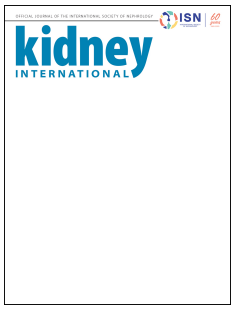
Journal Pre-proof



A pragmatic, open-label, randomized controlled trial of Plasma-Lyte-148 versus standard intravenous fluids in children receiving kidney transplants (PLUTO).

Wesley N. Hayes, MBBChir, Emma Laing, Rosemary Brown, Laura Silsby, Laura Smith, Helen Thomas, Fotini Kaloyirou, Rupa Sharma, James Griffiths, Helen Hume-Smith, MD, Prof Stephen D. Marks, MD, Nicos Kessaris, MD, Martin Christian, MD, Jan Dudley, PhD, Mohan Shenoy, MD, Michal Malina, MD, Mordi Muorah, MD PhD, Nicholas Ware, MD, Pallavi Yadav, MD, Ben Reynolds, PhD, William Bryant, PhD, Anastassia Spiridou, PhD, Jo Wray, PhD, Prof Mark J. Peters, PhD

PII: S0085-2538(23)00760-3

DOI: https://doi.org/10.1016/j.kint.2023.09.032

Reference: KINT 3631

To appear in: *Kidney International*

Received Date: 12 May 2023

Revised Date: 7 September 2023

Accepted Date: 24 September 2023

Please cite this article as: Hayes WN, Laing E, Brown R, Silsby L, Smith L, Thomas H, Kaloyirou F, Sharma R, Griffiths J, Hume-Smith H, Marks SD, Kessaris N, Christian M, Dudley J, Shenoy M, Malina M, Muorah M, Ware N, Yadav P, Reynolds B, Bryant W, Spiridou A, Wray J, Peters MJ, A pragmatic, open-label, randomized controlled trial of Plasma-Lyte-148 versus standard intravenous fluids in children receiving kidney transplants (PLUTO)., *Kidney International* (2023), doi: https://doi.org/10.1016/j.kint.2023.09.032.

A pragmatic, open-label, randomized controlled trial of Plasma-Lyte-148 versus standard intravenous fluids in children receiving kidney transplants (PLUTO).

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Population

138 pediatric kidney transplant recipients
Median age 11 (IQR 6-14) years

Randomized 1:1

Intervention

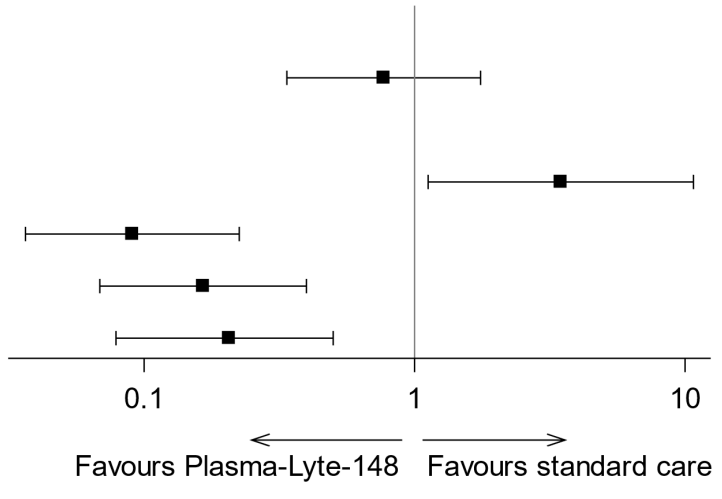
Peri-operatively:
Plasma-Lyte-148

Control

Peri-operatively:
Standard fluids, including:
0.45% NaCl ± glucose
0.9% NaCl ± glucose
Human Albumin Solution
Others

Outcomes

	Odds ratio (95% CI)	*P* value
Primary outcome		
Acute hyponatremia	0.77 (0.34, 1.75)	0.5274
Secondary outcomes		
Hypernatremia	3.47 (1.12, 10.74)	0.0223
Non-anion gap acidosis	0.09 (0.04, 0.22)	< 0.0001
Hyperchloremia	0.17 (0.07, 0.40)	< 0.0001
Hypomagnesemia	0.21 (0.08, 0.50)	0.0001



IV fluid changes

Fewer changes with Plasma-Lyte-148
Rate ratio 0.52 (0.40-0.67), p<0.0001

Other secondary outcomes

No significant differences
for all other secondary outcomes

Hayes WN, 2023

CONCLUSION

Perioperative Plasma-Lyte-148 did not change the proportion of children who experienced acute hyponatremia compared to standard fluids. Fewer fluid prescription changes were made with Plasma-Lyte-148 and hyperchloremia and acidosis were less common.

[QUERY TO AUTHOR: title and abstract rewritten by Editorial Office – not subject to change]

A pragmatic, open-label, randomized controlled trial of Plasma-Lyte-148 versus standard intravenous fluids in children receiving kidney transplants (PLUTO).

Running Head: Plasma-Lyte vs Standard Fluids in Pediatric Kidney Transplantation

Wesley N Hayes, Emma Laing, Rosemary Brown, Laura Silsby, Laura Smith, Helen Thomas, Fotini Kaloyirou, Rupa Sharma, James Griffiths, Helen Hume-Smith, Stephen D Marks, Nicos Kessaris, Martin Christian, Jan Dudley, Mohan Shenoy, Michal Malina, Mordi Muorah, Nicholas Ware, Pallavi Yadav, Ben Reynolds, William Bryant, Anastassia Spiridou, Jo Wray, Mark J Peters

Department of Pediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom (WN Hayes MBBChir, Prof SD Marks MD)
University College London Great Ormond Street Institute of Child Health, UK (WN Hayes MBBChir, Prof SD Marks MD, Prof MJ Peters PhD)
National Health Service Blood and Transplant Clinical Trials Unit, Cambridge, UK (E Laing, R Brown, L Smith, L Silsby, H Thomas, F Kaloyirou, R Sharma, J Griffiths)
Department of Anesthetics, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK (H Hume-Smith MD)
Department of Transplant Surgery, Guys and St Thomas NHS Foundation Trust, London UK (N Kessaris MD)
Department of Pediatric Nephrology, Nottingham Children's Hospital, Nottingham, UK (M Christian MD)
Department of Pediatric Nephrology, Bristol Children's Hospital, Bristol, UK (J Dudley PhD)
Department of Pediatric Nephrology, Glasgow hospital for Sick Children, UK (B Reynolds PhD)
Department of Pediatric Nephrology, Manchester Children's Hospital, Manchester, UK (M Shenoy MD)
Department of Pediatric Nephrology, Great North Children's Hospital, Newcastle, UK (M Malina MD)
Department of Pediatric Nephrology, Birmingham Children's Hospital, Birmingham, UK (M Muorah MD PhD)
Department of Pediatric Nephrology, Evelina Childrens Hospital, London, UK (N Ware MD)
Department of Pediatric Nephrology, Leeds Teaching Hospitals NHS Foundation Trust, Leeds, UK (P Yadav MD)
Department of Data Research Innovation and Virtual Environments, Great Ormond Street Hospital for Children, London, UK (W Bryant PhD, A Spiridou PhD)
Department of Psychology, Great Ormond Street Hospital for Children, London, UK (J Wray PhD)
Pediatric Intensive Care Unit, Great Ormond Street Hospital for Children, London, UK (Prof MJ Peters PhD)

Correspondence to: Dr Wesley N Hayes, Department of Pediatric Nephrology, Great Ormond Street Hospital NHS Foundation Trust, London, WC1N 3JH, United Kingdom Wesley.Hayes@gosh.nhs.uk

Telephone (++44) 02074059200 extension 0369

Abstract

Acute electrolyte and acid-base imbalance is experienced by many children following kidney transplant. This is partly because doctors give very large volumes of artificial fluids to keep the new kidney working. When severe, fluid imbalance can lead to seizures, cerebral edema and death. In this pragmatic, open-label, randomized controlled trial, we randomly assigned (1:1) pediatric kidney transplant recipients to Plasma-Lyte-148 or standard of care perioperative intravenous fluids (predominantly 0.45% sodium chloride and 0.9% sodium chloride solutions). We then compared clinically significant electrolyte and acid-base abnormalities in the first 72 hours post-transplant. The primary outcome, acute hyponatremia, was experienced by 53% of 68 participants in the Plasma-Lyte-148 group and 58% of 69 participants in the standard fluids group (odds ratio 0·77 (0·34 - 1·75)). Five of 16 secondary outcomes differed with Plasma-Lyte-148: hypernatremia was significantly more frequent (odds ratio 3·5 (1·1 – 10·8)), significantly fewer changes to fluid prescriptions were made (rate ratio 0·52 (0·40-0·67)), and significantly fewer participants experienced hyperchloremia (odds ratio 0·17 (0·07 – 0·40)), acidosis (odds ratio 0·09 (0·04 - 0·22)) and hypomagnesemia (odds ratio 0·21 (0·08 – 0·50)). No other secondary outcomes differed between groups. Serious adverse events were reported in 9% of participants randomized to Plasma-Lyte-148 and 7% of participants randomized to standard fluids. Thus, perioperative Plasma-Lyte-148 did not change the proportion of children who experienced acute hyponatremia compared to standard fluids. However fewer fluid prescription changes were made with Plasma-Lyte-148, while hyperchloremia and acidosis were less common.

Key Words

Pediatric nephrology, transplantation, hyponatremia

Lay Summary

In the first few days after a kidney transplant, children can develop harmful changes in the balance of salt, water, and acid in the bloodstream. This is because doctors give very large volumes of artificial fluids into the veins to keep the new kidney working.

This research compared the standard fluids used after a transplant operation with an alternative called Plasma-Lyte.

One hundred and thirty-eight children from nine hospitals took part. Half of them were randomly allocated to have standard fluids, and half of them to have Plasma-Lyte during and after their transplant operation.

The number of children who developed low levels of sodium (the main salt in the blood) was similar with standard fluids and Plasma-Lyte. More children developed abnormal chloride and acid balance with standard fluids. More changes to fluid prescriptions were made by doctors for children allocated to standard fluids.

Introduction

Transplantation is the treatment of choice for children with kidney failure.[1] Acute electrolyte and acid-base imbalance is experienced by many pediatric recipients in the post-operative period.[2] Abnormalities include acute hyponatremia, hyperkalemia, hyperchloremia and metabolic acidosis; smaller recipients of deceased donor kidneys are most at risk.[2]

Acute hyponatremia is associated with clinical complications including cerebral edema, seizures and death.[3,4] Pre-pubertal children are at greater risk of complications from acute hyponatremia because of the relatively low ratio of cerebrospinal fluid and brain volume compared to older children and adults.[5,6] Acute hyponatremia also contributes to symptoms such as nausea, vomiting and headaches.[7,8]

In many other clinical circumstances, children receiving isotonic fluid rather than hypotonic fluid experience less hyponatremia.[9-14] National guidance recommends isotonic fluid for children in general pediatric care.[15] This guidance was not widely adopted in pediatric transplantation due to uncertainty about its applicability in this population, and intravenous fluids are changed regularly in response to results of frequent blood tests.

Plasma-Lyte-148 is an isotonic, gluconate-acetate buffered intravenous fluid containing 140 mEq sodium, 5 mEq potassium, 3 mEq magnesium, 98 mEq chloride, 27 mEq acetate, and 23 mEq gluconate per liter.[16] There is a physiological basis to expect that Plasma-Lyte would reduce the incidence of clinically significant electrolyte and acid-base abnormalities in children following kidney transplant compared to standard fluids. In critically ill adults, use of Plasma-Lyte reduced the incidence of a composite outcome of death, new kidney replacement therapy or persistent kidney dysfunction compared to 0·9% sodium chloride, however a subsequent study showed no difference in death or acute kidney injury in this population.[17,18] In noncritically ill adults, hospital free days did not differ with use of Plasma-Lyte compared to 0·9% sodium chloride.[19] A randomized trial in children with sepsis comparing major adverse kidney events with use of balanced fluid versus 0·9% sodium chloride is currently underway.[20]

The aim of the PLUTO trial was to determine whether the incidence of clinically significant plasma electrolyte and acid-base abnormalities in pediatric kidney transplant recipients differs with Plasma-Lyte-148 compared to the existing standard of care intravenous fluids.

Methods

Study Design and Setting

PLUTO was an investigator initiated, open-label, randomized controlled trial comparing Plasma-Lyte-148 to current intravenous fluids in children receiving kidney transplants, conducted in 9 UK pediatric kidney transplant centers. A national Research Ethics Committee approved the study (HRA reference 19/LO/1866). Recruitment started on June 8, 2020 and completed August 9, 2022. The trial protocol was published previously.[21]

Participants

Patients under 18 years of age receiving a kidney-only transplant from either a living or deceased donor were eligible to participate. Multi-organ transplants were excluded. The trial was discussed with patients and parents/guardians in advance of kidney transplant, and they gave informed written consent and assent as appropriate, which was confirmed on the day of transplant. Baseline

demographic data were obtained directly from the UK Transplant Registry, held by NHS Blood and Transplant (NHSBT).

Randomization

Participants were randomized 1:1 to the intervention or control groups on the day of transplant using an online system. Randomization was stratified by transplant center and patient weight (<20kg vs ≥20kg), and further balanced within blocks of varying, undisclosed sizes. The randomization list was produced by the trial statistician using SAS statistical software.

Procedures

Participants randomized to the intervention group received either Plasma-Lyte-148 or Plasma-Lyte-148 & Glucose 5%, which could be administered interchangeably at the discretion of the clinical team, both intraoperatively and postoperatively. Participants randomized to the control group received standard intravenous fluids used at the site. Standard IV fluid practice varied between sites and included 0.45% and 0.9% sodium chloride solutions, Hartmanns, Human Albumin and colloid solutions. All sites changed the composition of IV fluid in response to regular blood test monitoring. Neither Plasma-Lyte-148 nor Plasma-Lyte-148 & Glucose 5% could be administered in the control group. The volume and rate of infusion of intravenous fluid, and the time to change from intravenous to enteral fluid, were decided by the treating clinician.

With the exception of intravenous fluid composition, all participants received standard clinical transplant care.

Participants were assessed daily in hospital for the first 72 hours post-transplant, at hospital discharge, and at their 3-month clinic follow-up visit. Clinical data and adverse events were captured using a secure web-based electronic case report form in the trial database (MACRO). Laboratory results for 72 hours following the start of the transplant operation were downloaded directly from the laboratory information management systems at each site, then uploaded to a secure web-based platform. Three month follow up data were obtained directly from the UK Transplant Registry. Data quality was assured by regular independent central and on-site monitoring.

Outcomes

The primary outcome measure was acute hyponatremia within the first 72 hours post-transplant, defined as any laboratory plasma sodium concentration <135mmol/L.

Secondary outcomes included hypernatremia (defined as plasma sodium concentration >145mmol/l), hyperkalemia (plasma potassium >5·5mmol/L), hypokalemia (plasma potassium <3·5mmol/L), non-anion-gap acidosis (plasma bicarbonate <20mmol/L and anion gap <20mmol/L), hyperglycemia (random blood glucose >5·5 mmol/L), hypomagnesemia (plasma magnesium <0·7mmol/L), hyperchloremia (plasma chloride >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), symptoms of hyponatremia, maximum and minimum systolic blood pressure, degree of fluid overload (defined as maximal proportional increase in weight from pre-transplant weight), time to discharge from hospital, transplant kidney function (estimated glomerular filtration rate at 1, 3 and 7 days) and the number of changes in intravenous fluid (defined by changes to the type of fluid prescribed and administered) within the first 72 hours post-transplant.

Safety reporting included notification of Serious Adverse Events (SAEs) to NHS Blood and Transplant Clinical Trials Unit within 24 hours. We used the Common Terminology Criteria of Adverse Events classification. A list of pre-defined SAEs unrelated to fluid composition were excluded from reporting

including surgical, infective, immunological and medication related complications.[21] Serious adverse events were monitored regularly by the independent data monitoring committee to ensure ongoing safety of trial participants.

Statistical Analysis

On the basis of published cohort data and a Cochrane meta-analysis, we assumed a 59% incidence of hyponatremia in the standard fluid group with a reduction to 29·5% with Plasma-Lyte-148 fluid.[2,9] The sample size required to detect this difference with 90% power using a two-sided test, 5% type I error and 1:1 allocation allowing for two formal interim analyses for harm or benefit was 128 participants. Allowing for 10% attrition, the total number of participants required was 144. The sample size was based on an unadjusted log odds ratio test (with interim analyses as described above).

For all analyses, participants were analyzed according to their allocated arm. Analysis for all efficacy outcomes was performed in a modified intention to treat cohort which included all randomized participants who received a transplant (excluding those who were not transplanted and therefore had no outcome data). An additional per protocol analysis was performed of the primary outcome, which also excluded those withdrawn, randomized in error or who had a protocol deviation. Safety analyses included all randomized, transplanted participants.

The proportion of participants who experienced hyponatremia was analyzed using a logistic regression model adjusting for donor type (living vs deceased donor), participant weight (<20kg vs ≥20kg pre-transplant) and transplant center as a random effect. A pre-specified subgroup analysis of the primary outcome split the standard fluids group into participants who received >50% versus ≤50% 0·9% sodium chloride fluid by total volume. Two pre-specified sensitivity analyses of the primary outcome were performed: an unadjusted analysis, and acute hyponatremia as identified in plasma or blood gas, rather than plasma alone.

Secondary outcomes which assessed the incidence of other electrolyte and acid-base disturbance were analyzed using the same model as the primary outcome, though adjustment factors differed based on model convergence, following a pre-defined approach. Adjusted normal linear regression models were used to assess differences in the continuous secondary outcomes, adjusting for repeated measures (by additionally incorporating a participant random effect within sites) where appropriate; an adjusted negative binomial model was used to compare number of changes in the intravenous fluid composition and an adjusted Cox proportional hazards model was used to assess differences in time to discharge.

An independent Data Monitoring Committee oversaw the safety data and interim analyses. To preserve the overall 5% Type I error rate for the trial and allow early stopping of the trial in the case of strong evidence for harm or benefit, the trial used a group sequential design with O'Brien Fleming boundaries, resulting in a significance level of $P < 0.0422$ at the final analysis. Two formal interim analyses were conducted after 70 and 100 randomizations, after allowing time for primary outcome data to be obtained. The stopping boundaries were used as a guideline alongside other safety data available to the committee and used as part of their overall assessment of the trial.

The statistical analysis plan was finalized before data were made available and results were analyzed. Statistical analyses were performed using SAS version 9·4M5. For all analyses, $P < 0.05$ was considered statistically significant. No adjustments were made to account for multiple testing, so results for secondary outcome analyses should be considered hypothesis generating only. The trial is registered with the ISCTRN registry (ISRCTN: 16586164), the European Union Clinical Trials Register (EudraCT: 2019-003025-22) and the Cochrane Central Register of Controlled Trials (CN-02070104).

Funding
The study was funded by the National Institute for Health and Care Research (project reference number NIHR200512).

Results

Between June 8, 2020 and August 9, 2022, 238 children were assessed for trial eligibility (**Figure 1**). One hundred and forty-eight consented and 144 were randomized (72 (50%) to the Plasma-Lyte-148 group and 72 (50%) to the standard fluids group, **Figure 1**). One hundred and thirty-eight proceeded to transplant in the study period and were included in the modified intention to treat cohort, of whom one participant did not have sufficient blood test data for inclusion in the primary analysis. Baseline participant and transplant characteristics are summarized in **Tables 1 and 2** respectively. The volumes and types of intravenous fluids received are summarized in **Table 3**; participants in the standard fluids group received predominantly 0.45% sodium chloride and 0.9% sodium chloride solutions. Medication and blood products received are summarized in **Supplementary Table S1**.

In the primary modified intention to treat analysis, 36/68 (53%) participants in the Plasma-Lyte group and 40/69 (58%) participants in the standard fluids group experienced acute hyponatremia (OR 0·77 (0·34 - 1·75); *P* = 0·53, **Table 4, Figure 2**). Similarly, per-protocol analysis of the primary outcome showed no difference in acute hyponatremia; 31/52 (60%) in the Plasma-Lyte group vs 38/62 (61%) in the standard fluid group (OR 0·80 (0·32 - 2·01), *P* = 0·63, **Table 4**). A sub-group analysis that divided participants randomized to standard fluids into groups who received >50% vs ≤50% 0·9% sodium chloride, and sensitivity analyses that included all blood gas sodium results and an unadjusted analysis, confirmed no significant difference in acute hyponatremia between participants randomized to Plasma-Lyte-148 versus standard fluids (**Supplementary Tables S2, S3**). Symptoms of hyponatremia, time to hyponatremia, duration of hyponatremia and magnitude and rate of change of plasma sodium concentration were similar between groups (**Supplementary Tables S4, S5**). The distribution of lowest plasma sodium concentration per participant per day is illustrated in **Figure 3**.

The proportion of participants who experienced non-anion gap acidosis was significantly lower in the Plasma-Lyte group: 12/63 (19%) participants in the Plasma-Lyte group vs 44/64 (69%) participants in the standard fluid group (OR 0·09 (0·04 - 0·22), *P* < 0·0001, **Table 5, Figure 2**). Fewer participants in the Plasma-Lyte group developed hyperchloremia (36/68 (53%)) than the standard fluid group (59/69 (86%)) (OR 0·17 (0·07 – 0·40), *P* < 0·0001, **Table 5, Figure 2**).

Hypomagnesemia was less frequent in the Plasma-Lyte than standard fluid group (10/67 (15%) vs 31/69 (45%) participants; OR 0·21(0·08 – 0·50) *P* = 0·0001, **Table 5, Figure 2**). Hypernatremia was more frequent with Plasma-Lyte, 17/68 (25%) compared to 8/69 (12%) in the standard fluid group (OR 3·5 (1·1 – 10·8) *P* = 0·022, **Table 5, Figure 2**). There were no differences between groups for hyperkalemia, hypokalemia, excessive rate and excessive magnitude of reduction in plasma sodium concentration (**Table 5, Figures 2 and 3**). When blood gas results were considered as a pre-specified sensitivity, differences observed between the two treatment groups were comparable to those seen in plasma alone (**Supplementary Table S6**).

The mean number of changes of fluid composition was 2·6 in the Plasma-Lyte group and 4·6 in the standard fluid group. When adjusted for donor type, pre-transplant weight, site, and hours at risk of event, there was a significant difference in the number of changes between the two treatment groups, with a rate ratio of 0·52 (95% CI: 0·40-0·67, *P* < 0·0001).

The median length of stay was 11 days in both treatment groups. No significant difference in the hazards of discharge between Plasma-Lyte and standard care groups was found (HR 1·32 95% CI: (0·93-1·86), *P* = 0·12, **Supplementary Table S7**). The mean degree of fluid overload was 7.8 (SD 7.8)% in the standard fluids group, and 7.7 (SD 7.4)% with Plasma-Lyte-148 (**Supplementary Table S8**).

Transplant function measured by estimated glomerular filtration rate on days 1, 3 and 7 post-transplant was similar between groups (**Supplementary Table S9**, Mean Ratio: 1·11 95% CI: (0·90-1·36), *P* = 0·34). Maximum and minimum systolic blood pressure percentiles were also similar between groups (**Supplementary Table S10**). Hyperglycemia was not assessed due to a high rate of data missingness (30%).

A total of 13 serious adverse events were reported in 6 (9%) of 69 participants randomized to Plasma-Lyte and 5 (7%) of 69 randomized to standard fluids (**Supplementary Table S11**). Pre-specified safety outcomes of acute severe hyponatremia (reduction of >10mmol/L from pre-transplant level or rate of reduction >1mmol/L/hour averaged over 6 hours on laboratory or blood gas samples) or severe hyperkalemia (> 6·5mmol/l on laboratory or blood gas samples) were identified in 15 (22%) participants in the Plasma-Lyte group and 24 (35%) in the standard care group. Three kidney transplants failed in the first 90 days in the standard fluids group, and none in the Plasma-Lyte group. One participant in the Plasma-Lyte group died from an unrelated surgical complication.

Discussion

The present trial shows that for children receiving kidney transplants, perioperative administration of Plasma-Lyte-148 fluid did not reduce the incidence of hyponatremia compared to standard fluids. Standard fluids were changed more frequently than PlasmaLyte-148, and had higher rates of metabolic acidosis, hyperchloremia and hypomagnesemia.

The equivalence of hyponatremia with use of both isotonic and predominantly hypotonic standard fluids in children receiving kidney transplants contrasts existing data from other clinical settings.[9-13] This may relate to unique aspects of pediatric kidney transplant practice. The volume of fluids administered to participants exceeded three times usual maintenance amounts. Compounding this, the post-operative antidiuretic response limits water excretion. Clinically significant fluid overload was observed in most participants, with a mean increase in weight of 7.7% after transplant. Water overload may therefore underlie the markedly higher incidence of hyponatremia in the present study compared to the general pediatric population, and the lack of a difference with isotonic fluid. It is also possible that the trial lacked sufficient power to detect a difference in hyponatremia. The sample size was based on a systematic review comparing 0.9% sodium chloride to hypotonic fluid, and did not include studies conducted in pediatric transplant recipients.[9] The tonicity of Plasma-Lyte-148 is lower than 0.9% sodium chloride, and the control group in our study received a combination of fluids. These factors may have diluted a difference in hyponatremia. Nevertheless, this trial does reduce uncertainty about the effect size with the first randomized data in this population.

Hypernatremia was more frequent with Plasma-Lyte-148 than standard fluids in the present study, consistent with data in children with acute illness.[22] The clinical relevance of this is unknown; no related adverse events were reported.

The type of intravenous fluid administered was changed a mean of 4·6 times in 72 hours in the standard fluid group, and 2·6 times in the Plasma-Lyte group. Very frequent blood tests and changes to fluids consumes significant healthcare resource. The present trial did not include a health economic

analysis, however the potential cost benefit of reducing fluid changes and blood tests with use of Plasma-Lyte-148 could be evaluated in future research.

The present trial found less hyperchloremia and less metabolic acidosis with Plasma-Lyte-148 than standard fluids. This finding is consistent with a systematic review and subsequent randomized trial in adult kidney transplant recipients, and a randomized trial in children on intensive care.[23-25] A recent randomized trial in deceased donor kidney transplant recipients found that Plasma-Lyte-148 reduced the incidence of delayed graft function compared with 0.9% sodium chloride; our study did not assess this outcome in children.[26] We observed no difference in transplant kidney function, graft or patient survival between the Plasma-Lyte-148 and standard fluid groups, although the study was not powered for these outcomes. This concurs with findings from a recent clinical trial in critically ill adult patients that compared acute kidney injury and patient survival with Plasma-Lyte-148 to 0·9% sodium chloride fluid, and contrasts with previous data suggesting a benefit to kidney and survival outcomes from balanced fluid.[17,18]

A perceived risk of hyperkalemia from the potassium content of Plasma-Lyte concerned some pediatric nephrologists, however the incidence of hyperkalemia was no greater with Plasma-Lyte-148 than predominantly potassium-free standard fluids in the present trial. This is consistent with data in adult kidney transplant recipients.[23,24,27] Previous concerns about an increased risk of hyperkalemia with use of Plasma-Lyte-148 appear not to be justified.

Hypomagnesemia is an independent risk factor for new onset diabetes after transplant in adult kidney recipients, however the association in children has not been established.[28,29] In the present study, fewer participants experienced hypomagnesemia with Plasma-Lyte-148 than standard fluids. Insufficient blood glucose data were available to examine the secondary outcome of post-transplant hyperglycemia in the present trial; the possibility of a benefit from Plasma-Lyte-148 on post-transplant diabetes mellitus could be evaluated in future research.

Our study had a number of strengths: it recruited a high proportion of eligible children from the majority of UK children's kidney transplant centers. Of the 179 pediatric kidney transplants performed during the period each site was open, 138 (77%) were randomized in the trial with a diverse range of heritage backgrounds. We used a pragmatic approach with intervention and comparator treatments that reflect care as it is delivered in real-world clinical practice. Limitations included the open label design; blinding was not considered feasible which may have impacted the treatment effect. Plasma sodium levels were a focus of clinicians' postoperative management, as reflected by multiple changes to the type of intravenous fluids used in the standard fluids group. Furthermore, standardization of fluids administered in the control group was not feasible due to variation in the fluid regimens used between different clinicians and sites, and the established practice of changing fluid in response to frequent blood test monitoring. Postoperative urine output data were not collected. Per protocol and subgroup analyses to account for different types of fluid used in both the intervention and control groups confirmed the primary results, although the study was not powered for these analyses.

The primary result of our study was unexpected because it contrasts with evidence in other populations. Post-operative hyponatremia is common in children receiving transplants, and the lack of improvement with balanced isotonic fluid warrants further evaluation; whether lower volumes of intravenous fluid would reduce the incidence of hyponatremia in this population is unknown.

In conclusion, Plasma-Lyte-148 fluid did not change the incidence of acute hyponatremia in children receiving kidney transplants compared to standard intravenous fluids. Fewer fluid prescription changes were made with Plasma-Lyte-148 and hyperchloremia and acidosis were less common.

Disclosure Statement
The authors have no competing interests.

Acknowledgements
This project was funded by the National Institute for Health and Care Research (NIHR) under its Research for Patient Benefit (RfPB) Program (Grant Reference Number NIHR200512). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The study was sponsored by Great Ormond Street Hospital for Children NHS Foundation Trust and supported by the Data Research Innovation and Virtual Environments Team at Great Ormond Street Hospital.

Our thanks to patient and parent representatives who have contributed to the design of this study, and to the NIHR Great Ormond Street Hospital Young Person's Advisory Group for research (YPAG) for co-designing patient information resources.

We are grateful to members of the trial oversight committees who supported delivery of the study: Karen Stevenson (NHS Greater Glasgow and Clyde), Prof Christopher Watson and David Inwald (Cambridge University Hospitals NHS Foundation Trust), Kerri Barber (ICON plc), Simon Knight (Nuffield Department of Surgical Sciences, Centre for Evidence in Transplantation), Francesca Clemons and Renate Hodge (National Health Service Blood and Transplant Clinical Trials unit), Mandy Wan and Rachel Hilton (Evelina Children's Hospital), Mairead Convery (Belfast Health and Social Care Trust), Shivaram Hegde (University Hospital of Wales Cardiff), Henry Morgan and Philip Arnold (Alder Hey Children's NHS Foundation Trust), Shuman Haq (University Hospital Southampton NHS Foundation Trust), Helen Dalgleish and Angela Branson (Manchester University NHS Foundation Trust), Ilyas Ali (Great Ormond Street Hospital for Children NHS Foundation Trust) and Nicholas Prince (St George's Hospital).

Contributors
WNH developed the idea for this study, drafted this manuscript and had oversight of the study delivery with mentorship from MJP. WNH, EL, LSm, HT and MJP applied for funding and developed the trial protocol. HHS, SDM, NK, MC, JD, MS, M Malina, M Mourah, NW, PY, WB, JW and AS are co-investigators and contributed to delivery of the trial. EL, FK, JG are the trial managers, RS the data manager and RB, LSi, LSm and HT the trial statisticians at NHSBT Clinical Trials Unit, all of whom had direct access to the data, and verified the data and the statistical analyses. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data Sharing Statement
Data requests should be submitted to the corresponding author (PLUTO Chief Investigator Dr Wesley Hayes (wesley.hayes@gosh.nhs.uk)) or the PLUTO Trial Manager (PLUTO@nhsbt.nhs.uk). A full data sharing request form will be required which will be reviewed by the sponsor and/or the relevant NHSBT research group, depending on the scope. Full anonymized datasets will be available no later than 18 months after the last participant was recruited. The study protocol has previously been published (doi: 10.1136/bmjopen-2021-055595), and the statistical analysis plan is included in the supplementary material. The types of analyses and mechanisms are to be agreed as part of the data request prior to data sharing, and a contract is mandatory before data is shared with a third party.

Supplementary Materials

Protocol versions 1.0, 1.1, 2.0 and summary of changes
Statistical Analysis Plan version 1.1
Supplementary Tables S1 – S11
Trial Management Group
Independent Trial Steering Committee
Independent Data Monitoring Ethics Committee
Supplemental statistical methods

References

1. Roach JP, Bock ME, Goebel J. Pediatric kidney transplantation. *Seminars in pediatric surgery* 2017; **26**(4): 233-40.
2. Hayes W, Longley C, Scanlon N, et al. Plasma electrolyte imbalance in pediatric kidney transplant recipients. *Pediatr Transplant* 2019: e13411.
3. Cansick J, Rees L, Koffman G, Van't Hoff W, Bockenhauer D. A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation. *Pediatr Nephrol* 2009; **24**(6): 1231-4.
4. Drake K, Nehus E, Goebel J. Hyponatremia, hypo-osmolality, and seizures in children early post-kidney transplant. *Pediatr Transplant* 2015; **19**(7): 698-703.
5. Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *Bmj* 1992; **304**(6836): 1218-22.
6. Ayus JC, Achinger SG, Arieff A. Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. *Am J Physiol Renal Physiol* 2008; **295**(3): F619-24.
7. Gankam Kengne F, Decaux G. Hyponatremia and the Brain. *Kidney Int Rep* 2018; **3**(1): 24-35.
8. Giuliani C, Peri A. Effects of Hyponatremia on the Brain. *J Clin Med* 2014; **3**(4): 1163-77.
9. McNab S, Ware RS, Neville KA, et al. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. *Cochrane Database Syst Rev* 2014; (12): CD009457.
10. Foster BA, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. *J Pediatr* 2014; **165**(1): 163-9 e2.
11. Wang J, Xu E, Xiao Y. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. *Pediatrics* 2014; **133**(1): 105-13.
12. Choong K, Kho ME, Menon K, Bohn D. Hypotonic versus isotonic saline in hospitalised children: a systematic review. *Arch Dis Child* 2006; **91**(10): 828-35.
13. McNab S, Duke T, South M, et al. 140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial. *Lancet* 2015; **385**(9974): 1190-7.
14. Ratnjeet K, Pallavi P, Jhamb U, Saxena R. 0.45% Versus 0.9% Saline in 5% Dextrose as Maintenance Fluids in Children Admitted With Acute Illness: A Randomized Control Trial. *Pediatr Emerg Care* 2022; **38**(9): 436-41.
15. Intravenous fluid therapy in children and young people in hospital. London; 2020.
16. Electronic medicines compendium. Plasma-Lyte 148 (pH 7.4) solution for infusion.
17. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. *N Engl J Med* 2018; **378**(9): 829-39.

18. Finfer S, Micallef S, Hammond N, et al. Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. *N Engl J Med* 2022; **386**(9): 815-26.
19. Self WH, Semler MW, Wanderer JP, et al. Balanced Crystalloids versus Saline in Noncritically Ill Adults. *N Engl J Med* 2018; **378**(9): 819-28.
20. Weiss SL, Balamuth F, Long E, et al. PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FlUid in Sepsis: study protocol for the PRoMPT BOLUS randomized interventional trial. *Trials* 2021; **22**(1): 776.
21. Hayes W, Laing E, Foley C, et al. Multicentre randomised controlled trial: protocol for Plasma-Lyte Usage and Assessment of Kidney Transplant Outcomes in Children (PLUTO). *BMJ Open* 2022; **12**(3): e055595.
22. Lehtiranta S, Honkila M, Kallio M, et al. Risk of Electrolyte Disorders in Acutely Ill Children Receiving Commercially Available Plasmalike Isotonic Fluids: A Randomized Clinical Trial. *JAMA Pediatr* 2021; **175**(1): 28-35.
23. Wan S, Roberts MA, Mount P. Normal saline versus lower-chloride solutions for kidney transplantation. *Cochrane Database Syst Rev* 2016; (8): CD010741.
24. Weinberg L, Harris L, Bellomo R, et al. Effects of intraoperative and early postoperative normal saline or Plasma-Lyte 148(R) on hyperkalaemia in deceased donor renal transplantation: a double-blind randomized trial. *British journal of anaesthesia* 2017; **119**(4): 606-15.
25. Raman S, Gibbons KS, Mattke A, et al. Effect of Saline vs Gluconate/Acetate-Buffered Solution vs Lactate-Buffered Solution on Serum Chloride Among Children in the Pediatric Intensive Care Unit: The SPLYT-P Randomized Clinical Trial. *JAMA Pediatr* 2023; **177**(2): 122-31.
26. Collins MG, Fahim MA, Pascoe EM, et al. Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): a pragmatic, double-blind, randomised, controlled trial. *Lancet* 2023.
27. Adwaney A, Randall DW, Blunden MJ, Prowle JR, Kirwan CJ. Perioperative Plasma-Lyte use reduces the incidence of renal replacement therapy and hyperkalaemia following renal transplantation when compared with 0.9% saline: a retrospective cohort study. *Clin Kidney J* 2017; **10**(6): 838-44.
28. Huang JW, Famure O, Li Y, Kim SJ. Hypomagnesemia and the Risk of New-Onset Diabetes Mellitus after Kidney Transplantation. *Journal of the American Society of Nephrology : JASN* 2016; **27**(6): 1793-800.
29. Chanchlani R, Joseph Kim S, Kim ED, et al. Incidence of hyperglycemia and diabetes and association with electrolyte abnormalities in pediatric solid organ transplant recipients. *Nephrol Dial Transplant* 2017; **32**(9): 1579-86.

Figure Titles and Legends

Figure 1: Trial Profile

Figure 2: Primary and Secondary Electrolyte Outcomes - Tornado and forest plot illustrating the number and proportion of participants that experienced the outcome alongside the adjusted odds ratio and 95% confidence interval

Figure 3: Other outcomes: Lowest plasma sodium per participant per day, highest plasma chloride per participant per day, and highest plasma potassium per participant per day, for the first 72 hours post-transplant

Table 1 **Baseline characteristics**
Data are n (%) for categorical variables and median (IQR) for continuous variables

	Randomized Treatment		
Participant characteristic	**Standard care (n=69)**	**Plasma-Lyte-148 (n=69)**	**Total (n=138)**
Age (years)	11 (6 - 14)	10 (6 - 15)	**11 (6 - 14)**
Male	39 (57)	37 (54)	**76 (55)**
Ethnic origin			
Asian	10 (14)	9 (14)	**19 (14)**
Black	5 (7)	7 (11)	**12 (9)**
Mixed	1 (1)	2 (3)	**3 (2)**
White	47 (68)	38 (58)	**85 (63)**
Other	2 (3)	4 (6)	**6 (4)**
Unknown	4 (6)	6 (9)	**10 (7)**
Cause of end stage kidney disease			
Tubulointerstitial disease (CAKUT/non-CAKUT)	29 (42)	29 (42)	**58 (42)**
Glomerular disease	4 (6)	8 (12)	**12 (9)**
Hereditary nephropathies	6 (9)	6 (9)	**12 (9)**
Systemic diseases	2 (3)	6 (9)	**8 (6)**
Other	28 (41)	20 (29)	**48 (35)**
Native urine output (ml/kg/24 hours)	16 (0 - 43)	5 (0 - 29)	**10 (0 - 37)**
Dialysis type			
Hemodialysis	24 (35)	27 (39)	**51 (37)**
Peritoneal dialysis	25 (36)	30 (43)	**55 (40)**
Pre-emptive	20 (29)	12 (17)	**32 (23)**
Weight (kg)	33 (18 - 48)	32 (17 - 48)	**32 (17 - 48)**
Height (cm)	140 (106 - 155)	135 (108 - 156)	**139 (106 - 155)**
BMI (kg/m^2)	17 (16 - 20)	17 (15 - 19)	**17 (15 - 19)**
Systolic blood pressure[a]	119 (108 - 128)	120 (110 - 131)	**120 (109 - 130)**
Blood group			
O	28 (41)	29 (43)	**57 (42)**
A	29 (42)	19 (28)	**48 (35)**
B	6 (9)	17 (25)	**23 (17)**
AB	6 (9)	3 (4)	**9 (7)**
Recipient waiting time in days (if deceased donor transplant)	671 (346 - 1011)	680 (329 - 1230)	**671 (333 - 1084)**
cRF (%)[b]	0 (0 - 47)	0 (0 - 3)	**0 (0 - 33)**
Graft number			
First	61 (88)	65 (96)	**126 (92)**
Second	8 (12)	3 (4)	**11 (8)**

[a]Maximum of three measurements at baseline for each participant.
[b]Calculated Reaction Frequency
Summary of missing data: Ethnicity is missing for 3 participants; Native urine output is missing for 12 participants; Height and BMI are missing for 4 participants; Systolic blood pressure, blood group, cRF, and graft number are missing for 1 participant; Age, sex, cause of end stage kidney disease, dialysis type, weight, and waiting time are missing for no participants.

Table 2 **Transplant characteristics**
Data are n (%) for categorical variables and median (IQR) for continuous variables

	Randomized Treatment		
	Standard care (n=69)	**Plasma-Lyte-148 (n=69)**	**Total (n=138)**
Cold ischemia time (hours)[a]			
Deceased donor	11 (9 - 13)	12 (11 - 15)	**11 (9 - 14)**
Living donor	4 (3 - 5)	4 (3 - 5)	**4 (3 - 5)**
HLA mismatch (at A, B, DR locus)			
000	6 (9)	6 (10)	**12 (10)**
[0 DR and 0/1 B]	29 (45)	21 (35)	**50 (40)**
[0 DR and 2 B] or [1 DR and 0/1 B]	26 (41)	32 (53)	**58 (47)**
[1 DR and 2 B] or [2 DR]	3 (5)	1 (2)	**4 (3)**
Graft placement			
Intra-abdominal	16 (23)	8 (12)	**24 (17)**
Extraperitoneal	53 (77)	61 (88)	**114 (83)**
Destination of transfer from operation theatre			
PICU	32 (46)	37 (54)	**69 (50)**
Ward	37 (54)	32 (46)	**69 (50)**
Donor characteristics			
Donor type			
DBD	25 (36)	20 (29)	**45 (33)**
DCD	4 (6)	6 (9)	**10 (7)**
Living	40 (58)	42 (62)	**82 (60)**
Donor age (years)	38 (32 - 47)	38 (30 - 42)	**38 (31 - 43)**
Donor ethnicity			
Asian	5 (7)	11 (16)	**16 (12)**
Black	3 (4)	2 (3)	**5 (4)**
Mixed	0 (0)	0 (0)	**0 (0)**
White	55 (82)	50 (75)	**105 (78)**
Other	4 (6)	4 (6)	**8 (6)**
Unknown	0 (0)	0 (0)	**0 (0)**
Donor BMI	24 (21 - 28)	27 (23 - 30)	**26 (22 - 29)**
Blood group match			
Identical	54 (78)	55 (81)	**109 (80)**
Compatible	14 (20)	9 (13)	**23 (17)**
Incompatible	1 (1)	4 (6)	**5 (4)**

[a]Elapsed time from start of perfusion to time kidney perfused with recipient's blood
Summary of missing data: Cold ischemia time is missing for 7 participants; HLA mismatch is missing for 14 participants; Donor BMI is missing for 15 participants; Donor type, donor age, and blood group match is missing for 1 participant; Donor ethnicity is missing for 4 participants; Graft placement and destination of transfer from operation theatre is missing for no participants.

Table 3	**Volume of intravenous fluids received**			
		Randomized Treatment		
		Standard care (n=69)	**Plasma-Lyte-148 (n=69)**	**Total (n=138)**
Summary of IV fluid volume received				
N (%) participants who received at least one IV fluid		69 (100)	69 (100)	**138 (100)**
Median (IQR) intravenous fluid volume (ml/kg body weight) per participant per occasion		19 (9 - 52)	23 (10 - 63)	**20 (9 - 58)**
Total intravenous fluid volume received per participant (ml/kg body weight) by time period, Median (IQR)				
Intraoperatively		73 (50 - 98)	77 (55 - 104)	**74 (53 - 101)**
Day 1		132 (99 - 221)	149 (91 - 215)	**137 (94 - 219)**
Day 2		54 (15 - 104)	51 (25 - 86)	**52 (17 - 92)**
Day 3		18 (7 - 46)	20 (13 - 38)	**19 (11 - 40)**
All (intraoperatively to 72 hours post-transplant)		284 (195 - 371)	267 (201 - 385)	**273 (195 - 385)**
Total intravenous fluid volume per participant (ml/kg body weight) by fluid type, N Median (IQR)				
Plasma-Lyte-148	N	5	68	**73**
	Median (IQR)	43 (9 - 55)	248 (180 - 342)	**242 (168 - 318)**
Plasma-Lyte-148 & 5% glucose	N	0	38	**38**
	Median (IQR)		32 (12 - 51)	**32 (12 - 51)**
0·9% sodium chloride	N	59	7	**66**
	Median (IQR)	87 (41 - 172)	30 (7 - 36)	**83 (33 - 164)**
0·9% sodium chloride with 5% glucose	N	11	0	**11**
	Median (IQR)	22 (10 - 58)		**22 (10 - 58)**
0·45% sodium chloride	N	40	1	**41**
	Median (IQR)	57 (22 - 178)	63 (63 - 63)	**61 (23 - 169)**
0·45% sodium chloride with 2·5% glucose	N	41	1	**42**
	Median (IQR)	71 (19 - 140)	92 (92 - 92)	**78 (19 - 140)**
0·45% sodium chloride with 5% glucose	N	19	0	**19**
	Median (IQR)	26 (17 - 55)		**26 (17 - 55)**
10% glucose	N	10	4	**14**
	Median (IQR)	11 (2 - 32)	6 (5 - 9)	**7 (4 - 15)**
4·5% Human Albumin solution	N	7	1	**8**
	Median (IQR)	30 (15 - 52)	17 (17 - 17)	**24 (16 - 47)**
5% Human Albumin Solution	N	3	3	**6**
	Median (IQR)	20 (11 - 39)	5 (5 - 8)	**9 (5 - 20)**
Hartmann's (Ringer lactate) solution	N	38	3	**41**
	Median (IQR)	63 (44 - 93)	90 (18 - 192)	**64 (44 - 93)**
Geloplasma	N	0	0	**0**
	Median (IQR)			
Other	N	10	2	**12**
	Median (IQR)	9 (4 - 13)	7 (4 - 9)	**9 (4 - 13)**

N is calculated only for those with fluid volumes reported. Instances where fluids were reported without corresponding volumes were excluded.

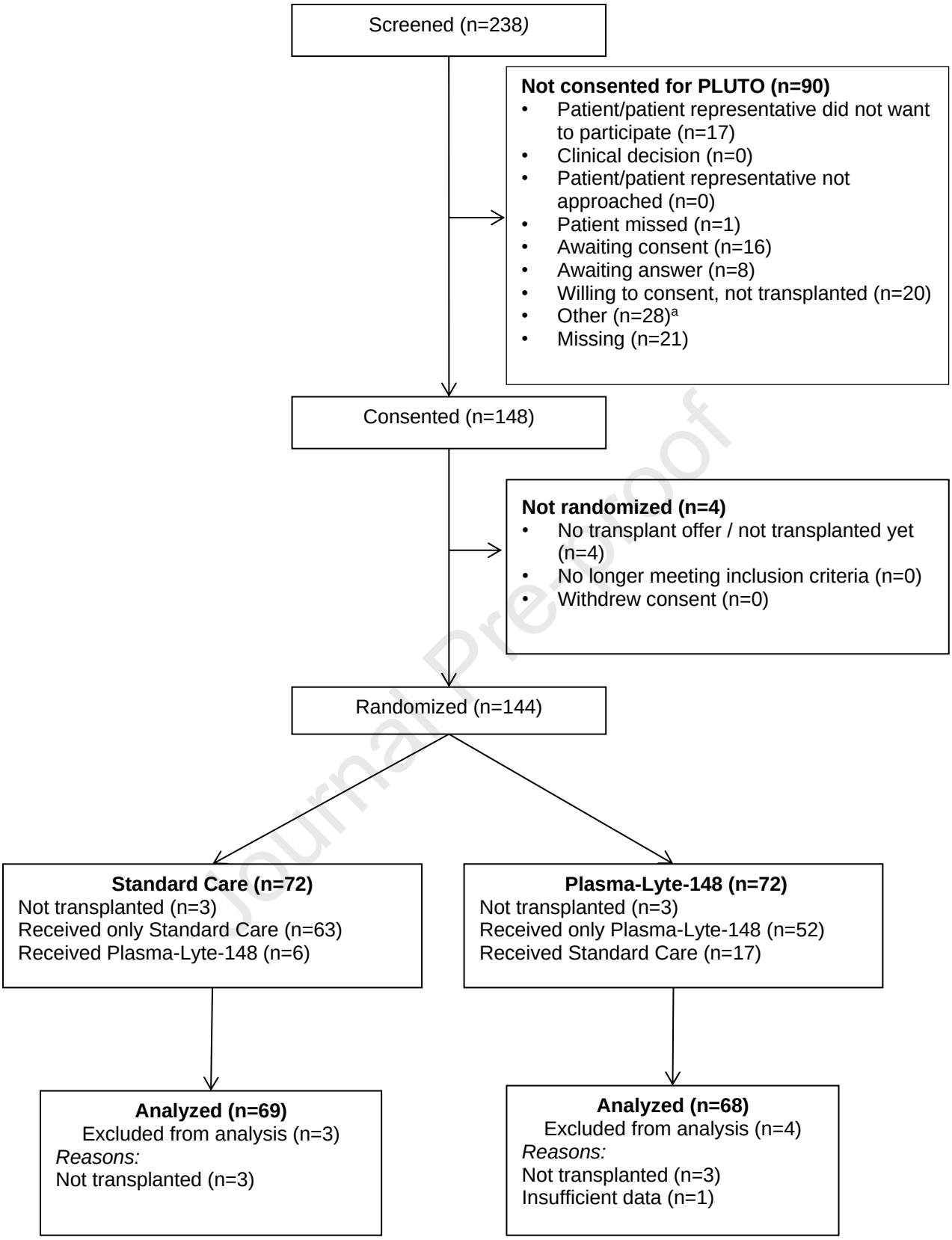
Table 4 Primary outcome - acute hyponatremia			
	Randomized Treatment		
	Standard care (n=69)	**Plasma-Lyte-148 (n=68)**	**Total (n=137)**
Modified intention-to-treat			
N/Total N (%)	40/69 (58)	36/68 (53)	**76/137 (55)**
OR (95% CI)[a]		0·77 (0·34 - 1·75)	
p-value[b]		0·5274	
Unadjusted risk difference (95% CI)		-5% (-22%, 12%)	
Median (IQR) number of events[c]	1·0 (1·0 - 2·0)	1·0 (1·0 - 2·0)	**1·0 (1·0 - 2·0)**
Per-protocol[d]			
N/Total N (%)	38/62 (61)	31/52 (60)	**69/114 (61)**
OR (95% CI)[a]		0·80 (0·32 - 2·01)	
p-value[b]		0·6287	
Median (IQR) number of events[c]	1·0 (1·0 - 2·0)	1·0 (1·0 - 2·0)	**1·0 (1·0 – 2·0)**

[a]Mixed logistic regression model adjusted for site, participant weight pre transplant and donor type.
[b]p-value from the likelihood ratio test when including and excluding the treatment term from the model.
[c]Per participant with at least one event
[d]Per-protocol analysis excluded those withdrawn (n=1), randomized in error (n=0), and who had a protocol deviation (n=24, of which 23 were fluid deviations). Participants may fall into more than one of the exclusion criteria.

Table 5 Secondary outcomes – other electrolyte and acid-base abnormalities			
	Randomized Treatment		
	Standard care (n=69)	**Plasma-Lyte-148 (n=69)**	**Total (n=138)**
Other electrolyte abnormalities within the first 72 hours post transplantation			
Hypernatremia			
N/Total N of participants (%)	8/69 (12)	17/68 (25)	**25/137 (18)**
OR (95% CI)[a]		3·47 (1·12 - 10·74)	
p-value[f]		0·0223	
Median (IQR) number of events[i]	1·0 (1·0 - 2·0)	1·0 (1·0 - 2·0)	**1·0 (1·0 - 2·0)**
Hyperkalemia			
N/Total N of participants (%)	17/69 (25)	18/68 (26)	**35/137 (26)**
OR (95% CI)[a]		1·23 (0·52 - 2·88)	
p-value[f]		0·6369	
Median (IQR) number of events[i]	1·0 (1·0 - 2·0)	1·0 (1·0 - 1·0)	**1·0 (1·0 - 2·0)**
Hypokalemia			
N/Total N of participants (%)	19/69 (28)	21/68 (31)	**40/137 (29)**
OR (95% CI)[b]		1·23 (0·57 - 2·68)	
p-value[f]		0·5904	
Median (IQR) number of events[i]	1·0 (1·0 - 2·0)	1·0 (1·0 - 2·0)	**1·0 (1·0 - 2·0)**
Non-anion gap acidosis			
N/Total N of participants (%)	44/64 (69)	12/63 (19)	**56/127 (44)**
OR (95% CI)[a]		0·09 (0·04 - 0·22)	
p-value[f]		<0·0001	
Median (IQR) number of events[i]	1·0 (1·0 - 2·0)	1·5 (1·0 - 2·0)	**1·0 (1·0 - 2·0)**
Hypomagnesemia			
N/Total N of participants (%)	31/69 (45)	10/67 (15)	**41/136 (30)**
OR (95% CI)[c]		0·21 (0·08 - 0·50)	
p-value[g]		0·0001	
Median (IQR) number of events[i]	1·0 (1·0 - 2·0)	1·0 (1·0 - 1·0)	**1·0 (1·0 - 2·0)**
Hyperchloremia			
N/Total N of participants (%)	59/69 (86)	36/68 (53)	**95/137 (69)**
OR (95% CI)[a]		0·17 (0·07 - 0·40)	
p-value[f]		<0·0001	
Median (IQR) number of events[i]	1·0 (1·0 - 2·0)	1·0 (1·0 - 1·0)	**1·0 (1·0 - 2·0)**
Excessive rate of reduction in plasma sodium concentration			
N/Total N of participants (%)	2/69 (3)	1/68 (1)	**3/137 (2)**
OR (95% CI)[d]		0·51 (0·01 - 9·84)	
p-value[g]		1·0000	
Median (IQR) number of events[i]	1·0 (1·0 - 1·0)	1·0 (1·0 - 1·0)	**1·0 (1·0 - 1·0)**
Excessive magnitude of reduction in plasma sodium concentration			
N/Total N of participants (%)	5/68 (7)	0/68 (0)	**5/136 (4)**
OR (95% CI)[e]			
p-value[h]			
Median (IQR) number of events[i]	1·0 (1·0 - 1·0)		**1·0 (1·0 - 1·0)**

Table 5 Secondary outcomes – other electrolyte and acid-base abnormalities			
	Randomized Treatment		
	Standard care (n=69)	Plasma-Lyte-148 (n=69)	Total (n=138)

[a]Mixed logistic regression model adjusted for site, participant weight pre transplant and donor type.
[b]Mixed logistic regression model adjusted for site and participant weight pre transplant.
[c]Exact logistic regression model adjusted for participant weight pre transplant and donor type.
[d]Exact logistic regression model adjusted for participant weight pre transplant.
[e]No regression model could be fitted.
[f]p-value from the likelihood ratio test when including and excluding the treatment term from the model.
[g]p-value from the conditional exact score test when including and excluding the treatment term from the model.
[h]No regression model could be fitted.
[i]Per participant with at least one event



Time could have elapsed between patients being approached in clinic and confirmed assent or consent at transplantation (depending on site practice). Therefore, not all approached patients had been consented or randomized when recruitment was stopped.

[a]Other reasons included: screened by sites for eligibility and approach, approached but no further details provided, and where no reason for decline or further details were provided.