Statistical Analysis Plan

Great Ormond Street Hospital for Children NHS Foundation Trust

NHS Blood and Transplant

PLUTO

Plasma-Lyte usage and assessment of kidney transplant outcomes in children

NIHR | National Institute for Health Research

Version: Final v1.1

Date: 20/12/2022

CTU Ref: 18/118
ISRCTN: ISRCTN16586164
REC: 270431
MHRA CTA: 2019-003025-22

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1. Background and Design

The main characteristics of this trial have been summarised using PLUTO Protocol v2.0 from 23/03/2021. Please refer to this Protocol for full details. All essential documents for the trial are held in the Trial Master File.

1.1 Trial Summary and Objective

To determine whether the incidence of clinically significantly abnormal plasma electrolyte levels will be different with the use of Plasma-Lyte 148 compared to intravenous fluid with current standard composition in children following kidney transplant.

1.2 Patient Eligibility Criteria

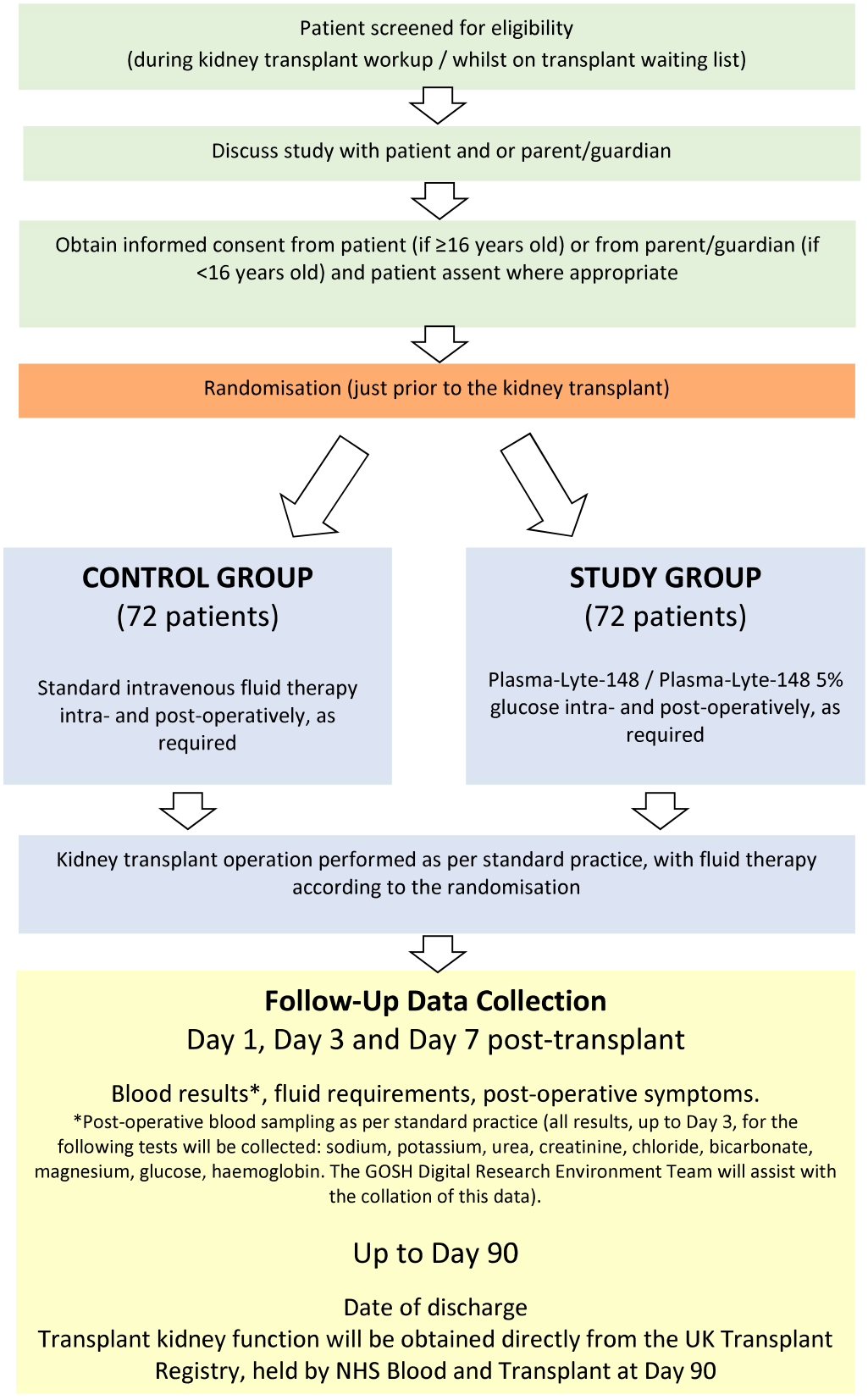
Inclusion criteria

1. Patients under 18 years of age at the time of transplantation with valid patient/parental consent
2. Patients receiving a kidney only transplant from either a living or deceased donor, in a participating UK centre

Exclusion criteria

1. Multi-organ transplant recipients

1.4 Trial Intervention



1.5 Randomisation and Blinding Procedures

Eligible patients who have consented to participate in the PLUTO trial will be randomised via an interactive web response system, provided by Sealed Envelope. Participants will be randomised in a 1:1 ratio, to the intervention and control groups. Participants will be randomised on admission to hospital for the transplant, once the trial team are confident that the transplant will be proceeding. Before performing the randomisation, the team must re-confirm the consent/assent (it may have been several weeks since initial consent was provided). The eligibility criteria should also be re-checked prior to randomisation and the site name and patient weight must be known. Upon randomisation, the site will be provided with the allocation (Plasma-Lyte or Standard fluid therapy) and the participant's randomisation number, which will be used to identify participants throughout the trial. This number will take the form RXXXX where XXXX is a four digit participant number.

The randomisation will be stratified by transplant centre and patient weight (<20kg vs ≥20kg pre-transplant). Randomisation will further be balanced using blocks of varying, undisclosed sizes. The randomisation list will be produced by the trial statistician using SAS statistical software.

1.6 Sample size calculation

The sample size required for this trial is 144 participants randomised. Analysis of 76 paediatric transplants performed at Great Ormond Street Hospital between 1 January 2015 and 31 March 2018 showed that 45 children (59%) experienced hyponatraemia within the first 72 hours post-transplant when managed with 0.45% saline 5% glucose fluid (1). This was used as the baseline rate. In the Cochrane systematic review by McNab S et al. (2), a 50% reduction in risk of hyponatraemia was shown. A greater effect size is anticipated because the rate of fluid delivery to children following kidney transplant significantly exceeds maintenance requirements (3). Using the 50% effect size from the Cochrane review, the assumed incidence of hyponatraemia would be reduced to 29.5%. A two-sided test with 90% power, 5% type I error and 1:1 allocation and allowing for two formal interim analyses for harm or benefit would require 128 patients. After allowing for 10% drop out, for example if a transplant cannot proceed due to a positive cross match, the total number of participants required is 144.

2. Data Handling

2.1 CRF descriptions and data collection schedule

Form No.	Form Title / Description of Form	Tick if Optional
1	**Screening Form**	☐
2	**Eligibility assessment**	☐
3	**Baseline Characteristics**	☐
4	**Randomisation**	☐
5	**Transplant Operation**	☐
6	**Day 1**	☐

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7	**Day 2**	☐
8	**Day 3**	☐
9	**Fluids**	☐
10	**Medication & Blood Products**	☐
11	**Day 7**	☐
12	**End Of Study**	☐
13 A	**SAE**	☒
13 B	**SAE Narrative**	☒
14	**Additional Medications (for SUSARs)**	☒
15	**SAE CTU Use**	☒
16	**Withdrawal**	☒

The Trial Visit Schedule shows details of assessments to be performed as follows:

VISITS									
	Screening	**Baseline (Pre-Tx)**	**At Tx**	**Day 1 Post-Tx**	**Day 2 Post-Tx**	**Day 3 Post-Tx**	**Day 7 Post-Tx**	**Month 3 Post-Tx**	**Hospital Discharge**
ENROLMENT									
Eligibility assessment	**X**								
Informed consent		**X**							
Baseline Characteristics*			**X**						
Re-confirm consent			**X**						
Randomisation			**X**						
TREATMENT									
Administration of trial fluid**			**X**	**X**	**X**	**X**			
ASSESSMENTS									
Transplant Operation Data			**X**						
Blood Results***		X	X	X	X	X			
Blood Gas Results (venous)		**X**	**X**	**X**	**X**	**X**			
Patient Weight		**X**	**X**	**X**	**X**	**X**			

Fluid Data			X	X	X	X			
Medication Data				X	X	X			
Symptom Assessment				X	X	X			
Safety Reporting (see section 13)			X	X	X	X			
Transplant Graft Function*							X	X	
Discharge Date									X

2.2 Procedures for recording and reporting outcomes

CRFs will be used to collect the majority of data from study entry. Screening log number or randomisation number, and participant initials will be used on all CRFs. Data will be recorded by electronic data capture (EDC). Data for this trial are also being collected via the Digital Research Environment (DRE) at Great Ormond Street and the UK Transplant Registry (UKTR) held by NHS Blood and Transplant. The DRE are collating all blood data and data will be extracted from the UKTR on donor and transplant characteristics and survival post-transplant. Prime responsibility for the complete collection of data for each centre will reside with the local Principal Investigator but may be delegated (for example to a Research Nurse). Overall responsibility for collating data from all centres will reside with the Trial Manager.

2.3 End-point Review Panel assessments/SAE Review

None.

2.4 Other assessments

None.

2.5 Trial Data Management and Verification

Quality control of data entered and data cleaning will be performed by the trial data manager and will be detailed in the Data Management Plan (FRM4727). This will include performing range, data completeness and consistency checks. Once this stage is finished, the trial dataset will be declared frozen and exported from the MACRO database for final data review and validation checks by a statistician, who will raise data queries with the trial manager or data manager. Once the trial statistician, data manager, and trial manager are satisfied that all queries have been resolved, the database will be locked. The locked database will be extracted into a statistical software package and used for final analysis.

3. Detailed Analysis Plan

3.1 Interim analysis and sample size re-estimation

The trial has a traffic light system incorporated at 15 months to assess progression from the internal pilot phase to full trial. Criteria for the traffic light system are based upon

recruitment rates (both number of sites and participants) and adherence to the intervention and control. If the red criteria are met, the trial would stop at this point. Full details can be found in section 16.3 of the protocol.

The trial will use a group sequential design with O'Brien-Fleming boundaries to inform early stopping of the trial in the case of strong evidence of harm or benefit, while preserving the overall 5% type I error rate for the trial. Two interim analyses to test for harm or benefit will be conducted after 70 and 100 patients have been recruited into the trial with primary outcome data. The stopping rules will be used as a guideline, alongside the other safety data available to the DMC, and used as part of their overall assessment of the trial.

3.2 Analysis principles

The population used for efficacy analyses will be a modified intention to treat population including all randomised participants who received a transplant. Although it is a very unlikely scenario for a participant to not receive a transplant after being randomised, it would be illogical to include those participants who have not been transplanted as no outcome data would be available. Participants will be analysed according to the trial arm to which they were randomised. This will be the primary analysis for the trial.

Participants who were not transplanted will be listed with reasons for not being transplanted. The number and percentage of these occurrences will also be tabulated by trial arm. As this number is expected to be small (<14 participants, which is 10% of the total sample size) no statistical test will be conducted to test for differences between trial arms.

Participants who did not meet all the inclusion criteria and/or met the exclusion criteria will be considered as randomised in error. There is no minimum amount of treatment, of the intervention or control, required in this trial. Non-compliance is defined as any participant randomised to the standard arm who receives any Plasma-Lyte intra-operatively or post-operatively in the first 72 hours post-transplant and any participant randomised to the intervention arm who receives any other intravenous fluid intra-operatively or post-operatively in the first 72 hours post-transplant. These occurrences will be counted as protocol deviations. In addition, protocol deviations may also occur which do not involve intravenous fluid. A decision will be made for each occurrence in a blinded manner (if possible) whether it will be classified as a protocol deviation in the analysis. All protocol deviations will be reviewed and discussed by the TMG in a blinded manner (if possible) and monitored throughout the trial.

Any participant, or their parent/guardian, who withdrew consent to participate in the trial and any withdrawal of a participant by their clinician for medical reasons, will be considered as a withdrawn participant.

- If a participant withdraws their consent prior to randomisation (participants will be approached for inclusion in the trial when they are on the deceased donor transplant waiting list or in the living donor assessment stage and then consent is reconfirmed prior to randomisation), then the participant will not be included in the primary nor secondary outcome analysis as no data will be collected.
- Withdrawal from the trial post-randomisation will not result in exclusion of the data for that participant from analysis, unless the participant or their family has requested the data already collected is removed.

- If a participant is randomised but then the transplant does not proceed, the participant should be withdrawn from the trial.

Participants randomised in error, protocol deviations and withdrawn participants will be tabulated separately with reasons. A summary will also be presented showing the percentage of participants who experienced each of these (randomised in error, protocol deviations and withdrawn) and whether any participants were co-enrolled in other trials when they were also a participant in PLUTO.

Participants randomised in error, participants with protocol deviations, those withdrawn or lost to follow up will be included in the modified intention to treat analysis where possible. A withdrawn randomised participant will only be excluded if they withdrew their consent for their data to be used in the trial.

The primary outcome will also be analysed per protocol. This analysis will exclude any randomised participant who did not receive a transplant, was randomised in error, had a protocol deviation or was withdrawn from the trial.

Statistical tests will be performed to compare primary and secondary outcomes between treatment arms. This study has only been powered to detect a difference between treatment arms in the primary outcome. All analyses specified will test a superiority hypothesis.

All tests will be two-sided, p-values of less than 0.05 will be considered as evidence of a difference between treatment arms, and conditional effects will be reported. P-values will be reported to four decimal places with p-values less than 0.0001 as <0.0001. All confidence intervals presented will be 95% and two-sided. Exact confidence intervals will be used for binary data, where exact models have been used. Multiple comparisons will be performed and this may increase the probability of observing a statistically significant result by chance. No adjustments will be made to account for multiple testing. The statistical package SAS will be used to conduct analyses.

The key demographics and clinical condition of the participants will be presented for each arm of the trial to describe the cohort. In addition, a summary of transplant characteristics will be presented for each arm of the trial. A CONSORT diagram will be presented to show how participants progressed through the trial.

All analyses and accompanying tables will be presented by the treatment to which the participant was randomised. All odds, hazard and rate ratios will be presented as Plasmalyte arm versus Standard arm. A ratio which is greater than 1 indicates that the odds, hazard or rate of the event is greater in the Plasmalyte arm. 95% confidence intervals will be presented with all ratios.

P-values for regression models will be obtained by comparing models with and without the treatment term using the likelihood ratio test. In analyses where mixed models are performed, the log-likelihood will be estimated using pseudo-likelihood methods.

All analyses will be adjusted for the stratification variables (site and participant weight pre transplant: <20kg and ≥20kg) and donor type: deceased and living, as this was also felt to be an important factor which could affect the outcomes of interest. Site will be

accounted for by including a random effect and participant weight and donor type by a fixed effect in each model.

Although PLUTO is a definitive trial, the total sample size is relatively small, hence:

- In the adjusted analyses we may observe separation of data points for outcomes with lower event rates. If this occurs, we would initially drop donor type from the model. If this does not resolve the problem, then site will be removed and a fixed effects regression model adjusting for participant weight pre transplant and donor type will be used. If this does not resolve the problem, then we would additionally drop donor type from the fixed effects regression model. If this is not suitable, then an unadjusted analysis will be performed. If the initial model is a mixed logistic regression model, then if site is removed, an exact logistic regression model will be used, where computationally possible. If exact regression is not possible, then a fixed effects logistic regression model with a Firth correction to reduce bias in the parameter estimates will be used. For each analysis, table footnotes will be used to indicate the final model type and the variables adjusted for.
- It is anticipated that in some tables and frequencies, the number presented will be less than 5. It was agreed by the TMG that all data will be presented as observed within the Data Analysis Report (as this report is only shared amongst the trial teams) but within any publications, data less than 5 will be presented as <5.

3.3 Analysis of primary outcome measures

The number and percentage of participants who experience acute hyponatraemia (defined as plasma sodium concentration <135mmol/L) within 72 hours post-transplant will be presented by trial arm and overall. This will be analysed using a mixed logistic regression model adjusting for donor type (living vs deceased donor), participant weight (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. A superiority hypothesis will be tested and the results from the adjusted analysis will be considered the primary analysis. The adjusted odds ratio for treatment, with 95% confidence interval, will be presented from this model, with the p-value from the likelihood ratio test when including and excluding the treatment term from the model. This will be the primary analysis. The median and interquartile range of the number of each event experienced by each participant will also be presented, but no further statistical testing will be conducted on these. As outlined above, this will be analysed using the modified intention to treat population, which includes all participants randomised and transplanted. This outcome will also be analysed in the per protocol population, which additionally excludes those randomised in error, with a protocol deviation, or withdrawn from the trial.

3.4 Analysis of secondary outcome measures

Symptoms of acute hyponatraemia (nausea, vomiting, headache, seizures) within the first 72 hours post-transplant

The number and percentage of participants experiencing each symptom will be presented by trial arm and overall. The proportion of participants experiencing each symptom at least once will be compared with exact logistic regression, because the number experiencing these symptoms may be small. The model will be adjusted for donor type (living vs deceased donor) and participant weight (<20kg vs ≥20kg pre-transplant).

The degree of fluid overload experienced

This outcome is defined as proportional increase in patient weight between pre-transplant weight and maximum weight in the 72 hours post-transplant. The mean proportional weight increase, with standard deviation, will be presented for each trial arm and overall. A Normal linear regression model will be used to assess whether mean proportional weight increase is different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. Residual plots from the normal linear regression will be examined. If there is any evidence of skew or non-constant variance, normal linear regression of log-transformed proportional weight increase will be used to assess whether mean log- proportional weight increase are different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect.

Time to discharge from hospital

This outcome will be measured from transplant operation start time ("knife to skin") till discharge from hospital, measured in days and will be estimated using competing risks analysis. Discharge from hospital will be considered as the event and death prior to discharge will be considered as the competing risk. Median (IQR) hospital stay from the cumulative incidence curve will be reported for each trial arm and overall. Although if there are no deaths, the Kaplan-Meier method will be used. To accommodate a random centre effect and adjustment for participant weight and donor type, Cox regression analysis with a frailty term will be used to compare time to discharge between treatment arms. Participants who have not been discharged will be censored at the point of last contact. Participants who die will be censored. The estimate of the hazard of discharge from this model should be interpreted with caution because it does not properly account for the competing risk of death. However, since the number of deaths is predicted to be small, the impact of the competing risk is likely to be negligible. This will be explored by examining the cumulative incidence function for death.

Transplant kidney function at 1, 3, 7 and 90 days

This will be calculated using the creatinine-based univariate Schwartz formula (4) to determine eGFR:

$$eGFR = 36.5 \times (\text{height} / \text{plasma creatinine concentration})$$

where height is measured in cm and plasma creatinine in micromol/L (1mg/dl = 0.01131222 micromol/L). For day 1 and 3, this data will be obtained from the blood data measurements taken routinely. If multiple measurements are recorded on the same day, then we will use the last measurement taken for each day, as this is likely to be the lowest and gives most time for creatinine to be in steady state. For day 7 and 90 a single measurement is being collected via the MACRO database and UK Transplant Registry respectively. For day 1, 3 and 7, the participant height recorded at transplant will be used. For 90 days, the participant's height at this timepoint will be used, which will be obtained from the UKTR. The mean and standard deviation of eGFR at each timepoint will be presented by trial arm and overall.

A repeated measures mixed Normal linear regression will be used to assess whether kidney function over days 1,3 and 7 are different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and day of measurement. In addition, two random

effects will be included in the model to account for individual participant effects and transplant centre. Residual plots from the normal linear regression will be examined. If there is any evidence of skew or non-constant variance, repeated measures mixed normal linear regression of log-transformed eGFR will be used to assess whether mean log- eGFR are different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and participant and transplant centre as random effects.
A separate mixed Normal linear regression will be used to assess whether mean eGFR is different between the two treatment arms at day 90, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. Residual plots from the normal linear regression will be examined. If there is any evidence of skew or non-constant variance, mixed normal linear regression of log-transformed eGFR at 90 days will be used to assess whether mean log-eGFR are different between the two treatment arms, adjusting for adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect.

Other electrolyte abnormalities within the first 72 hours post transplantation
This includes the following:

- Hypernatraemia (defined as plasma sodium concentration > 145mmol/l)
- Hyperkalaemia (defined as plasma potassium concentration > 5.5mmol/L)
- Hypokalaemia (defined as plasma potassium concentration < 3.5mmol/L)
- Non anion-gap acidosis (defined as plasma bicarbonate < 20mmol/L and anion gap < 20mmol/L. Anion gap will be calculated as the sum of plasma sodium and plasma potassium, minus the sum of plasma chloride and plasma bicarbonate). Where possible, these components should be obtained simultaneously, but where this is not possible, samples should be collected within an hour.
- Hyperglycaemia (defined as random blood glucose > 5.5 mmol/L)
- Hypomagnesaemia (defined as plasma magnesium concentration < 0.7 mmol/L)
- Hyperchloraemia (defined as plasma chloride concentration > 107mmol/L)
- Excessive rate of reduction in plasma sodium concentration (defined as >1mmol/L/hour averaged over 6 hours)
- Excessive magnitude of reduction in plasma sodium concentration (defined as > 10mmol/L from pre-transplant level)

The number and percentage of participants who experience each of these events will be presented by trial arm and overall, alongside the median and interquartile range of the number of each event experienced. To test for differences in the proportion of participants experiencing each event, separate mixed logistic regression models will be used. These will be adjusted for donor type (living vs deceased donor), participant weight (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. The adjusted odds ratio for treatment, with 95% confidence interval, will be presented from this model, with the p-value from the likelihood ratio test when including and excluding the treatment term from the model.

Maximum and minimum systolic blood pressure
The minimum and maximum systolic blood pressure will be taken for each day, for the first 3 days post-transplant (the measurement recorded in the database will have been sustained on 3 repeated values on each day). The values will be normalised to age and height percentile by the statistician, using the process as specified in https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf and

https://www.who.int/toolkits/growth-reference-data-for-5to19-years will be used to determine the height percentiles. Heights in cm will be converted to inches by dividing by 2.54 and will utilise the height at transplant. The mean minimum and maximum normalised systolic blood pressure, with standard deviation, will be presented separately for each trial arm and overall, for each day. A repeated measures mixed Normal linear regression will be used to assess whether mean percentiles over the three days are different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and day of measurement. In addition, two random effects will be included in the model to account for individual participant effects and transplant centre. Residual plots from the normal linear regression will be examined. If there is any evidence of skew or non-constant variance, repeated measures mixed normal linear regression of log-transformed percentile will be used to assess whether mean log- percentile are different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and participant and transplant centre as random effects.

Number of changes in intravenous fluid composition within the first 72 hours post-transplant

A change to intravenous fluid composition will be defined as any modification to the composition of the fluid administered to the participant. The number of changes in fluid will be counted as follows:

- If the participant is initially given something different to which they were randomised, this will be counted as the first change
- Subsequent changes will be counted based on the fluid being administered before the change.
- Diluent used for drug infusions, will not be counted.

For example:

- if the participant was randomised to standard arm, was first administered Hartmann's solution, then 0.9% sodium chloride, and then Hartmann's solution again, this would be counted as two changes.
- If the participant was randomised to Plasma-Lyte, was first administered 5% glucose, then received Plasma-Lyte 148 and then Plasma-Lyte® 148 & Glucose 5%, this would count as three changes.

The mean and standard deviation of the number of changes experienced will be tabulated by treatment arm and overall, alongside the percentage of participants who had a least one change. The number of changes will be compared by treatment arm using a negative binomial model. The model will be adjusted for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. The model will also include an offset to account for the number of hours the participant was at risk of the event, up to 72 hours post transplant.

3.5 Other outcome measures

Investigation into acute hyponatremia and plasma sodium concentration

- *Time to first develop acute hyponatremia*

  This outcome will be measured from transplant operation start time ("knife to skin") till the first time the plasma sodium concentration drops below 135mmol/L. The maximum time will be 72 hours post-transplant and the time will be measured in hours. It will be estimated using competing risks analysis. Acute

hyponatremia will be considered as the event and death prior to the event will be considered as the competing risk. Median (IQR) time to first develop acute hyponatremia from the cumulative incidence curve will be reported for each trial arm and overall. Although if there are no deaths, the Kaplan-Meier method will be used. To accommodate a random centre effect and adjustment for participant weight and donor type, Cox regression analysis with a frailty term will be used to compare time to first develop acute hyponatremia between treatment arms. Participants who have not experienced the event by 72 hours will be censored at this point, as will any participants who die or were withdrawn prior to 72 hours post transplant. The estimate of the hazard of acute hyponatremia from this model should be interpreted with caution because it does not properly account for the competing risk of death. However, since the number of deaths is predicted to be small, the impact of the competing risk is likely to be negligible. This will be explored by examining the cumulative incidence function for death.

- *Duration of acute hyponatremia*
  For those participants who experience acute hyponatremia, the total time between transplant operation start time and 72 hours post-transplant when the participant's plasma sodium concentration is below 135mmol/L will be calculated in hours. The start time of an acute hyponatraemia event in this period will be taken as the time of the first test where plasma sodium is <135mmol/L. The corresponding end time will be the time of the first test after this where plasma sodium is ≥135mmol/L, or 72 hours post-transplant, whichever occurs first. For each participant, these event durations will then be totalled. The mean duration, with standard deviation, will be presented for each trial arm and overall. A Normal linear regression model will be used to assess whether mean duration is different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. Residual plots from the normal linear regression will be examined. If there is any evidence of skew or non-constant variance, normal linear regression of log-transformed duration will be used to assess whether mean log- duration are different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect.
- *Magnitude of variation in plasma sodium concentration in first 72h*
  For each participant, the difference between their maximum and minimum plasma sodium concentration between transplant operation start and 72 hours post transplant, will be calculated. This outcome is clinically important as variation leads to fluid shifts, brain oedema and seizures. The mean magnitude of variation, with standard deviation, will be presented for each trial arm and overall. A Normal linear regression model will be used to assess whether mean magnitude of variation is different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. Residual plots from the normal linear regression will be examined. If there is any evidence of skew or non-constant variance, normal linear regression of log-transformed magnitude of variation will be used to assess whether mean log- magnitude of variation are different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect.
- *Maximum rate of change of plasma sodium concentration in first 72h*

For each participant, all plasma sodium concentrations measurements which are ≥5mmol/l and which were taken between transplant operation start and 72 hours post-transplant will be compared. The rate of change will be calculated, for tests taken at least six hours apart, by taking the difference between the measurements and dividing by the number of hours between the measurements. The maximum decrease of these will be selected for each participant. The mean maximum rate, with standard deviation, will be presented for each trial arm and overall. A Normal linear regression model will be used to assess whether mean maximum rate is different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. Residual plots from the normal linear regression will be examined. If there is any evidence of skew or non-constant variance, normal linear regression of log-transformed maximum rate will be used to assess whether mean log- maximum rate are different between the two treatment arms, adjusting for donor type (living vs deceased donor), participant weight pre transplant (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect.

Serious adverse events

Serious adverse events will be tabulated by classification (Acute severe hyponatraemia – symptomatic and non-symptomatic (separately), severe hyperkalaemia, seizures and other) and treatment arm. The number of participants who experienced at least one SAE will also be presented. Following the implementation of protocol v2.0, SAEs relating to electrolytes were no longer required to be reported by sites. Therefore, both acute severe hyponatraemia and severe hyperkalaemia will also be identified through all participants' plasma and blood gas results, including those SAEs which occurred prior to the protocol change. Acute severe hyponatraemia is defined as: a fall in plasma or blood gas sodium concentration of ≥10mmol/L from the pre transplant level or a rate of fall of plasma or blood gas sodium concentration exceeding 1mmol/L/hour averaged over 6 hours. A plasma or blood gas potassium concentration >6.5mmol/L will be used to identify acute severe hyperkalaemia. No statistical testing will be conducted.

Graft and patient survival at 90 days

This outcome will be measured from transplant operation date till 90 days post transplant, measured in days and the Kaplan-Meier method will be used to separately to estimate the graft and patient survival at 90 days with 95% confidence interval. For graft survival, deaths will be censored and graft failure will be considered as the event.
For patient survival death will be considered as the event. No statistical testing will be conducted.

Volume of intravenous fluid received

A summary of the volume of intravenous fluid received will be presented, by treatment arm and overall. The total intravenous fluid volume received overall and by fluid type, will also be tabulated. No statistical testing will be conducted.

Medication and blood products

A summary table showing the medication and blood products received will be compiled by treatment arm. No statistical testing will be conducted.

Primary outcome events confirmed by additional blood gas

For the primary outcome it was specified, where feasible, a concurrent blood gas should be performed to confirm the result, although this was not compulsory. Confirmatory blood gas sodium measurements should be +/-30mins from lab sample taken at the onset of event. The number of primary outcome events confirmed by a blood gas result will be tabulated by treatment arm and overall, with percentages.

3.6 Sub-Group analyses

A subgroup analysis will be performed for the primary outcome to assess whether the treatment effect differs according to the fluid regimen used in the standard arm. Analysis will be performed using the same methods as for the primary outcome, except the treatment term will be grouped as follows:

- Randomised to Plasmalyte
- Randomised to control and predominantly (defined as >50% total intravenous fluid volume) received 0.9% sodium chloride
- Randomised to control and received 0.9% sodium chloride less than or equal to 50% of their total intravenous fluid volume.

It is anticipated that 0.9% sodium chloride may decrease the number of participants experiencing acute hyponatraemia.

3.7 Sensitivity analyses

Three sensitivity analyses of the primary outcome will be conducted. Firstly, an unadjusted analysis will be presented, which will present the odds ratio, 95% confidence interval and p-value from an unadjusted logistic regression model. Secondly, although very unlikely, a participant may be transplanted but then require a re-graft during the trial period (i.e. because their previous graft failed). Hence the participant may be randomised twice into the trial and there will not be independence between observations in the data (an assumption of the logistic regression model). If this situation does occur, then we will conduct a separate, second sensitivity analysis, which will utilise the model from the primary analysis but also include a nested random effect for participant in the logistic regression model, to assess for any effects of this. Thirdly, the definition of acute hyponatraemia will be expanded to include plasma or blood gas sodium concentration <135mmol/L. This will be analysed using a mixed logistic regression model adjusting for donor type (living vs deceased donor), participant weight (<20kg vs ≥20kg pre-transplant) and transplant centre as a random effect. The number and percentage of participants who experience acute hyponatraemia will also be presented by whether the event occurred in plasma or blood gas by trial arm and overall, alongside the median and interquartile range of the number of each event experienced.

For the secondary outcome of other electrolyte abnormalities within the first 72 hours post transplantation, their definitions will also be expanded to include blood gas results. As magnesium is only collected in plasma, hypomagnesaemia will not be included in these sensitivity analyses. The numbers and percentage of participants who experience each of these events will also be presented by whether the event occurred in plasma or blood gases by trial arm and overall, alongside the median and interquartile range of the number of each event experienced. No further statistical testing will be conducted.

- Hypernatraemia (defined as sodium concentration > 145mmol/l)
- Hyperkalaemia (defined as potassium concentration > 5.5mmol/L)
- Hypokalaemia (defined as potassium concentration < 3.5mmol/L)
- Non anion-gap acidosis (defined as bicarbonate < 20mmol/L and anion gap < 20mmol/L. Anion gap will be calculated as the sum of sodium and potassium, minus the sum of chloride and bicarbonate)
- Hyperglycaemia (defined as glucose > 5.5 mmol/L)
- Hyperchloraemia (defined as chloride concentration > 107mmol/L)
- Excessive rate of reduction in sodium concentration (defined as >1mmol/L/hour averaged over 6 hours)
- Excessive magnitude of reduction in sodium concentration (defined as > 10mmol/L from pre-transplant level)

Where multiple test results are required to meet the criteria for an abnormality, events will only be identified in either all plasma results or all blood gas results (e.g. determining an excessive magnitude of reduction in sodium concentration will compare plasma sodium results against the pre-transplant plasma sodium, and blood gas sodium results against the pre-transplant blood gas sodium).

3.8 Procedures for handling Missing Data

Any missing primary and secondary outcome data will be summarised. For the primary outcome and other blood test results, the result will be considered missing if there are no results for that measurement within the 72-hour period post transplant. It is anticipated that missing data for the primary outcome will be rare, as the plasma sodium measurement is also used to determine one of the key SAEs within the trial, which mandates immediate reporting. Missing data due to death or withdrawal are also anticipated to be very rare: data from the UKTR showed that the 1-year patient survival rate for those transplanted between 2015-2018 was 99% (95% confidence interval 96-100) for paediatric kidney transplants from living and DBD donors (5). Primary and secondary outcome measures will not be imputed and these will be treated as missing data and excluded from the relevant analyses. If outcome data is missing for more than 25% of participants, outcomes will not be reported.

To explore if missing values have an undue impact on the primary outcome result, a sensitivity analysis using multiple imputation will be performed if the primary outcome is missing in more than 5% of the participants included in the modified intention to treat analysis. Variables will be included in the imputation model if they have a completeness of ≥65% and these variables are:

- Donor: type, age, ethnicity, BMI
- Trial participant/Recipient: age, sex, ethnicity, cause of end stage kidney disease, native urine output, dialysis type, weight and height at transplant, systolic blood pressure, blood group, calculated reaction frequency, graft number
- Transplant: blood group match, transplanting centre, cold ischaemic time, HLA mismatch between donor and recipient, graft placement.

Forty imputations will be used and the average across the imputations will be calculated. The model specified in section 3.3 will be utilised.

If the proportion of participants with a missing primary outcome is less than or equal to 5% then this sensitivity analysis will not be performed.

All the risk adjustment factors will always be known, as weight and site are required for randomisation and donor type is mandatory data required by the UKTR.

4. Data Analysis Tables

Data analysis will be based on the following tables.

4.1 Screening, Recruitment and Follow-up tables

4.1.1 Recruitment by Centre

Table XX Recruitment by Centre

Site	**Total number screened**	**Number eligible**	Number consented	**%** consented from eligible	**Number randomised**	% rand. from eligible
Belfast						
Birmingham						
Bristol						
GOSH						
Evelina						
Leeds						
Manchester						
Newcastle						
Nottingham						

4.1.2 Participants withdrawn

Table XX Participants withdrawn*

Randomisation number	Randomised treatment	Reason for withdrawal	Level of withdrawal (from treatment or follow up)	Timing of withdrawal	Is the participant included in mITT analyses?

*Excludes cases which were randomised but not transplanted.

mITT=modified intention to treat (primary analysis population)

Table XX	**Participants randomised but not transplanted**
Randomisation number	Randomised treatment

4.1.3 Participants randomised in error

Table XX	**Participants randomised in error**	
Randomisation number	Randomised treatment	Detail of error

4.1.4 Participants entered in trial more than once and co-enrolled in other trials

Table XX		**Participants entered into the trial more than once**		
Randomisation number		Randomised treatment		Reason for multiple enrolments
First	Second	First	Second	

Table XX	**Participants co-enrolled during the trial**	
Randomisation number	Randomised treatment	Names of the co-enrolled trials

4.1.5 Protocol Deviations

Table XX	**Protocol deviations**			
Randomisation number	Randomised treatment	Description of and reason for deviation	Clinical significance of deviation	Included in mITT analysis?
mITT = modified intention to treat (primary analysis population)				

Table XX	**Summary of withdrawn, randomised in error, co-enrolled and protocol deviations n (%)**		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Withdrawn*			
Randomised in error			
Co-enrolled			
Protocol deviations			
Randomised but not transplanted			
*Excludes cases which were randomised but not transplanted.			

4.2 Baseline Characteristics tables

Table XX Baseline characteristics- at time of randomisation
Data are no. (%) for categorical variables and median (IQR) for continuous variables

	Randomised Treatment		
Participant characteristic	**Standard care (n=)**	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Age (years)			
Male			
Ethnicity			
Asian			
Black			
Mixed			
White			
Other			
Unknown			
Cause of end stage kidney disease			
Tubulointerstitial disease (CAKUT/non-CAKUT)			
Glomerular disease			
Hereditary nephropathies			
Systemic diseases			
Other			
Native urine output (ml/kg/24 hours)			
Dialysis type			
Haemodialysis			
Peritoneal dialysis			
Pre-emptive (no dialysis)			
Patient weight at transplant (kg)			
Patient height at transplant (cm)			
BMI (kg/m^2)			
Systolic blood pressure[1]			
Blood group			
O			
A			
B			
AB			
Recipient waiting time in days (if deceased donor transplant)			
cRF[2] (%)			
Graft number			
First			
Second			

[1]Maximum of three measurements at baseline for each participant.
[2]Calculated Reaction Frequency
Summary of missing data:

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Table XX Transplant characteristics
Data are no. (%) for categorical variables and median (IQR) for continuous variables

	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Cold ischemia time (hours)*			
Deceased donor			
Living donor			
HLA mismatch (at A, B, DR locus)			
000			
0/1 B and 0 DR			
[2 B and 0 DR] or [0/1 B and 1 DR]			
[2 B and 1 DR] or [2 DR]			
Graft placement			
Intra-abdominal			
Extraperitoneal			
Destination of transfer from operation theatre			
PICU			
Ward			
Donor characteristics			
Type			
DBD			
DCD			
Living			
Age (years)			
Ethnicity			
Asian			
Black			
Mixed			
White			
Other			
Unknown			
BMI (kg/m^2)			
Blood group match			
Identical			
Compatible			
Incompatible			

*Elapsed time from start of perfusion to time kidney perfused with recipient's blood
Summary of missing data:

4.3 Primary Outcome table

Table XX Primary outcome, acute hyponatraemia			
	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Modified intention-to-treat			
N/Total N (%)			
OR (95% CI)[1]			
p-value[2]			
Median (IQR) number of events[3]			
Per-protocol			
N/Total N (%)			
OR (95% CI)[1]			
p-value[2]			
Median (IQR) number of events[3]			

[1] Mixed logistic regression model adjusted for site, participant weight pre transplant and donor type.
[2] p-value from the likelihood ratio test when including and excluding the treatment term from the model.
[3] Per participant

4.4 Secondary Outcome table(s)

Table XX Secondary outcome – symptoms of acute hyponatraemia			
	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Symptoms of acute hyponatraemia within the first 72 hours post-transplant			
Nausea			
N/Total N (%)			
OR (95% CI)[1]			
p-value[2]			
Vomiting			
N/Total N (%)			
OR (95% CI)[1]			
p-value[2]			
Headache			
N/Total N (%)			
OR (95% CI)[1]			
p-value[2]			
Seizures			
N/Total N (%)			
OR (95% CI)[1]			
p-value[2]			

[1] Adjusted for site, participant weight pre transplant and donor type.
[2] p-value from the likelihood ratio test when including and excluding the treatment term from the model.

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Table XX Secondary outcomes - fluids			
	Randomised Treatment		
	Standard care (n=)	Plasma-Lyte 148 (n=)	Total (n=)
The degree of fluid overload experienced			
Mean proportional weight increase (Standard Deviation)[1]			
Mean difference (95% CI)[2]			
p-value[3]			
Number of changes in intravenous fluid composition within the first 72 hours post-transplant			
N at least one change /Total N (%)			
Mean (Standard deviation) number of changes[1]			
Rate ratio (95% CI)[2,4]			
p-value[3,4]			

[1] Unadjusted
[2] Adjusted for site, participant weight pre transplant and donor type.
[3] p-value from the likelihood ratio test when including and excluding the treatment term from the model.
[4] Adjusted for number of hours the participant was at risk of the event

Table XX Secondary outcome – time to discharge			
	Randomised Treatment		
	Standard care (n=)	Plasma-Lyte 148 (n=)	Total (n=)
Time to discharge from hospital (days)			
Median (IQR)[1,2]			
Hazard ratio (95% CI)[3]			
p-value[4]			

[1] Unadjusted
[2] Using competing risks analysis
[3] Adjusted for site, participant weight pre transplant and donor type.
[4] p-value from the likelihood ratio test when including and excluding the treatment term from the model.

Table XX Secondary outcome – transplant kidney function			
	Randomised Treatment		
	Standard care (n=)	Plasma-Lyte 148 (n=)	Total (n=)
Transplant kidney function at 1, 3, 7 and 90 days			
Day 1 Mean eGFR (Standard Deviation)[1]			
Day 3 Mean eGFR (Standard Deviation)[1]			
Day 7 Mean eGFR (Standard Deviation)[1]			
Mean difference (95% CI)[2]			
p-value[3]			
Day 90 Mean eGFR (Standard Deviation)[1]			
Mean difference (95% CI)[2]			
p-value[3]			

[1] Unadjusted
[2] Adjusted for site, participant weight pre transplant and donor type.
[3] p-value from the likelihood ratio test when including and excluding the treatment term from the model.

Table XX Secondary outcome – other electrolyte abnormalities			
	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Other electrolyte abnormalities within the first 72 hours post transplantation			
Hypernatraemia			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			
Hyperkalaemia			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			
Hypokalaemia			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			
Non anion-gap acidosis			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			
Hyperglycaemia			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			
Hypomagnesaemia			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			
Hyperchloraemia			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			
Excessive rate of reduction in plasma sodium concentration			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			
Excessive magnitude of reduction in plasma sodium concentration			
N/Total N of participants (%)			
OR (95% CI)[2]			
p-value[3]			
Median (IQR) number of events[1]			

[1] Per participant
[2] Adjusted for site, participant weight pre transplant and donor type.
[3] p-value from the likelihood ratio test when including and excluding the treatment term from the model.

Table XX Secondary outcome – systolic blood pressure			
	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Maximum and minimum systolic blood pressure (percentile)[1]			
Maximum			
Day 1 Mean (Standard Deviation)[2]			
Day 2 Mean (Standard Deviation)[2]			
Day 3 Mean (Standard Deviation)[2]			
Mean difference (95% CI)[3]			
p-value[4]			
Minimum			
Day 1 Mean (Standard Deviation)[2]			
Day 2 Mean (Standard Deviation)[2]			
Day 3 Mean (Standard Deviation)[2]			
Mean difference (95% CI)[3]			
p-value[4]			

[1] Blood pressure is normalised to age and height percentile
[2] Unadjusted
[3] Adjusted for site, participant weight pre transplant and donor type.
[4] p-value from the likelihood ratio test when including and excluding the treatment term from the model.

4.5 Other Outcome summary tables

Table XX Other outcome measure -			
	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Investigation into acute hyponatremia and plasma sodium concentration			
Time to first develop acute hyponatremia (hours)			
Median (IQR)[1,2]			
Hazard ratio (95% CI)[3]			
p-value[4]			
Duration of acute hyponatremia (hours)			
Mean (Standard Deviation)[1]			
Mean difference (95% CI)[3]			
p-value[4]			
Magnitude of variation in plasma sodium concentration in first 72h (mmol/L)			
Mean (Standard Deviation)[1]			
Mean difference (95% CI)[3]			
p-value[4]			
Maximum rate of change of plasma sodium concentration in first 72h (mmol/L/hours)			
Mean (Standard Deviation)[1]			
Mean difference (95% CI)[3]			
p-value[4]			
Primary outcome events confirmed by additional blood gas			
n/N (%)[5]			

[1] Unadjusted
[2] Using competing risks analysis
[3] Adjusted for site, participant weight pre transplant and donor type.
[4] p-value from the likelihood ratio test when including and excluding the treatment term from the model.
[5] N is the number of primary outcome events

Table XX Other outcome measures – serious adverse events and survival			
	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Serious adverse events			
Total number of events			
Acute severe hyponatraemia (symptomatic) n(%)[1]			
Acute severe hyponatraemia (non-symptomatic) n(%)[1]			
Severe hyperkalaemia n (%)[1]			
Seizures n(%)			
Other n(%)			
Number of participants experiencing at least one SAE (% of total number of participants)			
Serious adverse events (identified from plasma and blood gas results)[2]			
Total number of events			
Acute severe hyponatraemia n(%)			
Excessive rate of reduction in sodium concentration n(%)			
Excessive magnitude of reduction in sodium concentration n(%)			
Severe hyperkalaemia n(%)			
Number of participants experiencing at least one SAE (% of total number of participants)			
Survival at 90 days			
Graft % (95% CI)			
Patient % (95% CI)			
[1] Only reported for participants prior to implementation of v2.0 of the protocol (23rd June 2021). [2] Includes events reported prior to v2.0 of the protocol.			

Table XX Other outcome measure – volume of intravenous fluid received			
	Randomised Treatment		
	Standard care (n=)	Plasma-Lyte 148 (n=)	Total (n=)
Summary of IV fluid volume received			
N (%) participants who received at least one IV fluid			
Median (IQR) intravenous fluid volume (ml/kg body weight) per participant per occasion			
Total intravenous fluid volume received per participant (ml/kg body weight) by time period, Median (IQR)			
Intraoperatively			
Day 1			
Day 2			
Day 3			
All (intraoperatively to 72 hours post-transplant)			
Total intravenous fluid volume per participant (ml/kg body weight) by fluid type, Median (IQR)			
Plasma-Lyte 148			
Plasma-Lyte 148 & 5% glucose			
0.9% sodium chloride			
0.9% sodium chloride with 5% glucose			
0.45% sodium chloride			
0.45% sodium chloride with 2.5% glucose			
0.45% sodium chloride with 5% glucose			
10% glucose			
4.5% Human albumin solution			
5% Human Albumin Solution			
Hartmann's (Ringer lactate) solution			
Geloplasma			
Other			

Table XX Other outcome measure – medication and blood products			
	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Medication - n/N (%)			
Induction Immunosuppression			
Intravenous methylprednisolone			
Basiliximab			
Alemtuzumab			
ATG			
Other			
Corticosteroids			
Prednisolone			
Methylprednisolone			
Calcineurin Inhibitors (CNI)			
Tacrolimus			
Ciclosporin			
Anti-proliferative Immunosuppressants			
MMF			
Azathioprine			
Other Immmunosuppression received			
Immunoadsorption			
Double filtration plasmapheresis			
Rituximab			
Immunoglobulin			
Inotropes			
Dopamine			
Adrenaline			
Noradrenaline			
Dobutamine			
Other			
Diuretics			
Furosemide			
Bendroflumethiazide			
Chlorothiazide			
Amiloride			
Spironolactone			
Mannitol			
Insulin			
Antiemetics			
Electrolyte Supplement			
Magnesium			
Potassium			
Sodium bicarbonate			
Sodium Chloride			
Blood products received- n/N (%)			
Packed red cell			
Platelets			
Fresh Frozen Plasma			
Other			

4.6 Sub-group analysis table

Table XX Subgroup analysis, acute hyponatraemia				
	Standard care (n=)		Plasma-Lyte 148 (n=)	Total (n=)
	>50% 0.9% sodium chloride	≤50% 0.9% sodium chloride		
N/Total N (%)				
OR (95% CI)[1]				
p-value[2]				

[1] Mixed logistic regression model adjusted for site, participant weight pre transplant and donor type.
[2] p-value from the likelihood ratio test when including and excluding the treatment term from the model.

4.7 Sensitivity analysis table

Table XX Sensitivity analysis – primary outcome			
	Randomised Treatment		
	Standard care (n=)	Plasma-Lyte 148 (n=)	Total (n=)
Unadjusted			
N/Total N (%)			
OR (95% CI)			
p-value[2]			
Primary outcome with nested random participant effect			
N/Total N (%)			
OR (95% CI)[1]			
p-value[2]			
Primary outcome with multiple imputation			
N/Total N (%)			
OR (95% CI)[1]			
p-value[2]			
Primary outcome identified in blood or blood gas sodium			
Plasma			
N/Total N (%)			
Median (IQR) number of events[3]			
Blood Gas			
N/Total N (%)			
Median (IQR) number of events[3]			
All			
N/Total N (%)			
OR (95% CI)			
p-value[2]			
Median (IQR) number of events[3]			

[1] Mixed logistic regression model adjusted for site, participant weight pre transplant and donor type.
[2] p-value from the likelihood ratio test when including and excluding the treatment term from the model.
[3] per participant.

Table XX Sensitivity analysis – other electrolyte abnormalities			
	Randomised Treatment		
	Standard care (n=)	Plasma-Lyte 148 (n=)	Total (n=)
Other electrolyte abnormalities within the first 72 hours post transplantation			
Hypernatraemia			
Plasma			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Blood Gas			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
All			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Hyperkalaemia			
Plasma			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Blood Gas			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
All			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Hypokalaemia			
Plasma			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Blood Gas			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
All			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Non anion-gap acidosis			
Plasma			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Blood Gas			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
All			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Hyperglycaemia			
Plasma			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Blood Gas			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
All			
N/Total N of participants (%)			

Median (IQR) number of events[1]			
Hyperchloraemia			
Plasma			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Blood Gas			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
All			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Excessive rate of reduction in plasma sodium concentration			
Plasma			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Blood Gas			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
All			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Excessive magnitude of reduction in plasma sodium concentration			
Plasma			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
Blood Gas			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
All			
N/Total N of participants (%)			
Median (IQR) number of events[1]			
[1] Per participant			

4.8 Missing data analysis table

Table XX Summary of missing data for primary and secondary outcomes– n/N (%)			
	Randomised Treatment		
	Standard care (n=)	**Plasma-Lyte 148 (n=)**	**Total (n=)**
Blood measurements (No measurement in 72 hours post-transplant)			
Sodium level (mmol/L)			
Plasma			
Blood Gas			
Potassium level (mmol/L)			
Plasma			
Blood Gas			
Urea level (mmol/L)			
Creatinine level (micromol/L or umol/L)			
Chloride level (mmol/L)			
Plasma			
Blood Gas			
Bicarbonate level (mmol/L)			
Plasma			
Blood Gas			
Magnesium level (mmol/L)			
Calcium level (mmol/L)			
Plasma			
Blood Gas			
Phosphate level (mmol/L)			
Glucose level (mmol/L)			
Plasma			
Blood Gas			
Symptoms of acute hyponatraemia			
Nausea			
Vomiting			
Headache			
Seizures			
Other			
Weight pre transplant			
Weight in 72 hours post-transplant			
Height at transplant			
Date of discharge			
Minimum systolic blood pressure			
Maximum systolic blood pressure			

4.9 Figures

Figure XX Consort diagram

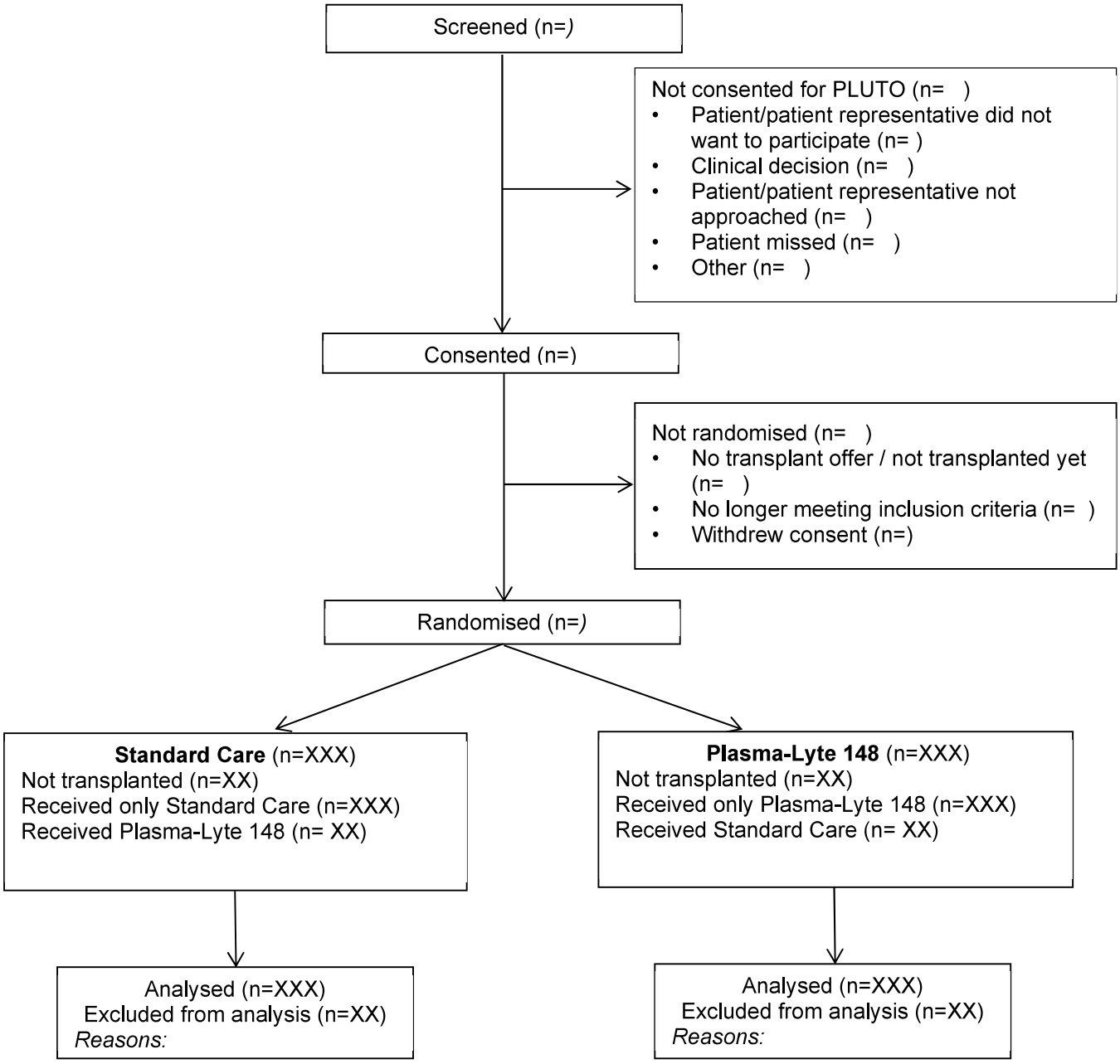

Figure XX Time to first acute hyponatraemia

A cumulative incidence curve showing the time to first developing acute hyponatraemia (defined as plasma sodium concentration <135mmol/L) within 72 hours post-transplant, by arm. Acute hyponatremia will be considered as the event and death prior to the event will be considered as the competing risk. Although if there are no deaths, the Kaplan-Meier method will be used.

Figure XX Lowest plasma sodium concentration by day

For each participant, the lowest plasma sodium measurement each day will be obtained and of these the median and interquartile range will be plotted by day and treatment arm. These will be plotted as box plots, for baseline and for the three days post-transplant. Any outliers will also be populated.

Figure XX Highest plasma chloride level by day

For each participant, the highest plasma chloride measurement each day will be obtained and of these the median and interquartile range will be plotted by day and treatment arm. These will be plotted as box plots, for baseline and for the three days post-transplant. Any outliers will also be populated.

Figure XX Highest potassium level by day

For each participant, the highest plasma potassium measurement each day will be obtained and of these the median and interquartile range will be plotted by day and treatment arm. These will be plotted as box plots, for baseline and for the three days post-transplant. Any outliers will also be populated.

5. Statistical Analysis Plan Amendments

Revision History:

Version	Author	Date	Reason for revision
1.1	Rosie Brown	20/12/2022	Updating sensitivity outcomes to incorporate blood gas results as well as plasma. Updating blood pressure outcome to normalised percentile in Table 4.4 in line with text. Separated secondary outcome tables into multiple smaller tables. Clarified some statistical methods/model fitting criteria, including how the planned models will be modified if issues with model fitting.

6. References

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