Evaluation of Efficacy, Outcomes and Safety of a New Infant Haemodialysis and Ultrafiltration Machine in Clinical Use.

(**I**nfant **KI**dney **D**ialysis and filtration) –

The **I-KID** Study

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2 Protocol signatures

2.1 Protocol authorisation signatories

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the UK Policy Framework for Health and Social Care, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as applicable.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

Representative of the Research Sponsor

Name: Sean Scott

Position: Regulatory Compliance Manager

Signature: _____ Date:

Chief Investigator

Name: Dr Heather Lambert

Signature: _____ Date:

Statistician

Name: Professor John Matthews

Position: Senior Statistician

Signature: _____ Date:

Newcastle Clinical Trials Unit (NCTU)

Name: Professor Helen Hancock/Rebecca Maier

Position: co-Director/Deputy Lead, Newcastle Clinical Trials Unit (NCTU)

Signature: _____ Date:

2.2 Principal Investigator signature page

Short Study Title: I-KID

Principal Investigator

I have carefully read and understood protocol version 5.0 dated 19th October 2018. I agree to conduct the study in compliance with Good Clinical Practice and all required regulatory requirements.

Name:

(print) _____

Site name/I.D: _____

Signature: _____ Date: _____

3 Contents Page

4 Glossary of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
ACT	(glass) Activated Clotting Time
AE	Adverse Event
AR	Adverse Reaction
CAPA	Corrective and Preventive Actions
CI	Chief Investigator
CNS	Central Nervous System
CRRT	Continuous Renal Replacement Therapy
CRT	Cluster Randomised Trial
CRF	Case Report Form (paper)
CTU	Clinical Trials Unit
CVL	Central Venous Line
CVVH-D	Continuous Veno-Venous Haemofiltration Dialysis
DD	Device Deficiency
DMC	Data Monitoring Committee
e-CRF	electronic Case Report Form
EU	European Union
g	Gram
GCP	Good Clinical Practice
GEE	Generalised Estimating Equations
GP	General Practitioner
HD	Haemodialysis
HRA	Health Research Authority
ID	Identification
IMD	Investigational Medical Device
ISF	Investigator Site File
Kg	Kilogram
MHRA	Medicines and Healthcare products Regulatory Agency
ML	Millilitre
Nidus	Newcastle Infant Dialysis Ultrafiltration System
NUTH	The Newcastle Upon Tyne Hospitals NHS Foundation Trust
PCPI	Patient Carer Public Involvement/Input
PD	Peritoneal dialysis
PI	Principal Investigator
PICAnet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
PIS	Participant Information Sheet

Abbreviation	Definition
PPI	Patient and Public Involvement
PR	Parental Responsibility
R&D	Research and Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
RRT	Renal Replacement Therapy
RVI	Royal Victoria Infirmary
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SOP	Standard Operating Procedure
SRM	Selected Reaction Monitoring
SW	Stepped Wedge
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
UF	Ultra Filtration
UK	United Kingdom
USADE	Unanticipated Serious Adverse Device Effect
USM	Urgent Safety Measure

5 Responsibilities

Sponsor: The Newcastle Upon Tyne Hospitals NHS Foundation Trust will act as the research Sponsor for this study.

Funder: Efficacy and Mechanism Evaluation Programme

Trial Management: A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by Newcastle Clinical Trials Unit.

Principal Investigator: This is a multi-centre study and the Principal Investigator will have overall responsibility for the conduct of the study at a particular trial site.

Trial Management:

The following functions falling under the responsibility of the Sponsor will be delegated to Dr Heather Lambert:

- Ethics Committee Opinion (including application for research ethics committee favourable opinion, notification of protocol amendments and end of trial, site specific assessment & local approval)
- HRA Approval and agreement with participating sites
- Good Clinical Practice and Trial Conduct (including Good Clinical Practice (GCP) arrangements, data monitoring, emergency & safety procedures)
- Administration of funding for the study

Trial conduct at site:

Investigator responsibilities:

- Study conduct and the welfare of study subjects
- Familiarity with the study intervention(s).
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events and serious adverse device effects.
- Screening and recruitment of subjects
- Ensuring all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event
- Obtaining local approval before any research activity begins and abiding by the policies of Research Governance
- Compliance with the Principles of GCP, the UK Policy Framework for Health and Social Care Research, the Data Protection Act and any other relevant legislation and regulatory guidance.
- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent.

- The Principal Investigator (PI) shall be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. S/he shall provide a current signed & dated curriculum vitae as evidence for the Trial Master File.
- Ensuring Study Site team members are appropriately qualified by education, training and experience to undertake the conduct of the study.
- Availability for Investigator meetings, monitoring visits and in the case of an audit.
- Maintaining study documentation and compliance with reporting requests
- Maintaining a site file, including copies of study approval, list of subjects and their signed informed consent forms
- Documenting appropriate delegation of tasks to other study personnel e.g. Research Nurse, Co-Investigator(s), Trial Coordinators, Data Managers
- Ensuring data collected is accurate, timely & complete
- Providing updates on the progress of the trial
- Ensuring subject confidentiality is maintained during the project and archival period
- Ensuring archival of study documentation for a minimum of 5 years following the end of the study, unless local arrangements require a longer period

6 Protocol Summary

Short title:	I-KID
Protocol version:	4.0
Protocol date:	28th September 2018
Chief Investigator:	Dr Heather Lambert
Sponsor:	The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Funder:	Efficacy and Mechanism Evaluation Programme
Study design:	A multi-centre, randomised clinical investigation using a cluster stepped-wedge design with one way crossover study with each unit acting as their own control
Study Intervention:	Control: current renal replacement therapy (either Peritoneal Dialysis or Continuous Veno-Venous Haemofiltration)
	Experimental intervention: renal replacement therapy using the Newcastle Infant Dialysis Ultrafiltration System (Nidus)
Primary objective:	To compare the use of a novel haemodialysis device with conventional renal replacement therapy in babies under 8kg treated in Paediatric Intensive Care Units
Secondary objective:	To compare the use of a novel haemodialysis device with conventional renal replacement therapy using the secondary outcome measures
Primary outcome:	Accuracy of fluid removal compared with prescription
Secondary outcomes:	Haemodynamic status Biochemical clearances Number of ventilator free days Survival Completion of intended renal replacement therapy course Need for additional vascular or dialysis access Unplanned change in circuits Exposure to blood transfusion Bleeding events Anticoagulant use Parent/Guardian experience Staff acceptability and usability of device
Number of study sites:	6
Study population/size:	95
Study duration:	30 months

7 Background

7.1 Rationale

Small young babies requiring renal replacement therapy (RRT) present specific therapeutic challenges because of their small size and the current technology available. Recurrent themes emerge from publications indicating similar problems faced by clinicians world-wide and proposing the need for improved device technology to provide some solutions.

This clinical investigation is designed to determine the clinical efficacy, outcomes and safety of a novel Non-CE marked infant haemodialysis machine, the Newcastle Infant Dialysis Ultrafiltration System (Nidus), compared to currently available therapy. Nidus is specifically designed for use in small babies between 0.8 and 8 kilogram (kg). Nidus offers the possibility of RRT for the smallest babies when other forms of dialysis may not be possible or is inadequate. There is evidence from a previous single centre pilot study to anticipate Nidus has the potential to contribute significant benefits to the health of small babies needing RRT in the short and long term.

The proposed clinical investigation is a result of a committed multicentre effort by collaboration between front line clinicians, scientists, academics and manufacturers, with significant parent and public involvement, throughout its development. The results will be applicable not just in the UK but worldwide and changes in clinical practice could take place rapidly.

The high quality training package developed as part of this study will contribute to better understanding of RRT and safer introduction of new RRT technology in other units after completion of the study. A team of specialist dialysis nurses will be developed who have been selected from each of the recruiting hospitals and are familiar with a number of dialysis circuits, machine and modalities.

The Nidus machine uses a smaller circuit volume, with less exposure to blood products, and more precise control of ultrafiltration and dialysis. Pilot data has suggested improved management of fluid overload and renal failure. This may contribute towards lower morbidity and mortality, and may reduce length of time of ventilator dependency or length of stay in paediatric intensive care units (PICU). This would be valuable for National Health Service (NHS) resources and society. Nurses have reported ease of use of the Nidus which is important in a busy PICU.

7.2 Research Treatments

Over the past 10 years at least 265 children under 10kg or under 1 year (including 84 babies under 5kg) are reported in the literature as receiving RRT in PICU, and have indicated similar problems faced by clinicians world-wide. They all describe difficulties with vascular access and blood flows, fluid balance, rapid clotting, loss of circuits and hypotensive episodes at initiation.

This study will contribute to the current knowledge base and further understanding of the effects of RRT. Improved understanding may influence approaches to fluid balance management. There is a well-described need for improved technology to provide RRT effectively and safely for small babies [13].

Current Population

The first population of babies treated with RRT are sick infants in PICU. Most of these babies do not have intrinsic renal disease and therefore have good potential for renal recovery. Although mortality and morbidity in PICU varies and is related to the underlying diagnosis, survival of babies in PICU is worse in those with fluid overload [1] or needing RRT, of whom

up to 20-40% may die [2]. RRT is supportive until kidney recovery and although most survivors are independent of RRT at discharge from PICU, up to 30% may have chronic renal sequelae. Babies requiring RRT in PICU have been reported to have longer length of stay and required more days of ventilator support. There are over 300 infants per year in the UK receiving treatment with continuous RRT in PICU. Many of these babies have multi-system disease which includes acute renal failure – for example, babies with severe sepsis.

The second population of babies are in the post-operative period, especially after cardiac surgery whose major problem is an acute kidney insult and fluid overload and poor urine output.

The I-KID study will approach the parents/ guardians of babies (referred to as patients for the study) from these two population groups.

A third population of babies treated with RRT are those with an inborn error of metabolism for example urea cycle defects causing hyperammonaemia. They require, as an emergency, very rapid removal of toxic metabolites to prevent irreversible CNS damage with associated high morbidity and mortality [9]. This small group (about 15 per year in the UK) do not normally have renal impairment and are not included in the study because of their unpredictable, and sometimes much higher than routine dialysis requirements that may be required to clear toxins.

Another population of babies requiring RRT are those with intrinsic renal disease, which is often congenital, who are normally treated with peritoneal dialysis (PD). There are only around 10 of these babies a year. Although not always straightforward, this form of therapy is well established and frequently works well in the chronic situation. However some babies fail treatment with PD because of technical problems like catheter leakage; others cannot be treated with PD because of abdominal wall problems like gastroschisis or abdominal surgery; some get recurrent peritonitis or peritoneal failure. Outcome for those very small babies is poor as, unlike for adults and older children, there have not been alternative options like intermittent haemodialysis. These populations of babies are not included in the study.

Current Therapy

PD is used frequently to support infants after open-heart surgery [14]. PD is technically simpler than haemodialysis (HD); there is no lower size limit but complications are common in the smallest patients [2]. Ultrafiltration (UF) is unpredictable, and chemical clearance less efficient, especially in unstable babies who develop splanchnic vasoconstriction and who also risk developing necrotising enterocolitis. This renders PD impossible, as does abdominal surgery and congenital abdominal wall defects. Larger critically ill infants with multi-organ failure are often treated with a variety of continuously delivered haemodialysis (HD) modalities (continuous renal replacement therapy, CRRT) [2]. Vascular access for HD modalities including Continuous Veno-Venous Haemofiltration (CVVH) is problematic as the size of central venous line (CVL) required for adequate blood flow is disproportionately large for the size of the baby especially when a double lumen line is needed (Poiseuille's law: flow is proportional to the fourth power of the internal radius).

Conventional HD and CRRT machines are unlicensed as they are CE marked for use in adults and bigger children. They cannot control fluid balance better than ±30 ml/hour [15], and therefore are not licensed for babies weighing <8 kg (or approved for use in children of <20 kg in the US). The recommended minimum 7-French, dual-lumen vascular access lines and continuous 40 ml/minute blood flows are difficult to achieve in the smallest babies. Their relatively large circuit volume (50-70ml) produces sudden dilution of blood on commencing treatment if crystalloid primed, and increases the risk of anaemia with circuit loss. Hypotension on connection is a problem [3, 7, 8]. Blood priming risks exposing the baby abruptly to aberrant chemical and pH changes, which are reduced by pre-dialysing the circuit [10]. Exposure to blood transfusions increases the risk of developing tissue-type sensitisation which may be important if renal function does not recover and renal or other solid organ transplant is considered in the future.

Alternative Technology

In 1995, the Newcastle group designed a novel HD circuit, which operated by different principles. It was driven by syringes, and uncoupled the baby's blood flow capacity from the requirements of the dialysis filter [17]. In 2005, they reported the results of automating this as a miniaturised machine (circuit volume less than 10ml), with which four babies were treated weighing between 800 g and 3.4 kg, using a single-lumen access line, and without the need for blood-priming [18]. This device was subsequently developed into Nidus [4].

7.3 Risks

Risks of Current Therapy

CVVH machines are not approved for use in babies weighing <8 kg because their technology is inherently imprecise and only capable of controlling fluid removal to within ±300 ml daily – a relatively large potential error with risk of dehydration or fluid overload for small babies.

Risk of Using Nidus

This is a Clinical Investigation of a Non-CE Marked Device as the CE marking of the Nidus device is in progress.

Nidus has been developed over years of collaboration between scientists, engineers, clinicians and nurses, using human factors science to develop a safe system, which is resilient to unanticipated events. The design has been modified several times to better aid those using it, with ease and clarity of use to improve safety.

Safety monitoring is an important focus of this study. The Nidus makes a downloadable constant recording of all activity data including volumes, flows, pressures, alarms and response to alarms so any alarm or event, however small, can be subsequently analysed. The Nidus potentially provides a safer way of performing CVVH on babies by using a novel circuit that allows precise ultrafiltrate control thus reducing the potential for errors in ultrafiltrate removal that would be trivial for larger children but are not for a baby. It's small circuit volume (<10mls) avoids the need for blood priming with stored blood which has associated immediate risks and long term risks of developing sensitising antibodies.

8 Objectives

Study Aim

The overall aim of the I-KID clinical investigation is to compare the use of a novel haemodialysis device, Nidus, with conventional RRT in patients under 8kg treated in paediatric intensive care, using a randomised stepped-wedge design.

The study aims to evaluate the efficacy of Nidus in improving accuracy of ultrafiltrate fluid removal, as well as reducing the incidence and severity of adverse effects of renal replacement use of blood product transfusion. It will also generate a safety profile in the application of Nidus in the clinical environment.

Objectives

The objective is to recruit 95 patients from 6 study centres over 20 months. There will be stepwise cross-over from conventional RRT (control period) to Nidus (intervention period) in participating centres. The use of RRT will be documented in each of the 6 centres and events such as access line changes and blood transfusions will be recorded via the already established daily PICAnet enhanced renal audit reporting system. In addition, blood and fluid biochemistry will be recorded, as well the weight of the dialysate bags pre and post dialysis to enable clearances and accuracy of fluid removal to be calculated. Parents/guardians will be asked about their experience using a questionnaire and staff will be asked about acceptability and usability of the RRT device using a questionnaire. Patients will be reviewed at a single routine clinic visit approximately 1 month after start of their RRT, some will still be in hospital and for others this will be done at a convenient clinical follow up.

8.1 Summary of research objectives

Hypothesis:

Fluid balance control will be improved using Nidus with good clearances and fewer adverse effects than conventional RRT.

Primary Objective:

To compare the use of a novel haemodialysis device with conventional renal replacement therapy in babies under 8kg treated in paediatric intensive care

Secondary Objective:

To compare the use of a novel haemodialysis device with conventional renal replacement therapy in patients under 8kg treated in paediatric intensive care in relation to the secondary outcome measures as listed in section 9.3.

9 Study Design

This is a multicentre study using a randomised stepped-wedge cluster design [5].

In a stepped-wedge (SW) cluster design, the trial is divided into successive treatment periods and in this clinical investigation there will be three different treatment sequences. Each centre will be randomly allocated to one of the sequences in the design, with two centres allocated to each sequence. In all sequences, the treatment in the first period will be conventional therapy, while in the last treatment period all units will use Nidus. The sequences differ in the timing at which the change from conventional therapy to Nidus occurs, as shown in figure 1. There will be a training period immediately before the centre changes to Nidus. Data from the first patient in the training period will be collected but not be used in the main analysis of the study. Competency will be assessed after this first case and then, if required, after each case in the training period until the site is deemed competent. Intervention data will then be collected and used from the next recruited patient. The design means that all participating centres will have the chance to use both treatments during the course of the study. Unlike a conventional cluster-randomised design, a SW design allows treatment estimates to be based on within-centre comparisons.

The stepped wedge design has been chosen over a conventional randomised control trial with individual patient randomisation for reasons of safety, ethics and acceptability. The method of randomising the centre, rather than the patient, has been supported by a Research Consumer Group, parents who have been consulted and health professionals. This study is taking place in the paediatric intensive care environment, necessitating a level of urgency to recruit, consent and initiate RRT without compromising the patients' health further which raises ethical concerns [21].

For all study periods, in an emergency situation, dialysis may commence at the discretion of the responsible clinician before consent is obtained if it is in the patient's best interest to not delay treatment. The patients' parents or legal guardians will be approached for signed consent, as soon as practicable after starting RRT, ideally within 48 hours, (deferred consent). The current best practice guidance from the CONNECT study, gives detailed recommendations which the I-KID study will follow [22]. Consenting to the study will not affect whether the patient receives dialysis or not. The method of randomising the centre, rather than the patient, has been supported by a Research Consumer Group, parents who have been consulted and health professionals.

Sequence	Period 1	P2	P3	P4	P5	FU
S1	C	T	I	I	I	FU
S2	C	C	T	I	I	FU
S3	C	C	C	T	I	FU

S1, S2, S3 = sequences in SW design – two centres randomized to each sequence
C = conventional treatment in unit (control period)
T = training period (results not used – until deemed competent)
I = intervention whole unit uses Nidus (intervention period)
Each of the data collection periods in each sequence will be 4.5 months long.
FU = Follow Up

Figure 1: I-KID study design sequence

9.1 Study Duration and Setting:

The total study duration will be 30 months.

1 – 3 months: The first 3 months will be used to develop a high quality training competency package which will enable staff to become competent in undertaking I-KID study procedures.

A training launch event will take place for all participating sites.

4- 24 months: There will be a recruitment period of 20 months in which to consent a target of 95 patients across the 6 participating centres.

Each centre will include a control recruitment period, a 2 month training period, followed by an intervention recruitment period and an additional 1 month to complete patient follow up.

There will be additional support provided by the experienced Nidus support team and the Nidus Lead Nurse. PICU nurses will need to be competency assessed before each site can begin using the intervention. Competency of sites in using the machine will then be assessed every 6 months.
Data collected for the first patient enrolled into the study during the designated training period, at each site, will not contribute to the primary analysis. Once a site is deemed competent, the data will be collected and used for the study analysis. The site competency will be signed off by members of a Competency Subgroup which will include the Chief Investigator, the training lead and members of the TMG as delegated by the CI.

All 6 centres will be randomised and after appropriate training and competency assessment, the study intervention will be introduced as per the design. Using questionnaires, parents/guardians will be asked about their experiences and staff will be asked about acceptability and usability of the device. Staff will approach parent/guardians about the UK Renal Registry for long term data collection. This is in line with current UK Department of Health policy to collect data on cases of acute dialysis.

Recruitment will be reviewed at the end of month 1, and regularly thereafter at study TMGs and Trial Steering Committees (TSC).

25-30 months: This time will be used for site close down visits, statistical analysis of data, writing reports and dissemination of results to the scientific, medical and nursing community as well as to parent/public interest groups. Submission of abstracts will continue beyond this period to target specific conferences and publications.

9.2 Primary Outcome Measure:

Accuracy of fluid removal compared with prescription – a measure that includes fluid removal precision of the dialysis system.

- Does the dialysis methodology provide the hourly fluid removal that the clinical team wanted?

9.3 Secondary Outcome Measures:

- Haemodynamic status (drop in blood pressure after connection requiring intervention)
- Biochemical clearances
- Number of ventilator free days
- Survival

- Completion of intended renal replacement therapy course
- Need for additional vascular or dialysis access
- Unplanned change in circuits
- Exposure to blood transfusion
- Bleeding events
- Anticoagulant use
- Parent/guardian experience measured using questionnaires
- Staff acceptability and usability of device measured using questionnaires

9.4 Definition of end of study:

The end of the study will be defined as the locking of the eCRF database. All data queries will have been raised and resolved, with no further changes to the data.

10 Subject Population

Participants will be patients in PICU in 6 NHS Hospital Trusts which have tertiary nephrology units in the UK. Participating sites include Birmingham Children's Hospital, University Hospitals Bristol, Great Ormond Street Hospital, Newcastle upon Tyne Hospitals (including Royal Victoria Infirmary and Freeman Hospital), University Hospital Southampton and Evelina London Children's Hospital.

10.1 Inclusion criteria

- Patients in PICU with a body weight of 0.8kg – 7.99kg (note: includes estimated body weight emergency situation) who require continuous RRT for acute renal insufficiency or fluid overload as part of their standard clinical care.
- *Person with legal parental responsibility (PR) for the patient provides written informed consent for the patient to take part in the study.

*This may be after the patient has started dialysis in an emergency situation so as not to delay treatment. See section 11.3.

10.2 Exclusion criteria

- Patient with known chronic renal failure already on established adequate RRT
- Patient already established on adequate RRT for whom entry into the study would require additional central venous access, if that access is not clinically indicated.
- Patient has an underlying metabolic diagnosis, including hyper ammonaemia
- Clinician makes a clinical decision that the patient should not receive RRT using Nidus

11 Screening, recruitment and consent

11.1 Identification and screening of participants

- Potential participants will be identified as they present on PICU by the doctor or nurse at site with delegated responsibility. They will be screened against the study inclusion and exclusion criteria using the patient medical notes.
- As part of standard care, all parents/guardians will be told about the clinical need for the patient to receive dialysis treatment. They will be told that the PICU at their hospital is taking part in the I-KID study.
- The initial approach will be done sensitively by communicating carefully with clinical staff, taking into consideration how the parents/guardians are feeling at that time and the individual situation of the patient.
- A log will be completed to document all patients who fulfilled the eligibility criteria for the study. This includes those who were approached and were subsequently included or excluded, as well as those who were not approached and the reasons why.

11.2 Recruitment procedures

The decision to start the patient on RRT will always be clinical. As part of standard care, staff will discuss with the parent/ guardian the need for dialysis and the current methods of RRT being used within the PICU. This will include the Nidus during the Intervention period.

After a clinical decision has been made to start a patient on RRT, parents/guardians will be given the appropriate Summary and the Additional Usual Treatment/Intervention Parent/Guardian Information sheets. It will be explained to the parent/guardian that they must read and consider the Summary Information Sheet as a minimum in order to make a decision about the patient taking part in the study. They may choose to read the Additional Information Sheet at the same time or at a time of their choosing. This ensures that all information is made available and the parent/guardian can decide what level is most appropriate for them.

All parents/ guardians will be given as long as is reasonably possible before the Investigator or person with delegated responsibility returns to discuss the study and answer any questions. The length of time given to consider the summary information will vary depending on the urgency of the situation and the health of each patient. Parents/guardians will always be given as long as is reasonably possible before seeking consent.

11.3 Consent procedures

The centre will have been randomised to a particular sequence in the SW cluster design, which removes the need for individual participant randomisation.

Parents/guardians will be asked to consent for the patient to take part in the I-KID study. In an emergency situation, dialysis may commence at the discretion of the responsible clinician before consent is obtained if it is in the patient's best interest to not delay treatment. If dialysis occurs prior to consent being taken for the patient to enter into the I-KID study, it will be noted in the patients' medical records that the decision to start treatment for the patient as part of the I-KID study has been made by the clinician caring for the child. The time that this decision was made, and the fact that consent has not yet been obtained from the parents / legal guardians will also be recorded in the patients' medical records. The patients' parents or legal guardians will be approached for signed consent, as soon as practicable, ideally within 48 hours, (deferred consent). Existing dialysis methods will be used during the control (usual treatment) period, and the Nidus used during the Intervention period. Informed consent discussions will be undertaken by appropriate site staff (as per the delegation log) involved in the study with the opportunity for the parent/guardian to ask any questions.

Parents/guardians who provide consent will still be given further opportunities to discuss the study and ask questions. All parents/guardians have the right to withdraw the patient from the study at any time without having to give a reason.

If consent is not received, the method of dialysis used will be/have been decided by the clinician considering the best option for that patient and what methods are available in the PICU at that time. The patient will not enter/or continue with the I-KID study and no I-KID data will be collected.

Consent Form:

One signature will be required on the consent form from a parent or legal guardian with legal parental responsibility (PR). If two persons are present with legal PR who cannot agree on the patient taking part in the trial, they will be encouraged to speak with medical staff about any concerns they may have. They may be given more time if needed. If both cannot agree, then consent would not be taken and the patient would not be included in the study.

Full written informed consent will be provided by signing, dating and initialling the consent form, which will be witnessed by the Investigator or staff member who has delegated responsibility to do so.

The original signed consent forms will be retained in the Investigator Site File (ISF), with a copy filed in the patient's clinical notes and a copy provided to the parent/guardian. The parent/ guardian will specifically consent to the patients' GP being informed of their participation in the study.

The parent/guardian has the right to refuse continued participation on behalf of the patient at any time without giving a reason and this will be respected.

11.4 Questionnaires

All parents/guardians of the patient (both, if two are present) will be given the opportunity to answer a short questionnaire about their experiences of having a baby on dialysis and how they found taking part in the study. The questionnaire will be completed face to face whilst the parents/guardians are in the unit, with a member of the team talking through the written document and supporting with completion, if required. Consent for the questionnaire will be implied by answering the questions and completing the form.

Staff using the Nidus machine will be asked to complete a paper questionnaire about the acceptability and usability of the RRT device. Consent for the questionnaire will be implied by completing the form. The aim will be for at least 50% of the questionnaires given to be returned completed, and it will be the responsibility of the Lead Nurse at site to ensure they are distributed appropriately.

12 Study intervention

Parents/guardians will continue to receive full supportive care as required whether the patient receives the control or intervention therapy. The initial requirement for the patient to have RRT will be made by the lead clinician in PICU and will be initiated according to the usual indications practiced by the attending clinical team. The control and intervention therapies will be administered by the NHS clinical team ordinarily treating the child with support from research nurses.

Control Therapy (Usual Treatment)

Patients will be treated with current RRT options available at the participating centre at that time during the usual treatment period. This will be either PD or CVVH, and measurement of fluid removal by the dialysis device will take place. PD is mainly used in smaller patients, and CVVH mainly for larger patients. Staff in PICU are already trained and competent in these RRT methods.

There are several machines available and in use currently, including the Gambro Prismaflex and Baxter Aquarius. In the absence of suitable and safe alternatives, these machines are used during standard care. The Nidus machine will not be available for use during the control period.

Control therapy will be used in the control period according to usual clinical practice until changeover to Nidus according to the stepped-wedge cluster randomised design. Eligible patients who decline consent to the I-KID study will still receive standard control therapy.

Intervention Therapy (Nidus)

With consent from the parent/guardian, patients with a weight of 0.8 – 7.99kg (estimated in emergency situations) will receive dialysis using the Nidus machine. The Nidus will only be available for use by trained staff during the intervention period.

Nidus has been specifically developed for use in patients under 8kg.The Nidus withdraws approximately 5-10mls of blood from the patient each time, cleaning it and removing excess fluid before returning the blood to the patient. It withdraws water from the patient therefore allowing appropriate fluids and nutrition. It operates at lower blood flows with a 10ml circuit which means that blood pre-filling is not needed.

The Nidus makes a constant recording of all activity data, including volumes, flows, pressures, alarms and response to alarms, downloadable for safety purposes. The length of time each patient will require dialysis will vary from a few hours to a few weeks depending on clinical need, and they may need the bags of fluid changing several times in a day.

Commercial company Allmed are responsible for the manufacture of the Nidus device, circuit and filters. They are loaning the machines to all 6 participating centres free of charge for the duration of the study. Each centre will receive 2- 3 machines, which will be at sites in sufficient time to allow staff training before the intervention period will start. This will also allow for the possibility of multiple cases needing treatment at the same time.

All 6 centres have a tertiary nephrology unit, and there will be provision of PICU and Nephrology nurse time for the duration of recruitment in each unit. All teams using Nidus will have received standardised training with a mandatory set of competencies, and have access to a 24hour support phone line.

During the intervention period, control therapy will continue to be used for those patients who do not meet the criteria for the Nidus machine (dry weight of under 8kg) and where consent is not received from the parent/ guardian for the patient to take part in the I-KID study.

Clinicians caring for patients under 8kg who have started on conventional dialysis methods and it has failed will have the option to use /switch to the Nidus machine on compassionate grounds outside of this study during the intervention period. Local and MHRA processes for

compassionate use should be followed by sites and I-KID Trial Managers, CI and Sponsors must be informed by copying in to correspondence.

13 Randomisation

As the clinical investigation requires the participating centres to be randomised, as opposed to individual patients, the units of randomisation are known at the start of the trial and will be randomised by the trial statistician using a random number generator in the package Stata [23]. As the numbers of patients that we expect to recruit varies between the centres, the randomisation will be stratified to ensure that over the trial as a whole the expected numbers of patients on the two treatments will be the same.

14 Blinding

All parents/ guardians will be fully aware and informed of the treatment that the patient is receiving. The treatment received will be dictated by the hospital and clinician along with parent/ guardian consent.

15 Study Data

15.1 Table 1 Schedule of Events:

Event	Before dialysis starts*	RRT Day 1	RRT day 1time 0 Baseline data Confirmation of eligibility	RRT time +6 hours	RRT first 48hours Fixed 12 hourly intervals	RRT from 48hours to end of RRT or discharge from PICU	Discharge day from PICU	Approximately 1 month Follow Up
		Renal Replacement Treatment						
Control Period: Summary and Additional Usual Treatment Parent/Guardian Information Sheet and Consent Form.	x							
Intervention Period: Summary and Additional Intervention Parent/Guardian Information Sheet and Consent Form.	x							
Access to daily PICAnet data		x	x	x	x	x	x	
Access to daily enhanced renal PICAnet data		x	x	x	x	x	x	
Additional study data recorded		x	x	x	x	x	x	x
Adverse Event and Device Deficiency recording			x	x	x	x	x	x
Access to data from routine clinical assessments			x	x	x	x	x	x
Access to results from routine blood tests			x	x	x	x	x	x

Event	Before dialysis starts*	RRT Day 1	RRT day 1time 0 Baseline data Confirmation of eligibility	RRT time +6 hours	RRT first 48hours Fixed 12 hourly intervals	RRT from 48hours to end of RRT or discharge from PICU	Discharge day from PICU	Approximately 1 month Follow Up
		Renal Replacement Treatment						
Weighing of dialysis fluid bags in			x	x	x			
Weighing of dialysis fluid bags out			x	x	x			
Biochemistry tests on waste fluid Enzymatic creatinine, urea, phosphate			x	x	x			
Access to results from routine weight, BP, blood & urine.								x
Nurse acceptability questionnaire					x			
Parent Questionnaire						x		

*Unless deferred consent is used.

Collection and Recording of Information

Table 2. Data Collection and Phases

	Dialysis Function Measurements a) Weighing dialysis bags or PD equivalent. b) Collecting waste dialysate and blood for clearance measurements.	***Clinical Data Collection*** a) PICAnet data. b) Enhanced Renal PICAnet data. c) Dialysis-related events.
Phase 1 Primary outcome.	**X** at 0 hours and +6 hours	**X**
Phase 2 Detailed data from +6 hours up to 48 hours.	**X** twice daily [e.g. 08:00 and 20:00] until 48hours has passed	**X**
Phase 3 Clinical data during RRT, collected for up to and including 28 days.	—	**X**

Data will be collected for the study in 3 distinct phases from the start of dialysis for each patient in PICU.

I-KID study data will be captured and entered at sites on electronic Case Report Forms (eCRFs). The eCRFs will be accessed by the Newcastle Clinical Trials Unit for monitoring purposes.

Phase 1 (0 hours to +6 hours):

- Data collected during phase 1 will address the primary outcome.
- Data will be recorded at the time that RRT is started (as '0 hours') and again as close to 6 hours later as it practically possible (+ 6 hours). The precise times will be recorded (24:00 format).
- For clearance measurements, a sample of effluent (waste) dialysate fluid will be collected at the same time (approximately +/- 1 hour) as blood is collected to measure the clinical biochemistry. These will be sent together to the laboratory for analysis.
- Data collection will include recording the ultrafiltration.
    - For CVVH/D or Nidus, the ultrafiltration is measured by weighing the unused and used dialysate fluid bags.
    - For PD the ultrafiltration is measured volumetrically by the nurse at the bed side.
- Data collection will include recording the dialysis device settings.
- PICAnet (daily and enhanced) data will be recorded as well as dialysis related events

Phase 2 (+6 hours to 48 hours):

- More detailed data will be collected during phase 2 (until 48 hours after RRT was started)
- After the first 6 hours, the same data will be recorded as in Phase 1 except this will be undertaken at fixed 12 hourly intervals e.g. 08:00 and 20:00 until 48 hours has lapsed from the start of RRT.
- PICAnet (daily and enhanced) data will be recorded as well as dialysis and device related events
- After completing Phase 2, no more dialysis clearance or UF data will be collected.

Phase 3 (0 hours until RRT stops, or 28 days after RRT):

- Long term data will be collected in phase 3 to address secondary outcomes
- Data will be collected daily until RRT ends, or up to 28 days after the start of RRT.
- PICAnet (daily and enhanced) data will be recorded as well as dialysis and device related events
- At discharge from PICU, extra information will also be collected, including the date of discharge and the location after discharge e.g. home, another ward.

For all phases:

- Extra clinical data will be recorded for dialysis related events, in addition to the PICAnet data. These will include requirements for blood transfusion and cardiovascular instability during this period.
- Staff at site will request access to the daily information collected and uploaded to the PICAnet system as part of the national PICAnet audit. This will include the enhanced renal data which is also collected at the participating sites. Data will only be requested for patients who have been consented to the I-KID study.
- The downloaded dataset will include a unique I-KID participant identification (ID) number, the patient identifiable information will be date of birth and may include NHS number. The data download will be sent centrally using a secure network to the database Manager at the Newcastle Clinical Trials Unit for upload to MACRO.

Follow Up Visit:

- Staff will request access to the information recorded when the parent/guardian attends the follow up visit at the hospital (or a local hospital). If the patient has been discharged home by this point, they would be required to come back to hospital to attend this visit as part of standard care. This is usually around 1 month after dialysis was started, or in line with local practice, but must be no longer than 3 months after dialysis was started.

Biochemical Tests:

- Waste fluid produced from dialysis that is usually discarded will be collected and sent to the local labs along with blood samples, for the measurement of urea, phosphate and enzymatic creatinine, as well as any other blood tests undertaken for clinical reasons. A different process is in place for samples collected at Southampton, on section 15.3.

Adverse Event (AE) and Device Deficiency (DD) Recording:

- All AEs, other than those considered consistent with the usual clinical pattern for patients requiring renal replacement therapy in PICU and observed DDs will be collected and recorded in both the medical notes and eCRF.

- See section 19 for reporting requirements for AEs that fulfil the criteria of a Serious Adverse Event, Serious Adverse Device Effect or Device Deficiency that could lead to a Serious Adverse Device Effect.

Parent and Staff Questionnaires:

- All parents/guardians of patients who took part in I-KID will be given the opportunity to answer an optional questionnaire about the experience of having their on dialysis and how they found taking part in the I-KID study. This will be completed face to face with a member of the research team.
- Parents/guardians will be asked at an appropriate time before the patient is discharged from the unit. This can be any time up to the day of discharge.
- Staff using the Nidus machine will be asked to complete an optional questionnaire about the acceptability and usability of the RRT method.
- Consent will be implied through the act of completing the questionnaire.
- Staff will approach parent/guardians about taking part in the UK Renal Registry to allow for long term data collection (outside of the I-KID study).

15.2 Study Samples

No additional samples will be taken from the patient for the purposes of this study. This study will access the results from routine tests.

Fluid removed during dialysis that would usually be discarded as part of standard care will be sent to the local hospital labs for biochemical testing. The sample for testing will be prepared by gently mixing the fluid in the waste dialysate bag. An aliquot of approximately 2mL will be added to a Universal container, via the tap on the collection bag and sent to the lab.

The fluid will be destroyed once the testing has been completed. No samples will be kept beyond the end of the study.

15.3 Biochemical Testing

Waste fluid removed during dialysis would usually be discarded. This will be collected and sent to the local NHS lab for testing. Fluid will be tested for enzymatic creatinine, urea and phosphate. The results of the tests will be recorded and compared to the patient routine blood test results.

Fluids and Biochemical testing for Southampton

The creatinine assay currently used in Southampton is a non-enzymatic (Jaffe) method. Enzymatic creatinine analysis is required for the I-KID study. Therefore, special arrangements have been made for dialysate fluid and excess plasma to be securely stored and appropriately transported for appropriate enzymatic assay.

15.4 Data Handling and Record Keeping:

Data will be downloaded from the PICAnet system to each site for patients who have been consented to the study. This will contain patient identifiable information, including date of birth and may include hospital number. Each patient will be allocated a unique participant ID number at site when they are enrolled into the study. All subsequent records will be identified using this ID number – including any work sheets and eCRFs. The downloaded data will be sent by sites to the Newcastle Clinical Trials Unit for upload to the MACRO database.

Additional data will be captured by research staff at sites using eCRFs designed specifically for the I-KID study. All data is entered on to a secure validated clinical data management system with an auditable data trail.

Data will be handled, computerised and stored in accordance with the Data Protection Act 2018. All original consent forms will be held in the ISF, with a copy in the clinical notes and a copy given to the participant.

Caldicott approval will be obtained from all local sites as part of the local NHS permission to enable the collection of personal identifiable information as part of this trial. The quality and retention of study data will be the responsibility of the CI. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

A Database Manager will be responsible for developing the eCRFs and database using MACRO. This will be used for trial specific data capture, raising and resolving data queries, cleaning and preparing the data for analysis, archiving and data sharing. The central Trial Management team will also have access to any worksheets used by sites and eCRFs in order to monitor recruitment and data entry.

16 Statistical Considerations

16.1 Statistical Analysis

Statistical analysis will take place during months 25 to 27.

The analysis of the study will allow for clustering by the use of generalised estimating equations (GEEs) with an assumed independence working correlation matrix. The assumed variance will be constant for continuous outcomes but for the binary and categorical outcomes, suitable variance functions will be assumed. In addition to a treatment effect the fitted statistical model will include effects for each of the treatment periods of the SW design, to allow for any trends over time [5]. Patients receiving treatment during more than one period will be ascribed the period effect corresponding to the period during which the patient started treatment.

The principal analysis for each variable will compare Nidus and conventional therapies, with a secondary analysis which will estimate contrasts comparing i) Nidus vs PD and ii) Nidus vs CVVH.

16.2 Variables

The main aim of the trial is to compare how close the actual fluid removal (X) is to that prescribed by the treating physician (A), so attention is focussed on the variability of the difference between X and A, as measured by its standard deviation, SD. The primary variable to be analysed is Y=log (|X-A|), where the vertical bars in |X-A| indicate that the sign of the difference is ignored. The log transformation means that the ratio of the SDs of the treatments being compared can be assessed through the difference in means of the Y variable.

In the primary analysis X and A will refer to the fluid removal during the first six hours of treatment. In a further analysis X and A will refer to the fluid removal over the first 48 hours of treatment, or discontinuation of RRT, whichever occurs first.

As the primary variable considers only the first six hours of treatment, it is anticipated that the number of patients unable to provide a primary variable based on six hours of fluid removal (e.g. due to death or technical problems with the RRT) will be minimal. As such the primary analysis will be based only on those patients who do provide six hours of data. A supplementary analysis will include all eligible patients who commence RRT, but in these analyses the duration of RRT will be included as a covariate to allow for differences in duration which might arise between the treatment groups.

Analyses will also be performed on the secondary variables listed in Section 6. These include the following biochemical clearances based on determinations at 6 hours and 48 hours after the start of RRT, and will use the same GEE used to analyse the fluid removal. The parent experience questionnaire be analysed using simple tabulation and using a suitable GEE. The other variables listed will be tabulated by treatment. More sophisticated analyses using GEEs may be impractical in many cases if there is little variation in the response (e.g. if there are few unplanned changes in the circuits). As this is a study with complete follow-up over a relatively short period, survival will be analysed as a binary outcome indicating if the patient survived until discharge.

16.3 Sample size calculations

This study will look to recruit for 20 months, as outlined in Section 9 and during this period we expect to recruit 95 patients across the 6 participating PICUs.

The sample size calculation follows the method of Hussey and Hughes1 [5], adapted to accommodate unequal cluster sizes.

The primary outcome is Y=log |X-A| and this will be distributed, at least approximately, as log SD + log |Z|, where Z has a standard Normal distribution. It is assumed that the Z responses in a PICU are from a multivariate standard Normal distribution where all pairs have a common

correlation, such that the implied common correlation of the Ys is R. Responses in different PICUs are assumed to be independent. Under these assumptions the difference in means between the treatments is log (SDconv/SDNIDUS). We seek to demonstrate that Nidus offers a three-fold improvement in SD. The variances and parameters in our model can be identified with those in the formula of Hussey & Hughes, which allows us to determine the power that a study recruiting 95 patients can attain.

The design is a SW cluster design and the correlation R is the intraclass correlation. In common with many cluster-randomized designs we have limited prior knowledge of the value of R. However, because this is a SW cluster design, in which a good deal of within-cluster information is available for the estimation of treatment effects, the sample size estimates are much less sensitive to the value of R than is the case for ICC in conventional cluster-randomized trials. Calculations show that using a 5% two-sided Type I error, the power of a trial recruiting 95 patients is 80% for R=0.1 and this becomes 84% for R=0.05 For cluster-randomized trials an ICC as large as 0.1 is unusual, so the study will have adequate power. The power will also vary slightly depending on the sizes of the units allocated to sequences S1, S2 and S3, however for the randomization schemes anticipated variation in power is less than 1%.

From analysis of PICANet audit data, in 2011-13, approximately 200 children under 1 year old are provided with renal support (CVVH, PD or both) annually in the participating PICUs. Of these about 50%) were under 1 month. PICANet data does not currently include weight but all those under 1 month will weigh under 8kg weight and around 70-80% of the older group will weigh less than 8 kg. Overall, it is thought that 35 - 40% of these children will received CVVH or CVVH + PD. Taking account of these figures and making conservative allowance for those refusing consent or dropping out for clinical reasons, it is believed that I-KID will be able to recruit about 63 babies a year from the combined units. This allows the target of 95 patients to be recruited in 20 months. It is possible to bring additional sites on board if there are any issues with recruitment at participating sites.

17 Compliance and withdrawal

17.1 Assessment of compliance

All eligible participants will be patients in PICU on dialysis and are staying as part of their standard clinical care. Clinical and research staff will be closely monitoring the patients for the full duration of their dialysis treatment, with information collected and recorded daily.

The dialysis method used will be determined by the hospital and doctor(s) as well as receiving parent/ guardian consent. Dialysis will be administered by trained staff who will have their competency assessed every 6 months.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

17.2 Withdrawal of participants

All parents/guardians will have the right to withdraw the patient from the study at any time for any reason, and without giving a reason. If the parent/guardian withdraws the patient from the study, they will be asked to complete a confirmation of withdrawal document. They will be asked if they would be happy for the reason for the decision to withdraw to be recorded, and if any data collected so far can still be used in the study analysis.

The clinician has the right to change the therapy after RRT has started due to concerns regarding their safety or a change in their condition. Should a patient therapy be changed within the first 6 hours of RRT starting, data collection will not continue for the study and it will be counted as a withdrawal. The reason for withdrawal will be documented as thoroughly as possible. If the therapy is changed after the + 6 hours data collection time has been completed, and consent has been obtained for the study, data collection will continue and the patient will remain in the study.

There is a high mortality rate in the patient population eligible for this study. Data that has been collected and recorded after consent will still be used for the study no matter what the outcome for the patient, unless consent is withdrawn. This is clearly stated in the information sheet and consent form.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

18 Data monitoring, quality control and quality assurance

18.1 Discontinuation rules

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Trial Steering Committee, Sponsor, or regulatory authority.

18.2 Monitoring, quality control and assurance

The trial will be managed and supervised through the Trial Management Group (TMG) based at Newcastle Clinical Trials Unit (CTU). The Trial Management Group (TMG) will include the CI, Senior Trial Manager, Trial Manager, Trial Administrator, Trial Statistician, Database Manager and Co-Investigator(s).

The Newcastle Clinical Trial Manager will provide day to day support for the site, and provide training through site initiation visits and routine monitoring visits.

The Principal Investigator will be responsible for the day-to-day study conduct at site.

Quality control will be maintained through adherence to Newcastle CTU and Sponsor SOPs, study protocol, the principles of GCP, UK Policy Framework for Health and Social Care Research and clinical investigation regulations.

Trial Steering Committee (TSC)

As agreed by the study Sponsor and Funder, a Trial Steering Committee (TSC) will be convened. The TSC will consist of an Independent Chair, two other independent members, a Principal Investigator and independent consumer representatives. In addition, representatives of the Trial Management Group, Sponsor and Funder will be invited to attend or dial in via teleconference as needed.

TSC responsibilities will be outlined in a TSC terms of reference.

The TSC will meet a minimum of three times over the course of the study. The role will be monitor progress and supervise the trial to ensure it is conducted to high standards in accordance with the protocol, the principles of GCP, relevant regulations and guidelines. The TSC will advise on whether to continue or discontinue the study and make a recommendation to the Sponsor. If the study is prematurely discontinued, the parents/guardians of participants will be informed and no further trial data will be collected.

Data Monitoring Committee (DMC)

A DMC of all independent members will be convened to undertake independent review. The purpose of this committee will be to monitor safety. At the first meeting, the DMC will agree on its charter of operation, and possible adoption of a formal stopping rule for safety.

The DMC will convene a minimum of three times over the course of the study.

A written charter will be agreed and used by the DMC and TSC.

Study Monitoring

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken on behalf of the study Sponsor by the Newcastle CTU, in agreement with the CI. The main areas of focus will include consent, serious adverse events, serious adverse device effects and essential documents in study files. A monitoring plan will be written, agreed and signed by the Sponsor and monitor.

Site monitoring will include:

- Original consent forms will be reviewed as part of the study file. The presence of a copy in the patient hospital notes will be confirmed for all participants
- Original consent forms will be compared against the study participant identification list

- Reported serious adverse events and serious adverse device effects will be verified against treatment notes/medical records (source data verification)
- The presence of essential documents in the ISF and study files will be checked
- Source data verification of eligibility for all participants entered in the study

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness before submission
- All documentation essential for study initiation will be reviewed before the site is authorised and approved to start
- Copies of consent forms will be checked to ensure they have been completed correctly

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The study may be subject to inspection and audit by NUTH under their remit as Sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

19 Adverse Event Monitoring and Reporting

19.1 Safety Reporting Definitions

Term	Definition
Investigational Medical Device (IMD)	A medical device being assessed for safety or performance in a clinical investigation.
Device Deficiency (DD)	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may be due to malfunction, misuse, user error, inadequate labelling or insufficient information provided by the manufacturer.
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention under study.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: a) Results in death b) Led to serious deterioration in the health of the participant, that either resulted in: 1) A life threatening illness or injury or* 2) A permanent impairment of a body structure of body function, or 3) In-patient prolonged hospitalisation c) Medical of surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function or d) Led to foetal distress, foetal death or a congenital abnormality or birth defect. e) Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences *AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent any of the outcomes listed, **should still be considered as serious.**
Adverse Device Effect (ADE)	Adverse event related to the use of the investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a use error or intentional misuse. Any unexpected physiological response of the participant does not in itself constitute a use error.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the **Investigator Brochure or Protocol section 19.2.3 (Table of Adverse Events and Possible Relationship to Nidus Use or Misuse)** as an effect that could lead to an SADE.

19.2 Reporting Exclusions

Adverse events judged by the Investigator responsible for patient care, as consistent with the usual clinical pattern for patients requiring renal replacement therapy in PICU, do not meet the definition of a reportable AE. All other adverse events which occur, should be assessed and reported in compliance with applicable procedures outlined below in section 19 of the protocol.

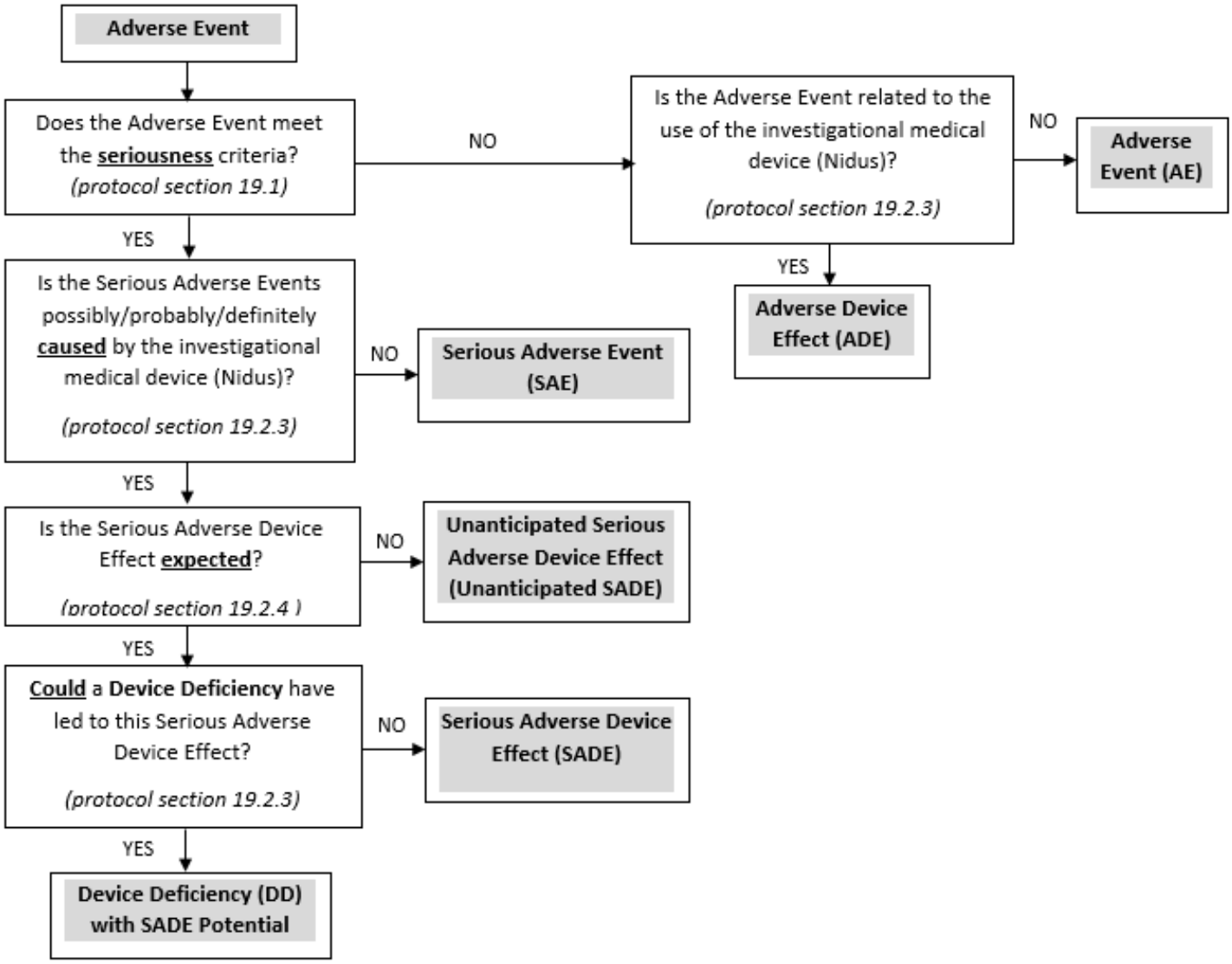
Babies in PICU requiring RRT are unstable and their clinical course commonly involves:

- multi-organ involvement or failure requirement for mechanical ventilator support or supplemental oxygen
- fluid overload with pulmonary or generalized oedema
- blood pressure fluctuation - hypertension or hypotension (e.g. on connection to RRT circuit or with fluid shifts)
- coagulation problems resulting in bleeding, requirement for blood transfusion
- complications of central venous lines including blockage/clotting and infection
- complications of peritoneal dialysis catheter including leakage, infection, peritonitis
- neurological problems like encephalopathy or fitting.

The clinical course and status of children in PICU is routinely recorded on a daily basis in the notes and in PICANet audit returns.

19.3 Assessment of Adverse Events (AEs)

Flow Diagram: Assessment of AEs



The PI at site, or designee, is responsible for the identification of any AE as defined in the protocol. Each AE must be assessed for **severity (19.3.1), seriousness (19.3.2), causality (19.3.3) and expectedness (19.3.4)** as follows:

19.3.1 Assessment Severity:

An assessment of severity is required (**mild, moderate, severe**) to determine if an event is at a severity not usually seen. The investigator, or designee, should make an assessment of severity for each AE according to their clinical judgement and knowledge of the participant. This will be recorded in the electronic case report form (eCRF) and in serious cases on SAE/SADE Report Forms.

19.3.2 Assessment of Seriousness:

The PI or designee must make an assessment against the standard definition in the Safety Reporting Definitions section 19.1.

19.3.3 Assessment of Causality:

The relationship between the use of the investigational medical device (Nidus) and the AE must be assessed by the PI or designee using clinical judgement to determine the causal relationship. Other factors such as medical history of underlying diseases, concomitant therapy

and any other relevant risk factors must be considered. The PI or designee must also consult the Investigators Brochure (IB), and current version of the protocol including the table of 'Adverse Events and Possible Relationship to Nidus Use or Misuse' later in this section.

Categorisation of Causality:

All **SAEs** must be categorised according to the following five different levels of causality:

Categorisation	Categorisation Description
Not Related	A relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis when applicable; - harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. For examples of adverse events and serious adverse events see table below - Table of Adverse Events and Possible Relationship to Nidus Use or Misuses.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained. For examples of adverse events and serious adverse events see table below - Table of Adverse Events and Possible Relationship to Nidus Use or Misuses.

Categorisation	Categorisation Description
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that; - the investigational device or procedures are applied to; - the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. For examples of adverse events and serious adverse events see table below - Table of Adverse Events and Possible Relationship to Nidus Use or Misuses.

Assessment of Causality:

All AEs must be assessed to determine the causal relationship to the investigational medical device (Nidus). The tables below list examples of AEs/SAEs that may occur in this patient population, and ways in which they may possibly be related to the use or misuse of the Nidus machine.

TABLE OF ADVERSE EVENTS AND POSSIBLE RELATIONSHIP TO NIDUS USE OR MISUSE

Adverse Event (AE) / Serious Adverse Event (SAE)	**Possible Nidus related action (including misuse) causing event, leading to ADE/SADE Classification**
Sudden and unexpected drop in patient blood pressure (hypotension)	Nidus removing more ultrafiltration (UF) than is set or it is reporting resulting in significant hypotension. User has set too high UF rate for patient resulting in significant hypotension. User has set stroke volume too high for patient size resulting in significant hypotension. Nidus withdrawing higher stroke volume then set by user. Blood loss from Nidus or Nidus tubing set (either leak or loss) resulting in significant hypotension.
Patient acquired infection	Nidus tubing not sterile (packaging damaged or not sealed correctly) resulting in patient acquiring infection.
Patient given antibiotics to pre-empt infection	Nidus tubing failed exposing blood line to air resulting in pre-emptive use of antibiotics
Air infusion/possible air emboli, Patient given emergency scan	Nidus tubing failed (possible air embolus to patient) resulting in patient needing emergency scan. Nidus device pushed significant air embolus to the patient without alarm/stopping. Bubble alarm acknowledged, and machine restarted by user without following corrective action as indicated, due to inadequacy of on screen information.
Patient lost excessive blood requiring additional blood transfusion.	Repeated filter clots when using Nidus causing kit changes. Due to ACT being kept too low (user error). Nidus pushed patients' blood to waste bag resulting in excessive loss of blood to patient. Nidus tubing set or filter fails causing blood leak/loss. (If this is undetected it would be a SADE).
Clot returned to patient	Nidus pushed clot back to patient, without pressure alarm or stall alarm or stopping.

Adverse Event (AE) / Serious Adverse Event (SAE)	Possible Nidus related action (including misuse) causing event, leading to ADE/SADE Classification
Patient has excessive bleeding	Nidus device infusing heparin at higher rate than user has set, resulting in excessive bleeding. Heparin rate incorrectly set too high by user, ACTs were too high and inadequate action taken by user, resulting in excessive bleeding. ACTs incorrectly taken/analysed, leading to incorrect heparin rate setting resulting in excessive bleeding.
Patient injured by force on catheter line	Nidus device brakes fail and patient is injured due to force on catheter line. User forgets to apply brakes and Nidus device moves and patient is injured due to force on catheter line.
Patient has dramatic and inexplicable change in blood chemistry	Catastrophic Nidus filter failure resulting in direct mixing of dialysate and blood and return to patient. User selects inappropriate fluid and/or additives and connects to Nidus dialysate connection contrary to Instructions for use. User selects inappropriately high dialysate-rate, coupled with high access rate, for the size of baby (in particular <1.5kg), resulting in too higher clearance rate.
Electrocution	Nidus generating dangerous electrical currents resulting in electrocution of patient.
Burns	Device power/battery failure causing fire and burns to patient.

19.3.4 Assessment of Expectedness:

All SAEs and SADEs must be assessed for expectedness (classified as **anticipated/ unanticipated**) by the PI or designee according to the following:

Event Term	Assessment Description
SADEs	The **Investigator Brochure (IB) and the Table of Adverse Events and Possible Relationship to Nidus Use or Misuse in section 19.3.3** of this protocol will be used by the PI or designee as a basis for identifying anticipated/unanticipated. ADEs should be characterised by their nature, incidence, severity and outcome. The PI or designee must note the version of the IB and Protocol that is used to perform this assessment on the Report Form.
SAEs	The following are SAEs that could be reasonably expected to occur in this population of vulnerable and sick patients during the course of the study or form part of the outcome data: - Death (unless unexpected in specific population) - Multi-organ failure - Requirement for mechanical ventilator support or supplemental oxygen - Pulmonary oedema - Severe generalized oedema and fluid overload - Hypertension requiring treatment - Hypotension requiring treatment with fluid bolus or inotropes - Severe bleeding - Requirement for blood transfusion - Central venous line complications, blockage, infection or clotting - Peritoneal dialysis catheter complications, leakage or infection - Peritonitis (if on PD) - Encephalopathy/fitting

19.4 Quarantine of Device

If an ADE is defined as serious (SADE) or a DD that could have potentially led to a SADE (anticipated or unanticipated) then the investigator must quarantine the device as soon as possible.

Until the Medicines and Healthcare products Regulatory Agency (MHRA) have carried out an investigation:

- The device should not be discarded, repaired or returned to the manufacturer.
- All material evidence i.e. parts removed, replaced or withdrawn from use following an incident including relevant instructions, records and packaging materials or any other means of batch identification must be:
    - Clearly identified and labelled
    - Stored securely
- Evidence should not be interfered with in any way, except for safety reasons or to prevent loss. Where relevant, a record of all readings, settings, positions of switches, valves, dials, gauges and indicators, along with any photographic evidence and eye witness reports should be retained.

19.5 Recording and Reporting of Adverse Events

19.5.1 Site Requirements

The following AEs must be recorded and reported by the **participating site** in accordance with the table below:

Event Term	Recording and Reporting
AEs and Observed DDs:	Unanticipated AEs and device deficiencies for the Nidus, must be recorded, with details of the assessment, in both the patient medical notes and the eCRFs from day 1 of dialysis until the end of dialysis (+24hours) or day 28 if this is sooner. A complete record of unanticipated AEs for the study will be maintained in the eCRFs (database).
All SAEs	SAEs that are related to the device are reported as SADEs. SAEs that are due to the critical condition of the baby are expected and do not need to be reported, see section 19.2. All other SAEs are to be recorded on a provided SAE log and reported by the PI or designee to the CI, Newcastle CTU and Sponsor on a monthly basis in accordance with procedure outlined by the MHRA (Ref CI/2017/0066 – 27th Feb 2018) no later than 5 working days prior to the sponsor MHRA monthly reporting deadline.
All SADEs or a DD that could lead to an SADE	Must be reported by the PI or designee to the CI, Newcastle CTU and Sponsor **ideally within 24 hours and no later than 3 calendar days** after the site learn of its occurrence using the SAE/SADE Report Form. ***Initial Report***: if necessary can be made by telephone or email to Newcastle Clinical Trials Unit. The PI or designee must then complete the agreed Report Form and send via secure system to Newcastle CTU / CI / nominated Sponsor contact. ***Follow Up Report:*** In the case of incomplete information at the time of initial reporting, or follow up information, a new Report Form must be completed and sent via secure system as soon as possible. All SADEs will be tracked until they are resolved.
	Please send the completed and signed SAE/SADE report form(s) and any SAE summary logs using the I-KID secure distribution email: **nctu.IKID-sae@nhs.net**

19.5.2 Sponsor Requirements

The following AEs must be recorded and reported by the **study Sponsor** in accordance with the table below:

Regulatory Body	Event Description	Recording and Reporting
MHRA	The following events are considered as requiring expedited reporting to the MHRA by the Sponsor • All SAEs that are deemed to be either device related or possibly device related (SADEs) • Any DD that might have led to an SADE if: a) Suitable action had not been taken b) Intervention had not been made c) If circumstances had been less fortunate • New findings/updates in relation to already expedited reported events	For all reportable events where there is an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding in relation to such events, the Sponsor will report to the MHRA immediately, but no later than **2 calendar days** after Sponsor become aware of such an event or new information in relation to an already reported event. Any other reportable events as outlined above or any new finding/update in relation to them must also be reported immediately, but no later than **7 calendar days** after the Sponsor becomes aware of them.
	All SAEs that are **not** related to the device.	Will be reported to the MHRA by the Sponsor **once a month** by a summary report.
REC/HRA	Unanticipated SAEs and SADEs occurring from day 1 of dialysis until the end of dialysis (+24hours) or day 28 if this is sooner.	Will be reported to the REC/HRA by the Sponsor within **15 calendar days** of Sponsor becoming aware of the event using the appropriate reporting form. Any relevant follow-up information should be sought from site and reported by Sponsor as soon as possible after the initial report.
	All SAEs/SADEs/DDs that are reported to Sponsor.	A report on the safety of participants will be included in the **annual** progress report submitted by NCTU, including Investigator notifications of any SAEs/SADEs/DDs that are reported. Document evidence of investigator review of these will be filed in the Investigator Site File.
PI's	Unanticipated SAEs and SADEs occurring from day 1 of dialysis until the end of dialysis (+24hours) or day 28 if this is sooner.	Will be notified to all PIs participating in the study on an ongoing basis.

19.5.3 Serious Breaches

It is the responsibility of the CI to ensure that the clinical investigation is run in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team but the CI and PI will retain overall responsibility. Any actual or suspected

breaches must be reported to the Sponsor within 24 hours of identification. Where a serious breach has been identified, it is the responsibility of the Sponsor to notify the REC and MHRA within **7 calendar days** of determining that a serious breach has occurred.

Deviations from the protocol and GCP occur in clinical investigations and the majority of these events are technical deviations that are not serious breaches. These events should be documented in the electronic Case Report Form (eCRF) and on the protocol deviation log, in order for Corrective and Preventive Actions (CAPA) to be taken.

19.6 Clinical Safety Sub Group

Following receipt of SAEs/SADEs from site, they will be reviewed by members of the clinical safety sub-group, comprising Dr Heather Lambert, Dr Malcolm Coulthard and Mr Michael Whitaker, to confirm agreement with causality and expectedness assessment, prior to reporting to the MHRA. This assessment must be communicated to the Trial Manager and sponsor representative immediately and documented and filed in the TMF.

Please note: Timelines for this review will be determined based on the required dates for sponsor reporting to the MHRA.

Timelines for Review	
SAEs	Within 5 working days of receipt from site
SADEs	Within 1 working day of receipt from site

19.7 Protocol Specifications

For purposes of this protocol:

- Adverse events (AEs) not consistent with the usual clinical pattern for patients requiring RRT in PICU and observed device deficiencies (DDs) will be collected and recorded, together with an assessment in the medical notes and in the electronic CRF.
- All such adverse events will be recorded from day 1 of dialysis until the end of dialysis (+24hours) or day 28 if this is sooner and SAEs and SADEs tracked until they are resolved.

19.8 Responsibilities

Principal Investigator:

- Checking for AEs and ADEs when participants attend for treatment or follow-up.
- Recording every AE not consistent with the usual clinical pattern for patients requiring renal replacement therapy in PICU and observed DD with an assessment in the medical notes and eCRFs.
- If it is determined that an AE fulfils the criteria of a SADE or a DD that could lead to an SADE, the Investigator must ensure it is reported to NCTU/CI/study Sponsor without any unjustifiable delay.
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events using the Investigator Brochure and Protocol approved for the study.
- Ensuring that all SADEs recorded and reported to the Sponsor ideally within 24 hours (and no later than 3 days) of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that all SAEs, unless they are due to the critical condition of the babies being recruited, are reported by the PI or designee to the CI, Newcastle CTU and Sponsor on a monthly basis on the provided SAE log within the timelines agreed with sponsor.

Chief Investigator

- Clinical oversight of the safety of study participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all SADEs
- Confirmation of causality and expectedness assessments for all SAEs/SADEs reported by site
- Review of specific SAEs/SADEs in accordance with the study risk assessment and protocol.

Sponsor

- Reporting to MHRA any SADE, and DD which might have led to an SADE and new findings or updates in relation to already reported events.
- Any adverse incident involving a medical device undergoing clinical investigation must be reported to the manufacturer, or directly to the Medicines & Healthcare Products Regulatory Agency via the online system (www.mhra.gov.uk). Reportable SAEs/SADEs will be reported to REC.

TSC/DMC

- Regular review of safety data collected to date to identify any trends

20 Ethics & Regulatory Issues

20.1 Research Ethics Committee Review and Reports

Favourable ethical opinion will be sought prior to commencement of the study and for all subsequent amendments as appropriate. Local approvals will be sought before recruitment may commence.

Study Information sheets will be provided to parents/guardians of all eligible patients. Tailored consent will be obtained appropriate to the phase of the study at the time of consent.

The Newcastle CTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained.

An annual progress report will be submitted each year to the REC by the Newcastle CTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The Newcastle CTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

20.2 Ethics Considerations

20.2.1 Patient, Care and Public Involvement (PCPI)

PCPI has heavily shaped the study design.

Feedback was sought from a group of parents with children on dialysis in Newcastle upon Tyne where considerable support was given to the study and the step wedge design. It was felt that obtaining consent for the type of dialysis method to be used would add to families' stress and anxiety. Also, that parents were likely to default to the position of the medical team. The step wedge design was considered to be a good compromise where the hospital and medical team were randomised, with individual consent sought at a later date for collection and recording of information only for the study.

Parent and co-applicant Chris Boucher has been involved in the study development from the start to ensure that methods are acceptable and sensitive.

I-KID will have an advisory Consumer Advisory Group to provide additional trial oversight and PPI input. This group will include a parent, lay member, Chris Boucher and a Sponsor PPI representative wherever possible. PPI representatives from participating sites will also be invited to attend when appropriate.

Discussion with the Newcastle Researcher Consumer Group demonstrated how important they felt this study would be. They held favourable views on the step wedge design and delayed consent to collect and record information for the study.

21 Confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the sites will identify participants by their initials and a unique study identification code only. The study will comply with the Data Protection Act, 2018. All study records and Investigator Site Files will be kept at sites in a locked filing cabinet with restricted access.

The research team will be requesting access to patient identifiable information from the PICAnet system, which will include date of birth and NHS hospital number. A patient identification number will then be allocated at sites to all patients enrolled in the study.

22 Insurance and Finance

Conduct

The Newcastle Upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study at site.

Management

The Newcastle Upon Tyne Hospitals NHS Foundation Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management.

Design

Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

Payment

Parents/guardians will not be paid for taking part in this study. The patient will be staying in the PICU as part of their clinical care, and will not be required to attend any additional research visits.

Declaration of Interest:

The inventor of Nidus and the nursing lead for Nidus will both receive royalties from its sales. Both have driven the engineering and clinical development of the machine since 1995.

23 Study Report / Publications

The data will be the property of the Chief Investigator and Co-Investigator(s). Publication will be the responsibility of the Chief Investigator.

It is planned to publish this study in peer review articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Individual participants will not be identified from any study report.

Parents/Guardians will be informed about the patient's contribution to the study at the end of the study, including a lay summary of the results.

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