (%) A, V, P, U
- Restless or irritable, sunken eyes, return of skin pinch, unable to take or retain oral fluids, thirsty: n (%) yes, no

Clinical history of current illness

- History of fever, bloody diarrhoea, history of vomiting, cough, passing dark urine, convulsions in this illness: n (%) yes, no
- *Number of days of convulsions: median (IQR) of those with convulsions*

Past medical history

- *Ever treated for TB, admitted to hospital in last 12 months, known epilepsy, known HIV: n (%) yes, no*
- *Number of times admitted to hospital in last 12 months: n (% of those with admission) once, twice, three times, more than three times*
- *Currently on treatment for epilepsy: n (% of those with known epilepsy) yes, no*
- *On HIV care: n (% of those on care for HIV) yes, no*

Recent and current medical treatment

- Taken liquids in this illness, currently taking antibiotics, currently on anti-malarial medication, currently on anti-retroviral medication, currently receiving traditional medicines: n (%) yes, no
- Type of liquid taken: n (% of those who have taken liquids) plain water, oral rehydration solution (ORS), home-made ORS, Ribena, Lucozade, other
- Type of antibiotic: n (% of those currently taking antibiotics) amoxicillin, cotrimoxazole, metronidazole, cephalexin or similar, unknown name, other
- Duration of antibiotic treatment: median (IQR) of those taking antibiotics

Chronic conditions present at enrolment

- *Cerebral palsy, TB, chronic cough (>1 month), diarrhoea in last 6 months: n (%) yes, no*
- *Description of diarrhoea: n (% of those with diarrhoea in last 6 months) short episode, recurrent, persistent*

Feeding and malnutrition history

- *Age food was introduced (months): median (IQR)*
- *Still breastfeeding: n (%) yes, no*
- *Born prematurely, previous admission for malnutrition, admitted to another facility in this illness, currently on RUTF: n (%) yes, no, don't know*
- *Appetite (1-10 scale): median (IQR)*

Developmental milestones

- *Able to sit unsupported before this illness, known neurological condition: n (%) yes, no*

- *Able to walk unsupported before this illness: n (%) yes, no, N/A*
- *Neurological condition: line listing*

Clinical examination

- *Indrawing, deep breathing, severe palmar pallor, jaundice, enlarged liver, ascites, splenomegaly, flaky paint skin, desquamation, candida, angular kelosis, mouth sores, generalised lymphadenopathy: n (%) yes, no*
- *Crackles: n (%) none, unilateral, bilateral*
- *Liver size below costal margin: n (% of those with enlarged liver) ≤2cm, >2cm*

Ward test results

- Glucose (mmol/L), lactate (mmol/L): n (%) not missing, median (IQR)
- Hypoglycaemia (glucose <3 mmol/L), hyperlactaemia (lactate ≥3 mmol/L): n (%)
- HIV, malaria rapid diagnostic test: n (%) positive, negative, invalid, not done

Blood test and biochemistry results

- *White blood cell count (10^9/L), red blood cell count (10^{12}/L), haemoglobin (g/dL), haematocrit (%), platelet count (10^9/L), lymphocyte count (10^9/L), neutrophil count (10^9/L),* sodium (mmol/L), potassium (mmol/L), *chloride (mmol/L), bicarbonate (mmol/L), serum osmolarity, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), troponin: n (%) not missing, median (IQR)*
- Severe hyponatraemia (sodium <125 mmol/L), severe hypokalaemia (potassium <2.5 mmol/L), hypernatraemia (sodium >145 mmol/L), severe anaemia (haemoglobin <5 g/dl), thrombocytopenia (platelet count < 160 x 10^9/L), leukocytosis (white blood cell count > 12.5 x 10^9/L): n (%)
- *Blood culture: n (%) not missing, n (% of non-missing values) positive, negative.*

8.4 Description of follow-up

Completion of follow up visits

The following will be presented by IV rehydration arm for children in stratum A, and by oral rehydration arm for all children (strata A and B combined).

- Visits considered complete, defined as attended or died before the visit took place, at 7 days and 28 days: n (%)
- Visits that took place outside visit window (as defined in section 7), at 7 days and 28 days: n
- Child status at 7 days and 28 days: n (%) visit done, died, withdrawn, lost to follow up, missed visit.
- *Reasons for withdrawal: n (%) moved to another area; transport problems; no longer interested; moved to live with another carer/relative; work commitments of carer; child too ill to travel; social problems; other; unwilling to disclose.*

Completeness of data for primary outcomes

The following will be presented by IV rehydration arm, and for the Plan C and Slow arm combined, for children in stratum A.

- Vital status known at 96 hours: n (%)

The following will be presented by oral rehydration arm for children in strata A and B combined.

- Sodium levels considered complete at both baseline and 24 hours, defined as a non-missing entry or died before the time point: n (%)
- Record status at 24 hours: n (%) sodium level recorded at both baseline and 24 hours, form entered- no sodium level recorded at one or both timepoints, died, LTFU/absconded, no form entered

8.5 Adherence to treatment and protocol deviations

IV rehydration strategy

The following will be presented by IV rehydration arm for children in stratum A.

- Number of children in shock: n (%)
- Number receiving a bolus: n (% of children in shock)
- Total volume of bolus fluids received: median (IQR)
- Time from randomisation to start receiving fluids: median (IQR)
- Fluid (mls/kg) received at 1hr, 2hrs, 4hrs, 6hrs, 8hrs, 24hrs from baseline: median (IQR) by age <1 yr, >1yr for WHO plan C arm

Oral rehydration strategy

The following will be presented by oral rehydration arm for children in strata A and B separately, and in both strata combined.

- Time from randomisation to of start oral rehydration (minutes): median (IQR)
- Duration of ORS (hours): median (IQR)
- Total ORS given (mls/kg): median (IQR)

Protocol deviations

- Protocol deviations: n (%) major, minor

8.6 Primary outcomes

IV rehydration

- Mortality at 96 hours

Number and proportion of deaths at 96 hours will be summarised by arm and a chi-squared test will be used to test for a difference between arms. The effect size will be described using the risk ratio adjusted for site by a Mantel-Haenszel type of adjustment. A secondary analysis will use time to event methods, with hazard ratios and 95% confidence intervals calculated using Cox proportional hazard models, adjusted for site.

The proportional hazards assumption will be checked using the Grambsch-Therneau test, and if the assumption does not hold ($p<0.05$) an alternative method suitable for non-proportional hazards, such as restricted mean survival time (RMST), will be used. Kaplan-Meier curves will be plotted and log-rank tests will be performed.

Oral rehydration

- Change in sodium at 24 hours

Change in sodium (mmol/L) from randomisation to 24 hours will be analysed using normal linear regression, adjusting baseline sodium (measured at randomisation). Children who died within 24 hours of randomisation will be excluded from analysis. This gives an estimate of the change in sodium among the principal stratum of children surviving at least 24 hours, under the assumption that there is no

difference in 24 hour mortality between the two ORS strategies. Mean change in each arm, and mean difference between treatment arms, with 95% confidence intervals, will be presented.

8.7 Secondary outcomes

The following outcomes will be analysed for both the IV and oral rehydration comparisons, unless otherwise specified. Analysis comparing IV rehydration strategies will be adjusted for site. Analyses comparing oral rehydration strategies will be adjusted for site and strata.

- Change in sodium levels from post-IV levels to 24 hours (Stratum A only)

Post-IV sodium is only captured by the measurement at 8 hours and therefore this analysis will use the 8 hour value as baseline. Mean change in sodium levels (mmol/L) from 8 hours to 24 hours by arm will be calculated using normal linear regression, adjusting for the value measured at 8 hours. Mean difference between arms will be presented. Time from end of IV to 8 hours will also be summarised.

- Pulmonary oedema or heart failure

Cases of pulmonary oedema and heart failure will be analysed using time to event methods through day 28 counting in-hospital death as a competing risk. Subhazard ratios and 95% confidence intervals will be calculated and cumulative incidence functions will be plotted. If events occur in <5 children, numbers will be tabulated (rather than using time to event methods) and Fisher's exact test used to test for a difference between arms.

- Change in weight (kg), weight-for-age (z-score), MUAC (cm) and MUAC-for-age (z-score) from baseline to day 7

Normal linear regression adjusted for absolute baseline values will be used to calculate mean changes from baseline to day 7 and mean difference between the treatment arms. Generalised estimating equations will be used to jointly model changes during admission.

- Day 28 survival

Survival to day 28 will be analysed using Cox proportional hazard models to calculate hazard ratios and 95% confidence intervals. The proportional hazards assumption will be checked using the Grambsch-Therneau test, and if the assumption does not hold ($p<0.05$) an alternative method suitable for non-proportional hazards such as restricted mean survival time (RMST) will be used. Kaplan-Meier curves will be plotted and log-rank tests will be performed to test for difference between arms.

- Severe hyponatraemia (<125 mmol/L) or hypokalaemia (<2.5 mmol/L)

Number and proportion of children with hyponatraemia and hypokalaemia will be tabulated at 8 and 24 hours, and 7 days. Time to event methods will be used to analyse the time to correction of severe hyponatraemia and hypokalaemia through to day 7, treating death as a competing risk. Subhazard ratios and 95% confidence intervals will be presented.

- Urine output at 8 hours

Normal linear regression will be used to estimate mean urine output (mls/kg/hour) up to 8 hours and the mean difference between arms.

8.8 Other analyses

The following outcomes will be analysed for both the IV and oral rehydration comparisons, unless otherwise specified.

- Serious adverse events

The number and proportion of children ever having a serious adverse event, and the number of events, will be tabulated by randomised group and by body system. Chi-squared or Fisher's exact tests will be used to test for differences between arms. The number of events will also be tabulated by SAE criteria (fatal, life threatening, caused or prolonged hospitalisation, persistent or significant disability, other), and by body system. Relatedness to the IV and oral rehydration strategies will also tabulated.

- Serious adverse events definitely/probably/possibly related to randomisation

The number and proportion of children having a serious adverse event definitely, probably or possibly related to the IV or oral rehydration strategies will be tabulated by randomised group and by relatedness, and also by body system.

- *Change in consciousness level or seizures during admission*

The number and proportion of children who experience a deterioration in consciousness level, or have observed convulsions during admission, will be tabulated. Chi-squared or Fisher's exact tests will be used to test for differences between arms. Time to event methods such as Kaplan-Meier plots will be considered.

- *Neurological SAEs*

The number and proportion of children having an SAE recorded as a suspected neurological event will be tabulated. Chi-squared or Fisher's exact tests will be used to test for differences between arms. Time to event methods such as Kaplan-Meier plots will be considered.

- *Development of shock*

The number and proportion of children who did not have shock at the time of randomisation, but went into shock following randomisation, will be tabulated. Chi-squared or Fisher's exact tests will be used to test for differences between arms. Time to event methods such as Kaplan-Meier plots will be considered.

- *Change in sodium and potassium at 8 hours and 7 days*

Change in sodium (mmol/L) and potassium (mmol/L) at 8 hours and 7 days will be analysed using normal linear regression, adjusting for baseline sodium (measured at randomisation). Mean change in each arm and mean difference between arms will be presented.

- *Hypernatraemia (>145 mmol/L)*

The number and proportion of children with hypernatraemia will be tabulated at 8 and 24 hours, and 7 days. Chi-squared or Fisher's exact tests will be used to test for differences between arms.

8.9 Subgroup analyses

Interaction tests will be performed to check for heterogeneity of effects in the two primary outcomes according to the other randomised allocation (oral rehydration for the mortality outcome, and IV rehydration for change in sodium).

Subgroup analyses will also be performed for each primary outcome in the following subgroups:

- *Age (<1 year, ≥1 year)*
- *Consciousness level*
- *Respiratory distress*
- *HIV status*
- *Strata (GASTROSAM A vs B) for the oral rehydration outcome*

9 References

1. Mramba L, Ngari M, Mwangome M, et al. A growth reference for mid upper arm circumference for age among school age children and adolescents, and validation for mortality: growth curve construction and longitudinal cohort study. *BMJ.* 2017;358:j3423.

Certificate Of Completion

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Signer Events	Signature	Timestamp
Elizabeth George elizabeth.george@ucl.ac.uk Security Level: Email, Account Authentication (Optional)	Signed by: Elizabeth George B9A848352424412... Signature Adoption: Pre-selected Style Using IP Address: 86.174.22.190	Sent: 17 December 2024 | 16:25 Viewed: 18 December 2024 | 08:19 Signed: 18 December 2024 | 08:19
Electronic Record and Signature Disclosure: Accepted: 18 December 2024 | 08:19 ID: 48ec651f-6808-43d4-b629-25592fa68502		
Kath Maitland kathryn.maitland@gmail.com Imperial College, London Security Level: Email, Account Authentication (Optional)	DocuSigned by: Kath Maitland 4FEBBA0BB1BD4CC... Signature Adoption: Pre-selected Style Using IP Address: 46.234.224.20	Sent: 17 December 2024 | 16:25 Viewed: 17 December 2024 | 17:53 Signed: 17 December 2024 | 17:53
Electronic Record and Signature Disclosure: Accepted: 17 December 2024 | 17:53 ID: 9869e2ab-335e-4c29-925a-766a5da578fb		
Roisin Connon r.connon@ucl.ac.uk Statistician University College London Security Level: Email, Account Authentication (Optional)	DocuSigned by: Roisin Connon 1671D28A21C9466... Signature Adoption: Pre-selected Style Using IP Address: 128.40.216.23	Sent: 17 December 2024 | 16:25 Viewed: 17 December 2024 | 16:25 Signed: 17 December 2024 | 16:25
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	17 December 2024 | 16:25
Certified Delivered	Security Checked	17 December 2024 | 16:25
Signing Complete	Security Checked	17 December 2024 | 16:25
Completed	Security Checked	18 December 2024 | 08:19

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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