UCL INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children
NHS Foundation Trust

PLUTO

Plasma-Lyte Usage and assessment of kidney Transplant Outcomes in children

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Signatures

The Chief Investigator, Principal Investigators and Sponsor have discussed this protocol. All have agreed to perform the investigation as written and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief Investigator

W Hayes
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Signature

Date: 25/Mar/2021

Sponsor

Great Ormond Street Hospital for Children NHS Foundation Trust
Clinical Trials Manager
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Signature

Date: 25-MAR-2021

1 Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	17/01/2020	W Hayes / E Laing / C Foley	Update of protocol to define comparator arm fluids as IMPs.
2	2.0	23/03/2021	W Hayes / E Laing / C Foley / L Pankhurst	Change to one of the secondary outcome measures, additional clarity on symptom assessment, blood testing and approaching patients/electronic consent procedures, changes to safety reporting requirements.

2 Abbreviations

AE	Adverse event
AR	Adverse reaction
ALT	Alanine Transaminase
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
EMEA	European Medicines Agency
ESKD	End Stage Kidney Disease
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
GP	General Practitioner
IB	Investigators Brochure
ICF	Informed Consent Form
ISF	Investigator Site File
ICH	International Conference of Harmonisation

IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
QP	Qualified Person for release of trial drug
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UKTR	UK Transplant Registry

3 Participating Sites and Local Principal Investigators

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4 Study Synopsis

Title of clinical trial	Plasma-Lyte 148 usage and assessment of kidney transplant outcomes in children (PLUTO trial)
Sponsor name	Great Ormond Street Hospital for Children NHS Foundation Trust
EudraCT number	2019-003025-22
Medical condition or disease under investigation	Kidney transplantation, end stage kidney disease (ESKD)
Purpose of clinical trial	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.
Study Design	A multi-centre open label randomised controlled trial
Summary of eligibility criteria	Inclusion criteria: - Patients under 18 years of age at the time of transplantation with valid patient/parental consent - Patients receiving a kidney only transplant from either a living or deceased donor, in a participating UK centre Exclusion: - Multi-organ transplant recipients
Investigational medicinal products and dosage	Either Plasma-Lyte® 148 solution for infusion or Plasma-Lyte® 148 & Glucose 5% w/v solution for infusion (both of these products can be used in the intervention arm). Dosage/rate of IV fluid at discretion of clinical care team.
Comparator (IMP) products	Standard intravenous fluid (varies between hospitals) is a combination of: 0.45% sodium chloride 0.45% sodium chloride 2.5% glucose 0.45% sodium chloride 5% glucose 0.9% sodium chloride 0.9% sodium chloride 5% glucose 10% glucose Hartmann's (Ringer lactate) solution Geloplasma 4.5% Human Albumin Solution 5.0% Human Albumin Solution
Study Endpoints	**Primary endpoint:** Acute hyponatraemia in the first 72 hours post kidney transplant **Secondary endpoints:**

	• Symptoms of acute hyponatraemia (nausea, vomiting, headache, seizures) within the first 72 hours post-transplant • The degree of fluid overload experienced • Time to discharge from hospital • Transplant kidney function at 1, 3, 7 and 90 days • Other electrolyte abnormalities within the first 72 hours post transplantation: ○ hypernatraemia ○ hyperkalaemia ○ hypokalaemia ○ non anion-gap acidosis ○ hyperglycaemia ○ hypomagnesaemia ○ hyperchloraemia ○ excessive rate of reduction in plasma sodium concentration ○ excessive magnitude of reduction in plasma sodium concentration • Maximum and minimum systolic blood pressure (normalised to age and height percentile) sustained on 3 repeated values on each day, for 3 days post-transplant • Number of changes in intravenous fluid composition within the first 72 hours post-transplant For further detail, including definitions, see Section 8.
Sample Size	144 participants randomised
Route(s) of administration	Intravenous infusion
Maximum duration of treatment of a participant	72 hours
Screening & Enrolment	All patients <18 years old, with end stage kidney disease awaiting kidney transplantation, will be screened for participation. Eligible patients will be fully informed about the study by the clinical care team during the pre-transplant preparation period. Informed consent and patient assent will be taken by the PI or delegated members of the clinical care or research team.
Qualitative sub-study	A Process Evaluation will be undertaken to explore patients' and families' perceptions of the participant information, recruitment and consent process and acceptability of the trial.
Baseline	Clinical observations and baseline blood tests as per routine pre-transplant clinical care. Includes height, weight, blood pressure and baseline blood tests.
Treatment period and data collection	• Blood results as per routine post-transplant clinical care for first 72 hours post-transplant (all results), including sodium, potassium, creatinine, bicarbonate, chloride, magnesium, glucose, haemoglobin, pH, blood gases.

	• Daily weights as per routine post-transplant care. Symptom assessment (nausea, vomiting, headache, seizures) for first 72 hours post-transplant. • Data on all fluids (including comparator products) and relevant medications will also be captured on the electronic Case Report Form (eCRF).
Follow-up period	• Kidney Function at Day 7 post-transplant (+/- 1 day) • Month 3: Serum creatinine • Hospital Discharge: date of discharge from hospital
End of Study	3 months post-transplant
Definition of end of trial	The End of Trial is defined as the date follow-up data is completed for all participants.

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5 Introduction

5.1 Background

PLUTO is a multi-centre randomised controlled trial that will provide evidence for safe intravenous fluid management after kidney transplant in children.

5.1.1 What is the problem being addressed?

Acute hyponatraemia is closely associated with important clinical complications in children after transplant: cerebral oedema, seizures(1) and death(2). Hyponatraemia (defined as plasma sodium concentration < 135mmol/l) is a common problem experienced by 59% of children receiving kidney transplants in the first 72 hours following transplant(3). Approximately 8% of children suffer hyponatraemia-related seizures following kidney transplantation with standard fluid therapy(1). Pre-pubertal children are at particular risk of brain damage or death from acute hyponatraemia because of the relatively low ratio of cerebrospinal fluid (CSF) and brain volume compared to older children and adults(4, 5).

In addition to these serious problems, acute hyponatraemia also predicts symptoms which influence children's experience following transplant. These include nausea and vomiting, headaches, breathlessness and reduced conscious level(6, 7).

Several factors predispose children to acute hyponatraemia following kidney transplant:

Firstly, very large volumes of intravenous fluid are administered to children following kidney transplantation in order to establish and maintain blood flow to the adult donor kidney. Small children typically receive up to 200ml/kg intravenous fluid intra-operatively, and further fluid to replace post-operative urine losses(8).

Secondly, hypotonic intravenous fluid (with sodium concentration lower than the bloodstream) is currently used in the majority of UK paediatric kidney transplant centres. There is no evidence base for this practice. Hypotonic fluid has largely disappeared from other areas of paediatric practice following recognition of the risks of severe hyponatraemia (low blood sodium concentration) and death(9).

Thirdly, the post-operative period is an especially high risk time for acute hyponatraemia because of the typical antidiuretic response(7, 9). This limits the kidney's capacity to excrete water, and thereby predisposes to lower plasma sodium concentration.

National guidance now recommends isotonic fluid (with similar sodium content as the bloodstream) for children(10). However this guidance has not been adopted in transplant clinical practice because of a view that the period following kidney transplantation differs from other situations in terms of the volume of fluid administered and the associated sodium and chloride load. Hence, hypotonic fluid is still routinely administered to children following kidney transplantation(1, 3) and the use of isotonic fluid in this context requires evaluation.

0.45% sodium chloride 5% glucose contains equal quantities of sodium and chloride with additional glucose. Its sodium concentration is approximately half that of bloodstream levels; it is hypotonic.

Plasma-Lyte-148 is an isotonic, balanced intravenous fluid(11). It is licenced in children and used in paediatric intensive care, surgical, and general paediatric wards. Plasma-Lyte-148 has an equivalent cost to standard intravenous fluids. Plasma-Lyte-148 contains sodium, chloride, potassium, magnesium with concentrations that match those of the bloodstream.

There is a physiological basis to expect that Plasma-Lyte-148 will reduce the incidence of dangerous electrolyte abnormalities in children following kidney transplantation compared to current standard fluid. The sodium, chloride, potassium and magnesium concentrations of Plasma-Lyte are balanced to those in the bloodstream. A perceived risk of hyperkalaemia (high bloodstream potassium concentration) from the potassium content of Plasma-Lyte concerns some paediatric nephrologists, although a systematic review in adult kidney transplant recipients demonstrated less hyperkalaemia with Plasma-Lyte compared to 0.9% sodium chloride(12). Given the national equipoise about intravenous fluid composition in paediatric kidney transplant recipients, a clinical trial is needed to evaluate robustly whether Plasma-Lyte will reduce dangerous electrolyte imbalance and associated symptoms, and improve transplant kidney function, in this group of patients.

5.1.2 Importance of this research

Unpleasant symptoms arising from electrolyte abnormalities are common after kidney transplantation. In a significant proportion of cases (8%), these progress to life-threatening encephalopathy and seizures. Newer balanced salt solutions may offer a safe and cost-effective intervention to both reduce risk and improve patients' experience of kidney transplantation.

Currently these risks are managed by very regular blood sampling and intensive input from senior staff. This requires significant nursing, laboratory and medical resource including 2 to 6 hourly blood sampling and analysis, communication of abnormal results, and frequent changes to intravenous fluid when abnormalities arise. A fluid regimen that reduces acute hyponatraemia would improve safety and reduce the intensity of monitoring required for the 130 children receiving kidney transplants each year in UK(13).

Kidney transplantation is the treatment of choice for children with end stage kidney disease(14), of whom there are approximately 1000 receiving renal replacement therapy in the UK(15). Currently, post-transplant acute electrolyte imbalance is experienced by most paediatric recipients(3).

This research will determine whether the incidence of abnormal and dangerous plasma electrolyte levels will be different with the use of Plasma-Lyte-148 compared to intravenous fluid with current standard composition. A positive result would provide high quality evidence to change current practice of administering hypotonic fluid to paediatric kidney transplant recipients.

5.1.3 Evidence for isotonic fluid vs. hypotonic fluid

Four systematic reviews demonstrate a lower risk of hyponatraemia in children in hospital who receive isotonic fluid as opposed to hypotonic fluid in scenarios other than kidney transplant(16-19). One subsequent randomised controlled double-blind trial confirmed a lower risk of hyponatraemia in children who received isotonic maintenance intravenous fluid compared to hypotonic fluid(20). National guidance recommends isotonic or near isotonic maintenance fluid for children(10). Despite this guidance, there remains a unique tension between general recommendations and specialty practice in paediatric kidney transplantation. This uncertainty about the relevance of the guidelines arises from the extremely high volumes of intravenous fluids given in this situation. These can be as high as 7 times the amounts given in a more typical post-operative period. Plasma-Lyte-148, the proposed intervention in this trial, is isotonic and consistent with NICE guidance for intravenous fluid in children(10).

5.1.4 Evidence for balanced fluid vs. 0.9% sodium chloride

A Cochrane systematic review concluded that the risk of hyperchloraemic metabolic acidosis is lower in adult kidney transplant recipients with balanced intravenous fluids compared to 0.9% sodium chloride(12). One randomised trial and a retrospective analysis in adult kidney transplant recipients both found a lower risk of hyperkalaemia with Plasma-Lyte-148 compared to 0.9% sodium chloride(21, 22). One randomised trial in children with sepsis comparing balanced fluid to 0.9% sodium chloride is currently underway (Pragmatic Pediatric Trial of Balanced vs Normal Saline Fluid in Sepsis (PRoMPT BOLUS) study, Clinicaltrials.gov NCT03340805)(23). Taken together, data from adult kidney transplant recipients support the use of Plasma-Lyte-148 as the intervention.

5.2 Introduction to investigational treatment

Plasma-Lyte 148 is an isotonic, balanced intravenous fluid. It is licenced in children and used in paediatric intensive care, surgical, and general paediatric wards. Plasma-Lyte 148 has an equivalent cost to standard intravenous fluids. Plasma-Lyte 148 contains sodium, chloride, potassium, magnesium with concentrations that match those of the bloodstream. It is consistent with NICE guidance for intravenous fluid in children(10). Further data can be found on the electronic medicines compendium(11).

In this trial, use of Plasma-Lyte® 148 solution for infusion and Plasma-Lyte® 148 & Glucose 5% w/v solution for infusion is permitted within the intervention arm.

5.3 Clinical Data

5.3.1 Efficacy

One randomised controlled double-blind trial showed a lower risk of hyponatraemia in children who received isotonic maintenance intravenous fluid compared to hypotonic fluid(20). This was conducted in children on general paediatric wards, as opposed to kidney transplantation.

5.3.2 Safety and tolerability

Trials in adult kidney transplant recipients showed that administration of Plasma-Lyte 148 is safe with respect to potassium in adult patients with ESKD. The incidence of hyperkalaemia was lower in adult patients receiving Plasma-Lyte 148 compared to 0.9% sodium chloride(21, 22).

5.3.3 Pharmacokinetics & pharmacodynamics

Not applicable: Plasma-Lyte 148 contains no active drug.

6 Study rationale and purpose

The PLUTO trial will determine whether the incidence of abnormal and potentially dangerous plasma electrolyte levels in paediatric kidney transplant recipients will be different with the use of Plasma-Lyte-148 compared to intravenous fluid with current standard composition.

7 Trial Design

An open-label randomised controlled trial comparing Plasma-Lyte 148 (the intervention) to the current standard of care in paediatric kidney transplant recipients, conducted in 9 UK paediatric kidney transplant centres.

7.1 Rationale for the study design

An open-label randomised controlled trial was chosen to eliminate selection bias and mitigate confounding by unmeasured factors. Blinding the clinical team was not considered feasible as the randomisation arm will be evident to the clinical team from the trend in plasma sodium concentration. Participants and their families will also not be blinded to the trial treatment. The intervention is clearly labelled and could easily be read by participants or their families. Removing or hiding the labelling of the products was thought to be an added complication for the trial. In addition, the bias that could come from participants knowing the treatment allocation was thought to be minimal.

7.2 Rationale for choice of comparator

The comparator IMPs are the current standard intravenous fluid regimen used in the paediatric transplant centre. Current standard of care involves switching between various intravenous fluids to balance the blood electrolyte levels. Comparator IMP fluids include a combination of the following products which will be administered according to the discretion of the treating physician:

- 0.45% sodium chloride
- 0.45% sodium chloride 2.5% glucose
- 0.45% sodium chloride 5% glucose
- 0.9% sodium chloride

- 0.9% sodium chloride 5% glucose
- 10% glucose
- Hartmann's (Ringer lactate) solution
- Geloplasma
- 4.5% Human Albumin Solution
- 5.0% Human Albumin Solution

For the majority of centres this is Hartmann's fluid or 0.9% sodium chloride intraoperatively, followed by a combination of 0.45% sodium chloride and 0.9% sodium chloride with varying concentrations of glucose postoperatively. Some centres use 4.5% Human Albumin Solution in addition. The variability in standard clinical practice has arisen from the lack of evidence to inform choice of intravenous fluid in this patient population. This research will compare the alternative therapy, Plasma-Lyte 148, to the current standard of care at each participating centre. For this pragmatic trial, permitting variation in the control arm is necessary to achieve a robust comparison of the intervention to current standard clinical care. Given that hypotonic intravenous fluid predominates in most centres, this variability should not significantly impact the trial outcomes.

8 Trial Outcomes

Primary Outcome Measure

Acute hyponatraemia in the first 72 hours post-transplant (defined as plasma sodium concentration < 135mmol/L). Where feasible, a concurrent blood gas should be performed to confirm the result, although this is not compulsory.

Secondary Outcome Measures

- Symptoms of acute hyponatraemia (nausea, vomiting, headache, seizures) within the first 72 hours post-transplant. This will be obtained via direct questioning, where feasible in relationship to the patient's age and developmental stage.
- The degree of fluid overload experienced (defined as proportional increase in patient weight between pre-transplant weight and maximum weight in the 72 hours post-transplant weight)
- Time to discharge from hospital (measured from transplant operation start time ("knife to skin")), measured in days
- Transplant kidney function at 1, 3, 7 and 90 days (using creatinine-based univariate Schwartz formula(24) to determine eGFR)
- Other electrolyte abnormalities within the first 72 hours post transplantation:
    - 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)
    - 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)
- Maximum and minimum systolic blood pressure (normalised to age and height percentile) sustained on 3 repeated values on each day, for 3 days post-transplant
- Number of changes in intravenous fluid composition within the first 72 hours post-transplant

9 Assessment and Management of Risk

A detailed Risk Assessment has been conducted which acknowledges the potential risks to the trial. This section provides an overview of the Quality Assurance (QA) and Quality Control (QC) measures that will be put in place to ensure the trial is performed and data generated and recorded in accordance with the principles of ICH GCP.

9.1 Potential Benefits and Risks of the Intervention

The risks of current standard care are significant. Acute hyponatraemia occurs in 59% children in the immediate post-transplant period(3) and can result in seizures or death in extreme cases(1, 2). These risks are mitigated by frequent (2 to 6 hourly) blood sampling in clinical practice. This practice will be followed in both arms of the clinical trial.

Clinical data in children outside of the transplant setting and in adult kidney transplant recipients suggests a lower risk of acute electrolyte imbalance with isotonic balanced IV fluid such as Plasma-Lyte 148 compared to the current standard of care. Specifically, the risk of hyponatraemia is expected to be lower (16, 20), and the risk of hyperkalaemia are expected to be lower in the intervention arm (21, 22). Nevertheless, the same frequency of blood tests and monitoring is used in the intervention arm as the current standard of care.

In summary, the risk of acute hyponatraemia is considered to be lower with the intervention than the current standard care; the risk of hyperkalaemia is not considered to be higher than standard care. Frequent blood test monitoring will mitigate the risk of acute electrolyte imbalance in both arms of the trial.

10 Selection of Participants

This trial will be conducted in paediatric patients with ESKD undergoing kidney transplantation.

10.1 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

10.2 Exclusion Criteria

1. Multi-organ transplant recipients

10.3 Screening

All patients <18 years old, with ESKD awaiting kidney transplantation, should be screened for participation and added to the Patient Log and electronic Screening Log. Reasons for non-inclusion will be recorded.

All patients must be allocated a Screening ID Number: this will take the form S**XXX**-**YY** where **XXX** is the three-digit site code, and **YY** is a two digit sequential number. This ID number will identify the patient on the qualitative sub-study questionnaires (see Section 10.5) and on the consent/assent form(s) and eCRF before randomisation (for those who consent to participate).

10.4 Recruitment

CONFIRMING ELIGIBILITY / DISCUSSING TRIAL

Eligibility for PLUTO must be confirmed by the Principal Investigator (PI) or other medically-qualified person who is authorised on the study delegation log. Once eligibility has been confirmed:

For patients aged <16 years

Authorised trial staff (doctors or nurses) will approach parents/guardians to invite their child to take part in the trial. The Parent/Guardian Information Sheet (PIS) will be provided which identifies the title of the trial, the Chief Investigator and includes information about: the purpose of the trial, the consequences of participating, or not (i.e. none), participant confidentiality, use of personal data, data security and the future availability of the results of the trial.

The child must also be informed about the trial and their wishes should be taken into account. The appropriate PLUTO PIS should be used (based on the child's age and level of understanding):

- Under 6 years
- 6-10 years
- 11-15 years

The information must be given by a member of staff who has experience of working with children.

For patients aged ≥16 years

Authorised trial staff (doctors or nurses) will approach the young person to invite them to take part in the trial. The Young Person Information Sheet (16-18 years) should be provided.

It is good practice to involve the family in the process, however, if the young person objects, their privacy should be respected.

Any young person, aged 16 or over, who is not capable of giving consent, should only be included in a CTIMP in the UK in line with the adult provisions of the Medicines for Human Use (Clinical Trials) Regulations. If this occurs in the PLUTO trial, and if appropriate, a relative or friend of the patient should be approached and provided with the information sheet. Contact the Chief Investigator / Trial Manager for further advice.

There is also a study website which patients and their families can also access for information (www.pluto-study.co.uk). Patients and families must be given adequate time to consider their participation. The trial should be introduced during the process of transplant preparation, which will allow several weeks to consider participation. They must also be given the opportunity to ask any questions they may have about their/their child's participation in PLUTO. It is acceptable for the discussion(s) about the study to be conducted remotely.

CONSENT/ASSENT

For patients aged <16 years

Under Clinical Trial Regulations, a person under the age of 16 years is deemed to be a 'minor' and an appropriate adult* must give consent for that child to take part. The wishes of the child must form part of the decision-making process.

The appropriate adult must sign the Parent/Guardian Consent Form. If parents/guardians are unable to sign, a thumbprint will be taken in lieu of a signature.

The child's assent should be recorded on the assent form. It is usually inappropriate to ask young children (e.g. under seven years) to sign an assent form. A child's refusal to participate, or continue, in a study should always be respected.

**Appropriate adult may be i) a person or local authority with parental responsibility for that child or ii) a Nominated Legal Representative.*

For patients aged ≥16 years

The patient must sign the Young Person Consent Form (16-18 years).

It is recommended that informed consent is obtained in person. However, in certain circumstances (e.g. for patients who are under the care of the local authority) and if a reduced number of face-to-face hospital consultations are taking place due to ongoing COVID-19 restrictions, it is acceptable to obtain consent electronically. Following real-time discussion with the patient/parent/guardian, the consent form can be sent to complete and return via email. The person taking informed consent is responsible for confirming the identity of the patient or parent/guardian who will be giving informed consent. The patient or parent/guardian giving consent can either type directly onto the consent form or print and return a scanned copy of the signed form. It is also acceptable for consent forms to be signed and returned by post. This procedure is in line with MHRA/HRA guidance for Type A CTIMPs, where any simple electronic signature is permitted.

A fully signed copy of each consent/assent form will be given to the patient and/or parent/guardian, a copy placed in the participant's medical notes, and a copy kept in the Investigator Site File. If consent was obtained electronically, the patient and/or parent/guardian must receive a fully signed copy of their consent form.

PLUTO participants will not be randomised until the date of the kidney transplant operation. Depending on transplant waiting time, there may be a long period of time between initial consent and randomisation (especially for patients awaiting deceased donor transplant). For this reason, consent should be re-confirmed during the hospital admission for the transplant operation (before randomisation occurs). Also towards the end of the study, Research Teams will be asked to start informing all patients they approach that they may not end up being included in the study (if sample size is reached before they are randomised). This will be managed by NHSBT CTU.

If a participant turns 16 whilst in the study, the consent previously received from their parent/guardian will no longer be valid. The participant must be asked to provide their own consent.

If a participant turns 18 after consenting (prior to randomisation), they are no longer eligible for the trial and must be withdrawn. A Withdrawal Form should be completed on the eCRF.

If a participant turns 18 after randomisation and prior to the End of Study, the participant does not need to be withdrawn.

10.5 Process Evaluation (Qualitative Sub-Study)

A process evaluation will be undertaken to explore patients' and families' perceptions of the participant information, recruitment and consent process and acceptability of the trial. A mixed-methods approach will be used, comprising questionnaires and telephone interviews.

Recruitment and sampling
Followingthe initial approach for participation in PLUTO (after the patient/family have made their decision on whether or not to participate), authorised trial staff will also give each family a short questionnaire (Questionnaire 1 – see Appendix B). It will be made clear that completion of the questionnaire is voluntary.

For all families who provide initial consent for the PLUTO trial, a follow-up questionnaire will be given at Day 4-7 post-transplant (Questionnaire 2 – see Appendix B), including to any families who subsequently changed their mind about participation in the trial. This will explore the patient / family's experience of being involved in the trial.

All questionnaires will be provided with pre-stamped, pre-addressed envelopes for return to the Centre for Outcomes and Experience Research in Children's Health, Illness and Disability (ORCHID) team at Great Ormond Street. The screening log ID will be the only identifier on the questionnaire. The questionnaire data will be entered onto a database (RedCap) by the ORCHID team.

Both questionnaires also include an option for patients / families to opt-in (tick box) to being contacted for a telephone interview. Telephone interviews will only be conducted with older children (over 16 years old) and parents. Interviews will take place within 4 weeks of initial discussion about the trial and/or within 4 weeks after hospital discharge following kidney transplantation. Flexibility will be offered for this in terms of evenings and weekends.

Questionnaires
Brief questionnaires have been developed for parents for each of the two time points at which approach for consent is made (initial approach and on the day of transplant). Questions predominantly include Likert-scale responses with one open question to enable free-text comments. Questions include topics related to recruitment and consent, information and decision making about participation (or not). Questionnaires do not contain any identifying information but will be pseudo-anonymised through use of a screening log ID number.

Sampling for interviews
Consent to be approached for interview will be documented on the returned questionnaire(s). Between 8 and 10 parents or older children from each of the questionnaire time points will be recruited. A sampling matrix will be used to select participants from those who have consented for interview to ensure diversity in terms of treating centre, type of transplant (living/deceased donor) and whether or not families consented to participate in PLUTO. Sampling will continue until no new themes are being identified.

Interviews
An interview topic guide has been developed for the study which draws on published literature and expert guidance and includes questions on experience of recruitment and consent, participant information, motivation for participation (or reasons for not participating) and reasons for changes in decision making (for parents who withdraw from

the trial having initially provided consent). Interviews will be participant-led to ensure that participants' own perspectives and priorities remain central but the topic guides will be used to steer the interviews. Topic guides will be revised throughout the interview phase to reflect any new topics raised either in the interviews or through questionnaire responses. All interviews will be recorded with participant permission and transcribed verbatim. Participants will be asked to provide verbal consent at the time of interview for the conduct and recording of the interview.

If as part of the process evaluation, a family shares concerns regarding the conduct of the trial, their consent will be sought to share this information with the Chief Investigator, and site staff if necessary. The Chief Investigator will ensure that these are followed-up accordingly.

Analysis

Thematic analysis, based on the approach of Braun and Clark, will be used to analyse the interviews, with themes being inductively derived from the data. Questionnaires will be analysed using appropriate descriptive and, if appropriate, inferential statistics.

11 Randomisation

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 R**XXXX** where **XXXX** is a four digit sequential participant number. The PI/delegate should use this number on all Case Report Forms, including their centre's Patient Log.

RANDOMISATIONS

www.sealedenvelope.com/access

Choose PLUTO from the drop down list and log-on as instructed.

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

If difficulties are experienced using the randomisation website during working hours, then please contact the Trial Manager, who will be able to randomise the patient on your behalf.

12 Treatment

12.1 Name and description of investigational medicinal products

Plasma-Lyte® 148 and Plasma-Lyte® 148 & Glucose 5% w/v are balanced isotonic intravenous fluids which are licenced for use in children(11). The Marketing Authorisation holder is Baxter Healthcare Ltd, Caxton Way, Thetford, Norfolk, IP24 3SE.

12.2 Route of Administration

Intravenous infusion.

12.3 Maximum dosage allowed

No maximum dose to be specified.

12.4 Maximum duration of treatment of a subject

Maximum duration of treatment 72 hours post-transplant. For children still requiring fluid therapy >72 hours post-transplant, it will be the clinician's decision of which fluid to use.

12.5 Comparator investigational medicinal products

Comparator IMP fluids include a combination of the following products which will be administered according to the discretion of the treating physician:

- 0.45% sodium chloride
- 0.45% sodium chloride 2.5% glucose
- 0.45% sodium chloride 5% glucose
- 0.9% sodium chloride
- 0.9% sodium chloride 5% glucose
- 10% glucose
- Hartmann's (Ringer lactate) solution
- Geloplasma
- 4.5% Human Albumin Solution
- 5.0% Human Albumin Solution

12.6 Dosage modifications

N/A

12.7 Presentation of the drug

Intravenous fluid bag.

12.8 Known Drug reactions

No known reactions (crystalloid fluid, no active component).

12.9 Drug storage and supply

To be sourced from local hospital stock and will be stored and handled according to local policy.

12.10 Compliance with Trial Treatment

All fluid intake will be recorded on the electronic CRF. 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 receive any of the other intravenous fluids specified in section 12.5 intra-operatively or post-operatively in the first 72 hours post-transplant (any medications given intravenously e.g. Mannitol will not be classified as non compliance).

Kidney transplantation carries a risk of hyperkalaemia, with small children and deceased donor recipients being most at risk.(3) Continuation of the intervention in the presence of hyperkalaemia, as opposed to switching to standard intravenous fluid, is considered safe for two main reasons. Firstly, there is a physiological rationale that the balanced composition of Plasma-Lyte-148 should preserve physiological pH of plasma, thereby preserving the main mechanism of short-term extracellular potassium control, namely cellular buffering. Secondly, clinical data from trials in adult kidney transplant recipients show a lower incidence of hyperkalaemia in patients receiving Plasma-Lyte 148 compared to 0.9% sodium chloride(21, 22).

Significant non-compliance with the treatment allocation is defined as follows:

- Plasma-Lyte-148 used intra-operatively and post-operatively in <75% intervention group

AND/OR

- Adherence to current standard care in < 75% control group

Adherence to the intervention and control arms will be monitored by the TMG and DMC. If significant non-compliance were to occur, further training would be undertaken with the study team at the relevant centre, with closer subsequent monitoring. Closure of the site will be considered if the issue were to persist.

13 Schedule of Procedures

No additional tests are required for PLUTO trial participants. This table summarises the data required at each timepoint:

	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									
Qualitative Sub-Study – give Q1	**X**								
Eligibility	**X**								

assessment									
Informed consent		**X**							
Baseline Characteristics		**X**							
Re-confirm consent/assent			**X**						
Randomisation			**X**						
Qualitative Sub-Study – give Q2							**X**		
TREATMENT									
Administration of trial fluid			**X**	**X**	**X**	**X**			
ASSESSMENTS									
Transplant Operation Data			**X**						
Blood Results**		**X**	All results for 72 hours from transplant 'knife-to-skin'						
Blood Gas Results**		**X**	All results for 72 hours from transplant 'knife-to-skin'						
Patient Weight		**X**	All weights for 72 hours from transplant 'knife-to-skin'						
Fluid Data			All fluid for 72 hours from transplant 'knife-to-skin'						
Medication Data			All meds* for 72 hours from transplant 'knife-to-skin'						
Symptom Assessment				**X**	**X**	**X**			
Dialysis				**X**	**X**	**X**			
Blood Pressure		**X**		**X**	**X**	**X**			
Safety Reporting			**X**	**X**	**X**	**X**			
Transplant Graft Function							**X**	**X***	
Discharge Date									**X**

*Data must be collected on all inotropes, diuretics, immunosuppressives, insulin, anti-emetics and electrolyte supplements administered during this 72 hour period.

**Blood Results and Venus Blood Gas data will be obtained directly from the Trust Pathology System (*where possible*), anonymised and then transferred to the Digital Research Environment at GOSH. Further detail on this in Section 14 and Appendix C.

***Data will be obtained directly from the UK Transplant Registry, held by NHS Blood and Transplant (e.g. patient ethnicity, blood group, donor details, matching details, transplant graft function).

14 Data Collection

Please refer to the PLUTO Study Manual for further guidance on data collection. Unless otherwise specified, the data will be collected via a purposely designed MACRO database (access via www.ctu.nhsbt.nhs.uk/macro).

14.1 Baseline Assessments

Baseline assessments comprise those undertaken as part of routine clinical care prior to kidney transplant. The following data will be collected:

- **Eligibility Checklist**
- **Baseline Form (pre-transplant)**: details of the end stage kidney disease (cause, dialysis type, dialysis start date, native urine output), actual patient weight (kg), patient height (cm), blood pressure.

Baseline demographic data (patient age, patient sex, patient ethnicity) will be obtained directly from the UK Transplant Registry, held by NHS Blood and Transplant.

14.2 On Day of Transplant

- **Randomisation Form (on day of transplant)**: randomisation date/time, randomisation ID number, treatment arm
- **Pre-transplant blood test results** (see Table 1)

14.3 Post-Transplant (72 hours)

The 72 hour post-transplant period starts at the time of transplant operation "knife to skin".

- **Transplant Operation Form**: operation start time, duration, graft placement
- **Fluids**: all fluid input / output, and all patient weight measurements in the first 72 hours post-transplant
- **Blood Products**: all blood products administered in the first 72 hours post-transplant
- **Medications**: all inotropes, diuretics, immunosuppressives, insulin, anti-emetics and electrolyte supplements administered in the first 72 hours post-transplant
- **Symptom Assessment**: a symptom assessment should be carried out at the end of each 24-hour post-transplant period (i.e. once daily) for 3 days post-transplant to assess:
  - Nausea in last 24 hours (Y/N)
  - Vomiting in last 24 hours (Y/N)
  - Headache in last 24 hours (Y/N)
  - Seizure(s) (Y/N)
  - Highest pain score in last 24 hours. Pain is graded between 0-10 and age-appropriate scales (such as FLACC or Wong-Baker) can be used, as per local practice.
- **Blood Pressure**: Maximum and minimum systolic blood pressure sustained on 3 repeated values on each day, for 3 days post-transplant

- **Blood Test Results**: all results to 72 hours post-transplant will be collected (see Table 1.). No additional blood testing should be conducted for the study – routine clinical practice should be followed. The Digital Research Environment (DRE) Team, based at Great Ormond Street Hospital, will assist with the electronic collection of this data. Refer to Appendix C for further detail on this process.

Table 1. Blood Test Results

Test	Preferred Units
Plasma sodium level	mmol/L
Plasma potassium level	mmol/L
Plasma urea level	mmol/L
Plasma creatinine level	micromol/L
Plasma chloride level	mmol/L
Plasma bicarbonate level	mmol/L
Plasma magnesium level	mmol/L
Plasma calcium level	mmol/L
Plasma inorganic phosphate level	mmol/L
Blood glucose level	mmol/L
Haemoglobin mass concentration in blood	g/L
Blood pH	-
Blood gas – bicarbonate	mmol/L
Blood gas – chloride	mmol/L
Blood gas – sodium	mmol/L
Blood gas – potassium	mmol/L
Blood gas - ionised calcium	mmol/L
Blood gas - glucose	mmol/L

14.4 Follow-Up Data Collection

- **Post-Transplant Form**: need for dialysis post-transplant, creatinine at Day 7 post-transplant (+/- 1 day)
- **Hospital Discharge**: date of discharge from hospital

No additional outpatient visits will be required for the research study. Creatinine level at Month 3 (+/- 14 days) will be obtained directly from the UKTR, as will transplant and patient survival.

14.5 Treatment Duration

IV fluid (control or intervention) will be administered in the post-transplant period at the discretion of the treating clinician. The maximum treatment duration for the study will be 72 hr post-transplant. The decision to discontinue IV fluid and switch to enteral fluid will be made by the treating clinician.

14.6 Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant and their family have the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason. Standard clinical care procedures will continue to be undertaken if the intervention is withdrawn. If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. 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 to be removed. The reason for withdrawal will be recorded on the eCRF. If a participant is randomised but then transplant does not proceed, the participant should be withdrawn from the trial.

Although very unlikely, a participant may be randomised but then the transplant does not proceed; or the participant may be transplanted but then require a re-graft during the trial period (i.e. because their previous graft failed). If either of these situations occur, participants can be re-consented (if still eligible) and re-randomised into the trial. Participants should be given a new screening log and randomisation number, and their data in the trial will be treated as two separate events.

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. 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. They will have overall oversight and can recommend terminating the trial early for these or any other safety concerns.

14.7 Definition of End of Trial

The End of Trial is the date follow-up data is completed for all participants.

15 Assessment of Safety

15.1 Definitions

Table 2: Definitions Term	Definition
Adverse Event (AE)	Any untoward medical occurrence affecting a trial participant during the course of a clinical trial.
Adverse Reaction (AR)	Any adverse event when there is at least a possibility that it is linked to a trial drug or intervention.
Unexpected Adverse Reaction (UAR)	An unexpected occurrence of an adverse reaction
Serious Adverse Event (SAE)	A serious adverse event that: • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly/birth defect • other important medical event(s)***
Serious Adverse Reaction (SAR)	An SAE that is thought to be causally linked to a trial drug or intervention.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An unexpected occurrence of a SAR; there need only be an index of suspicion that the event is a previously unreported reaction to a trial drug or a previously reported but exaggerated or unexpected frequent adverse reaction.

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.
***Other events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (excluding new cancers or result of overdose).

15.2 Adverse Events

Non serious AEs will <u>not</u> be reported during this trial. Plasma-Lyte 148 and all comparator products are licensed products being used within their licensed indication.

15.3 Expected Serious Adverse Events

All patients eligible for PLUTO have ESKD and are at increased risk of experiencing SAEs due to the complexity of their condition. Many of these events are anticipated as a result of the patient's medical condition and standard treatment received in hospital.

15.3.1 Expected Serious Adverse Events to be notified

SAEs which are related to complications of transplantation (anticipated events) and listed in 15.3.2 do not have to be reported. All other SAEs must be notified within 24 hours to NHSBT CTU via a SAE report (on the eCRF) and monitored regularly by the DMC to ensure ongoing safety of trial participants. Additional safety monitoring is being conducted by the DMC and this is detailed in protocol section 19.1.

15.3.2 Expected Serious Adverse Events related to complications of transplantation excluded from notification

The following situations that are unrelated to the intervention, but fulfil the definition of an SAE, are excluded from notification:

1. **Surgical complications:**
    a. Return to theatre for exploration
    b. Haemorrhage
    c. Blood transfusion
    d. Transplant obstruction/dilatation/hydronephrosis
    e. Thrombosis (thrombosis of transplant, DVT, Pulmonary embolus, arteriovenous fistula)
    f. Transplant kidney arteriovenous fistula
    g. Transplant nephrectomy
    h. Haematuria
    i. cystoscopy for evacuation of haematoma or stent removal
    j. renal artery stenosis
    k. bowel injury, obstruction or ischaemia
    l. lymphocele/collection +/-drainage
    m. hernia
    n. urine leak
    o. nephrostomy

2. **Infective complications:**
    a. Viraemia (EBV, CMV, JC and BK viraemia)
    b. Bacteraemia
    c. Fever

3. **Immunological complications:**
    a. Acute rejection
    b. Transplant kidney biopsy

4. **Medication related complications:**
    a. Calcineurin inhibitor nephrotoxicity and neurotoxicity
    b. New onset diabetes

5. **Other:**
    a. Delayed graft function/primary non-function
    b. Thrombocytopenia/ thrombotic microangiopathy

15.4 Reporting Procedures for Serious Adverse Events

All SAEs (other than those defined in the protocol section 15.3.2 as not requiring reporting), occurring from the start of trial treatment until 72 hours post-trial treatment, must be reported on the SAE Reporting Form (on the eCRF) within 24 hours of the Site Study Team becoming aware of the event. Each report added to the eCRF will be automatically notified to NHSBT CTU. If the eCRF is unavailable for any reason, a paper version of the form should be emailed to serious_adverse_events@nhsbt.nhs.uk. NHSBT CTU will perform an initial check of the report, request any additional information if required. Additional and further requested information (follow-up or corrections to the original case) should also be added to eCRF using a new SAE Report Form. NHSBT CTU will ensure that all SAEs are reported to the Sponsor.

15.4.1 Assessment of causality

The Principal Investigator is responsible for assessing causality of events according to the following criteria:

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial drug or intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial drug or intervention). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	The evidence is clearly in favour of attributing the adverse reaction to the trial drug or intervention
Definitely	There is conclusive evidence beyond reasonable doubt attributing the adverse reaction to the trial drug or intervention.

15.4.2 Expectedness

For events which are considered possibly, probably or definitely related to an IMP,

expectedness must be assessed against section 4.8 (Undesirable Effects) of the relevant approved SmPC. NHSBT CTU, on behalf of the Sponsor, will undertake the expectedness assessment.

In cases where the nature or severity of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

15.5 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

15.5.1 Who should report and whom to report to?

NHSBT CTU on behalf of the Sponsor should report all the relevant safety information previously described to the concerned competent authorities and to the Ethics Committee concerned. NHSBT CTU shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

15.5.2 When to report?

Fatal or life-threatening SUSARs

The MHRA and the Research Ethics Committee should be notified as soon as possible but no later than 7 calendar days after NHSBT CTU has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the MHRA and the Ethics Committee within an additional eight calendar days.

Non-fatal and non-life threatening SUSARs

All other SUSARs and safety issues must be reported to the competent authority and the Ethics Committee in the concerned Member States as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt as follow-up reports. In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

15.6 Development Safety Update Reports

NHSBT CTU will submit an Annual Progress Report in lieu of a full DSUR throughout the clinical trial, to the Competent Authority (MHRA in the UK), Ethics Committee and the Sponsor.

16 Statistics

16.1 Number of Subjects to be enrolled

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(3). This was used as the baseline rate. In the Cochrane systematic review by McNab S et al. (16), 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(8). 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.

16.2 Interim analyses

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.

16.3 Internal Pilot Phase (Month 3-15)

The PLUTO trial will use a traffic light system to assess progression from the internal pilot phase to full trial at 15 months using the following criteria:

Green light (proceed to full trial)
1. A minimum of 7 sites are open to recruitment
2. Overall recruitment rate of >4 participants per month
3. Plasma-Lyte-148 used as per protocol in >75% intervention group
4. Adherence to current standard care in >75% control group

Amber light (develop and implement strategies to improve recruitment/adherence)
1. 4 - 6 sites are open to recruitment

2. Overall recruitment rate of between 2-4 participants per month
3. Plasma-Lyte-148 used as per protocol in 50 – 75% intervention group
4. Adherence to current standard care in 50 – 75% control group

Red light (do not proceed to full trial)
1. Fewer than 4 sites are open to recruitment
2. Overall recruitment rate of <2 participants per month
3. Plasma-Lyte-148 used as per protocol in <50% intervention group
4. Adherence to current standard care in <50% control group

16.4 Early termination of the trial

The Data Monitoring Committee (described in further detail in Section 19) can recommend premature closure of the study on safety grounds. On the basis of recommendations from the DMC, the ultimate decision on continuation of the study lies with the Trial Steering Committee.

16.5 Analysis

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

16.5.1 Inclusion in Analysis

The population used for efficacy analyses will be a modified intention to treat analysis which will include all randomised patients who receive 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. This will be the primary analysis for the trial. The primary outcome will also be analysed per protocol.

16.5.2 Statistical methods to be employed (plan of analysis)

Characteristics of all randomised patients will be tabulated by arm of the trial to describe the cohort. A CONSORT diagram will be presented to show the flow of patients through the trial.

Primary outcome: proportion of patients who experience hyponatraemia (defined as plasma sodium concentration <135mmol/L) within 72 hours post-transplant. This will be analysed using a logistic regression model adjusting for donor type (living vs deceased donor), patient weight (<20kg vs >=20kg pre-transplant) and transplant centre as a random effect. Subgroup and sensitivity analyses will be used to assess whether the treatment effect differs according to the fluid regimen used in the standard arm.

Secondary outcomes:
The secondary outcomes which assess the incidence of other electrolyte and acid-base disturbance within 72 hours post transplantation (hyperkalaemia, hypokalaemia, hypernatraemia, acidosis, hypomagnesaemia, hyperglycaemia and excessive rate and magnitude of fall in plasma sodium concentration) will all be analysed using the same model as the primary outcome. Exact logistic regression will be used to compare instances of nausea/vomiting, headache and seizures. Adjusted normal linear regression models will be used to assess differences in the continuous secondary outcomes and an adjusted Cox proportional hazards model will be used to assess differences in time to discharge. The number of changes in intravenous fluid composition within the first 72 hours post-transplant will be tabulated, by treatment arm.

16.5.3 Procedure to account for missing or spurious data

Any missing primary and secondary outcome data will be summarised. 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. 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.

16.5.4 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

These will be described, reported and justified in the final data analysis report.

17 Regulatory Compliance

17.1 Training Requirements

Staff involved in this trial must hold a valid GCP certificate. Additionally, protocol-specific training will be provided as part of the Site Initiation Visit. For detailed information on training requirements, please refer to the PLUTO Study Manual (www.pluto-study.co.uk/documents).

17.2 Central Monitoring at CTU

Study data will be checked regularly for missing or unusual values (range checks) and checked for consistency over time by NHSBT CTU. If any such problems are identified, the problem will be discussed with the local site for checking and confirmation or correction, as

appropriate. Adherence to the randomised treatment allocation will also be monitored centrally.

17.3 On-Site Monitoring

On-site monitoring visits will be conducted by NHSBT CTU. The frequency, type and intensity of monitoring visits will be detailed in a separate monitoring plan, in accordance with the trial Risk Assessment.

17.3.1 Direct Access to Patient Records

As part of the trial agreement between the Sponsor / NHSBT CTU and the clinical site, investigators and the investigators' institution will permit access to trial patients' medical records and all other records held at the site that pertain to the trial for the purposes of trial-related monitoring, audit, ethics committee review and regulatory inspection.

17.3.2 Confidentiality

Patient's names and/or addresses will not be disclosed. Individual participants will not be identified in the resulting publications and presentations from the trial. This trial will comply with the UK Data Protection Act (2018) and the General Data Protection Regulation.

17.4 Quality Assurance and Quality Control of Data

Protocol adherence will be monitored to check that patients receive the intervention as allocated.

17.5 Auditing

In addition to potential GCP inspections by the MHRA or audits by the local R&D department, the Sponsor / NHSBT CTU reserves the right to conduct site audits, either as part of its ongoing audit programme, or in response to adverse observations during monitoring visits.

18 Data Management

18.1 Source Documents

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent form, the participant will be referred to by their Screening ID number or Randomisation Number, not by name.

18.2 Direct Access to source data / documents

Only members of the trial research team and authorised representatives from the sponsor will have direct access to the source data and trial documentation. All source data and trial documentation will also be available to external auditors if and when required, and inspectors in the event of regulatory inspection. Access to the final data set will remain with the Chief Investigator.

18.3 Data Recording and Record Keeping

18.3.1 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Essential documents will be retained for a **minimum** of 25 years after completion of the trial. These documents will be retained for longer if required by the applicable regulatory requirements.

19 Oversight Committees involved in trial

The Trial Management Group (TMG) will be responsible for the day to day running and management of the trial. The TMG will meet at least four times yearly, more often during the set-up and close down phases of the trial. Members include the CI, the Trial Manager, trial statistician, trial data manager and a NHSBT CTU Clinical Operations Manager.

The Trial Steering Committee (TSC) will provide overall supervision for the trial and provide advice through its Independent Chair. The ultimate decision on continuation of the trial lies with the TSC.

19.1 Data Monitoring Committee (DMC)

This study will use a Data Monitoring Committee (DMC). The DMC will be responsible for on-going monitoring of the efficacy and safety of subjects in the study according to their Charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the TSC for a final decision. The Sponsor will forward such decisions to regulatory authorities, as appropriate. The DMC will be independent of the study team and will have no direct involvement in other aspects of the trial. The DMC will develop its own operation procedures in consultation with the sponsor which will be documented in the DMC charter.

In addition, on a six-monthly basis, the DMC will review and compare the incidence of acute severe hyponatraemia and severe hyperkalaemia (as defined below) between the two participant groups. All blood test results in the 72-hour post-transplant period are being collected for each trial participant, so this data can be collated by the Trial Statistician and

sent to the DMC for review.

Acute severe hyponatraemia is defined as a fall in plasma sodium concentration of ≥ 10mmol/L from the pre-transplant level, and/or a rate of fall of plasma sodium concentration exceeding 1mmol/L/hour averaged over 6 hours.

Severe hyperkalaemia is defined as plasma potassium concentration >6.5mmol/L. This occurs in 8% children with standard fluid therapy.

20 Quality Control (Monitoring) and Quality Assurance (Audit)

The Sponsor is responsible for implementing Quality Control and Quality Assurance.
The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. A Trial specific monitoring plan will be established and the trial will be monitored with the agreed plan.

Issues will be escalated to the Chief Investigator and Sponsor.

21 Ethical and Regulatory Approvals

21.1 Ethical Approval

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki, ICH Good Clinical Practice Guidelines and in accordance with the terms and conditions of the ethical approval given to the trial. A favourable opinion will be sought from the Research Ethics Committee before recruitment begins.

21.2 Regulatory Approval

A Clinical Trial Authorisation (CTA) will be sought from the MHRA before recruitment begins. The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

22 Patient Confidentiality & Data Protection

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a Screening ID Number / Randomisation Number on the eCRF. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. Data will be stored in a secure manner and in accordance with the General Data Protection Regulation and Data Protection Act 2018.

23 Serious Breaches

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the sponsor becoming aware of the breach. A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial”.
In the event that a serious breach is suspected NHSBT CTU must be contacted as soon as possible. NHSBT CTU, in conjunction with GOSH as Sponsor, will notify the regulatory authority according to the SOP on ‘Serious Breach Notification’.

24 Financial Information and Insurance

Cover for negligent harm will be provided by the Great Ormond Street Hospital for Children NHS Foundation Trust through the Clinical Negligent Scheme for Trusts (CNST). No-fault compensation insurance cover for any non-negligent harm will be provided by University College London (UCL).

25 Publications Policy

25.1 Dissemination

The final study data set will be analysed and results published as soon as possible following completion of study follow-up, final data checks and database lock. Individual Clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of publications.

Study findings will be presented to academic and non-academic groups. The PPI group will play an important part in disseminating the study findings into the public domain. Dissemination to non-academic audiences including service users, commissioners, clinicians and service providers will be facilitated through the use of existing networks e.g. email lists, social media.

All research teams and PPI members involved in the study will be invited to a close out meeting to discuss the findings of the study.

Open access, peer reviewed academic outputs and research reports together with associated summaries and key findings will be produced for funders, policy makers and NHS audiences and held on the study website.

Any publications arising from this study will adhere to the NIHR funding and support outputs guidance.

25.2 Authorship

Authorship for any publications arising from this study will follow the rules set out by the International Committee of Medical Journal Editors definitions of Authorship and Contributorship http://www.icmje.org/ethical_1author.html

25.3 Approvals

Study results will be embargoed and not disseminated until authorised by the CI and TSC. Final manuscripts and presentations will be approved by the CI and TSC prior to publication. Similarly, any subsequent sub-study analysis will require authorisation by the CI and TSC prior to publication. Sub-study manuscripts must not be published prior to the publication of the main study.

25.4 Identification

A trial identifier should be included on all presentations and publications (e.g. the ISCRTN).

25.5 Timing

It must be made clear that no data may be made public before publication and never without agreement from the CI.

25.6 Acknowledgements

For the main report of this study submitted for publication, together with associated methodology and health economic papers or posters/presentations, we will use the International Committee of Medical Journal Editors definitions of Authorship and Contributorship (http://www.icmje.org/ethical_1author.html). The members of the TSC and DMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication and the support of the NHSBT Clinical Trials Unit, and NIHR Funder acknowledged in all publications/presentations.

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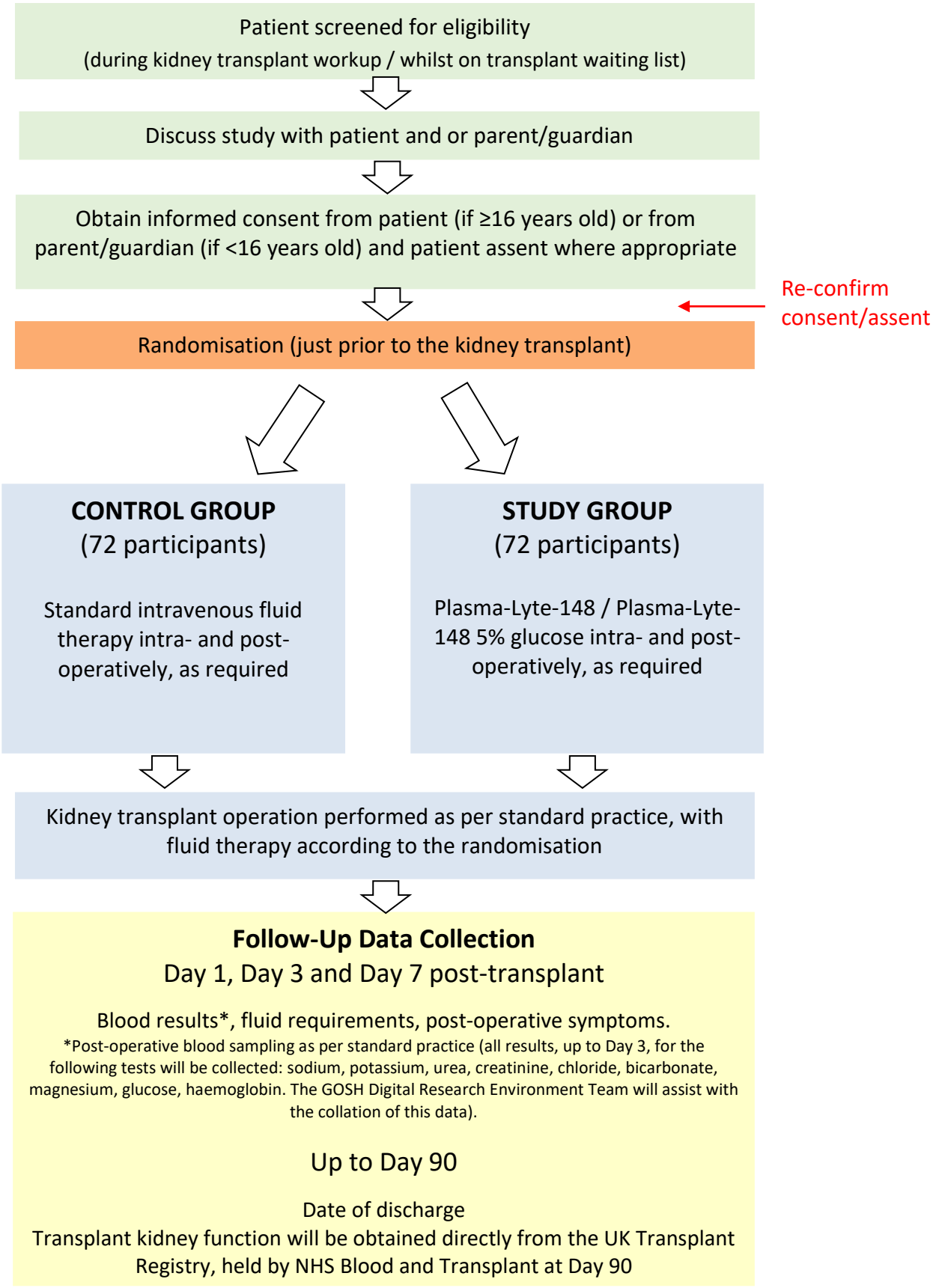
27 Appendix A: Trial Flow Chart



28 Appendix B: Qualitative Sub-Study Questionnaires

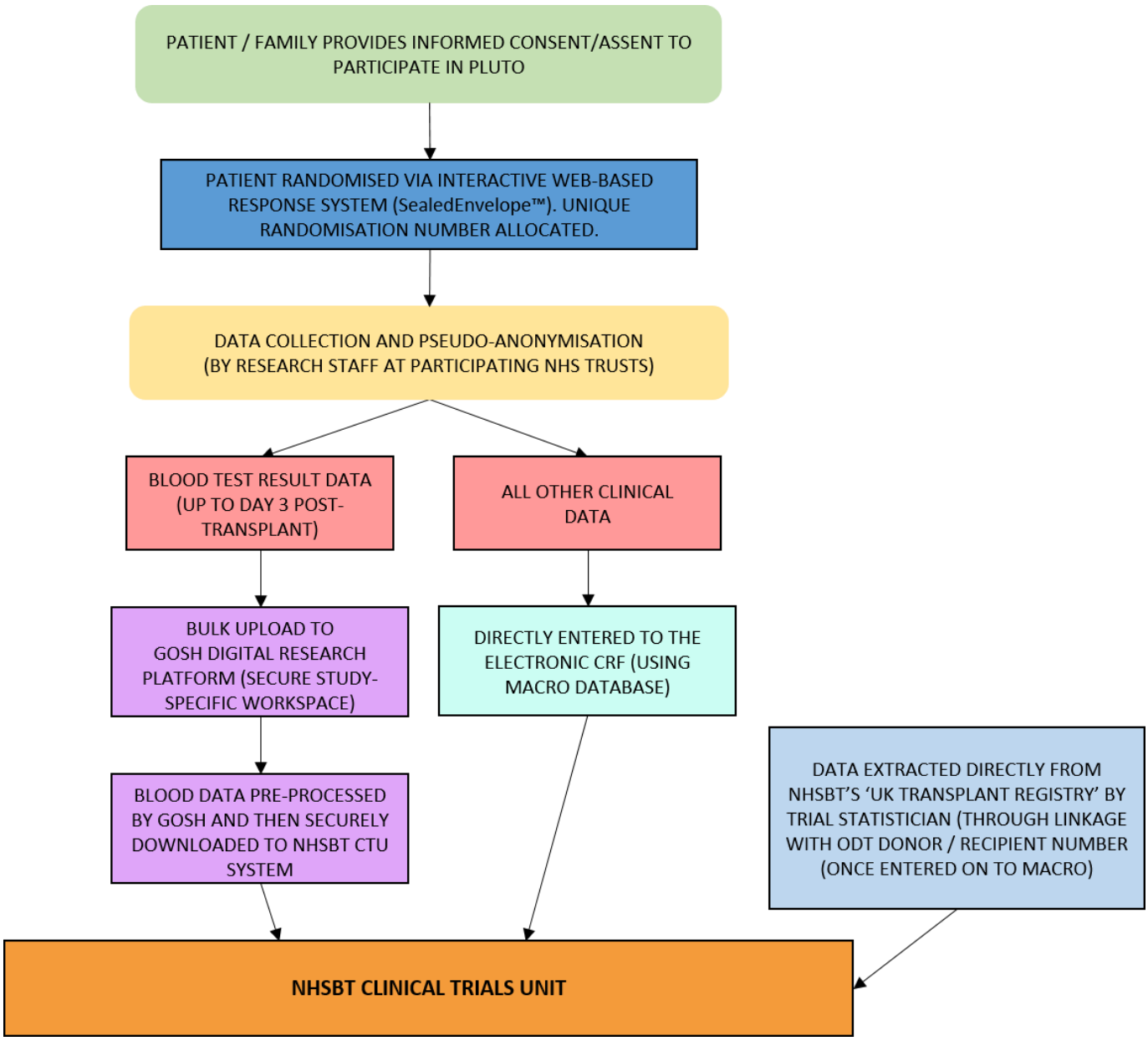
QUESTIONNAIRE 1 – PRE-TRANSPLANT

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I was satisfied with how I was **approached** about PLUTO	◯	◯	◯	◯	◯
I understood the **information** that I received from the doctor/research nurse about PLUTO	◯	◯	◯	◯	◯
I had sufficient opportunity to ask **questions** about PLUTO	◯	◯	◯	◯	◯
Any questions I had about PLUTO were answered in a way that I could **understand**	◯	◯	◯	◯	◯
I was satisfied with the **consent** process for PLUTO	◯	◯	◯	◯	◯
I had enough **time** to think about whether or not to consent to my child participating in PLUTO	◯	◯	◯	◯	◯

QUESTIONNAIRE 2 – POST-TRANSPLANT

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I was satisfied with how I was **approached** about PLUTO on the night of transplant	◯	◯	◯	◯	◯
I remembered the **information** I had previously been given about PLUTO	◯	◯	◯	◯	◯
I had sufficient opportunity to ask **questions** about PLUTO on the night of transplant	◯	◯	◯	◯	◯
Any questions I had about PLUTO were answered in a way that I could **understand**	◯	◯	◯	◯	◯
I was satisfied with the **re-consent** process for PLUTO on the night of transplant	◯	◯	◯	◯	◯
I was happy with my original **decision** to consent to my child participating in PLUTO	◯	◯	◯	◯	◯

29 Appendix C: Data Flow Diagram



Blood test result data will be collected electronically in collaboration with the Digital Research Environment (DRE) Team at Great Ormond Street Hospital. Where possible, blood test results will be downloaded from the laboratory reporting system at each site, and anonymised with the participant study number. Alternatively, blood test results can be entered manually from the laboratory reporting system. These data will be uploaded to a secure cloud based digital research platform maintained by the DRE at Great Ormond Street Hospital. Data will be pre-processed by the DRE, and then accessed securely by NHSBT CTU.