FULL TITLE OF THE TRIAL

The ASK Trial: a trial of a patient and family outreach service to improve AccesS to living-donor Kidney transplantation

SHORT TRIAL TITLE / ACRONYM

The ASK trial: improving AccesS to Kidney transplantation

PROTOCOL VERSION NUMBER AND DATE

Version1.2 26th September 2025

- Post approval changes to the document are listed with new version control in Appendix 4.

RESEARCH REFERENCE NUMBERS

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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 clinical investigation without the prior written consent of the Sponsor

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

For and on behalf of the Trial Sponsor:

Signature:

..signed electronically

Date:
.01/10/2025

Name (please print):

...Alia Ataya.....

Position: ...Sponsor Representative.....

Chief Investigator:

Signature: .

signed electronically.....

Date:
.02/10/2025..

Name: (please print):

..Pippa Bailey.....

Statistician:

Signature: .. signed electronically.....
.....

Date: .
.01/10/2025

Name: (please print):

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Position: ....Lead Trial Statistician.....
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KEY TRIAL CONTACTS

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i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

ABOi	ABO blood group incompatible
ATTOM	Access to Transplantation & Transplant Outcome Measures
BMI	Body Mass Index
CEAC	Cost-effectiveness acceptability curve
CI	Chief Investigator
CRF	Case report form
CTU	Clinical Trials Unit
DAC	Data Access Committee
DCEA	Distributional cost-effectiveness analysis
DDKT	Deceased-donor kidney transplant
DMC	Data Monitoring Committee
eCRF	Electronic case report form
GCP	Good Clinical Practice
HCP	Healthcare Professional
HLAi	Human leukocyte antigen incompatible
HRA	Health Research Authority
ICER	Incremental cost-effectiveness ratio
IMD	Index of Multiple Deprivation
ITT	Intention-to-Treat
LDKT	Living-donor kidney transplant
LKD	Living Kidney Donation
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
PAG	Patient Advisory Group
PAM	Patient activation measure
PI	Principal Investigator
QALY	Quality Adjusted Life Years
RCT	Randomised controlled trial
REACH	Renal Education and Choices @ Home
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage
SOP	Standard Operating Procedure

TIDieR	Template for Intervention Description and Replication
TMG	Trial Management Group
TSC	Trial Steering Committee
UKRR	UK Renal Registry
UoB	University of Bristol

iii. TRIAL SUMMARY

Trial Title	The ASK Trial: a hybrid effectiveness-implementation trial of a patient and family outreach service to improve AccesS to living-donor Kidney transplantation.	
Internal ref. no. (or short title)	The ASK trial: improving AccesS to Kidney transplantation	
Clinical Phase	Phase III	
Trial Design	i) A two-arm, parallel group pragmatic type 1 hybrid effectiveness-implementation trial of a patient and family outreach service to improve access to living-donor kidney transplantation. ii) A mixed-methods process evaluation.	
Trial Participants	Adults (age ≥ 18 years) with advanced kidney disease who: i) have been referred for transplant assessment and do not have a contraindication to transplantation, OR ii) are active on the UK kidney only transplant waiting list. Individuals are not eligible if they already have a potential living kidney donor undergoing surgical assessment for donation or approved for kidney donation.	
Planned Sample Size	A sample of 532 will allow us to detect a +10% difference in the primary outcome in the intervention arm (20% vs 10%) with α=0.05 and power=0.9. A sample of 592 will allow for 10% attrition.	
Treatment duration	Approximately 24 hours total over 3 months across 2-3 participant contact points	
Follow up duration	18 months	
Planned Trial Period	4 years (recruitment, intervention delivery and follow up data extraction)	
Objectives and outcome measures	Objectives	Outcome Measures
	To determine: - the effectiveness and cost-effectiveness of a multicomponent intervention to improve access to living-donor kidney transplantation.	Primary outcome: Proportion of participants who receive of a living-donor kidney transplant (LDKT) within 18 months of randomisation (excluding LDKT if from a non-directed altruistic donor outside the sharing scheme). Secondary outcomes: I) time to receipt of a LDKT (excluding LDKT if from a non-directed altruistic donor outside the sharing scheme)

		II) transplant candidates with at least one donor at each stage of assessment III) patient activation (PAM13) IV) perceived social support (ISEL-12) V) LDKT knowledge (R3K-T) VI) quality of life (EQ-5D-5L) VII) intervention adherence VIII) resource use (ModRUM)
Intervention components	The outreach service comprises: 1. Potential donor identification: The participant meets with a living kidney donation (LKD) specialist nurse to discuss their family members' awareness of their kidney disease, and potential donor candidacy. 2. NHS written outreach to potential donors: A standardized NHS letter to the participant's family and friends, accompanied by a plain language information sheet. 3. Home-based family engagement and education: An engagement and education session in the participant's home led by an LKD nurse specialist and a living kidney donor.	
Formulation, Dose, Route of Administration	• Letters sent by patient's clinical team to potential donors. • Home-based patient and family education delivered by a specialist nurse and a living kidney donor.	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
NIHR Health and Social Care Delivery Research (HSDR) **Grant reference NIHR160325** **postawardsetup@nihr.ac.uk**	This study/project is funded by the NIHR Health and Social Care Delivery Research (HSDR) (NIHR160325). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.
University of Bristol **Head of Research Governance – Mr Adam Taylor** **research-governance@bristol.ac.uk** **0117 3940177**	**Sponsorship**
North Bristol NHS Trust **Research & Innovation** **Floor 3 Learning & Research building** **Southmead Hospital** **Westbury-on-Trym** **Bristol, BS10 5NB** **research@nbt.nhs.uk** **0117 4149330**	**NHS partner/Host**
NHS Blood and Transplant Clinical Trials Unit **NHSBT CTU** **Long Road** **Cambridge** **CB2 0PT** **CTU@nhsbt.nhs.uk**	**Clinical Trials Unit**

v. ROLE OF SPONSOR AND FUNDERS

The Sponsor as the employer of the Chief Investigator (CI) is responsible for study design, study conduct, data analysis and interpretation. Study design was reviewed by the study funder at the time of application. The study funder will not be involved in the study's conduct, data analysis and interpretation, or manuscript writing. The Sponsor and the study funder may be involved in

dissemination of results through the publication and promotion of study findings on their website and twitter feed.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES, GROUPS & INDIVIDUALS

Trial Management Committees

Aim: To outline the various committees or groups involved in trial coordination and conduct.

- Trial Management Group

  The Trial Management Group (TMG) will comprise of Dr Pippa Bailey (CI), all Co-Investigators, the trial manager, trial coordinator, clinical operations manager, data manager and trial statisticians. It will meet on a regular basis to review progress (at least once every 3 months in the first 2 years, then approximately 6 monthly, with potential for additional ad hoc meetings, as required/indicated). Meetings will be by videoconference to minimise costs, environmental impact and to maximise attendance. These meetings will be chaired by the Trial Manager.

- Trial Steering Committee

  The role of the Trial Steering Committee (TSC) is to monitor and supervise the progress of the trial on behalf of the Sponsor and Funders and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. An independent TSC will be appointed and will meet for the first time by month 6 of the trial and then 6 monthly until the trial closes. The TSC will be chaired by an independent member and comprise a minimum of four additional independent members (covering expertise in transplantation and clinical trials and including people who have received a kidney transplant or donated a kidney). The CI (Dr Pippa Bailey) will also be a member of the TSC. Observers may also attend, as may other members of the TMG or members of other professional bodies, at the invitation of the Chair.

- Data monitoring committee

  An independent Data Monitoring Committee (DMC) will review the data at pre-specified intervals to ensure patient safety and the ethical running of the trial. The DMC will comprise of at least two independent clinicians and a statistician. The DMC can provide advice and make recommendations to the TSC.

- Patient Advisory Group

  A Patient Advisory Group (PAG) comprising 8 members will be established and meet 6 monthly. This will be co-chaired by Primrose Granville, patient co-applicant, and another co-chair to be appointed.

vii. Protocol contributors

The protocol was written by the CI Dr Pippa Bailey with input from co-investigators.

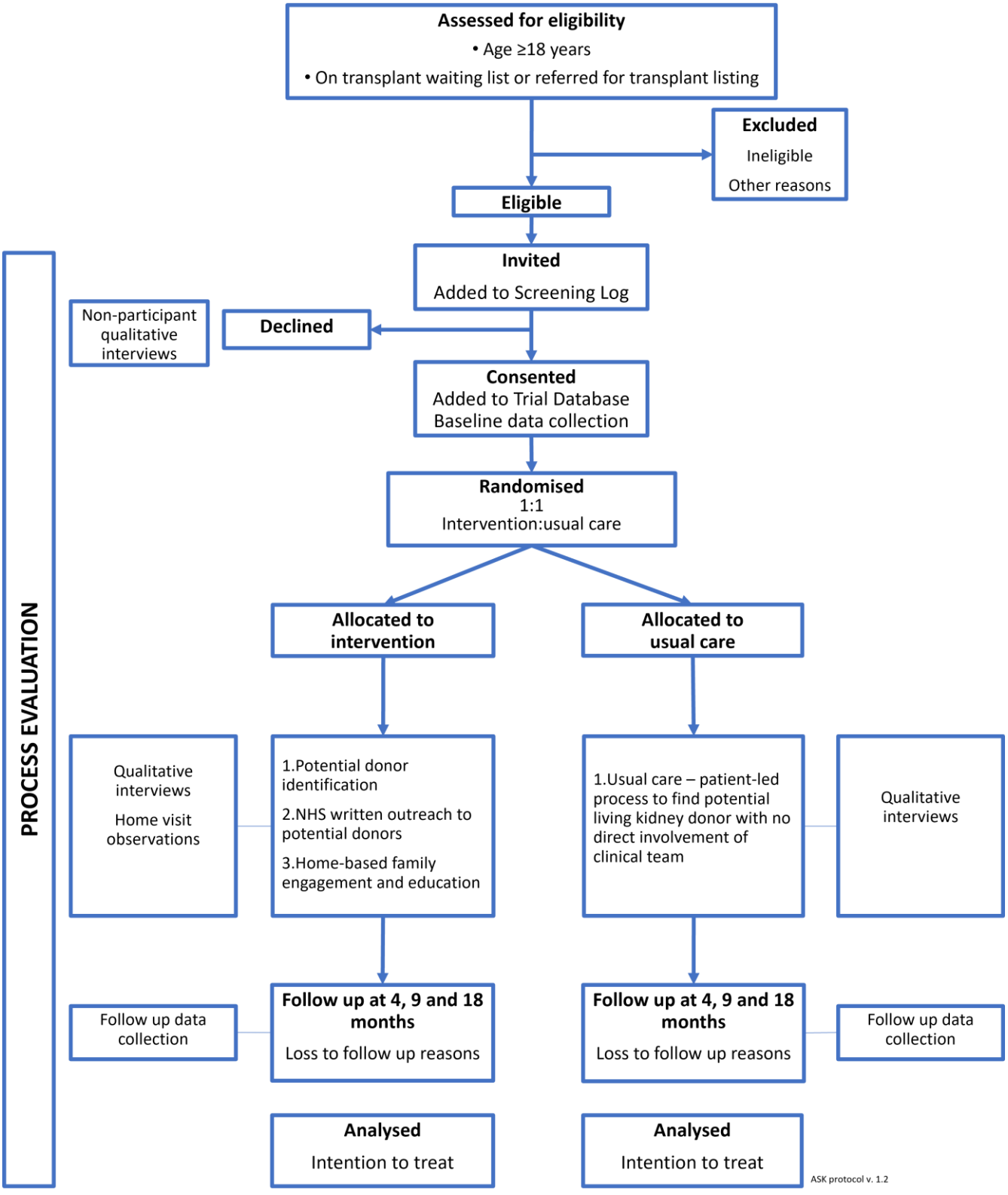
The protocol was reviewed by the study sponsor prior to submission for approval by the Research Ethics Committee (REC) and Health Research Authority (HRA).

viii. KEY WORDS

Randomised controlled trial; Complex intervention; Pragmatic trial; Living-donor kidney transplantation; Improving access;

ix. TRIAL FLOW CHART

Figure 1. Flow diagram for the ASK trial



x. GANTT CHART

Year	Year -1		Year 1				Year 2				Year 3				Year 4				Year 5			
Month	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Funding awarded																						
Preparation of study materials																						
REC and HRA approvals																						
Site confirmations and approvals																						
Appointment and training of intervention nurse at each site																						
Appointment and training of living kidney donors at each site																						
Sites 1-20 Site set-up																						
Sites 1-20 Recruitment																						
Intervention delivery																						
Process evaluation interviews																						
Follow-up assessments																						
Prepare protocol for publication																						
Process evaluation analysis																						
Trial effectiveness and cost-effectiveness analyses																						
Prepare findings for publication																						
Oversight committee meetings																						
Trial Management Group																						
Trial Steering Committee																						
Patient Advisory Group																						
Data Monitoring Committee																						

1 BACKGROUND

Kidney failure affects approximately 68,000 people in the UK, with more than 7500 newly diagnosed each year[1]. It is among the most severe of the chronic non-communicable diseases: survival at 1, 3 and 5 years is approximately 90, 70 and 60% respectively[2].

A living-donor kidney transplant (LDKT) describes a transplant in which a kidney has been donated from a living person, typically a relative or friend. A LDKT is the best treatment in terms of life expectancy and quality of life for people with kidney failure[3-5]. In the UK, 86% of adult LDKT recipients are alive 10 years after transplantation, compared to 74% of deceased-donor kidney transplant (DDKT) recipients[5]. Quality of life is better with a transplant compared to dialysis[3,4,6-9]. A LDKT is the most cost-effective treatment for kidney failure[10,11] saving the NHS £20,000 per year compared to dialysis[12]. The risks of donating a kidney are very small[13,14]. Mortality in living kidney donation is estimated to be between 0.01 and 0.03%[13,15,16]. Perioperative complications, such as wound infection and bleeding, occur in about 7.3% of cases[15]. Absolute 15-year incidence of kidney failure for most kidney donors is <1%, and the quality of life of donors returns to pre-donation levels after donation[9,17-19].

The UK's LDKT activity falls behind that of many other comparable countries, including the Netherlands, the USA, South Korea, New Zealand, Switzerland, Canada, Norway, Denmark, and Sweden[20]. All these high-income countries have active DDKT programmes. In 2019 the number of LDKTs per million population was 15 in the UK, 21 in the USA, and 29 in the Netherlands[21]. Between 2019-2022, before the disruption of COVID-19, 20% of the UK transplant waiting-list receive a LDKT annually[22] compared to 60% in the Netherlands[23].

1.1 Socioeconomic and ethnic inequity

Certain individuals with kidney disease are less likely to receive a LDKT. Socioeconomic disadvantage describes having less favourable social and economic circumstances than others in society, indicated by education level, employment, income and assets[24]. In the UK, socioeconomic disadvantage is associated with reduced access to living-donor kidney transplantation[25,26]: The most socioeconomically deprived people with kidney disease are 60% less likely to receive a LDKT than the least deprived[25]. There is also ethnic inequity[25,26]: people from UK minority ethnic groups constitute 36% of the transplant waiting list but only 18% of LDKT recipients[5]. Recent evidence suggests ethnic inequity is driven by deprivation[27].

1.2 Reasons for inequity

Our mixed-methods research has identified mediators of inequity and targets for intervention[28-32].

1.2.1 Mediators of socioeconomic inequity

Our primary research identified the following mediators of socioeconomic inequity:

- LDKT knowledge[29]
- Patient activation: the knowledge, skills and confidence a person has in managing their own health and care[29,33]
- Perceived social support: the emotional, practical, and informational help an individual perceives is available to them[29,34]

In addition, the Access to Transplantation and Transplant Outcome Measures (ATTOM) study identified health literacy as an additional mediator of socioeconomic inequity[35]: health literacy is the ability to obtain, understand and use information to make health decisions.

Socioeconomic disadvantage is associated with lower levels of LDKT knowledge, patient activation, perceived social support, and health literacy[28,29,36] which results in difficulties identifying and approaching potential living kidney donors[28].

1.2.2 Mediators of ethnic inequity

We undertook further primary research[31] in which we found that UK minority ethnicity is associated with:

- Limited LDKT knowledge[31]
- A culture of silence: difficulty discussing illness with family or friends[31]
- A lack of awareness that people living outside the UK can donate[31]
- Financial concerns particularly for non-UK donors[31]

These factors affect the initial steps in accessing a LDKT: people have limited knowledge about LDKT and experience difficulties discussing possible donation with family or friends.

1.3 Service intervention development

To address the identified barriers, an intervention needed to:

- Identify and directly engage with a patient's social network to address the lack of patient activation, culture of silence, and perceived low social support.
- Ensure information delivery on NHS donor reimbursement, including for non-UK donors.
- Use plain language, multimedia information, to address limited health literacy and lack of knowledge.

Before intervention development work, we reviewed the literature for existing services and interventions that targeted the barriers identified. A relevant scoping review had been undertaken in 2017[37]. The review identified a lack of evidence-based strategies to increase LDKTs, but there was weak evidence that home-based family engagement may be effective[37].

We then worked with patients, family members and healthcare professionals to co-produce an intervention with the required components including home-based family engagement[38]. The intervention comprises:

1. **Potential donor identification:** A transplant candidate meets with a LKD specialist to discuss LKD, their family members' awareness of their kidney disease, and potential donor candidacy.
2. **NHS written outreach to potential donors:** A standardized NHS letter to a patient's family and friends, accompanied by a plain language information sheet.
3. **Home-based family engagement and education:** Led by an LKD specialist and a previous living donor.

1.4 Previous randomised controlled trials (RCTs)

Intervention component 2 is standard practice in Norway[39] but has never been formally evaluated for effectiveness or harms. Intervention component 3 has been evaluated in small RCTs in the Netherlands and the USA[40,41]. Both reported more LDKTs in the intervention group compared with control but were underpowered to demonstrate effectiveness of home-visits to increase LDKTs. We performed a random-effects meta-analysis given intervention heterogeneity: the pooled estimate shows these small trials do not provide evidence of intervention effectiveness (Risk Ratio 2.08, 95% Confidence Interval 0.69-6.24, p=0.19). In addition, the healthcare systems and populations of the Netherlands and the USA are not directly comparable to those of the UK, and both have much higher existing rates of LDKT.

1.5 Feasibility trial

Our Wellcome Trust-funded feasibility trial of the developed intervention started in 2021 at 2 UK hospitals[42]. Actual recruitment (n=62) exceeded target (n=60) and was achieved 2 months ahead of schedule (Figure 1). Trial follow-up was completed in December 2023.

The feasibility trial determined the required population, recruitment period, intervention delivery time and costs for this proposal. The feasibility trial was undertaken at Bristol (a transplanting centre) and Gloucester (a referral centre). 51% of the eligible population at the feasibility study sites were from the most socioeconomically deprived deciles (Index of Multiple Deprivation (IMD) deciles ≤5) and 22% were from UK minority ethnic groups. The eligible population at 2 sites over 21 months was 300. 183 people were invited, and 62 (34%) agreed to participate, all of whom were randomised. Participants were representative of the eligible population with respect to sex, age and socioeconomic status. We over-recruited individuals of UK minority ethnicity: 27% of participants versus 22% of the eligible population.

This population representative sample, with more than a quarter of participants from UK minority ethnic groups, meant we were able to evaluate the delivery and acceptability of the intervention to people with different cultures. The process evaluation found that the intervention was acceptable to diverse patients and their families. Family members who attended the home visits mentioned that tailoring of the home-visit donor to them would have optimised the intervention further.

Feasibility trial attrition (withdrawal/loss to follow up/death) was <10%. 98% of participants completed nurse follow up assessment. 84% of participants completed the follow-up patient questionnaire. The questionnaire was poorly completed if it was emailed to participants rather than completed in person at a hospital visit. 21% of participants have (at the time of submission) received a DDKT, with disparity between the intervention arm (5/32, 16%) and the usual care arm (8/30, 27%). As a result, we will now stratify the randomisation in the proposed trial by minimisation factors that will predict participants who are more likely to receive a DDKT whilst on the trial. The feasibility trial was not powered to detect a difference in the planned primary outcome for the effectiveness trial, but the findings inform the sample size calculation for this trial. At the time of submission, 28% (9/32) of participants in the intervention arm had people contact the unit to be tested for kidney donation, compared to 10% (3/30) in the usual care arm. 6% (2/32) in the intervention arm have received a LDKT, compared to 0% in the usual care arm (0/30).

2 RATIONALE

2.1 Research priority

Improving equity in living-donor kidney transplantation has been highlighted as a UK and international research priority[43,44]. The UK Renal Research Strategy highlights the need to build *'the evidence base that will increase equitable access for patients to [the] best available treatment'*[43]. NHS Blood and Transplant's (NHSBT) strategy identifies a need to '*Promote patient awareness and engagement in living donation across all sectors of society'* by increasing '*transplant opportunities for patients who are currently disadvantaged*'[45]. The patient-initiated All-Party Parliamentary Group's Living Kidney Donor Summit called for *'a strategy for supporting kidney patients in finding potential living donors'*[46]. Our research addresses these strategic goals, building on our previous feasibility trial.

Our project addresses NIHR's HSDR call 23/89 '*Overcoming ethnicity-based inequities in access and experience of health and care services*'.

2.2 Evidence gap

As detailed above, a 2017 scoping review identified a lack of evidence-based strategies to increase LDKTs. Excluding our ASK feasibility trial, since 2017 nine relevant trials have been registered with WHO trials: 3 pilot RCTs, 5 effectiveness RCTs, 1 non-randomised trial. Six of these studies are based in the USA and three in Canada. None of the trials are based in the UK. The USA already has a higher rate of LDKTs than the UK, and the healthcare system is not comparable to the UK, hence the context of these trials is very different to the UK. None of the interventions under evaluation involve home-based education and engagement, which was highlighted in the 2017 scoping review as the only intervention for which there was weak evidence of effectiveness[37]. The large Canadian EnAKT LKD (Enhance Access to Kidney Transplantation and Living Kidney Donation) Cluster RCT (NCT03329521) has just published its findings[47]: this multicomponent intervention which comprised hospital-based patient education and opportunities for transplant recipients and living donors to share experiences with patients, but no family engagement or home-based education, did not increase access to LDKTs.

A similar intervention to our home-visit intervention component, REACH (Renal Education and Choices @ Home) was evaluated as a service quality improvement project in Edinburgh[48]. The home-based intervention service was based on the home education intervention developed in the Netherlands[40]. As a result of successful delivery of the service, and the findings of the previous Dutch and American trials, the REACH programme is being rolled out across all 10 Scottish renal units[48] but there is a lack of evidence of service effectiveness or cost-effectiveness to support roll out across the rest of the UK.

In summary, despite previous research in Europe and the USA, it is not known if a patient and family home-based outreach service is effective at increasing LDKTs, if it is cost-effective in the UK, or if it improves equitable access to living-donor kidney transplantation. The service components being evaluated here have not been evaluated together as a single intervention that targets multiple barriers to living-donor kidney transplantation. An adequately powered pragmatic RCT is required.

2.3 Assessment and management of risk

The intervention components have been selected after qualitative interviews and co-production work with patients, family members and healthcare professionals to ensure the components and resources are acceptable, and potential risks of harm have been identified and minimised. The intervention has been found to be deliverable and acceptable in a feasibility trial. Possible harms include family and

friends feeling pressure to donate, economic difficulties for donors, an increase in the number of people volunteering to donate that is not translated into increased numbers of actual donations, and a lack of cost-effectiveness. A parallel process evaluation will be undertaken including qualitative interviews with and questionnaire completion by participants (transplant candidates and potential donors) to collect data on the acceptability of the intervention.

Participants in previous home-based education trials have not reported that the intervention induced unacceptable pressure on the family/friends to donate a kidney[40,41]. On the contrary, some patients reported disappointment that the intervention did not result in an LDKT[40]. Management of patients' expectations regarding the outcome is key to minimise this harm. The minimal risks must be considered in light of the benefits of a LDKT detailed in the 'Background' section. This research is also necessary to prevent harm that could result from the adoption of interventions which have not undergone rigorous evaluation.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Objectives

The trial objectives are:

- to determine the effectiveness and cost-effectiveness of a multicomponent patient and family outreach service to improve access to living-donor kidney transplantation.
- to increase the proportion of eligible kidney patients that receive a LDKT by supporting disadvantaged individuals to overcome barriers to accessing a LDKT.

A process evaluation will assess delivery fidelity, acceptability, reach, the influence of context, and implementation barriers and facilitators.

3.2 Outcome measures/endpoints

3.2.1 Primary endpoint/outcome

Primary Outcome Measures	**Timepoint(s) of evaluation of this outcome measure**
Proportion of participants who receive a LDKT within 18 months of randomisation (excluding LDKTs from non-directed altruistic donors outside the sharing scheme)	•18 months

3.2.2 Secondary endpoints/outcomes

Secondary Outcome Measures	**Timepoint(s) of evaluation of this outcome measure**
Time to receipt of a LDKT (excluding LDKT if from a non-directed altruistic donor outside the sharing scheme) • Probability of receiving a LDKT as estimated by Kaplan-Meier methods	•18 months

Transplant candidates with at least one donor at each stage of assessment: 1. Initial evaluation by coordinators completed 2. Nephrological assessment completed 3. Surgical assessment completed 4. Registered to UK Living Donor Sharing Scheme (if applicable, and reason for entry into sharing scheme e.g., ABO blood group incompatible (ABOi), Human Leukocyte Antigen (HLA) incompatible (HLAi), better match required) 5. Donated/date set for donation • Total number and % in each stage • Descriptive statistics for number of donors per recipient registered to UK Living Donor Sharing Scheme, with reasons will be presented • Patient self-reported total number of donors at any of the above stages 1-4	•18 months
Patient activation (PAM13) • Mean[a] PAM score (0-100) and number and % of each PAM level (1-4)	• 4 months
Perceived social support (ISEL-12) • Mean[a] total ISEL-12 score (/36)	• 4 months
LDKT knowledge (R3K-T) • Mean[a] total R3K-T score (/11)	• 4 months
Quality of life (EQ-5D-5L) • Mean[a] EQ-5D-5L index value and mean EQ-VAS score (/100)	• 4, 9 and 18 months
Adherence Intervention group • Participants who have first intervention meeting (number and %) • Participants who have letters sent to family/friends (and number of letters sent per participant) (number and %) • Participants receiving home visits by intervention team (and number of home visits per participant) (number and %) • Content compliance (quantitative checklist for home visit content) (number and % with each item completed) Usual care group • Number and % who incorrectly received at least one component of intervention because of a research team error	• 4 months
Resource Use (ModRUM) (see section 10.4)	18 months

[a] Mean or median will be presented depending on distribution

3.2.3 Other endpoints/outcomes

Other Outcome Measures	Timepoint(s) of evaluation of this outcome measure
• Health Literacy (SILS-1)	• 4 months
• Transplant beliefs	• 4 months

4 TRIAL DESIGN

This is a two-arm, parallel group, pragmatic, individually-randomised type 1 hybrid effectiveness-implementation trial of a multicomponent patient and family outreach service to improve access to living-donor kidney transplantation. A type 1 hybrid focuses primarily on the effectiveness outcomes of an intervention while exploring the "implementability" of the intervention. A parallel process evaluation will use mixed-methods to investigate the implementation and mechanisms of impact of the intervention.

5 TRIAL SETTING

The trial will run at a minimum of 20 NHS hospitals in England and Wales. Selection of sites will be based on the presence of appropriate clinical research infrastructure and adequate staff to conduct the trial safely and per protocol. The site selection process will include an assessment of how many patients are likely to be eligible, and the site's potential rate of accrual given the site level resource. Site selection will include a review of any potential barriers to recruitment such as other trials recruiting from the same patient population.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Adults (age ≥ 18 years) are eligible if they:

a) Have been referred for/are being assessed for kidney only transplant listing
   Or
b) Are active on the UK kidney only transplant waiting list.

Individuals are assessed for kidney transplantation when they have advanced kidney disease (this includes chronic kidney disease stages 4, 5, 4T and 5T and those in receipt of dialysis).

6.2 Exclusion criteria

Individuals will be excluded from participation if they have any of the following:

a) Active malignancy

b) Signs or symptoms of active cardiac disease (e.g., angina, arrhythmia, New York Heart Association functional class 3/4 heart disease, symptomatic valvular heart disease)
c) Chronic intractable systemic infection
d) Active substance addiction/misuse
e) Body mass index (BMI) ≥ 40 kg/m^2
f) A transplant multidisciplinary team expectation that they are unlikely to be suitable for transplantation following pending investigations (e.g., cardiopulmonary)
g) A potential living kidney donor undergoing surgical assessment or approved for kidney donation.
h) A registration/planned registration on the UK transplant waiting list for multiple simultaneous organ transplants e.g., simultaneous pancreas-kidney or simultaneous liver-kidney transplants.

NB: Individuals who do not have capacity to consent to the trial are still eligible; a consultee will be approached.

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Screening for eligibility and participant identification

i) Patient participants

A list of all adults currently active on the UK kidney only transplant waiting list will be generated from the renal IT system (e.g., proton, diproton, vital data) and all those referred to the coordinators for assessment for transplantation. This initial list can be generated by the hospital's renal information technology lead, transplant coordinators, clinicians, or administrators. This list will be refreshed every 4-12 months as new referrals become eligible for participation. This list is then used by the site PI/research nurses to assess eligibility prior to approach, eligibility will then be confirmed prior to consent and baseline assessment. Patients identified as eligible during routine clinical practice, can also be given the patient information sheet. There is a separate information sheet for consultees of patients who do not have capacity.

The patient information sheet can be given to eligible patients:

- By the principal investigator (PI) or research team in person
- By the PI or research team via post or email following a phone call with the patient
- By Transplant coordinators, nephrologists, surgeons and specialist nurses (following discussion with the PI/research team), with a follow up call by the PI/research team to explain the study and answer any questions

If the patient does not have capacity to make this decision, a consultee will be approached.

The first invitation will be followed up with a phone call from or face-to-face meeting with a research staff member to offer further discussion about the study.

At the first invitation and the follow up phone call or meeting, the research staff member (e.g., research nurse) will explore the patient's current health state and any transplant decisions that have already been made. They will then explain the trial and in particular:

- Why the study is needed i.e. to see if approaches used outside the UK to help people receive living-donor kidney transplants are acceptable to people in the UK and whether they work.
- What randomisation means
- What being randomised to the usual care arm would mean for them
- What being randomised to the intervention arm would mean for them
- Other aspects of trial participation (e.g., follow up details, right to stop the trial intervention but remain in the trial and right to withdraw from the trial).

When the patient feels fully informed, they will be asked to make a decision about entering the RCT.

If they decide to enter the trial, the research staff member will:

- Receive consent for the RCT
- Conduct the baseline assessment including extraction of data from medical records and administration of the questionnaires.
- Randomise the patient to their treatment arm, i.e. usual care or the intervention. The participant will only be informed of their allocation after the collection of baseline data to avoid it influencing patient reported measures.
- Explain what will happen next in terms of (i) their clinical care and (ii) their research follow-up

Patients who decide not to enter the trial will be offered the opportunity of taking part in a qualitative interview exploring reasons underlying their decision to not take part.

All approached patients will be documented in a comprehensive screening database on OpenClinica. Screening will be designed with reference to the SEAR (Screen, Eligible, Approached, Randomised) framework[49], however data will only be entered by sites from the point of approach and data from NHSBT UK Transplant and the UK Renal Registries will be used to summarize age, sex, ethnicity and IMD quantile of an approximation of the eligible population to minimise the amount of data needed to be entered by sites. For all patients approached sex, age and ethnicity will be entered on the screening database. Sites will provide pseudo-anonymised data to the central study team with details of the population i) approached, and ii) randomised, and the statisticians will report summary statistics. This will enable assessment of those not reached by the study and allow discussion with the trial management group (TMG), TSC, and patient advisory group (PAG) regarding strategies to optimise recruitment. At the end of the trial this information will be used to assess how applicable study findings are to the truly eligible population.

ii) Family and friend participants

Patient participants allocated to the intervention arm will be asked to invite family members and friends to an education and engagement home visit. Family members and friends present at this home visit will be invited to participate in qualitative interviews. No family or friends will have their medical, social care or GP records screened before or after consent to participation in the qualitative interviews.

iii) Healthcare professionals

Healthcare professionals involved in delivering the intervention (e.g., the intervention healthcare professionals (HCPs)), contributing to the research study (e.g., renal research nurses, local PIs), or

those whose practice will be impacted by the intervention (e.g., transplant coordinators, transplant nephrologists, transplant surgeons) will be invited to participate in qualitative interviews. Healthcare professionals will be purposively sampled to include a range of professionals and study sites. No medical, social care or GP records of healthcare professional participants will be accessed.

7.1.2 Payment

Individuals will not receive any payment, reward or recognition for trial participation. Patient and family members who consent to participation in qualitative interviews will be given a £25 voucher for their time.

7.2 Consent

The PI retains overall responsibility for the conduct of research at their site, this includes the receiving of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Receiving consent will be delegated on the delegation of duties log to research staff who will be trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki. It will take place in several steps:

i) First contact

The Patient Information Sheet outlining the study will have given patients an opportunity to contact the clinical or research team to decline participation, before receiving a telephone call from or a face-to-face meeting with a member of the research team. A face-to-face meeting would be arranged to correspond with an existing clinical appointment. Participant information will be available as a printed information sheet and as a digital version.

Once a patient is sufficiently informed to be able to make a decision whether to take part in the study, the research team will assess the patient's understanding of the trial and their capacity to decide to participate. Individuals who lack the Mental Capacity to consent to the trial can still participate. An individual's Mental Capacity to provide personal consent to transplant surgery will already have been determined by their clinical team during transplant assessment (e.g., Is the patient able to understand the risks and benefits of transplantation and provide consent to surgery or is a clinical Consent form 4 required?). Individuals with a temporarily impaired Mental Capacity would not be considered suitable for transplantation: reversible causes of impaired capacity (e.g., infection, delirium, intoxication, mental illness, brain tumour) would mean someone is ineligible for transplantation for reasons related to transplant safety and not Mental capacity. Individuals who have been deemed suitable for transplantation but who have been deemed by their clinical teams to lack capacity will have irreversible reasons for a lack of capacity (e.g., learning disability, dementia, irreversible brain injury). Individuals who have been deemed not to have capacity to consent to transplantation will be deemed to lack the Mental Capacity to consent to the trial because the understanding required to consent to transplantation is essential to consent to trial participation. Individuals who lack capacity to provide personal consent will still be eligible for the trial: the opinion of a personal consultee on the perceived wishes of the individual will be sought.

If a patient who has provided consent to participation loses capacity to provide ongoing consent to participation, the opinion of a consultee on the perceived wishes of the individual will be sought. The opinion of the consultee will determine whether the participant receives any further trial intervention or contact from the research team. Data on outcomes for these individuals can be extracted from the medical records, UK Renal Registry (UKRR) or NHSBT if a consultee is happy for data collection but no further study contacts.

The consent form can be completed and signed on paper, or electronically. The participant's personal email address will be used when obtaining consent digitally, and it will stand as the verification that the person completing consent is who they say they are, as per the HRA guidance[50].

If a trial participant also gives consent to be contacted by the qualitative research team, the qualitative research team will reach out and contact the participant to give them further information and take consent for the qualitative study separately.

ii) When a potential participant declines participation in the trial

Patients who are eligible but not willing to be randomised will be asked if they would be willing to take part in an interview to understand the reasons underlying their decision. Research staff will explain that this interview is to help improve the clarity of information provided about the study, and to understand whether there was something about the study and/or intervention that participants found unacceptable or intrusive. They will be told about the intervention and asked if this became routine care, whether this is something they would engage with. This information will be used to improve the way future patients are approached and informed and no pressure will be exerted on patients who have already declined participation to change their mind. Written information will be provided about this qualitative study.

Trial non-participants who are happy to be interviewed will contact the qualitative researchers at the University of Bristol directly via email, phone or posted paper reply slip. The qualitative researchers will then make contact and arrange for a date for the interview.

Consent for the interview will be requested before the interview starts. As the interviews will be undertaken over the telephone, consent will be audio-recorded and the researcher who completes the consent form will sign to confirm the consent has been recorded. The recording of the consent will be transcribed along with the interview.

iii) Family/friends

Family/friends of participants invited by the patient participant to the home education session will be provided with an additional 'Home visit qualitative information sheet' outlining the opportunity to take part in a qualitative interview at a later date.

If they wish to take part in this, they will contact the qualitative researchers at the University of Bristol directly via email, phone or posted paper reply slip. The qualitative researchers will then make contact and arrange for a date for the interview. Consent for these qualitative interviews will be requested at the time of interview. Consent will be audio-recorded and the researcher who completes the consent form will sign to confirm the consent has been recorded. The recording of the consent will be transcribed along with the interview.

7.3 The randomisation scheme

Research staff will undertake randomisation of eligible individuals with concealed allocation using Internet-based Sealed Envelope™ software using minimisation. Participants will be allocated 1:1 to i) the intervention arm or ii) the usual care arm, stratified by site to ensure a balance in terms of local

differences. Minimisation will be used to ensure balance in sex, age group (≤ 55 years vs > 55 years), socioeconomic strata (IMD deciles 1–5 vs deciles 6–10), time on dialysis (≤ 5.5 years vs > 5.5 years) and ethnicity (White vs All other ethnic groups combined). We will use minimisation with probability weighting of 0.8 to reduce predictability. Due to the nature of the intervention, participants and those administering the intervention cannot be blinded to allocation.

7.3.1 Method of implementing the allocation sequence

All patients who enter the study will be logged on the trial database and given a unique participant ID. The research staff member (e.g., research nurse) will retrieve the information necessary for randomisation from the clinical record, i.e. site (stratified), sex, age group, IMD deciles, time on dialysis and ethnicity (minimised). Participant postcodes will be converted into IMD deciles using GB Postcode Deprivation Finder. Participants will then be randomly allocated 1:1 to the intervention or usual care arms.

Hospital staff will be informed about the allocation arm by the research staff member (e.g., research nurse), so that they can answer queries from participants and their relatives. Participants will be allocated a screening ID when entered on the screening database, if they proceed to randomisation, they will be allocated a participant ID which will be entered onto Sealed Envelope at randomisation and used as their randomisation number.

7.4 Baseline data

Demographic, social, clinical, and patient reported data will be collected by research staff at the baseline visit (following consent and prior to randomisation) and should be entered onto the database in a timely manner i.e. within a day of adding consent to the eCRF. The maximum visit window for collecting patient reported data (baseline questionnaires) is + 2 weeks, however every effort should be made to collect and enter the data within a day of adding consent to the eCRF. No blood or urine tests are required other than those that are being performed as part of routine care.

Table 1. Summary of baseline data collection

Demographics	Age, NHS number, date of birth, sex, ethnicity, religion, marital status +/- children, employment status, education level, housing tenure, IMD decile, car ownership, distance lived from renal unit, alcohol consumption, smoking history. Email address and phone number will be collected for the purposes of patient reported outcomes and contact for the qualitative study.
Clinical	Primary renal disease, date of current transplant listing if listed, co-morbidities, current stage of kidney disease (Pre-emptive, Haemodialysis, Peritoneal dialysis), dialysis start date, BMI.
Patient reported*	Renal and transplant knowledge (R3K-T[52]), social support (ISEL-12[53,54]), Patient Activation (PAM13[33,55]), health literacy (SILS[56,57]), transplant preference, transplant beliefs[58], quality of life (EQ-5D-5L[59]).
Laboratory	Blood group, matchability (score 1-10, if available), % calculated reaction frequency (if available)
Resource use	Modular resource use measure (ModRUM)[60]

* Baseline (+2 weeks)

7.5 Trial assessments

Clinical, laboratory, compliance with the intervention and patient reported data will be collected by research staff from secondary care clinical notes and during study contacts. No physical assessment of participants is required. No blood or urine tests are required other than those that will already have been performed as part of routine care. If a participant is not contactable at clinic appointments up to 3 attempts will be made to contact the person via phone. After 3 attempts to make contact, if the participant remains uncontactable, they will be considered lost to follow up. If a participant dies, family members will not be asked to complete a questionnaire on their behalf. Patients lost to follow up will not be replaced.

Study contacts for patient participants will be:

1. Baseline
2. Follow-up at 4 months
3. Follow-up at 9 months (short-term outcomes)
4. Follow-up at 18 months (long-term outcomes)

Purposively sampled patient participants will be invited to consider participating in qualitative interviews as part of the process evaluation. Further details are provided under **section 7.7**.

Study contacts for family/friend participants will be:

1. Immediately after the home visit family members/friends will be invited to consider participating in a qualitative interview at a later date. They will be provided with an information sheet and details of how to reply if they wish to be interviewed. Further details are provided under **section 7.7**.

Table 2. Summary of follow up data collection

		Time after baseline
Clinical	Current status on the transplant list (in assessment/active/suspended/ removed/ transplanted. If transplanted, the date and type of transplant will be recorded), co-morbidities, kidney disease stage, date and cause of death (if this occurred), number of living kidney donors undergoing assessment, and stage of assessment for donors (e.g., scheduled for surgery/completed assessment/registered in the UK living kidney sharing scheme)	9 months (+/- 2 weeks) and 18 months (+4/-2 weeks)
Laboratory	Matchability, % calculated reaction frequency	9 months (+/- 2 weeks) and 18 months (+4/-2 weeks)
Resource use (intervention arm only)	Records of home-visits by intervention team detailing: duration of visit, location and date/time of visit; length of travel in distance for intervention team, if interpreters were used, and the cost of interpreters.	At time of home visit

Resource use	ModRUM[60] Patient self-reported total number of donors at any of the stages 1-4 of assessment (1. Initial evaluation by coordinators completed, 2. Nephrological assessment completed, 3. Surgical assessment completed, 4. Registered to UK Living Donor Sharing Scheme, 5. Donated/date set for donation);	18 months (+4/-2 weeks)
Adherence to and acceptability of intervention (intervention arm only)	Number and % of participants who have first intervention meeting, number and % of participants who have letters sent to family/friends (and number of letters sent per participant), number and % of participants receiving home visits by intervention team (and number of home visits per participant), content compliance (quantitative checklist for home visit content)	At time of home visit
Patient reported: mediator variables	Renal and transplant knowledge (R3K-T[52]); social support (ISEL-12[53,54]); Patient Activation (PAM13[33,55]); health literacy (SILS[56,57]); transplant preference; transplant beliefs[58]	4 months (+/- 2 weeks)
Patient reported: quality of life	Quality of life (EQ-5D-5L[59]).	4 months (+/- 2 weeks), 9 months (+/- 2 weeks) and 18 months (+4/-2 weeks)

7.6 Extraction of data from national databases of routinely collected data

At the point of consenting to take part in the RCT, all participants will be asked to consent to linkage to existing healthcare databases held by the UKRR, NHSBT, NHS England and SAIL(Wales), using their NHS number and date of birth. These databases can provide data on commencement of renal replacement therapy, date and type of kidney transplant, date and cause of death, if this information is missing from the medical records. This will enable follow up of clinical outcomes for participants who lose capacity to continue providing consent, or are lost to follow up, including those who move to a renal unit not participating in the trial.

Clinical, laboratory and resource use outcomes will be extracted from medical records at the hospital sites, or from UKRR and NHSBT databases.

7.7 Process evaluation data collection

As a type 1 hybrid effectiveness-implementation trial[61] a secondary aim is to understand contextual barriers and facilitators to implementation. A type 1 hybrid trial combines effectiveness and implementation outcomes in one study, with the aim of reducing time for translation of research on effectiveness into routine practice[62]. A mixed-methods process evaluation will evaluate intervention delivery, acceptability, fidelity of implementation, reach, and how context affect implementation and

outcomes. It will be undertaken with reference to Medical Research Council Guidance[63] and the Promoting Action on Research Implementation in Health Services framework[64]. It will include:

- **Semi-structured interviews** (telephone or video) with up to 10 trial non-participants, 25 patient participants, 25 family/friend home-visit attendees, and 25 healthcare practitioners to understand reasons for (non)participation, experience of the interventions, impact on NHS care pathways, and barriers and facilitators to implementation from patient, family/friend and a range of healthcare professional perspectives. Data will be transcribed and analysed using reflexive thematic analysis[65].
- **Subjective intervention fidelity checklists** completed by the intervention LKD nurse specialists will record if any core components not delivered for a participant, and if not, the reasons for this.
- **Objective intervention fidelity observations:** Remote video observations by the CI and qualitative research associate of 3 home visits per site. Observations will allow researchers insight into the immediate response of those involved in the home visit to the information that is shared. Where possible, the findings from the analysis of observational data will be triangulated with the findings of data collected during interviews with the patients/family or friends/healthcare professionals involved in these visits.
- **Context analysis:** What centre factors support site set up, recruitment and intervention delivery? Information will be extracted on existing usual care pathways, resources, and pre-trial LDKT activity. These data will be triangulated with data collected during healthcare professional interviews.
- **Anonymised aggregated screening data** to assess inclusive participation described in Section 7.1.1 above.

Participation in the qualitative interviews is optional. Patients and family members who participate in a qualitative interview will be given a £25 voucher for each qualitative interview completed.

7.8 Withdrawal and discontinuation criteria

Participants can choose to discontinue from their allocated trial treatment at any time for any reason without affecting their usual care. Discontinuation of trial treatment is not considered a withdrawal and participants will remain in the study and continue to complete trial assessments and data collection.

Participants can withdraw from providing data to the trial, at any time for any reason without affecting their usual care. All efforts ethically appropriate will be made to report the reason for withdrawal as thoroughly as possible in free-text and from a list of categories on the case report form (CRF). Data already collected will be kept. Participants who have withdrawn can choose to continue to consent to follow-up assessments or to withdraw from follow-up. Clinical outcomes from hospital records and UKRR and NHSBT registries will be extracted if they choose to continue to consent to follow-up assessments. Participants may be removed from the transplant waiting list by their clinical team during the trial. If a participant in the intervention arm is removed from the transplant waiting list prior to receiving the intervention, and is unlikely to be re-listed within the next 6-months (as assessed by the Principal Investigator) they will not receive the intervention but follow-up assessments will occur.

If a participant in the intervention arm receives a DDKT during the trial prior to receiving the intervention then they will not receive the intervention, but they will remain in follow-up. If this fails before receiving the intervention, the participant can continue to receive the intervention.

Patients withdrawn from the trial will not be replaced. Individuals can only participate in the trial once.

7.9 End of trial

The trial will end 21 months after the final participant is recruited to the trial to allow for follow up data to be collected. Once the trial is closed all sites will be contacted and the CI and sponsor will notify the main research ethics committee of the end of the trial within 90 days of its completion.

Table 3. Example contact schedule for patient participants and data collection time points

Month	0 (+ 2 weeks)	1 (+/- 2 weeks)	3 (+/- 2 weeks)	4 (+/- 2 weeks)	9 (+/- 2 weeks)	18 (+4 /- 2 weeks)
Contact type	or	or		or or	or or	or or
Practitioner	PI/Assoc PI/research staff (e.g., research nurses)	Trained living donor nurse specialist	Trained living donor nurse specialist and a living kidney donor	PI/Assoc PI/research staff (e.g., research nurses)	PI/Assoc PI/ research staff (e.g., research nurses)	PI/Assoc PI/ research staff (e.g., research nurses)
Contact content for those allocated to intervention arm	Information giving, recruitment, consent, baseline questionnaires, and randomisation	Meeting with intervention HCP: intervention components 1 and 2	Patient and family home education and engagement: intervention component 3	Questionnaire follow up; Sample for qualitative interviews	Questionnaire follow up; Sample for qualitative interviews	Questionnaire follow up; Sample for qualitative interviews
Contact content for those allocated to usual care control arm	Information giving, recruitment, consent, baseline questionnaires, and randomisation	No contact	No contact	Questionnaire follow up; Sample for qualitative interviews	Questionnaire follow up; Sample for qualitative interviews	Questionnaire follow up; Sample for qualitative interviews
Data extracted from electronic medical records	Laboratory; Clinical	None	None	None	Laboratory; Clinical	Laboratory; Clinical
Data collected from participating site	Time to recruitment of first participant	Resource use associated with the intervention and adherence to the intervention.	Resource use associated with intervention arm and adherence to the intervention.	None	Compliance with and acceptability of trial	Resource use

= Postal contact = Telephone/Video call study contact = Home study visit = Face to face meeting at hospital

8 TRIAL TREATMENTS

Patient participants will be randomised to either i) the intervention arm or ii) usual care.

8.1 Intervention arm

The intervention has three components:

1. **Potential donor identification**: An LKD nurse specialist, or other appropriately trained and delegated member of the team, will meet with the participant to create a social network diagram and discuss the initial suitability of family and friends as possible donors. Personal barriers to LDKT will be elicited and misinformation addressed. The participant will meet with the LKD nurse ideally within 2-4 weeks of recruitment, but this meeting must take place within 4 months of randomisation. This first meeting should be undertaken in person/face-to-face but if the participant requests it, it can be undertaken over the telephone or a virtual platform. The date and duration of this visit, including travel, will be documented. Intervention component 1 will ensure all those in the intervention arm have received information about LDKTs that should be part of usual care but it will also provide an opportunity for the following which are not part of usual care:

    • Formal discussion of a patient's social network (family and friends), to understand with whom the patient has discussed their kidney disease, transplant options and living donation. The LKD nurse will ascertain the participant's close relationships with relatives and friends, and the estimated age, sex, and health of these individuals. In the feasibility trial this was the point at which misunderstandings or assumptions about LDKTs were identified and challenged e.g., there's an upper age limit for kidney donation, you can only donate to someone of the same ethnicity as you.

    • Identification of the relatives and friends the participant would like to receive posted written information on living donation.

    • Relationship and trust building with the LDKT specialist

    • Agreement as to which friends and family will be invited to the home visit. The LKD nurse will inform the participant about the home education and engagement visit. The LKD nurse will explain the proposed content of the home visit, and will agree with the participant i) which friends and family members will be invited to the home visit, ii) where the visit will take place (home preferred location but participants may ask for an alternative location such as a community space, a hospital meeting room. The meeting can happen as a virtual or hybrid meeting to allow people living outside the local area or UK to join. iii) a number of possible dates for the home visit in the next 1-3 months. At the end of the first session the intervention HCP will record the number of individuals that the participant wishes to invite for the second session.

    • Agreement as to which topics the participant is happy to discuss at the home visit

2. **NHS written outreach to potential donors:** The LKD nurse specialist and participant will agree which family and friends will be sent a:

    - Plain language information sheet about LKD developed with patients and patient charity Kidney Care UK[38].

    - Standardized NHS letter introducing the option of LKD with information on how to begin donor assessment.

The participant will then address envelopes for posting to selected family members and close friends. Postage will be paid. Alternatively, the participant can take home the envelopes and address these at home. Alternatively, if participants prefer, they will be provided with letters and information sheets that they can distribute to family and friends.

After intervention stages 1 and 2 the LKD nurse will record:

- The duration of the meeting
- The number of letters posted for that recipient
- The number of people invited to the home visit.

It is the participant's responsibility to invite family members and friends to the Home visit.

3. **Home-based family engagement and education**: A home visit will be undertaken by an LKD nurse specialist and a trained living kidney donor. The home visit should ideally happen within 3 months of randomisation. It can happen at the weekend or evening: whatever time best suits the participant and their guests. The importance of the home in enabling a relaxed environment and avoiding travel costs was stressed during intervention development[38] but the meeting can happen as a virtual hybrid to allow people living outside the local area or UK to join. The home visit will cover topics from the following list:

Kidney disease

Introduction to healthy kidneys

Introduction to kidney disease - specific to the participant

The psychosocial and physical consequences of kidney disease

Dialysis

The different forms of dialysis (haemodialysis (home or in-centre), peritoneal)

Transplantation

Introduction to transplantation

The various programs of donation and transplantation (DDKT and LDKT)

The number of DDKT and LDKT performed nationally and locally

The ethnic and socioeconomic differences regarding access to LDKT

The differences in graft survival between DDKT and LDKT

LDKT

Living kidney donation

Personal account of living kidney donation

Motivation and decision making

Donor assessment

The kidney donation operation

The personal, emotional and financial aspects of LDKT

The risks and psychosocial aspects associated with donor nephrectomy

Lifestyle after kidney donation

Common issues after kidney donation

Open discussion

Whether present individuals have any questions about kidney donation?

How do I let people know I am interested in donating?

After intervention stage 3 the LKD nurse will record:

- The duration of the visit (including travel)
- The number of family/friends present at the home visit
- Whether interpreters were used and the cost of these

The LDKT nurse specialists will be NHS employees (most likely specialist nurses or transplant coordinators). The LDKT specialists will receive trial specific training for this. LKD nurses and living kidney donors will be trained through an online training developed by the CI, and the nurse and living kidney donor who delivered the intervention in the feasibility trial. Cultural competency resources for NHS staff will be used. Training resources will be available throughout the trial.

LDKT nurse specialists from all recruiting sites will be invited to take part in regular online drop-in sessions delivered by the CI and co-investigators to discuss any problems encountered, provide updates on any national policy or guidance that impacts on practice, ensure up-to-date information is being shared, and / or share best practice amongst intervention delivery staff.

The LKD nurse will share their work telephone number and work email addresses with participants so that they can be contacted for further advice and support if required at any time during the trial participation.

8.1.1 Received intervention

In this pragmatic multicomponent trial participants allocated to the intervention arm will be allowed to decline offered components. Participants may decline elements of components 1 and 2, they may decline component 3, they may wish to receive component 3 as a personal home education session but decline to invite family and friends, they may invite family and friends who do not attend. The intervention components received will be recorded on the CRF by the research staff member (e.g.,

research nurse) or LKD nurse delivering the intervention components. The primary analysis will be an intention-to-treat analysis but a per protocol analysis will also be undertaken for comparison.

8.2 Trial restrictions and concomitant treatments

In this pragmatic trial, all treatment delivered as part of standard care will continue for both trial arms. No restrictions on concomitant treatments are specified.

8.3 Assessment of compliance and intervention delivery fidelity

A process evaluation will be used to study how the intervention is implemented and may provide information on contextual factors that affect the intervention. It will also provide information about the uniformity of delivery of the intervention to different participants in different locations, where the “same” intervention may be delivered and received in different ways. The integrated qualitative research will provide a more in-depth understanding of how the trial treatments and procedures are being delivered and received in practice.

The mixed-methods process evaluation will include:

- **Semi-structured interviews** (telephone or video) with participant and non-participant transplant candidates and family members to understand experience and acceptability of intervention, and with practitioners on experiences of delivery and to what extent they felt that delivery matched the intended intervention.
- **Subjective intervention fidelity checklists** completed by the intervention LKD nurse specialists will record if any core components are not delivered for a participant, and if not, the reasons for this.
- **Objective intervention fidelity observations:** Remote video observations by the CI and qualitative research associate of 3 home visits per site. This will allow assessment of fidelity of delivery against a quantitative checklist, and qualitative observation field-notes will be made.
- **Context analysis:** What centre factors support intervention delivery? Information will be extracted on existing usual care pathways, resources, and pre-trial LDKT activity.

Process information will be documented in the compliance log. For participants in the intervention arm, the research staff member (e.g., research nurse), an LKD nurse, or CI will use the quantitative intervention delivery checklist, recording the delivery of components of the intervention. For participants in the control arm compliance will be recorded at the end of the study by the research staff member (e.g., research nurse) recording whether the participant received any elements of the intervention from another source. From here compliance can be reported to the TSC and Sponsor.

The following will be recorded as protocol deviations:

1. If participants randomised to the intervention arm do not complete the first intervention meeting with a LKD specialist within 4 months of randomisation

2. If participants randomised to the usual care arm receive a home education and engagement visit as a result of a research team error

The primary analysis will be intention to treat. Those non-compliant will be included in this analysis. For this reason, even if a patient is documented as deviating from protocol or withdrawing from their randomised treatment they will be encouraged to continue with study visits/contacts and patient

questionnaires. Per-protocol analysis of the primary outcome will exclude participants who do not adhere to the trial intervention allocated to them (see section 10.3.2 for precise definitions of the per-protocol populations).

We will explore the reason for not complying with treatment as recorded in the risks and issues log and investigated through qualitative interviews. If participants who are non-compliant with their allocated treatment arm do not respond to attempts to collect patient reported outcome data, outcome data that can be extracted from medical records and national registries will be used.

8.4 Usual care

The comparator will be usual care. This typically comprises general kidney failure therapy education without specific screening of potential donors, or direct outreach to family and friends. There will be some heterogeneity within and across sites: a pragmatic trial must try to reproduce the circumstances under which an intervention will be used[66].

9 SAFETY

9.1 Definitions

Term	Definition
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

“Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Serious” is the regulatory definition supplied above.

This study will be looking at Serious Adverse Events (SAEs) that are **related to the study** (i.e. they resulted from application of any of the research procedures) and **unexpected** (i.e. not listed in the protocol as an expected occurrence).

9.2 Anticipated events excluded from reporting

Anticipated events due to the nature of advanced kidney disease and its treatments do not require reporting (this could include abnormal laboratory results that can be explained directly or indirectly by their advanced kidney disease, commencement of dialysis, death that can be explained directly or indirectly by their advanced kidney disease)

These expected events do not require reporting but will be recorded in the participant's medical records. However, anything the PI/CI deems unexpected and related to the intervention, must be reported.

Complications from living kidney donor surgery will not be reported as an SAE as these are accepted and recognised complications from the surgery.

Any medical conditions picked up as a result of testing for donation will not be reported as an SAE as this is a known complication of donation.

9.3 Recording and reporting of SAE

All reportable SAEs occurring from the time of consent until 30 days after the end of trial participation must be documented on the online SAE form via OpenClinica within 24 hours of the research team becoming aware of the SAE. Any SAEs that are related to the research procedures and unexpected will be reported to the Research Ethics Committee and the Sponsor by the Trial Manager, within 15 days of becoming aware of the event. For each SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial/intervention), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be updated on OpenClinica as soon as it is available or at least within 72 hours of the research team becoming aware. Events will be followed up until the event has resolved or a final outcome has been reached.

Each SAE must be reported separately and not combined on one SAE form. Any change of condition or other follow-up information relating to a previously reported SAE should documented on the appropriate form and the trial manager will email this securely to the Sponsor as soon as it is available or within at least 15 days of the information becoming available to the research team. Events will be followed up until the event has resolved or a final outcome has been reached.

A summary report will be submitted to the TSC on a regular basis.

9.4 Responsibilities

Principal investigators (PIs) and research staff

Principal investigators (PIs) and research staff at each site will be checking for SAEs when participants attend for treatment/follow-up; they will be responsible for:

- Using medical judgement in assigning seriousness, causality and expectedness.
- Ensuring that all SAEs are documented and reported within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased if a record of receipt is not received within 2 working days of initial reporting.

Chief Investigator

The CI will be responsible for:

- Clinical oversight of the safety of patients participating in the trial, 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.
- Using medical judgement in assigning expectedness.
- Immediate review of all reportable SAEs.

Trial Manager

The Trial Manager will be responsible for:

- Ensuring safety reports are prepared in collaboration with appropriate members for the main REC, TMG, DMC and TSC.
- Reporting safety information to the delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit.
- Reporting SAEs to the Sponsor.
- Expedited reporting of SAEs to the REC within required timelines.
- Notifying PIs of SAEs that occur within the trial.
- Central data collection of SAEs.

Sponsor

The sponsor will be responsible for:

- Overall oversight of the trial.

Trial Steering Committee and Data Monitoring Committees

These groups will be responsible for periodically reviewing safety data.

9.5 Notification of deaths

Only deaths thought to be a direct consequence of the intervention (and therefore a SAE) will be reported on OpenClinica. This will occur within 24 hours of notification of death.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

By the end of the feasibility trial, 10% of people in the usual care arm had a potential donor being tested. If 10% of people in the usual care arm receive a LDKT, to detect a +10% difference in the intervention arm with α=0.05 and power=0.9 we will require 532 participants. Allowing for 10% attrition, a sample of 592 is required to determine intervention effectiveness. Sites in the feasibility trial have recruited 18 participants/centre/year. 20 of the 54 English and Welsh renal units recruiting over 20 active site months will provide the required sample size. Due to the primary outcome being assessed at 18 months follow-up, no interim analyses for effectiveness will be conducted.

10.2 Planned recruitment rate

The work will take place over 60 months. Participant recruitment will start as soon as the first site is confirmed. Staggered set-up and opening of twenty sites will occur from month 9 over 18 months. Recruitment will occur until month 37. 20 sites will recruit for an average of 20 months per site (400 site-months of recruitment assuming 1.5 recruits per site per month). Follow up will continue until month 55, 18 months after the last recruit is randomised.

10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

Analysis and reporting will be in line with CONSORT guidelines[67]. Baseline characteristics of the two groups will be presented and a CONSORT diagram used to show participant flow through the study. The primary statistical analysis will be conducted on an intention-to-treat (ITT) basis. Baseline variables to be explored are those described in **section 7.4**. Patient-reported outcome scores based on standardised questionnaires will be calculated based on the developers' scoring manuals and missing and erroneous items will be handled according to these manuals. Continuous measures will be presented as means and standard deviations or medians and interquartile ranges depending on their distribution. Categorical data will be presented as frequencies and proportions.

10.3.2 Primary outcome analysis

The primary outcome is receipt of a LDKT (excluding LDKT if from a non-directed altruistic donor outside the sharing scheme) within 18 months of randomisation. We will use a multivariable logistic regression model for the binary outcome (LDKT=1/no LDKT=0) adjusted for minimisation factors (fixed effects) and centre (random effect). The odds ratio of receiving a LDKT and 95% confidence interval

will be presented, together with a p-value for the treatment effect. We will estimate the number needed to treat to achieve one additional LDKT, with 95% confidence interval. Our primary analysis will be an ITT analysis including every randomised participant. We will also undertake two per protocol analyses for comparison:

- Per protocol 1: All participants apart from:
    - Any participant allocated to the intervention arm who did not receive at least one component of the intervention
    - Any participant allocated to the usual care arm who, as a result of a research team error, received at least one component of the intervention (this will be recorded as a protocol deviation)
    - Any patient randomised in error or with other significant clinical protocol deviations

- Per protocol 2: All participants apart from:
    - Any participant allocated to the intervention arm who did not receive all three components of the intervention
    - Any participant allocated to the usual care arm who as a result of a research team error, received at least one component of the intervention (this will be recorded as a protocol deviation)
    - Any patient randomised in error or with other significant clinical protocol deviations

- An exploratory Bayesian analysis of the primary outcome may be performed at the final analysis stage in order to understand what the results would look like for a Bayesian trial design. A prior distribution for the probability of receiving an LDKT in each treatment arm will be elicited and agreed on and detailed in the SAP. In the final analysis, a posterior estimate for the odds ratio along with a 95% credible interval may be presented.

We will perform a sensitivity analysis for the primary outcome to account for the occurrence of DDKTs. Further details will be provided in the Statistical Analysis Plan.

10.3.2.1 Subgroup analysis

Subgroup analyses of the primary outcome will be conducted by including an interaction term in the mixed logistic regression model. These will include deprivation status, sex and ethnic group. All of these factors have been found to be associated with the likelihood of receiving an LDKT.

10.3.3 Secondary outcome analysis

- Time to receipt of LDKT (excluding LDKT if from a non-directed altruistic donor outside the sharing scheme)

- Transplant candidates with at least one donor at each stage of assessment

    1. Initial evaluation by coordinators completed
    2. Nephrological assessment completed
    3. Surgical assessment completed
    4. Registered to UK Living Donor Sharing Scheme (if applicable, and reason for entry into sharing scheme e.g., ABOi, HLAi, better match required)
    5. Donated/date set for donation

        - Number of donors per recipient registered to the UK living Donor Sharing Scheme with reasons
        - Patient self-reported total number of donors at any of the previously detailed stages 1-4
    - Patient activation (PAM13 score 0-100; PAM level 1-4)
    - Perceived social support (ISEL-12, score 0-36)
    - LDKT knowledge (subsection of R3K-T, 11 questions, max score 11)
    - Quality of life (EQ-5D-5L health utility score 0-1, level 1-5 for each dimension, visual analogue scale score 0-100)
    - Adherence: Number and % of participants who have first intervention meeting, number and % of participants who have letters sent to family/friends (and number of letters sent per participant), number and % of participants receiving home visits by intervention team (and number of home visits per participant), content compliance (quantitative checklist for home visit content)
    - ModRUM to estimate healthcare resource use before at the end of the trial

Patient-reported outcome scores from questionnaire data will be calculated based on the developers' scoring manuals, and missing and erroneous items will be handled according to these instructions.

Time to receipt of LDKT will be presented using Kaplan-Meier plots and analysed using Cox proportional hazards regression. Patient self-reported number of potential donors and adherence will be presented as descriptive statistics only. The remaining secondary outcome measures will use appropriate regression methods to compare arms, and all analyses will be adjusted for stratification and minimisation variables.

The status of the patient at the 18-month follow-up point will also be presented (never listed/active on transplant list/suspended/removed/LDKT/DDKT/died without transplantation). In our quality-of-life analysis we will adjust for baseline EQ-5D-5L scores. In our analyses of patient activation, perceived social support and LDKT knowledge we will adjust for the value of the outcome at baseline.

All hypothesis tests will be pre-specified in the statistical analysis plan and will be two-sided, with a p-value of <0.05 considered as providing strong evidence against the null hypothesis for the primary outcome analysis. There will be no adjustment for multiple testing.

10.3.4 Other outcomes

- Health Literacy (SILS-1, Likert scale 1-5)
- Transplant Beliefs (Qualitative statement responses – 5-point Likert, strongly disagree through to strongly agree.)

Health literacy and Transplant beliefs at 4 months will be summarised with descriptive statistics. The reason for inclusion of these outcomes is to understand the intervention effect mediators. We will investigate whether the intervention changes participant health literacy and transplant beliefs, or whether the intervention provides a 'work around' to these identified barriers to transplantation.

10.3.5 Interim analysis and criteria for the premature termination of the trial

Recruitment will be reviewed at every TMG, TSC, and DMC meeting. A continuation/progression criteria dashboard with red/amber/green thresholds is proposed to help assess whether the trial should continue (Table 4) with first assessment after 6 months of recruitment. Achieving all green

targets would almost certainly mean the trial continues to recruit, whereas achieving predominantly red targets would almost certainly indicate that the trial will not recruit to target in the proposed timelines and continuation needs to be reviewed.

Table 4. Trial continuation progression criteria dashboard

	The recruitment rate per active site month	The % of invited (approached in person and given information sheet) patients randomised	The % of randomised patients lost to follow-up at 3 months (no data recorded at hospital site or on national databases)
GREEN	1.0 pts/mth or more	30% or more	5% or less
AMBER	>0.7 and <1.0 pts/mth	>20 and <30%	>5 and <10%
RED	0.7 pts/mth or fewer	20% or less	10% or more

At the first DMC meeting, the committee will agree on its charter of operation and advise on the criteria for the need for interim analyses. The TSC and DMC will be responsible for assessing safety and efficacy; they will be responsible for recommending stopping the trial at any time if there are significant safety or ethical issues. Judgements will be made at their discretion.

10.4 Economic analysis

The primary economic evaluation will compare the costs and outcomes of the patient and family outreach service alongside usual care versus usual care for adults with advanced kidney disease. If the new service is effective, it will reduce rates of dialysis for this patient population in the medium to long-term; therefore a model-based economic evaluation, in which costs and benefits are estimated beyond the lifetime of the trial, is appropriate. Following an approach taken for a similar intervention in the Netherlands[68], a Markov model-based economic evaluation with a lifetime horizon will be developed to compare trial arms[69]. Discount rates will be applied to costs and benefits beyond the first year, consistent with the National Institute for Health and Care Excellence (NICE) economic evaluation reference case guidance (currently at a rate of 3.5% for costs and benefits). An NHS and Personal Social Services perspective will be taken in the economic evaluation, with Quality Adjusted Life Years (QALYs) as the primary outcome for the cost-effectiveness analysis. QALYs represent a composite measure of patient benefit capturing both quality and quantity of life in a single outcome[70].

The main data inputs from the trial will be:

i) the primary outcome (receipt of a LDKT within 18 months of randomisation), which will be used to predict future healthcare costs and benefits across trial arms in the model-based economic evaluation,

ii) health-related quality of life as measured by the EQ-5D-5L[59] to estimate short-term QALYs, and

iii) costs in terms of participants' healthcare resource use at the start and the end of the trial using the ModRUM[60], as well as the additional healthcare resource use associated with the new intervention.

The new intervention will be costed to account for the additional nurse and living kidney donor training time, service delivery time and travel costs, the costs of required interpreters, as well as the cost of testing family/friends for kidney donation and any subsequent surgery. Measurement of this resource use will be undertaken by records of nursing staff and patient self-reports of number of potential donors being tested for living kidney donation at 18 months. Patient trajectories through the model that are beyond the timeframe of the trial will be drawn from UKRR data. Medium to long-term data on costs and QALYs will be drawn from published sources for comparable cohorts of patients who are receiving dialysis or those with kidney transplants[4,71].

Results from the model-based economic evaluation will be presented in the form of incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs). Probabilistic sensitivity analysis will be undertaken to capture the uncertainty associated with model parameters: CEACs will show the probability of the new intervention being cost-effective at varying willingness to pay thresholds. The base analysis will use the NICE economic evaluation reference case willingness to pay thresholds of £20,000 and £30,000 per QALY gained[70]. An intervention that leads to more QALYs for less than £20,000 per QALY gain is usually considered a cost-effective use of NHS resources and recommended for use on the NHS[72]. We will explore multiple thresholds using Cost Effectiveness Acceptability Curves to examine the cost-effectiveness probability at different plausible willingness to pay thresholds for different stakeholders.

As the intervention aims to reduce health inequity, a distributional cost-effectiveness analysis (DCEA) will be conducted: this provides information about the equity impact of interventions and the possible trade-offs between equity and efficiency[73]. A DCEA requires information on the equity areas of concern to the decision-making context at hand. In this study, this will require specific information related to healthcare costs and outcomes by socioeconomic and/or UK minority ethnicity status for trial participants, given the described socioeconomic and ethnic inequity in access to LDKTs[25,26]. This form of economic evaluation allows decision-makers to consider simultaneously if a new treatment is cost-effective and improves equity (a "Win-Win") or if trade-offs in net population health impact and health inequalities may be required in decision-making[73]. The DCEA will allow decision-makers to see the predicted impact of the outreach service being offered universally compared to a more targeted approach for those with lower LDKT uptake to specifically address this inequity.

10.5 Process evaluation and qualitative analyses

Qualitative interviews and observation notes will be analysed using reflexive thematic analysis, as described by Braun and Clarke[65]. Transcripts will be read twice to gain familiarisation, and sections of text coded by assigning descriptive labels. Codes will be grouped based on shared properties and themes identified. Themes identified for each participant group (patients/family and friends/healthcare professionals) will be cross-compared iteratively during analysis to understand commonalities and

contrasts in perspectives, which are relevant for optimising delivery, acceptability, and understanding ways of overcoming any contextual barriers to implementation. All transcripts will be independently coded by the qualitative research associate with a sub-set independently coded by Senior Lecturer in Qualitative Health Science, Co-Investigator Dr Julia Wade. Codes will be discussed to maximise rigour, to identify areas of discrepancy and to refine the coding system. NVivo software will be used to aid analysis. Data collection and analysis will be iterative, taking place concurrently and informing further sampling. The exact sample size will depend on when the sample has delivered sufficient information power[74].

10.5.1 Integration of findings of process evaluation

We will present a descriptive analysis of quantitative information regarding fidelity, service components received ('dose'), and reach. We will integrate quantitative process measures into the trial outcomes dataset to understand how, for example, implementation variability affected outcomes (per protocol analyses). We will investigate if the qualitative interviews explain the quantitative findings regarding fidelity, 'dose', reach and impact of context. Process evaluation data will be analysed before the trial outcomes, and we will generate hypotheses as to whether, for example, certain individuals will benefit less from the intervention, which we can then investigate when analysing the trial outcomes[63]. We will investigate if trial outcomes differ by centre contextual factors. Qualitative findings will be used to clarify mechanisms of impact of the intervention.

10.6 Participant population

Using routinely collected UKRR and NHSBT registry data we can compare the % of LDKTs in the usual care arm with the % of LDKTs in individuals who would have been eligible for participation but who were not invited to participate. We can also compare usual care LDKT rates with pre-trial centre LDKT rates. This will allow us to investigate whether participating in the trial alone increased information provision to usual care participants. If there is a suggestion of contamination we will consider if a Complier Average Causal Effect sensitivity analysis is appropriate.

10.7 Procedure(s) to account for missing or spurious data

To limit missing patient reported outcome data, participants will have the opportunity to complete questionnaires on paper, online or via a telephone interview with a research staff member (e.g., research nurse).

The primary outcome will be receipt of a LDKT, which can be extracted from the UKRR or NHSBT datasets if people are lost to follow up. Patient consent will be sought for data linkage with the existing healthcare databases held by the UKRR and NHSBT. Linkage will enable follow-up of clinical outcomes for participants who move to a renal unit which is not participating in the trial.

Where other missing data exist for secondary outcomes, if appropriate according to the pattern of missingness, sensitivity analyses will be conducted using data imputed by multiple imputation based on full conditional specification.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

Data held at the University of Bristol (UoB) will be managed according to the UoB's Research Data Management policy: http://www.bristol.ac.uk/research/environment/governance/research-data-policy/

Data held at NHSBT will be managed according to a study specific data management plan.

Source documents are where data are first recorded, and from which eCRF data are obtained. In some instances, eCRF data may be considered source if this is where data is first recorded. Source data for the trial will be defined in a separate source document.

Data will be entered directly onto online electronic case report forms (eCRF), and participant questionnaires. Research staff may deviate from this to follow emergency procedures should there be a system failure making online data collection impossible.

PIs/Local site collaborators must keep records of all participants (sufficient to link records e.g., eCRFs and hospital records), all original signed informed consent forms and originals of any paper CRF pages.

Participants who have not returned a questionnaire as expected will be contacted via telephone by the research staff member (e.g., research nurse) to offer to complete the questionnaire over the phone. Up to three attempts to contact participants via telephone can be made.

11.2 Data handling and record keeping

11.2.1 Clinical and quantitative data

- The clinical data will be stored using OpenClinica. OpenClinica is a secure, web-based electronic data capture system designed for the collection of research data.
- OpenClinica is hosted in the cloud and accessed using any major web browser. Data are not stored locally by NHSBT and benefits from the rigorous cybersecurity and data loss prevention of a major cloud platform.
- OpenClinica is secure enough to store personally identifiable information when needed. For this study, in order to send out digital questionnaires to participants, as well as offer the option to complete digital consent, email addresses and phone numbers may be stored for participants.
- NHSBT Clinical Trials Unit (CTU) databases are designed to use the full capabilities of OpenClinica to ensure data quality is the best possible at the point of data collection. This will include using validation on numbers entered, logic checks against all possible relevant fields, calculated fields, and cross form logic.
- During the database development there are three phases of quality checks to ensure the database fits its purpose and is robust in the field. This includes internal testing by the designer, internal validation by a peer, and full external end user acceptability testing. OpenClinica supports the whole data lifecycle, including database design, data collection, validation, branching logic, data visualisation, analysis, reporting and storage. In addition, OpenClinica provides automated export procedures for seamless data downloads and can connect directly to common statistical packages.

- OpenClinica provides a full audit log cataloguing individual changes with date/time, old value, new value, reason for the change, and the identity of the user who made the change.
- OpenClinica user roles can be used in combination with access tags which can limit access to certain forms for users.
- Data entry can be performed by accessing NHSBT CTU's OpenClinica in a web browser or via a link sent to participants which takes them to a different view of the same web portal. To access the portal directly, users will be added to the system following request to the NHSBT data or operations team. It is the NHSBT data team's responsibility to ensure the appropriate training and delegation are complete before adding the new user to the live database.

11.2.2 Qualitative data

Qualitative data will be collected as encrypted digital audio files then transferred to a secure UoB server with access restricted to the qualitative researchers and CI within the ASK study team. Participants (health workers and friends/family members) will have a 14 day period during which they can withdraw their qualitative data and request the audio recording/transcript be destroyed. Due to the way in which qualitative data are analysed it will not be possible to guarantee deletion of an individual's data after 14 days, as the individual's data will have been coded and influenced the generation of analytical themes.

Audio files will be transcribed into word files through secure University of Bristol approved transcription services. Anonymised transcripts will be uploaded to NVivo software for analysis and audio files will be destroyed.

11.3 Access to Data

11.3.1 Source data

Participating investigators will allow monitors from the CTU/sponsor, persons responsible for the audit or monitoring, representatives of the REC and of the Regulatory Authorities to have direct access to source data/documents, in line with participant consent.

11.3.2 Anonymised trial data

The CTU and CI will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released.

Datasets will be uploaded to UoB's Research Data Repository: https://data.bris.ac.uk/data/. A summary of the data available will be detailed on the study website and all publications arising from the research. Potential new users can also actively search UoB's data repository.

Audiofiles of the recorded interviews will not be suitable for sharing as they carry a high risk of allowing the research participant to be identified, and the content of interviews will potentially be highly sensitive. Although the qualitative transcripts will be anonymised as personal issues will be discussed we cannot rule out the risk of identification. Therefore, access to these transcripts will be controlled. Requests for Controlled data through UoB are referred to an appropriate Data Access Committee (DAC) for approval, before data can be shared with researchers, after their host institution has signed a Data Access Agreement. The DAC comprises: Assistant Director of Research Services, Information Rights Officer, Head of Research Governance, Assistant Director IT Services, Research Contracts, Academics - the PI. The procedure for accessing data can be found here:

https://www.bristol.ac.uk/staff/researchers/data/accessing-research-data/

11.4 Archiving

Research data will be stored securely within NHSBT when the trial ends. Paper records (e.g., the trial master file) will be stored in locked offices/cabinets behind security accessed doors. Electronic data will be removed from the OpenClinica platform once archiving is authorised to start. Digital copies of the entire database and audit trail will be securely stored on a server managed by NHSBT Digital Data and Technology Services, accessible only by the research team. The final analysis dataset will be seen as the primary archived dataset although other files may also be archived. All personal identifiable data will be deleted at the time of archiving by the trial statisticians and data managers and the process evidenced in the trial master file. The University of Bristol is the study sponsor. Archiving will be authorised by the Sponsor following submission of the end of trial report and publication. Copies (paper or electronic) of completed case report forms will be kept for 10 years following the end of a study to enable audit of data used in publications. All essential documents will be archived following sponsor processes. Contracted organisations may be used for archiving.

Participating sites will archive site files via their usual arrangements.

12 MONITORING, AUDIT & INSPECTION

All trial related documents will be made available on request for monitoring and audit by the University of Bristol, the Research Ethics Committee and available for inspection by other licensed bodies.

Monitoring and audits undertaken by the University of Bristol, under their remit as sponsor, or individuals appointed responsibility for monitoring on their behalf, will ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition). NHSBT's CTU will also conduct remote monitoring based on information submitted by sites and will also undertake site monitoring visits. The frequency, type and intensity for routine site monitoring and the requirements for "for cause" monitoring will be detailed in a separate monitoring plan as agreed with the Sponsor.

The University of Bristol Research Governance department also regularly reviews its research portfolio. The University of Bristol has a Service Level Agreement with University Hospitals Bristol NHS Foundation Trust whereby the Trusts monitors 10% of the University's sponsored studies. University Hospitals Bristol NHS Foundation Trust has a Standard Operating Procedure (SOP 014 Monitoring and Oversight of Research) available at http://www.uhbristol.nhs.uk/research-innovation/for-researchers/run-a-study-and-closedown/monitoring/.

The CI, Dr Bailey, will take overall responsibility for managing the various components of the trial and will meet approximately monthly with the leads for each component. The CI will have overall responsibility for the budget. The Clinical Operations Manager will manage the CTU budget. The CI will review the budget with the Account Managers at the University of Bristol, North Bristol NHS Trust and CTU every 3 months.

NHSBT's Clinical Trials Unit, a UK Clinical Research Collaboration registered trials unit, will manage the trial on a day-to-day basis. Mrs Helen Thomas, Head of Clinical Trial Statistics will lead on the

clinical trial component of the study. A trial manager and a Clinical Operations Manager have been funded for the duration of the study. They will be supported by a trial coordinator and trial administrator. Data management will be the responsibility of a CTU Data Manager with support from a junior data manager. Statistical analysis will be led by a CTU senior statistician supervising a junior statistician, with oversight from Helen Thomas, Head of Clinical Trial Statistics.

The qualitative research will be led by Dr Julia Wade, Senior Lecturer in Qualitative Health Science who will supervise a qualitative research fellow. Dr Wade will sit on the TMG. Health economics evaluation will be led by Dr Paul Mitchell, Senior Lecturer in Health Economics and Health Policy Analysis who will supervise a health economics research fellow. Dr Mitchell will sit on the TMG.

A TMG will meet on a regular basis to review progress (at least once every 3 months in the first 2 years, then 6 monthly). Meetings will be by videoconference to minimise costs, environmental impact and to maximise attendance. A PAG comprising 8 members will be established and meet 6 monthly. This will be co-chaired by Primrose Granville, patient co-applicant.

An independent TSC will be appointed and will meet for the first time by month 6 of the trial and then 6 monthly. An independent Data Monitoring Committee will also be appointed prior to recruitment commencing with the purpose of reviewing the data at pre-specified intervals to ensure patient safety and the ethical running of the trial.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from an NHS REC and the Health Research Authority (HRA) for the trial protocol, informed consent forms and other relevant documents.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

The CI will notify the REC of the end of the trial. If the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer review

The proposal for this trial has been peer-reviewed through NIHR's HSDR peer-review process, which includes independent expert reviewers. In addition, the protocol has been reviewed by the Sponsor.

13.3 Public and Patient Involvement

Individual named patients, and the patient council of Kidney Care UK have been involved in the development of the study design. Their input has led us to offer the intervention to all rather than to just people who are socioeconomically disadvantaged, and they have advised regarding the wording and layout of patient information sheets. The trial follows a formal intervention development phase in which people with kidney disease and family members were interviewed regarding proposed intervention components to ensure the intervention being trialled is acceptable to participants.

Our key PPI contributor is Ms Primrose Granville. Primrose is a journalist, health campaigner and community advocate. She has lived experience of kidney disease and transplantation. She will co-chair a PAG comprising 8 people with experience of kidney failure, transplantation, or living kidney donation, and family members. Patient contributors will be recruited through the community groups with which Ms Granville works, Kidney Patient Associations, NHSBT's Patient and Public Advisory Group, and the national Kidney Voices for Research. They will be selected to ensure representation of individuals from UK minority ethnic and socioeconomically disadvantaged communities, and to ensure diversity with respect to age, sex, and experience of kidney disease. Patient collaborators will be reimbursed for their time according to the NIHR's guidance.

We will undertake four focus groups facilitated by the Centre for Ethnic Health Research with patients, family and the public from groups not represented in the feasibility trial, including people with East Asian heritage, and those with a Muslim faith. We will invite focus group participants to comment on whether the service delivery and resources need adaptation to ensure they are culturally concordant.

13.4 Regulatory Compliance

Before any site can enrol patients into the trial, the CI/PI or designee will obtain confirmation of capacity and capability for each site.

For all amendments the CI/PI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' research & development departments that permissions are ongoing.

13.5 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented and reported to the CI and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial.

The sponsor must be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per the appropriate SOP.

13.7 Data protection and patient confidentiality

The CI will be the data custodian. All data held in Bristol will conform to the University of Bristol Data Security Policy and in Compliance with the Data Protection Act 1998. Data will be managed according to the University of Bristol's Research Data Management policy:
http://www.bristol.ac.uk/research/environment/governance/research-data-policy/

13.7.1 Quantitative data

Any data collected on paper case report forms at study centres or as questionnaires from participants will be identifiable only by participant study number. These will be entered onto OpenClinica by the research team and stored in the site file in a secure location. Electronic data will be kept on password protected databases held on NHSBT servers, accessible only by the research team.

Data will be extracted from returned paper questionnaires or CRFs onto a password locked OpenClinica database on NHSBT's secure server. Questionnaires and CRFs completed online directly enter the data onto OpenClinica. Information capable of identifying participants will not be removed from the University of Bristol or clinical centres or made available in any form to those outside the study. Participants will be given a study code, a list of which will be kept at the participating NHS hospital site. This will be stored on OpenClinica to allow identification of the participant at the sites.

Long-term the data will be stored in the University of Bristol's Research Data Storage Facility: https://www.acrc.bris.ac.uk/storage.htm. Data will be stored for a minimum of 10 years.

13.7.2 Qualitative interview data

Qualitative data will be collected as encrypted digital audio files (mp3 files). Audio files will be uploaded to a secure access folder on the secure server of the University of Bristol's Population Health Sciences department. Once uploaded the audio files will be deleted from the recorder.

Recordings and transcriptions will be named with a study-assigned participant number, centre initials, and the date of recording. There will be no participant identifiers in files, databases, or transcripts, which will only be labelled with study assigned participant numbers. Coding keys matching the name of the participants with their study participation number will be stored in a password protected spreadsheet, which will be maintained and only accessed by the qualitative researchers.

All recordings will be securely transferred to a University of Bristol approved transcription company that has signed the required confidentiality agreements. Audio files will be transcribed and any potential participant identifiers removed from transcripts. Anonymised transcripts will be uploaded to NVivo software for analysis. Once qualitative data analysis is completed the audio files will be deleted from the secure server at the University of Bristol. Only the qualitative researchers working on this study will have access to secure folder containing the audio files and the transcripts.

Anonymised transcripts may still contain information which might allow the identification of participants by people known to them. Therefore, the transcripts although anonymised will be stored as encrypted word files in a restricted password accessible folder on the secure of server of the University of Bristol. Any personal data will only be collected, extracted, stored, and shared via the data.bris repository with the explicit consent of the participant. Paper versions of signed participant consent forms will be stored separately from the transcriptions, in a locked filing cabinet in a secure office at the University of Bristol.

Transcripts from the qualitative interviews and observations will be uploaded to the University of Bristol's Research Data Repository: https://data.bris.ac.uk/data/.

The anonymised qualitative data transcripts will be suitable for sharing to other researchers who may wish to undertake a thematic synthesis, or analyse the interviews using a different methodology to the one proposed in this study. When consent has been provided by the research participant, the anonymised transcript will be made available to other researchers. Requests for Controlled data through the University of Bristol are referred to an appropriate DAC for approval, before data can be shared with bona fide researchers, after their host institution has signed a Data Access Agreement. The University's DAC comprises the following: Assistant Director of Research Services (Library), Information Rights Officer (FOI, Data Protection), Head of Research Governance (ethics), Assistant Director IT Services (data security), Research Contracts (if commercially sensitive), Academics e.g., the PI. The procedure for accessing data can be found here: https://www.bristol.ac.uk/staff/researchers/data/accessing-research-data/.

If the DAC grants access to the data, a University of Bristol Data Access Agreement is drawn up and signed by the applicant, their host institution, and the University of Bristol. The University of Bristol's Research Data Service will oversee this.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

No competing interests have currently been identified for the CI and research team. The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

13.9 Indemnity

The necessary trial insurance is provided by the Sponsor. The University of Bristol has arranged Public Liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University.

This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff (including the Trust's responsibility for University of Bristol employees acting in connection with their NHS honorary appointments). Participating NHS sites will hold standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England.

The CI Dr Bailey holds an honorary appointment with North Bristol NHS Hospital Trust giving her the protection of the NHS indemnity scheme.

The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University.

13.10 Amendments

The Sponsor will determine whether an amendment is substantial or non-substantial. All amendments will be processed through the HRA and where appropriate the REC. Amendments will also be notified to NHS research & development departments of participating sites to confirm ongoing capacity and capability to deliver the study.

13.11 Post trial care

The intervention being evaluated is an intervention delivered over a fixed period of time, and there will be no ongoing delivery of support after the intervention has been delivered to study participants. If the trial finds the intervention to be effective and cost-effective, then the intervention will be recommended in policy for roll out across the UK.

13.12 Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Data will be uploaded to the University of Bristol's Research Data Repository: https://data.bris.ac.uk/data/.

The final qualitative and quantitative dataset will be accessible by the CI, the co-investigators, the trial statistician and the TSC. Local PIs will not have access to final dataset unless formally requested and approved by the TSC. The qualitative researchers will have access to the final qualitative dataset.

The anonymised qualitative data transcripts will be suitable for sharing to other researchers who may wish to undertake a thematic synthesis, or analyse the interviews using a different methodology to the one proposed in this study.

Consent for the sharing of the interview transcripts to other researchers will be explicitly sought from interviewees prior to the interview, and this confirmed with the interviewee following the interview. Transcripts will be anonymised with all personal identifiers and possible identifiers redacted. This includes details that may identify other people mentioned in the interview e.g., clinicians, family members. Participants will be informed that transcripts will be stored in accordance with the Data Protection Act and they will be asked to confirm in writing that they have understood this. If people decline to provide consent for sharing, the data will be used by the primary research team only. When consent has been provided by the research participant, the anonymised transcript will be made available to other researchers.

Although the qualitative transcripts will be anonymised, due to personal issues being discussed we cannot rule out the risk of reidentification and therefore as a double safeguard access to these transcripts will be controlled. Requests for Controlled data through the University of Bristol are referred to an appropriate Data Access Committee (DAC) for approval, before data can be shared with bona fide researchers, after their host institution has signed a Data Access Agreement. The University's DAC comprises the following: Assistant Director of Research Services (Library), Information Rights Officer (FOI, Data Protection), Head of Research Governance (ethics), Assistant Director IT Services (data security), Research Contracts (if commercially sensitive), Academics e.g., the PI. The procedure for accessing data can be found here: https://www.bristol.ac.uk/staff/researchers/data/accessing-research-data/

If the DAC grants access to the data, a University of Bristol Data Access Agreement is drawn up and signed by the applicant, their host institution, and the University of Bristol. The University of Bristol's Research Data Service will oversee this.

14 DISSEMINATION POLICY

14.1 Dissemination policy

The results of the study will be published in academic journals and all participants will be offered a plain English summary of the main findings of the study. The main trial report will be prepared and published with reference to the CONSORT guidelines[67]. Qualitative research reports will be prepared and published with reference to the COREQ guidelines[75]. Reports of this work will be submitted for presentation at national and international renal and transplant conferences. Intended papers include: i) Trial protocol published in a peer-reviewed journal; ii) Findings papers x 3 published in peer-reviewed journals: Effectiveness paper x1, Process evaluation x1, Cost-effectiveness analysis x2. We will aim to publish the process evaluation and implementation findings and RCT findings in parallel/simultaneous publications in the same peer-reviewed journal; and iii) Plain language summaries and visual abstracts.

On completion of the trial a final report will be prepared for the funder (NIHR). The funders will also be given formal notice of all publications, and the funder and sponsor will be acknowledged within the publications.

If the outreach service is effective at improving access to LDKTs, then we will described the core components of the intervention according to the Template for Intervention Description and Replication (TIDieR) checklist[76] for other centres to adopt and replicate.

Findings will be publicised in collaboration with the University of Bristol's and NHSBT's Communications and Media team.

We will create a plain language summary of findings, translated as required, and visual abstracts. The PAG will be the lead authors of these summaries. The summaries and visual abstracts will be made available on the study website. We will share them with participants, via the research nurses, and patients through existing local Kidney Patient Associations, and the national kidney patient charities Kidney Care UK and the National Kidney Federation. We will request findings are disseminated through their social media, newsletters and websites.

Findings will be shared with NHS healthcare professionals through the national Transplantation Clinical Studies Group which has representatives from all transplant centres in the UK. Findings will also be presented at medical conferences (British Transplantation Society and the European Society for Organ Transplantation conference).

14.2 Authorship eligibility guidelines and any intended use of professional writers

The trial report will be written by the CI with support from the TMG and all co-investigators. All TMG members and co-investigators who have contributed to the design, conduct, analysis and write up will be offered authorship on the final report.

On manuscripts arising from the trial, authorship will be on an individual authorship basis (rather than group authorship basis) with inclusion based on the recommendations of the International Committee of Medical Journal Editors.

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16 APPENDICES

16.1 Appendix 1 - Trial management / responsibilities

16.1.1 Patient registration/randomisation procedure

Patient registration will occur via the OpenClinica website. After an individual has provided consent for participation the research staff or PI at the participating site will log onto the Sealed Envelope study website, enter the participant details into the randomisation tool and this will then allocate the participant to one of the treatment arms. This should happen the same day as consent has been provided.

16.1.2 Data management

The CI holds overall responsibility for data management, including CRF checking, identifying missing data and attempt to complete missing entries, and addressing data queries/clarifications. Research staff and local PIs are responsible for data entry. Participants are also able to complete questionnaires online which enters data directly into the OpenClinica dataset.

16.1.3 Preparation and submission of amendments

The CI is responsible for submitting amendments for approval to first the Sponsor, then the REC and HRA as required. The CI is then responsible for informing participating sites of amendments.

16.1.4 Preparation and submission of Annual Safety Report/Annual

The CI is responsible for preparing and submitting the progress reports to the funders and Sponsor as required.

16.1.5 Data protection/confidentiality

The CI is responsible for ensuring Data Protection and confidentiality.

16.1.6 Trial documentation and archiving

The CI will be responsible for archiving trial documentation at the University of Bristol. Participating NHS sites are responsible for archiving local records held on participants e.g., copies of paper CRFs

16.2 Appendix 2 – Authorisation of participating sites

16.2.1 Procedure for initiating/opening a new site

Following initial approach, the CI will await confirmation of a site's capacity and capability to participate in the study. Prior to a green light being given by the Sponsor the CI will arrange a Site Initiation meeting which will be undertaken by the CI and intervention HCPs.

16.2.2 Principal Investigator responsibilities

The PI's legal responsibilities are listed in the Participating Site Agreement. PIs are expected to attend the site initiation meeting/teleconference, identify potential participants, ensure that the investigator site file is accurately maintained, disseminate trial related information to all stakeholders within their site, and ensure reporting of any adverse events to the CI.

16.3 Appendix 3 – Schedule of Procedures

Procedures	Visits				
			Treatment Phase		
	Screening	Baseline	1 Potential donor screen and invitation	2 Home visit	Follow Up
Eligibility assessment	X				
Informed consent		X			
Randomisation		X			
Demographics		X			
Clinical		X			
Laboratory		X			
Patient reported outcome measures		X			X
Resource				X	X
Compliance with trial			X	X	
Serious adverse event assessment and reporting		X	X	X	X

16.4 Appendix 4 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
Initial submission (never approved)	1.0	11 April 2025	n/a	n/a
Revised submission	1.1	14 May 2025	AE	Addition of SAIL (Secure Anonymised Information Linkage) data collection for Wales
NSA1	1.2	26 Sep 2025	PB, CB, VR	Changes to intervention delivery: addition of drop-in sessions for intervention delivery staff. Administrative changes to trial staff. Clarification of Baseline data collection time period. Revision of study flow diagram.