BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015971
Article Type:	Protocol
Date Submitted by the Author:	19-Jan-2017
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Renal medicine
Keywords:	Renal transplantation < NEPHROLOGY, Chronic renal failure < NEPHROLOGY, kidney, altruistic/ unspecified donation

Unspecified living kidney donation in the UK: barriers to implementation and delivery

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Abstract

Introduction: Living donation accounts for over one third of all kidney transplants taking place in the UK[1]. The concept of anonymously donating a kidney to a stranger (non-directed altruistic or unspecified kidney donation (UKD)) remains uncomfortable for some clinicians, principally due to concerns about the motivations and long-term physical and psychological outcomes in this donor group.

Aims: The research programme aims to provide a comprehensive assessment of the unspecified donor programme in the UK. It aims to identify reasons for variations in practice across centres, explore outcomes for donors, ascertain barriers and facilitators to UKD for those who have expressed a willingness to donate, and assess the economic implications of unspecified donation.

Methods: The research programme will adopt a mixed-methods approach to assessing UKD nationally using focus groups, interviews and questionnaires. Two study populations will be investigated. The first will include transplant professionals involved in unspecified kidney donation. The second will include a five-year prospective cohort of individuals who present to any of the 23 UK transplant centres as a potential unspecified living kidney donor. Physical and psychological outcomes will be followed up one year following donation or withdrawal from the donation process. A matched sample of specified donors (those donating to someone they know) will be recruited as a control group. Further qualitative work consisting of interviews will be performed on a purposive sample of unspecified donors from both groups (those who do and do not donate). **Dissemination:** The findings will be reported to NHS Blood and Transplant and the British Transplant Society with a view to developing national guidelines and a protocol for the management of those presenting for unspecified donation.

The study is registered with the International Standard Randomised Controlled Trial Number (ISCRTN) – 23895878

Strengths and Limitations of this study:

- This is a prospective, mixed methods study using both qualitative and quantitative methods to answer complex questions regarding barriers to service delivery
- This is a widely multi professional study drawing experiences from a variety of fields (surgery, medicine, psychology, psychiatry, ethics, NHS Blood and transplant)
- This study will assist in the development of national guidelines and a protocol in conjunction with NHS Blood and Transplant and The British Transplant Society.
- No economic analysis of unspecified kidney donation has previously been performed.
- There is a risk of not capturing individuals who are disengaged/ disappointed in the process of unspecified kidney donation
- The study relies on a large number of individuals participating and is based on the assumption that unspecified donation rates with continue to occur at the same rates as prior years

Introduction

Living donation remains the gold-standard treatment for individuals with end-stage renal failure. Currently over one third of all kidney transplants taking place in the UK are from living donors. A growing subset of living donors consists of individuals who choose to donate a kidney to someone that they have not previously met. These are called 'unspecified kidney donors' (UKDs) or 'non-directed altruistic' donors. Over 500 unspecified donations have taken place in the UK since the practice was introduced in 2006 and it currently accounts for approximately 11% of living donations per year[1].

Recipients of living donor kidneys are provided with a long lasting, high quality organ that is usually sufficient to avoid dialysis for an extended period of time[2]. Organs from UKDs can provide this opportunity for those without a living donor, some of whom would have a low chance of receiving a deceased donor organ from the waiting list due to sensitisation challenges. Additionally, UKD's organs can be further utilised by introducing them into the National Kidney Sharing Scheme. This involves kidney exchanges between pairs of donor and recipients who cannot otherwise proceed due to immunological incompatibility. A kidney from a UKD can be used to convert these exchanges into a 'chain' primed by the UKD (figure 1). In this way, the UKD donates to the first recipient, whose donor then subsequently donates to another recipient, and so on. The chain then terminates with donation to an individual on the deceased donor waiting list. In the US this has resulted in 30 transplants occurring from a single UKD[3]. In the UK, 47% of UKDs have been used to prime short chains of two transplants, and the UK Living Donor Strategy aims for 75% to be used for chains, with 3 transplants in each chain, by 2020[4].

Despite the increase in UKD in the United Kingdom the concept remains illegal in many European countries and is uncomfortable for some healthcare professionals, principally due to concerns about the motivations, characteristics and outcomes in this group of donors[5]. We have performed the largest quantitative study of psychosocial and physical outcomes in UKDs, where we sampled a national cohort of all 148 UKDs in the UK over the first five years of the programme and compared them with a regional sample of 148 specified kidney donors (SKDs - those who

donate to someone with whom the donor has an existing emotional relationship)[6]. All donors were sent a questionnaire which included a range of validated psychosocial outcome measures and questions specific to their donation. Physical outcome data were obtained from NHS Blood and Transplant. This study found that both physical and psychosocial outcomes were comparable between UKDs and SKDs, which suggests that clinician concerns may be unfounded. The limitations of this study were in its retrospective design and the inherent bias associated with this. Whilst we were able to analyse physical outcome data for the entire cohort, we were unable to determine whether those with poor psychosocial outcomes were within the non-responders and therefore not captured as part of the study. In addition, this study demonstrated a broad variation in donation rates across the country, with no obvious underlying reason.

A number of potential deterrents to UKD have been highlighted in our previous qualitative work and through consultation with UKDs in the development of this study.[7] For example, we have previously found that barriers to donation may exist within families where there is tension over the decision to donate altruistically and that there may be a role for transplant services to support families in this situation[7]. UKDs have also reported experiencing scepticism and resistance from some of the healthcare professionals they encountered. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also described as a difficult experience for UKDs who felt that they had to prove their sanity[7].

Aims and Objectives

The aim of this research programme is to perform a comprehensive assessment of the unspecified donor programme in the UK. Its objectives are to establish:

1. Whether variation in practice and attitudes across the UK is unnecessarily preventing some unspecified donation

2. Whether psychosocial and physical outcomes after unspecified donation are equal to those in specified donors

3. The economic benefit of unspecified donation

Ethical dimensions and implications of unspecified donation will also be explored. The programme's data will be used to develop national guidelines and inform transplant teams' decisions about potential donors.

Methods and Analysis

Design

This is a mixed methods research programme investigating unspecified kidney donation in the UK over a period of 5 years.

Research Questions

The study will be asking three main questions based on the research objectives listed above:

1. RQ1- Is there variation in transplant professionals' practice and attitudes, which is preventing some unspecified living kidney donations?
2. RQ2 - Are psychosocial and physical outcomes after unspecified donation equivalent to those after specified donation?
3. RQ3 - What is the economic benefit from unspecified donation?

In order to answer these three research questions we will utilise a mixed methods design, incorporating questionnaires to obtain quantitative data and interviews and focus groups to obtain qualitative data. The third question, related to health economics, will be answered using embedded data capture elements within the first two research questions.

RQ1 Transplant Professionals' Perspective

This sub-study defines transplant professionals (TP) as any healthcare professional that may come in contact with a potential unspecified donor. These include renal transplant physicians, surgeons, transplant co-ordinators, nurses involved in transplantation, psychologists and independent assessors, as well as administrative staff from all 23 UK centres. Answering this research question will involve three stages. The first stage will involve focus groups, led by qualitative researchers, in which the views of transplant professionals regarding UKD will be ascertained. Focus groups will be undertaken in four centres, chosen according to their volume of

donations. This will allow sampling from two centres with higher donation rates and two centres whose rates are amongst the lowest. The data obtained will undergo thematic analysis and the key themes identified will be extrapolated. This data will be used to inform the subsequent stages. The second stage will involve questionnaire development, from the themes generated by the focus groups. The questionnaires will form the basis of a series of prospective cohort studies which will help ascertain broader, nationwide attitudes towards unspecified kidney donation, as well as current working practices in the different transplant centres. The questionnaires will be disseminated using professional networks to all UK transplant professionals. The third stage will involve in-depth qualitative interviews that will be conducted with transplant professionals selected from six centres, again chosen according to their donation volume. These interviews will not only provide a more detailed understanding of professionals' views, but will additionally help add meaning to the data obtained from the prospective cohort studies (questionnaire based).

RQ2 Donors' Perspective

Two focus groups will be held to assist in informing the development of study-specific questionnaires. The first focus group will involve individuals that have proceeded to donate a kidney as an unspecified kidney donor, whilst the second will involve individuals who presented as potential unspecified kidney donors, but who did not proceed to donate. Themes emerging from the focus groups will again be analysed using thematic analysis and questions specific to UKD will be written and validated by the research team. These questions will subsequently become part of a larger questionnaires, which will include validated psychosocial outcome measures capturing data on a range of different factors [8-17]. Validated psychosocial outcomes measures will include: The Client service receipt inventory[8], Rosenberg self-esteem scale[9], Generalised anxiety disorder 7-item scale (GAD-7)[10], Multi-dimensional scale of perceived social support (MSPSS) [11], Ten-item personality measure[12], Decision regret scale[13], Patient health questionnaire (PHQ-9)[14], Satisfaction with life scale[15], Flourishing scale[16] and the Quality of life health survey (SF-12) [17].

The questionnaires will be used as part of a longitudinal cohort study with four intervention points, as determined by their progress through the donation pathway. All those presenting to a transplant centre as a potential UKD will complete a baseline

questionnaire. The second questionnaire will be given immediately prior to donation, or immediately after the donor is withdrawn from the assessment process. The final two questionnaires will be given at three and twelve months after donation or withdrawal.

The study population will consist of all those individuals approaching a transplant centre with an interest in becoming an unspecified donor, irrespective of whether they subsequently donated or not. Potential specified donors will be used as the control population. Due to the fact that not all those who present as potential donors go on to donate, the study will result in two test groups and two control groups (figure 3):

1. Test group 1: Potential unspecified donors who proceed to donation
2. Test group 2: Potential unspecified donors who do not proceed to donation (either due to personal choice or withdrawal by the clinical assessors)
3. Control group 1: Potential specified donors who proceed to donation
4. Control group 2: Potential specified donors who do not proceed to donation (either due to personal choice or withdrawal by the clinical assessors)

Qualitative interviews will also be completed with a sample of 15 UKDs who completed their donation, 15 UKDs who withdrew and 15 UKDs who were withdrawn from the process by the transplant team. Participants will be asked about their experience of the donation process and services, barriers and enablers to donation and outcomes from either donating or withdrawing from the process. These interviews will take place three months after donation or withdrawal from the donation process.

The data collected will be compared with and supplemented by each donor's NHS Blood and Transplant records. These will be used to provide physiological outcome data as well as information regarding the donation procedure for each participant. Physiological data will be collected before and after donation, as well as at 12-months following donation, as per national donor follow-up protocol. NHSBT data will be collected retrospectively once a participant completes the 12-month questionnaire, or earlier should they choose to withdraw from the study. Consent to

obtain NHSBT data will be obtained through the initial study participation consent form. Subsequent to this a formal request for data access from the NHSBT will be made.

RQ3 Economic outcomes of unspecified kidney donation

The economic effects of living kidney donation will be determined by examining the impact of donation on healthcare and societal costs for specified and unspecified donors, using the Client Service Receipt Inventory (CSRI) questionnaire[8]. The CSRI has been widely used and will be adapted and customised to reflect the healthcare services used in kidney donation. It will be administered in self-reported questionnaires to donors and will aim to determine the type and frequency of specific health services accessed.

Eligibility Criteria

Participants eligible for RQ1 recruitment include any transplant professional that has had contact with unspecified donors.

Participants eligible for RQ2 recruitment include any individual that makes contact with a transplant centre to enquire about unspecified donation and proceeds beyond the initial telephone conversation, as well as being able to give informed consent. Non-English speakers will be included and adequate translation facilities will be provided.

Individuals who have already begun the donation work-up process at the time of study commencement will also be eligible for recruitment provided they are more than 2 weeks away from donation. Control participants will be recruited from those individuals known to a transplant centre for the purposes of donating a kidney to a known individual (specified donors) using the same inclusion criteria.

Enrolment (Figure 4)

Recruitment to the questionnaire for Professionals study (RQ1) will be through professional networks. Local collaborators at specific centres will be established to assist with recruitment for the focus groups and interviews.

For the participant study (RQ2) all 23 centres across the United Kingdom will be set up as participant identification centres (PIC) sites. Any individual who makes contact with a living donor coordinator to enquire about donation will be informed about the study and recruitment options. If they are happy to receive information and provide verbal consent, the coordinator will either pass their contact details to the research team at Guy's Hospital or will provide the individual with the study co-ordinator's details. Once contact has been made the research team from Guy's Hospital will provide further information to the individual and be responsible for the recruitment and consent of participants.

Sample size calculation

Based on previous retrospective work[6], it is expected that a recruitment rate of 80% will be achieved. The study will aim to recruit 624 participants, of which 224 will go on to donate as unspecified donors. This recruitment rate is higher than is typical for longitudinal studies but justifiable given the population being studied. A sample size of 624 will provide sufficient precision to estimate the 95% confidence interval for proceeding to donation to within ±4% overall, and to within ±18% for each centre. In summary, the study aims to recruit 224 participants who have undergone unspecified donation (Test group 1) and 400 who did not donate (Test group 2).

The control group will recruit 200 individuals who are donating to friend or relative (specified donors - control group 1) and 200 individuals that intend to donate to a friend or relative but do not proceed (specified non-donors - control group 2). Based on our retrospective study we expect a recruitment rate of 80%. Therefore we will need to approach 500 specified donors. Given a stable rate of approximately 1000 specified donations per year across the UK, we anticipate that we will be able to recruit the control group using the same three-year recruitment window as the main cohort. If there is no difference between the unspecified altruistic and specified donors on the physical and psychological variables at 12 months, it will be possible to determine that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of a standardised mean difference of 0.3, which is deemed to be the smallest acceptable clinically meaningful difference – this allows for 20% missing data due to drop-out, at a significance level of 5% with 90%

power[18]. These individuals will be recruited through transplant co-ordinators nationally.

Study Set up

The research programme will be carried out at a national level, with sponsorship and monitoring provided by the Guy's Hospital Research and Development department. It has received funding from the National Institute of Health Research under HS&DR Project number 13/54/54.

Guy and St Thomas' NHS Foundation Trust is the lead site and are collaborating with Plymouth University, The University of Birmingham and King's College London. Twenty-three centres across the United Kingdom have been established as Patient Identification centres with all research activity being conducted centrally at Guy's Hospital.

Analysis plan

Qualitative Data Analysis

Data generated via the focus groups and staff interviews will be analysed using the Framework Approach. The framework approach was developed by the National Centre for Social Research[19]. It is a deductive form of analysis that is increasingly being used in healthcare research where the aim is to develop practical applications and target policy development. It starts deductively from the aims and objectives identified in the study. However, this approach is grounded and inductive, in that it is heavily based in participants' original accounts and the observations of those studied. Framework analysis largely conforms to the thematic analysis approach aiming to describe patterns in the data and provide a description of the data with an emphasis on making the process of identification clear and delineated[20]. The process of framework analysis enables interaction with the data set until a meaningful account is revealed with a conceptual framework, thus allowing the development to an explanatory account. Data will analysed in adherence with the five stages of data analysis using the framework approach as presented in Ritchie and Lewis (2003) and aided by the computer software program NVIVO (version.11).

Cohort Study Analysis

In addressing RQ1 concerning variables relating to an individual proceeding to donate, descriptive analysis will be used to describe the proportion of people who withdraw or proceed to donation, and the reasons for failing to proceed. Survival analysis will be used to identify predictors of proceeding to donation. The analysis will include all individuals enquiring about donation, with the dependent variable an indicator for each proceeding to donation. Centre-level structural and attitudinal factors identified in the study group's previous work[8] will be included in the models to determine whether these variables explain variation in donation rates. Individual level demographic variables at baseline (e.g. age, sex, education, and ethnicity) and time dependent psychological factors will be included to determine their association with outcome.

To address RQ 2 relating to outcomes after donation, descriptive analysis will be used to compare baseline variables for individuals in each of the specified donor (test) and unspecified donor (control) groups. Linear or logistic mixed-effects models will be used to estimate between group differences in outcome variables at the 3 and 12 months post-donation follow-up assessments. A three-level model will be specified with observations at each time-point (level 1) nested within individuals (level 2), who themselves are nested within centres (level 3). Group membership and follow-up assessment (time) will be included in the models as dummy variables. Interaction terms for group and time will allow for assessments of differences at individual time points. Models will adjust for potential individual level demographic confounders measured at baseline (e.g. age, sex, education, and ethnicity) and the baseline level of the outcome variable. Missing outcome data is under the assumption that data is missing at random. Sensitivity analysis will be performed to assess this assumption.

Economic Outcomes Analysis

The economic benefits of unspecified donation will be examined using decision analytical methods. Decision analytic models use mathematical relationships to define a series of possible consequences that flow from a set of alternative options being evaluated. Here the decision is to accept or not accept unspecified donation. If unspecified donation is accepted and an individual is assessed then there are a series

of events that can occur. These include refusal to proceed, being deemed unsuitable, successfully donating, and a recipient benefiting.

There are costs associated with these and the outcomes will be measured in terms of quality-adjusted life years (QALYs) for donors using the SF-12, and for recipients with QALYs derived from previous literature.

Data for the model will draw on a systematic literature review of published economic evaluations of kidney donation, as well as from the costing exercise described above and expert opinion. The model will take a lifetime horizon (with appropriate discounting) and will allow us to estimate the expected costs and QALY gain following the start of the process of unspecified donation. Given uncertainty around the model parameters, we will conduct a series of sensitivity analyses (deterministic and probabilistic) to assess its robustness. Key parameters to vary may include rejection and refusal rates and values placed on future QALY gains. The model will estimate costs and benefits for the donors. It will also estimate QALY gains for recipients and if possible we will incorporate future costs for recipients as well.

Discussion

The number of individuals considering living kidney donation to someone they have not previously met is becoming more common and has a significant potential to reduce the UK waiting list for kidney transplantation. Despite this trend, the concept of unspecified kidney donation (UKD) remains uncomfortable for some clinicians. Furthermore, the assessment and donation process may have scope for improvement from the donor's perspective. This study will provide a comprehensive assessment of the unspecified donor programme in the UK in order to determine the extent and reasons for variation in practice, ascertain barriers to donation, as well as the economic implications of unspecified donation. The study will also assess clinical outcomes after unspecified donation in order to facilitate evidence-based decision making regarding future unspecified donors, as well as inform the creation of national guidelines.

Acknowledgements

This study is funded by the National Institute of Health Research under Health Services & Delivery Research Programme project number: 13/54/54.

Authors would also like to acknowledge Jan Shorrock and Paul van den Bosch for their expert advice and support. The study team would also like to acknowledge the support of NHS Blood and Transplantation, The British Transplantation Society and all 23 transplant centres across the United Kingdom.

This research was supported in part by the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) based at Guy's and St. Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Footnotes:

Contributors: NM and HM conceived the idea for the project with input from AM and AC regarding the qualitative work and PMcC leading on the economic aspect of the project. RG, PG, HM, LB, AC, LW, SN, JC, PGibbs, AM, PMcC, HD and NM collaboratively contributed to the design of the study and its protocols. RG and PG led the writing of the manuscript. RG, PG, HM, LB, AC, LW, SN, JC, PGibbs, AM, PMcC, HD and NM have reviewed and revised the manuscript critically for important intellectual content.
RG, PG and NM take responsibility of the paper as a whole.

Funding: This project was funded by the National Institute for Health Research [Health Service and Delivery Research programme] (project number 13/54/54).

Competing Interests: None declared

Data sharing statement: We shall make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs

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Figures:

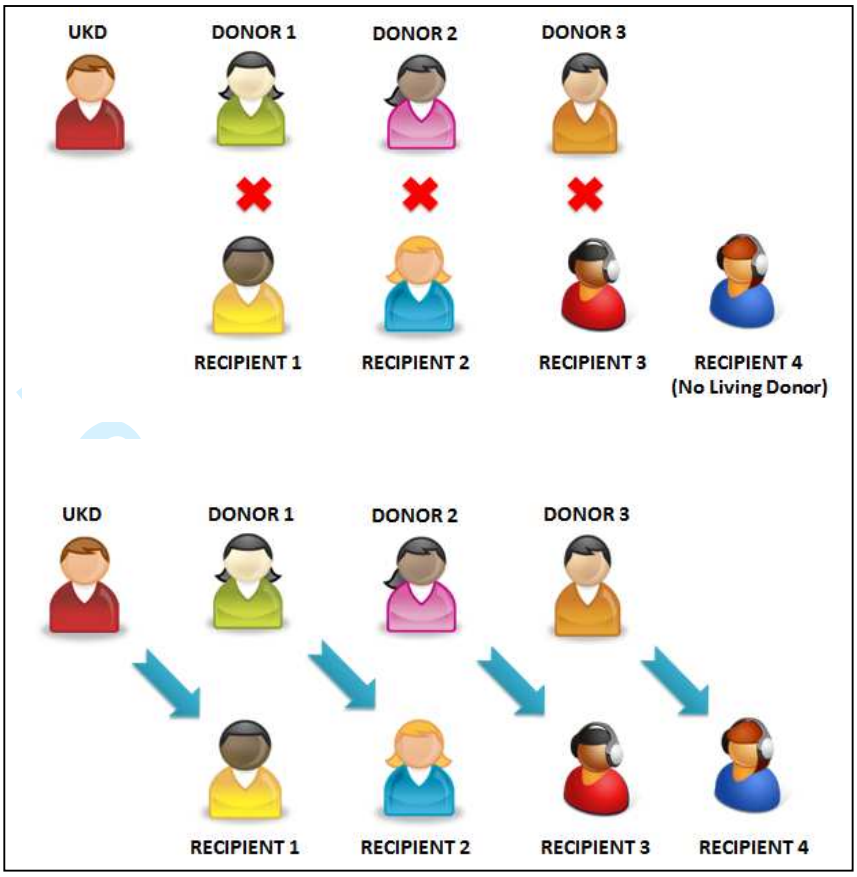

Figure 1: Illustration of an altuistic donor chain, primed by an unspecified donor

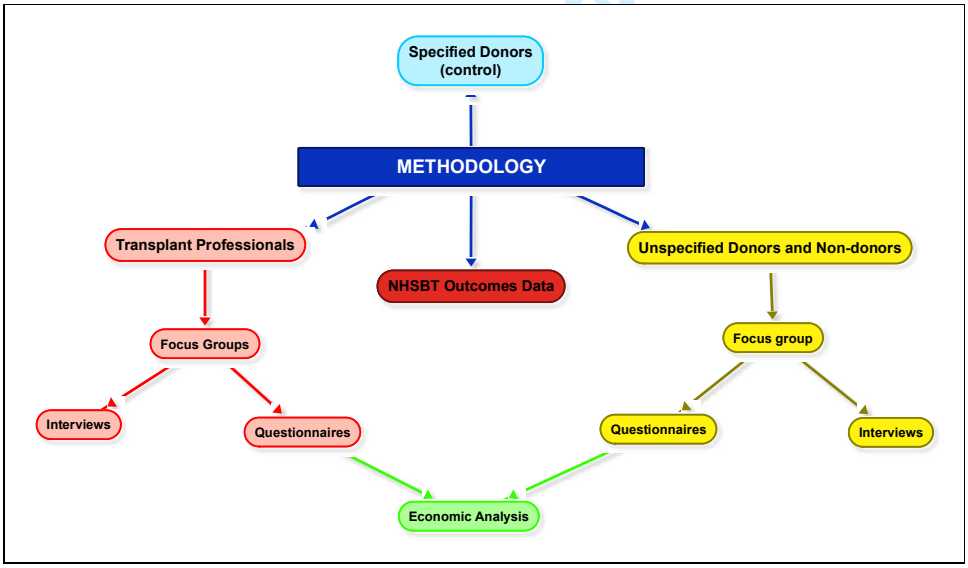

Figure 2: BOUnD Study methodology

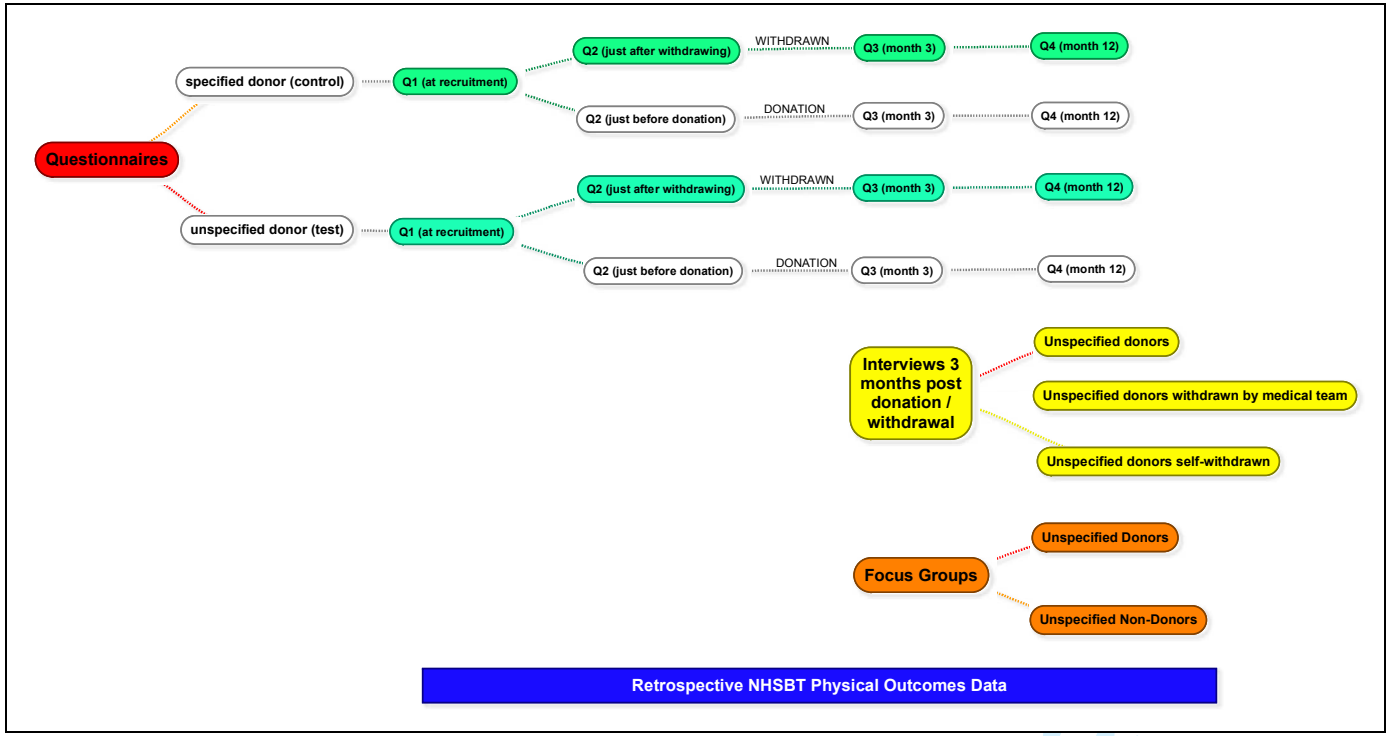

Figure 3: Research Question 2: Participant flow chart

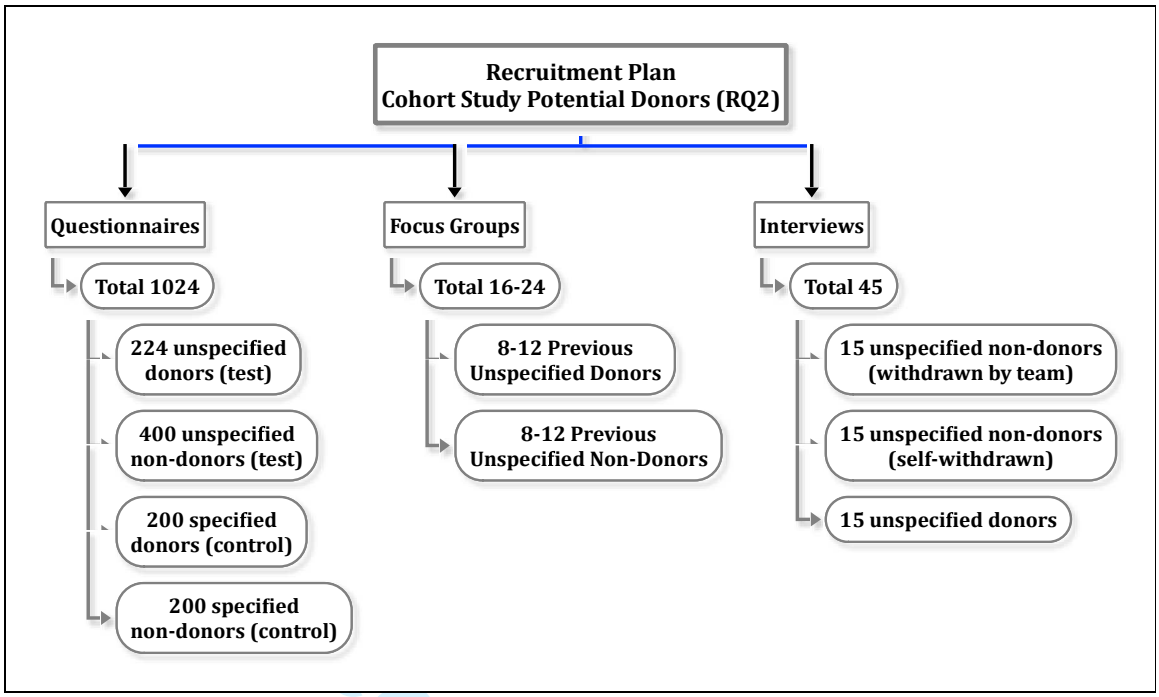

Figure 4: Study recruitment population

Unspecified living kidney donation in the UK: barriers to implementation and delivery
- Healthcare Professionals' Perspective -

1. Background

Over one third of all kidney transplants taking place in the UK today are from living donors. A growing subset of living donors are individuals who choose to donate a kidney to someone that they have not previously met; so called 'unspecified' or 'non-directed altruistic' donors. Over 200 unspecified donations have taken place in the UK to date since this was introduced in 2006 and this type of living donation is becoming more routine, currently accounting for approximately 7% of living donations (1).

Despite this increase, the concept of unspecified kidney donation (UKD) remains uncomfortable for some clinicians, principally due to concerns about the motivations, characteristics and outcomes of these donors. In a recent study of clinicians' views', 78% of French physicians were opposed to the practice of unspecified donation (2). In our previous qualitative work, we have found some evidence that this makes donation more difficult or stressful for some potential donors (3-5). Furthermore, we recently performed a large study of a national cohort of all 148 UKDs in the UK over the first five years of the programme, and compared them with a regional sample of 148 specified kidney donors (SKDs - those who donate to someone with whom they have an emotional relationship) (6). This study did not find an excess of poor psychosocial or physical outcomes in UKDs; however the response rate was 74%, with variable retrospective follow-up, and therefore it is impossible to be certain that donors with significant pathology were not missed- indeed, these are the very donors (for example, with depression) that might be expected to fail to respond. The study did highlight broad regional variations in the numbers of UKDs performed and has highlighted differences in the assessment process, which may explain the differences seen across the country. Indeed, 45% of all unspecified donations were performed in 3 centres. There is some evidence from other studies that attitudes from transplant professionals may be a barrier to donation (7-9). Both living donor nurses and psychiatric assessors involved in UKD have expressed concerns about the lack of practice guidance in this area; lack of clear guidance could be a further barrier to donation (4,5).
Through our qualitative work we have also found that barriers to donation may exist within families where there is tension over the decision to donate altruistically and there may be a role for transplant services to support families in this situation (3). We have recently been awarded a grant from the British Renal Society and

British Kidney Patients Association to explore this. This work is due to commence prior to this study and will inform this research.

The UKD participants in our PPI sessions and previous our qualitative study identified a number of issues in the process that they felt acted as deterrents and may have affected the decision by others to donate (3). They found difficulties in knowing how to make initial contact with the transplant centre. The negative attitudes of transplant professionals were also off-putting and this continued whilst donors were in hospital, with some experiencing ignorance and hostility from ward staff, which made them feel guilty for "choosing to become a patient". The length of the workup process was also commonly an issue, which donors found frustrating. Indeed, when considering living donor chains, most donors would have liked to have participated had it been easier and the timing more predictable. Many were working or had other commitments and the unpredictability of when the donation would take place meant that many were not in a position to oblige. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also a difficult experience for donors who felt that they had to prove their sanity (3).

Unspecified kidney donation is apparently more costly than specified donation, as it is resource intensive, with a large number of enquiries and assessments, and a low proportion that proceed to donate. In Portsmouth (the largest centre for unspecified donation), for example, of 149 referrals, 27 have donated and a further 27 are in work-up, giving a drop-put rate of at least 64%. Nevertheless, a kidney from a UKD may be a particularly valuable resource, since it can be used to provide a high quality, long lasting transplant to those who are otherwise difficult to transplant. The National Kidney Sharing Scheme, for example, involves kidney exchanges between pairs of donor and recipients who cannot otherwise proceed due to immunological incompatibility. A kidney from a UKD can be used to convert these exchanges into a 'chain' primed by the UKD; the UKD donates to recipient A, and her donor dates to recipient B, and so on (Appendix 2). In the US this has resulted in 30 transplants occurring from a single UKD (10). In the UK, 47% of UKDs have been used to prime short chains of two transplants, and the UK Living Donor Strategy aims for 75% to be used for chains, with 3 transplants in each chain, by 2020 (11). Thus, assuming UKDs rise to 200 per year, they would result in 450 transplants annually, which is almost half the current annual living donor transplantation rate. Despite this, no economic analysis of unspecified donation has been performed. This is particularly important since, if it is shown to have a significant economic benefit, extra resources could be allocated by NHS Blood and Transplant, as happened with SKDs over the last decade.

We therefore wish to perform an assessment of healthcare professionals' perspectives on the unspecified donor programme in the UK, in order to determine the extent and reasons for variation in practice and ascertain barriers to donation.

2. Aims

The study will specifically explore healthcare professionals' practice and attitudes to unspecified living kidney donation in transplant centres in the UK.

Research Question:

"Is there variation in transplant professionals' practice and attitudes, which is preventing some unspecified living kidney donations?"

3. Methods

The study will include three arms:

i) Focus groups

ii) Qualitative interviews and

iii) A questionnaire study of transplant professionals (surgeons, physicians, co-ordinators and others involved in transplantation in hospital) working with unspecified donors in the UK.

This is a mixed methods study, drawing on both qualitative and quantitative methods:

i) Qualitative information will be obtained by focus groups and individual interviews with transplant professionals in four centres. Sampling is purposive and centres will be chosen according to their numbers of completed donations, allowing us to sample from two centres which have amongst the highest rates of completed donations (Guys and St Thomas and Plymouth) and two centres whose rates are amongst the lowest (Birmingham and Leeds). These focus groups will contain key staff involved in the unspecified donation process (living donor nurses, psychological assessor, surgeons and nephrologists. These groups will be used to inform the approach in subsequent individual interviews with professionals from each discipline (surgeons, physicians, psychological assessors and donor coordinators). The interviews will involve centres chosen according to their number of completed donations. We will interview professionals at three sites which have the highest rates of completed donation (Guys and St Thomas, Plymouth and Manchester) and three centres with lower rates (Birmingham, Leeds and Bristol Southmead). It is anticipated that 60 transplant professionals in total will be interviewed.

ii) Quantitative study: Questionnaires will be sent to all transplant professionals working with unspecified donors across the UK, which will ascertain attitudes

towards unspecified kidney donation and current working practices. Both the focus groups described above and the patient representatives will inform the development of a questionnaire that explores working practices, knowledge of donation and staff attitudes incorporating salient points of interest from the data. This will be supplemented by an existing questionnaire (such as the Organ Donation Attitude [12]), which has been used previously in research to explore the impact of staff attitudes in organ donation.

Participants will be given an information sheet, adequate time to consider the study, and will be asked to give written consent.

If any evidence of distress is elicited in of the different parts of the study, access to a counselor will be offered, an approach we have adopted in a previous study (REC 09-H0804-31). We will ensure that data storage is annonymised and held in a secure fashion, according to Trust SOPs. Trial data will be archived at the end of the study, by our Clinical Trials Office. A trial manager will manage the trial, with help from a research fellow.

The data will be collected by collaborators from the Department of Psychology at Plymouth University. Focus group and individual interviews will be performed at sites most convenient for the healthcare professionals recruited. These may include NHS premises, individuals' homes, or other meeting venues (e.g. professional congresses).

The questionnaire data will be collected by postal or electronic means.

Analysis

Data generated via the focus groups and staff interviews will be analysed via the Framework Approach. The framework approach was developed by the National Centre for Social Research (13). It is a deductive form of analysis that is increasingly being used in healthcare research where the target is to develop practical applications and target policy development. It starts deductively from the aims and objectives identified in the study. However, this approach is grounded and inductive, in that it is heavily based in participants' original accounts and the observations of those studied.

Criteria for acceptance for UKD will be assessed across units in the UK, and requirements for work- up (such as psychiatric assessment) will be compared, in order to determine whether there are significant variations in practice. We will explore this in relation to the number of unspecified donation enquiries and completed donations.

Data from the questionnaire will be analysed using standard statistical tests to compare variations according to demographic factors, individual characteristics and centre effects.

4. Study Steering Committee

There will not be a Data Monitoring Committee, but there will be a Study Steering Committee (SSC), which will have the following responsibilities:
i) To provide advice, through its Chair, to the Chief Investigator, the Project Sponsor, the Project Funder, the Host Institution and the Contractor on all appropriate aspects of the project
ii) To concentrate on progress of the project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question
iii) The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society
iv) To ensure appropriate ethical and other approvals are obtained in line with the project plan
v) To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
vi) To provide advice to the investigators on all aspects of the project

The SSC will be constituted as follows: An independent chairperson, an independent statistician, one member (not directly involved with the study) from within the Trust, one member external to the Trust, and two service users. An observer from the sponsor and from the CLRN will be invited to attend.

The SSC will meet at 4 to 6 monthly intervals, or more frequently if the Chairperson deems this to be necessary.
There will be a Trial Steering Committee which will manage the project on a regular basis, and which will consist of the members of the project team. This will meet at 3 to 6 month intervals.

5. Data storage

A database will be constructed by the Guys and St Thomas Biomedical Research Centre. Online or paper questionnaires and interview transcripts will be transferred to the database, held on a secure server at either Guys Hospital or Plymouth University, in an anonymised fashion, with password protected access, limited to the study team. Back up will be performed automatically by the Trust systems, and data archiving will be undertaken by the Kings Health Partners Joint Clinical Trials Office, according to their standard operating procedures.

6. Outputs

The data collected will be used together with data from a concomitant NIHR study[1] to achieve several specific outputs, in addition to published manuscripts and conference presentations:

a) A report to NHSBT and the BTS, summarising the findings of the study
b) National guidelines, produced in conjunction with NHSBT and the BTS
c) A protocol for management of those presenting for unspecified donation
d) A report to the Renal Transplant Clinical Reference Group, which reports to NHS England (which commissions transplant services in England), and to the Scottish, Welsh and Northern Irish Departments of Health.

The process for developing these outputs (beyond the first, which will be written by the study team) is as follows:

National Guidelines

The transplant community is small, and there is a widespread desire for guidance on unspecified donation. Existing guidelines on living donation are extensively used by donor teams, and these have been important in changing culture. We recognize that guidelines are not, however, necessarily effective by themselves at changing practice- in this regard, the close liaison that one team member (LB) has with donor coordinators at all transplant centres, and the living donor forum which she organizes, will be vital.
The support of the BTS Clinical Trials Committee for this study is indicative of the close involvement and support of the BTS. There is an existing process for developing guidelines by the BTS, through the BTS Standards Committee. We will convene a small group, including NHSBT and BTS representatives, as well as service users, to draft a guideline, which can be sent to the BTS Standards Committee for consideration. Typically, this is opened for public consultation via the BTS website for a short period, revised and then disseminated to all units.

Commissioners' report

The Chief Investigator is a member of the Renal Transplant Clinical Reference Group (CRG) and has bee involved in drafting Service Specifications for transplantation. He will send a report, which will be drafted with the help of the study team, including service users, to the CRG for discussion and dissemination to NHSE and counterparts in other constituent countries.

[1] Unspecified living kidney donation in the UK: barriers to implementation and delivery - *Potential Donors Study*

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Guy's and St Thomas' NHS
NHS Foundation Trust

PROTOCOL TITLE:

Understanding barriers and outcomes of unspecified (altruistic) kidney donation (BOUnD); a multicentre prospective cohort study

BOUnD

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Study Synopsis

Title	**Understanding barriers and outcomes of unspecified (altruistic) kidney donation (BOUnD); a multicentre prospective cohort study.**
Protocol Short Title/Acronym	BOUnD (Barriers and Outcomes in Unspecified kidney Donation)
Protocol Version number and Date	RQ2 Protocol v2.1, 25/05/2016
Is the study a Pilot?	No
Study Hypothesis	(i) Regional differences in unspecified (altruistic) kidney donor rates will be explained by prospective donor experience e.g. depending on donor interaction with staff members, local expertise and resources. (ii) There is no detrimental impact of unspecified donation on mental and physical health.
Study Duration	December 2015 – April 2018
Methodology	Prospective, mixed-method cohort study recruiting unspecified potential donors (and a directed donor control group). Participants will be recruited to a prospective donor phase shortly after first enquiring about donation (hypothesis i). Those that proceed to donation will continue to a second phase focusing on outcomes over 1 year (hypothesis ii). Nested qualitative studies will explore experiences of the process in donors and non-donors using structured interviews. Focus groups will be used to guide questionnaire design and interview topic guide.
Sponsor name	Guy's and St.Thomas' NHS Foundation Trust R&D Office
Chief Investigator	Prof Nizam Mamode
REC number	15/SC/0637
Medical condition or disease under investigation	Unspecified (altruistic) living kidney donation
Purpose of study	To identify methods of improving the process of unspecified (altruistic) donation in the UK and inform the development of national guidelines
Primary objective	Physical and mental-health related quality of life, anxiety, depression, life satisfaction and self-esteem
Secondary objective (s)	1. Barriers to unspecified kidney donation 2. Economic outcomes of unspecified kidney donation
Number of Subjects/Patients	(i) 16 - 24 participants (focus groups); (ii) 1024 participants (questionnaires), as follows: Test group: 224 unspecified donors that proceed to donate and 400 unspecified donors that withdraw. Control group: 200 directed / specified donor controls that proceed to donate and 200 directed / specified potential donors who did not proceed; (iii) 45 participants (interviews),
Study Design	Prospective cohort study
Endpoints	(i) time from enquiry to donation (for those that proceed to donation) (ii) mental and physical health at 3 and 12 months post donation / withdrawal, compared to directed donor controls
Inclusion Criteria	Individuals contacting a UK transplant centre wishing to become specified or unspecified kidney donors or those that have already begun the work-up process
Exclusion Criteria	Foreign nationals that are unable to donate altruistically in their countries of residence or prisoners
Statistical Methodology and Analysis	Quantitative analysis: (i) Time-to-event analysis using Cox regression; (ii) propensity score weighted mean differences at 12 months using

	linear mixed effects models Qualitative analysis: Framework (thematic) approach

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Introduction

Over one third of all kidney transplants taking place in the UK today are from living donors. A growing subset of living donors are individuals who choose to donate a kidney to someone that they have not previously met; so called 'unspecified' or 'non-directed altruistic' donors. Over 200 unspecified donations have taken place in the UK to date since this was introduced in 2006 and this type of living donation is becoming more routine, currently accounting for approximately 7% of living donations (1).

Despite this increase, the concept of unspecified kidney donation (UKD) remains uncomfortable for some clinicians, principally due to concerns about the motivations, characteristics and outcomes of these donors. In a recent study of clinicians' views', 78% of French physicians were opposed to the practice of unspecified donation (2). In our previous qualitative work, we have found some evidence that this makes donation more difficult or stressful for some potential donors (3-5). Furthermore, we recently performed a large study of a national cohort of all 148 UKDs in the UK over the first five years of the programme, and compared them with a regional sample of 148 specified kidney donors (SKDs - those who donate to someone with whom they have an emotional relationship) (6). This study did not find an excess of poor psychosocial or physical outcomes in UKDs; however the response rate was 74%, with variable retrospective follow-up, and therefore it is impossible to be certain that donors with significant pathology were not missed- indeed, these are the very donors (for example, with depression) that might be expected to fail to respond. The study did highlight broad regional variations in the numbers of UKDs performed and has highlighted differences in the assessment process, which may explain the differences seen across the country. Indeed, 45% of all unspecified donations were performed in 3 centres. There is some evidence from other studies that attitudes from transplant professionals may be a barrier to donation (7-9). Both living donor nurses and psychiatric assessors involved in UKD have expressed concerns about the lack of practice guidance in this area, lack of clear guidance could be a further barrier to donation (4,5).
Through our qualitative work we have also found that barriers to donation may exist within families where there is tension over the decision to donate altruistically and there may be a role for transplant services to support families in this situation (3). We have recently been awarded a grant from the British Renal Society and British Kidney Patients Association to explore this. This work is due to commence prior to this study and will inform this research.

The UKD participants in our PPI sessions and previous qualitative study identified a number of issues in the process that they felt acted as deterrents and may have affected the decision by others to donate (3). They found difficulties in knowing how to make initial contact with the transplant centre. The negative attitudes of transplant professionals were also off-putting and this continued whilst donors were in hospital, with some experiencing ignorance and hostility from ward staff which made them feel guilty for "choosing to become a patient". The length of the workup process was also commonly an issue, which donors found frustrating. Indeed, when considering living donor chains, most donors would have liked to have participated had it been easier and the timing more predictable. Many were working or had other commitments and the unpredictability of when the donation would take place meant that many were not in a position to oblige. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also a difficult experience for donors who felt that they had to prove their sanity (3).

Unspecified kidney donation is apparently more costly than specified donation, as it is resource intensive, with a large number of enquiries and assessments, and a low proportion who proceed to donate. In Portsmouth (the largest centre for unspecified donation), for example, of 149 referrals, 27 have donated and a further 27 are in work-up, giving a drop-put rate of at least 64%. Nevertheless, a kidney from a UKD may be a particularly valuable resource, since it can be used to provide a high quality, long lasting transplant to those who are otherwise difficult to transplant. The National Kidney Sharing Scheme, for example, involves kidney exchanges between pairs of donor and recipients who cannot otherwise proceed due to immunological incompatibility. A kidney from a UKD can be used to convert these exchanges into a 'chain' primed by the UKD; the UKD donates to recipient A, and her donor dates to recipient B, and so on

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We therefore wish to perform a comprehensive assessment of the unspecified donor programme in the UK, in order to determine the extent and reasons for variation in practice, ascertain barriers to donation, and determine the economic costs and benefits of an unspecified donation. We will also assess outcomes after unspecified donation, in order to provide detailed evidence for transplant teams' decisions about potential donors.

2 Study Objectives and Design

2.1. Study Objectives

Aims: This study aims to perform a comprehensive assessment of unspecified altruistic donor programme in the UK to explore variation between centres and identify barriers and facilitators to donation for those that have expressed a willingness to do so.

Objectives:
(i) Identify and explain regional variations in unspecified kidney donation (UKD), based on donor interaction with staff members, local expertise and resources, and other economic variables
(ii) Establish prospectively the psychosocial, physical and economic outcomes of individuals undertaking unspecified kidney donation, compared to specified donors.

Outcomes

Primary outcomes: Physical and mental health-related quality of life.
Psychosocial health outcomes:

- quality of life (SF-12)
- anxiety (General Anxiety Disorder-7 (GAD-7)
- depressive symptoms (Patient Health Questionnaire-9 (PHQ-9)
- life satisfaction (Satisfaction With Life Scale)
- self-esteem (Rosenberg Self-Esteem Scale)
- Decision Regret Scale
- Flourishing Scale
- in house questionnaire

Physical health outcomes
NHSBT pre and post donation physiological and clinical outcomes

Secondary outcomes:
- Barriers to donation (qualitative data from interviews and focus groups)
- Healthcare resource utilisation data (Client Service Receipt Inventory (CSRI))

2.2 Recruitment Strategy

The primary study group will comprise all those who approach a transplant team in any UK transplant centre, offering to donate a kidney to a stranger over a three year period (2015 – 2018). Follow-up will take place up to 2020.
The control study group will comprise all those who approach a transplant team across the UK offering to donate a kidney to a family member or friend ("specified donors").
The study will use the same national professional transplantation network to collaborate with transplant co-ordinators and living donor nurses willing to participate in the recruitment process. Participant recruitment will take place subsequent to local R&D approval and transplant centres being identified and approved as participant identification centres (PIC).

UK Transplant co-ordinators will be briefed regarding the aims, objectives and recruitment criteria of the study. Communication and liaison with local transplant co-ordinators will be through Ms Lisa Burnapp (Lead Nurse - Living Donation, Organ Donation and Transplantation, NHSBT), who is a collaborator in the study.

Focus Groups Recruitment.

The Focus Groups represent the smallest aspect of the study and serve to help fine-tune the questionnaire design and interview topic guides. As such, only two focus groups will take place in centres such as Guy's Hospital (London) or Plymouth Derriford Hospital, where the study team has long-standing collaboration links with the donation teams. The local transplant co-ordinator or living donation nurse specialist (living donation team) will approach individuals that have recently donated or have withdrawn from donation and explore whether they would be interested in considering the study. Those that would be interested will be given the contact details of our research team or asked if they would agree to be contacted by us. The research team would then be able to provide further information and lead the consent and recruitment process.

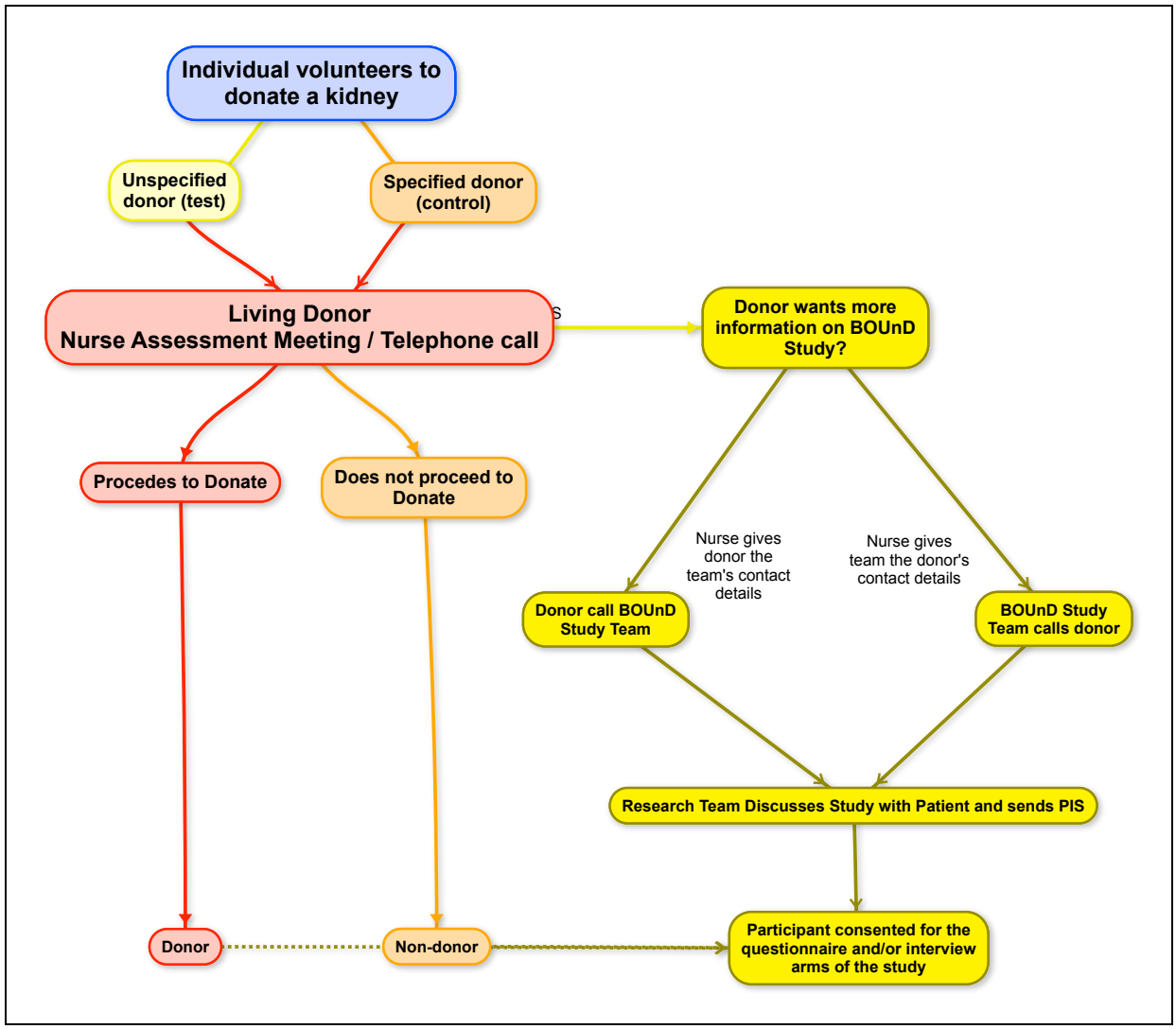
Interview and Questionnaire Recruitment

Transplant co-ordinators at each of the 23 UK transplant centres will ask potential donors approaching their units if they would be interested in participating in the study. This does not equate to being consented into the study, but simply facilitates further information gathering regarding our work. This will occur either at the initial telephone contact between the potential donor and the transplant centre or at the first clinic consultation with the transplant co-ordinator, depending on local practice protocols. Potential donors already being worked-up will also be given the opportunity to contact the study team for recruitment into the study.

Once a potential donor agrees to find out more about the study, the local transplant co-ordinator will facilitate contact with the research team by either giving the team's contact details to the potential donor, or (with the donor's permission) pass on their preferred contact details to the research team. The study's manager will be notified of individuals interested in the study. The research team will contact potential participants by phone, email or post to provide further information, discuss the study and provide participant information sheets. Those that indicate a willingness to participate will be enrolled in the study subsequent to completion of the relevant consent forms. The emphasis of the study is to cause minimal inconvenience to local transplant units and human resources. As such, once a transplant co-ordinator has facilitated the contact between the potential donor and the study team, no further involvement will be needed and all subsequent administrative and research work will be co-ordinated by the study's manager or investigators.

The control group will consist of individuals who are donating to friend or relative (specified donors). Control (specified) donors will be recruited in a similar consecutive manner by transplant co-ordinators. Control donors

that do not procede to specified donation will still be asked to participate in the study in order to provide robust data for comparison.



2.3 Study Design

Focus Groups

Two focus groups with potential donors will be undertaken. One focus group will involve those that have proceeded to donation. The other will involve potential donors that have withdrawn or been withdrawn from the donation process. 8-12 participants will take part in each focus group. The focus groups will not involve control participants. The physical location of the focus groups will be a suitable hospital venue, such as a conference room or a postgraduate centre. Recruitment will be undertaken as described above. The focus group discussion will be audio-recorded and transcribed for future analysis.

Data regarding socio-demographic (including the area postcode), physical, psychological characteristics, and resource use variables will be collected at baseline (shortly after contacting the transplant centre).

Questionnaires

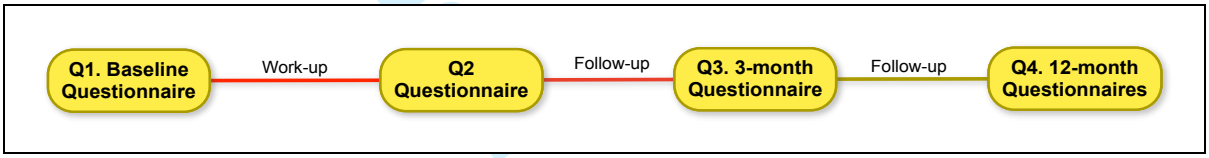
The questionnaire part of the study will have four research populations on which questionnaire data will be collected at four intervention points (Q1-Q4): baseline, preoperatively and at 3 and 12 months post-donation in the form of a study questionnaire bundle. Additional data (such as gender, age or ethnic group) will be collected at the time of recruitment into the study.

Q1. Baseline data will be collected within the first week of recruitment to assess the participant prior to the work-up process.

Q2. Pre-operative data will be collected in the 2 weeks preceding donation surgery (+/- 3 days). This will not be collected on the day of surgery in order to avoid confounding errors. This will mark the end of the work-up period. For those that withdraw from the study a longer period of time may be needed to capture these participants. In this case, the Q2 intervention point will span from the time of withdrawal to 3 weeks post withdrawal.

Q3. 3 months post donation or withdrawal

Q4. 12 months post donation or withdrawal



The four study populations will include:

1. Those that **proceed to donation** ('unspecified donors') – Test 1 population

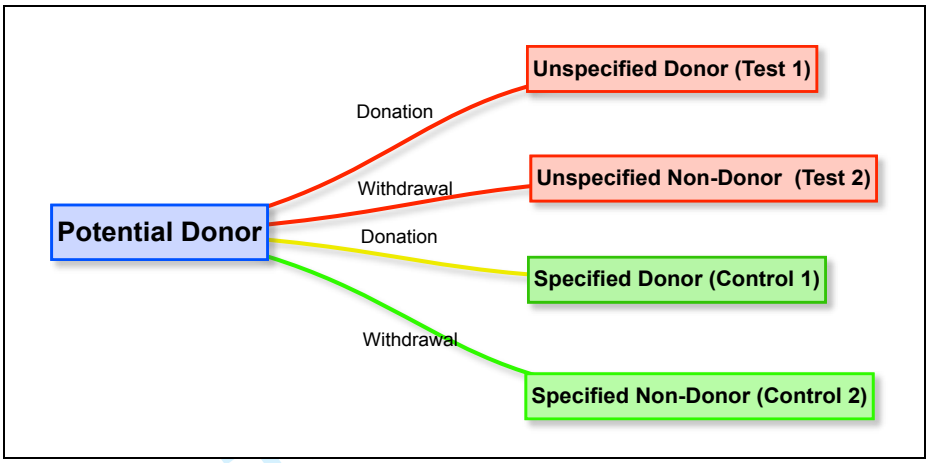
2. Those that **do not to donate** ('unspecified non-donors') due to donor's choice or withdrawal by the clinical assessors – Test 2 population

3. Those that undergo **living donation to a known individual** ('specified donors'), which will act as **control group 1**

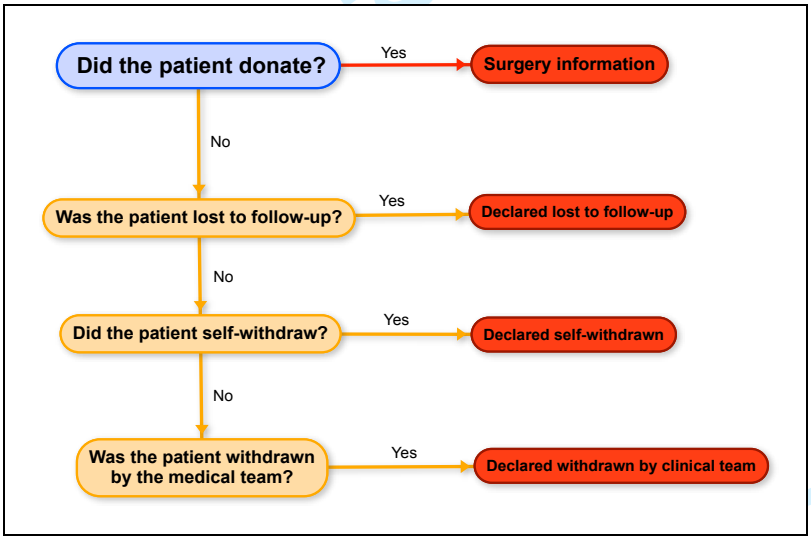
4. Those **intending to donate to a known individual that do not donate** ('specified non-donors'), which will act as control group 2

To ensure feasibility of the study questionnaire burden will be tested and considered in conjunction with the PPI group.

Questionnaire validation will be carried out by asking 20-30 volunteers that are previous kidney donors or future specified donors to review the in-house questionnaires. This will involve a facilitated think-aloud exercise to identify any face validity issues related to the newly developed questions. This exercise will result only in minor changes to the question structure, phrasing or answering methods. The questionnaire content validity will have already been validated by 15 members of the research team who will review the developed questionnaires on at least three occasions.



Participants who do not proceed to donation will be identified either by regularly checking with their local transplant coordinators (every two weeks) or by self-referral to the study team. The study researchers will then ascertain whether the patient self-withdrew or was withdrawn by the clinical team. The following data collection algorithm will be used:



Interviews

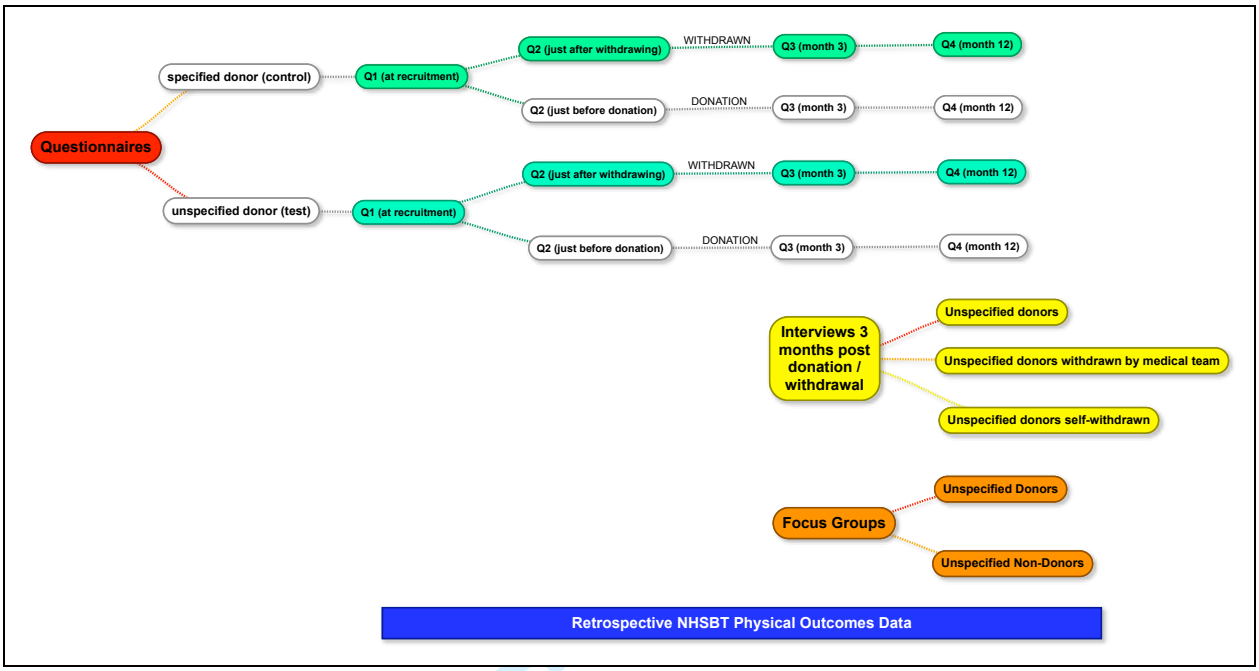
Qualitative interviews will also be completed with a sample of 15 donors who completed their donation, 15 who withdrew and 15 who were withdrawn by the transplant team from the process. Participants will be asked about their experience of the donation process and services, barriers and enablers to donation and outcomes from either donating or withdrawing from the process. The interview questions have been informed by our previous grounded qualitative work, focus groups and current research. Participants will be purposively sampled to ensure a range of demographics and experiences are captured.

Interviews will take place at 3 months following donation or withdrawal from the process.

Other Study Data

Linkage to the NHS Blood and Transplant records will provide physiological outcome data as well as information donation procedure for all donors. Physiological data will be collected pre- and post-donation, as well as at 12-months following donation, as per national donor follow-up protocol. This is described in Appendix 4. NHSBT data will be collected retrospectively once a participant completes the 12-month questionnaire, or earlier should they choose to withdraw from the study. Consent to obtain NHSBT data will be obtained through the initial study participation consent form. Subsequent to this a formal request for data access from the NHSBT will be made.

2.4 Study Outline



2.5 Trial Statistics and Data Analysis

The study endpoints will be:

i) time from enquiry to donation (for those that proceed to donation)

ii) mental and physical health at 3 and 12 months post donation, compared to directed donor controls

All primary analyses will be undertaken by the study statistician and investigator / research fellow in accordance with a predetermined analysis plan.

Descriptive analysis will be used to describe the proportion of people who withdraw or proceed to donation, and the reasons for failing to proceed. The analysis will include all individuals enquiring about donation, with the dependent variable an indicator for each proceeding to donation. Centre-level structural and attitudinal factors identified in our parallel study (IRAS 170483) will be included in the models to determine whether these variables explain variation in donation rates.

Descriptive analysis will be used to compare baseline variables for individuals that express an interest in donation that: i) the transplant team withdraw from donation; ii) those who decide not to proceed; iii) those that proceed to donation; and iv) the specified kidney donor control group, who either proceed or do not proceed to donate. Linear or logistic mixed-effects models will be used to estimate difference in outcome variables at the 3 and 12 months follow-up assessments between the groups at the outcome assessments. Group membership and follow-up assessment (time) will be included in the models as dummy variables. Interaction terms for group and time will allow for assessments of differences at individual time points. Models will adjust for potential demographic confounders measured at baseline (e.g. age, sex, education, ethnicity) and the baseline level of the outcome variable. Missing outcome data is under the assumption that data is missing at random. Sensitivity analysis will be performed to assess this assumption.

The analysis of qualitative data will be performed using the Framework (thematic) approach as described above.

3. Sample Size and Selection

Focus Groups

The two focus groups will recruit 8-12 potential or actual unspecified kidney donors each. These will be volunteers identified by UK transplant co-ordinators.

Questionnaires

Consecutive people contacting each of the transplant centres in the UK between April 2015 and Feb 2018 will be recruited to participate in the study. Based on current trends we conservatively estimate that there will be at least 279 kidney transplants from unspecified altruistic donors during that period. Indeed, there were 107 UKD in the UK in 2013. Assuming that the proportion of individuals contacting transplant centres who go on to donate remains stable (36%, based on data from Portsmouth in 2012), we expect that 780 people considering unspecified altruistic donation will contact transplant centres during that period. Based on our previous retrospective study, we expect at least a 80% recruitment rate- that is, 624 in total, of which 224 will go on to donate). This recruitment rate is higher than is typical for longitudinal studies but justifiable given the population being studied. A sample size of 624 will provide sufficient precision to estimate the 95% confidence interval for proceeding to donation to within ±4% overall, and to within ±18% for each centre. In summary we aim to recruit 224 who have undergone unspecified donation and 400 who failed to donate.

The control group will recruit 200 people who are donating to friend or relative (specified donors) and 200 individuals that intend to donate to a friend or relative but do not (specified non-donors). Based on our retrospective study we expect a recruitment rate of 80%. Therefore we will need to approach 500 specified donors. Given a stable rate of approximately 1000 specified donations per year across the UK, we anticipate that we will be able to recruit the control group using the same three-year recruitment window as the main cohort. If there is no difference between the unspecified altruistic and specified donors on the physical and psychological variables at 12 months, it will be possible to determine that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of a standardised mean difference of 0.3, which is deemed to be the smallest acceptable clinically meaningful difference – this allows for 20% missing data due to drop-out, at a significance level of 5% with 90% power (14). These individuals will be recruited through transplant co-ordinators nationally.

Interviews

Qualitative interviews will also be completed with a sample of 15 donors who completed their donation, 15 who withdrew and 15 who are withdrawn by the transplant team from the process. These individuals will be identified from the initial cohort of patients that approached transplant centres with the intention to donate altruistically.

Recruitment Targets

The following recruitment targets have been set:

Focus Groups: 2 focus groups of 8-12 previous donors and 8-12 non-donors.
Total: 16-24 participants

Questionnaires:
624 potential donors (test population)
224 who have donated
400 who did not donate

200 specified donors (control population 1) and 200 specified non-donors (control population 2)
Total: 1024 participants

Interviews:
15 potential donors that donated
15 potential donors that did not donate (self-withdrawn)
15 potential donors that did not donate (withdrawn by clinical team)
Total: 45 participants

Inclusion criteria

Any individual contacting a transplant centre to enquire about unspecified donation, who proceeds beyond the initial telephone conversation, and is able to give informed consent will be considered as a potential study participant. Non-English speakers will be included and adequate translation facilities will be provided. Individuals who have already begun the donation work-up process at the time of study commencement will also be eligible for recruitment provided they are more than 2 weeks away from donation. Control participants will be recruited from those individuals contacting a centre in order to donate to a known individual.

Exclusion criteria

Any individual who declines to participate at any stage will be excluded from the study. Individuals lacking capacity will also be excluded as will any individual not eligible to donate in UK. This includes foreign nationals who are unable to donate altruistically in their country of residence or prisoners.

4. Study procedures

4.1 Consent

The study research fellow or study manager will be notified of any eligible individuals by UK transplant co-ordinators. Potential participants will be invited to participate in the study by phone or post and will be provided with an information sheet prior to the consent process. Separate consent forms have been designed for each of the three study arms (focus groups, questionnaires and interviews). Where necessary these will be translated or explained by an interpreter. Individuals who agree to participate will be asked to complete a baseline assessment, in either paper or online format. Pre-operative assessments will be completed one week prior to donation.

The following study documents have been created (Appendix 5):

- PIS Unspecified Donors Focus Group
- PIS Unspecified Donors Questionnaire and Interview Group
- PIS Specified (Control) Donors Questionnaire and Interview Group
- Consent Form Unspecified Donors Focus Group
- Consent Form Unspecified Donors Interview Group

- Consent Form Unspecified Donors Questionnaire Group
- Consent Form Specified (Control) Donors Questionnaire Group

4.2 Follow up Procedures

Follow-up assessments will be sent by post (and made available to complete online). To minimise loss to follow up anyone who has failed to return their 12 month follow up assessments within 14 days will be contacted by phone with the aim of collecting information on at least the primary outcome variable.

4.3 Maximizing Response Rates

Unspecified donors are highly motivated individuals, who, in our experience, are enthusiastic about participation in studies that may help other donors. The response rate of 74% in our previous study, whilst too low for definitive conclusions in a retrospective study, is nevertheless higher than expected for a questionnaire survey (6).

However, it is vital that response rates are high enough to accurately capture outcomes, and we aim to achieve this as follows:

I. Participants presenting for donation will be contacted directly by the research fellow or study manager (usually by telephone or email). Non-responders will be contacted on 2 occasions, including using an alternative method (such as a written letter and/or telephone calls outside standard working hours).
II. Participants will be given the opportunity to return documents in a freepost envelope or by completing an online form.
III. The trial manager will contact all 23 transplanting centres on a regular basis to ensure that those who present for unspecified donation have been considered for inclusion in the study.
IV. One team member (LB) already has close and regular contact with donor co-ordinators (who are the first point of contact for any donor presenting at a transplant centre) in all transplanting centres. She will send reminders to all co-ordinators regularly to ensure continued referral of potential participants.

We will monitor the success of this approach using the internal pilot study described in the protocol.

4.4 End of Study Definition

Completion of the final questionnaire (at 12 months) of participants recruited in the 3-year period will mark the end of the study.

5. Laboratories

No laboratory facilities will be used for this study

6. Assessment of Safety

6.1 Emotional or Psychological Distress

If any clinical concern is identified by the research team from the questionnaires or interviews (for example suicidal thoughts, or severe depression) the local clinical team (transplant donor co-ordinator) will be informed with a view to referral to the local psychological or counselling service; we used this approach previously in our retrospective study. The provision of this facility is part of our commitment to good practice and we do not anticipate this will be needed. In the unlikely event that concern is raised about a participant who has withdrawn from the donation process early in the assessment period and has no further contact with their local transplant

unit, we will contact their GP directly. The GP contact details will be collected as part of the recruitment baseline data.

6.2 Impact of study on decision to donate

Focus Groups. The Focus Groups will be with altruistic kidney donors who have already completed or have withdrawn from the donation process. As such, the study will not be able to impact on their decision to donate from the perspective of the focus group alone.

Interviews. The qualitative interviews will be performed prospectively and take place three months after donation or withdrawal from the donation process. This is to avoid any undue influence on the participant's decision to donate. The interviews will be conducted by experienced qualitative researchers who have interviewed both altruistic kidney donors and donors withdrawn from the process. The REC applications associated with these previous projects are: Understanding Barriers and enablers to altruistic kidney donation v1.14/SW/1105 and 10/H0203/11-Understanding the experiences of altruistic kidney donors. (Clarke, A., Mitchell, A., & Abraham, C. 2013. Understanding donation experiences of unspecified (altruistic) kidney donors. British Journal of Health Psychology.)

Questionnaires. The questionnaires which will be used are validated and widely used research tools which are regularly employed in the fields of social science and psychology. We have previously used similar tools in our research with no significant impact on the participants' mental or physical health.

6.3 Sensitive questions

Additional questions that will be formulated as a result of the focus group data (in addition to the already validated questionnaires) will be discussed amongst the study research group that consists of psychologists, transplant surgeons and nurses who are highly aware and sensitive to the process of altruistic donation as a result of their extensive clinical experience. Furthermore, two members of the 'Give a Kidney Charity', who represent the altruistic donor community, will review and be involved in the development of any further questions. Any new questions that would potentially impact on the decision to donate will be excluded from the questionnaire bundle

6.4 Ethics Reporting

Reports of related and unexpected SAEs will be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. The form will be completed in typescript and signed by the chief investigator. The Coordinator of the main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt should be sent to the R&D Directorate.

No SAE are expected for this study.

7. Trial Steering Committee

7.1 Study Steering Committee

The study does not have a Data Monitoring Committee, but there is a Study Steering Committee (SSC), which will have the following responsibilities:

i) To provide advice, through its Chair, to the Chief Investigator, the Project Sponsor, the Project Funder, the Host Institution and the Contractor on all appropriate aspects of the project

ii) To concentrate on progress of the project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question

iii) The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society

iv) To ensure appropriate ethical and other approvals are obtained in line with the project plan

v) To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
vi) To provide advice to the investigators on all aspects of the project

The SSC will be constituted as follows: An independent chairperson, an independent statistician, one member (not directly involved with the study) from within the Trust, one member external to the Trust, and two service users. An observer from the sponsor and from the CLRN will be invited to attend.

The SSC will meet at 4 to 6 monthly intervals, or more frequently if the Chairperson deems this to be necessary.

The study steering committee has the following members:

Chair
Prof Kenneth Farrington
Consultant Renal Physician
ken.farrington@nhs.net

Independent statistician
Dr Matthew Robb
NHBST

One member (not directly involved with the study) from within the Trust
Dr David Game
Consultant Renal Physician

One member external to the Trust:
Dr Sian Griffin
Consultant Renal Physician

Previous Service Users
Mr Peter Cordwell

Mr Nicholas Crace

7.2 Trial Management Committee

The Trial Management Committee manages the project on a regular basis. It consists of members of the project team and meets at 3 to 6 month intervals. Minutes and agendas are issued in the regular manner. The committee has two permanent PPI members representing the 'Give a Kidney' Charity.

8. Ethics & Regulatory Approvals

15/SC/0637
South Central – Berkshire B Research Ethics Committee
Health Research Authority
Bristol HRA Centre, Level 3, Block B,
Whitefriars, Lewins Mead, Bristol BS1 2NT
HRA (Bristol Centre): 0117 342 1382 | www.hra.nhs.uk, nrescommittee.southcentral-berkshireb@nhs.net

9. Data Handling

Confidentiality

A database will be constructed by the Guys and St. Thomas Biomedical Research Centre. Online or paper questionnaires and interview transcripts will be transferred to the database, held on a secure server at either Guys Hospital or Plymouth University, in an anonymous fashion, with password protected access. Access to the database will be limited to the study researchers, Chief investigator and study manager. Participant data will be managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

Each patient will have a unique study identity number which will avoid the use of patients' hospital numbers, NHS numbers, dates of birth or names. The Chief Investigator will have a separate key linking the study identification number with identity of the study participants. The study key information will be kept in a separate password secure and locked environment.

Back-up will be performed automatically by the Trust systems, and data archiving will be undertaken by the Kings Health Partners Joint Clinical Trials Office, according to their standard operating procedures.

Record Retention and Archiving

All records will be kept in secure conditions. When the research trial is complete the records are kept for a further 5 years.

Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

Non-Compliance

The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

10. Finance and Publication Policy

10.1 Funding

The research is funded by the National Institute of Health Research (NIHR) HS&DR Award (13/54/54), with a total value of £872,756.

National Institute of Health Research
University of Southampton
Alpha House
Enterprise Road
Southampton
SO16 7NS

The funds will be managed centrally by the research team at Guy's Hospital and distributed to collaborating units according to a collaboration agreement, which has been negotiated by the relevant academic, financial and legal departments within the collaborating universities and hospitals.

10.2 Outputs

There will be several specific outputs in addition to published manuscripts and conference presentations:

a) A report to NHSBT and the BTS, summarising the findings of the study
b) National guidelines, produced in conjunction with NHSBT and the BTS
c) A protocol for management of those presenting for unspecified donation
d) A report to the Renal Transplant Clinical Reference Group, which reports to NHS England (which commissions transplant services in England), and to the Scottish, Welsh and Northern Irish Departments of Health.

The process for developing these outputs (beyond the first, which will be written by the study team) is as follows:

National Guidelines

The transplant community is small, and there is a widespread desire for guidance on unspecified donation. Existing guidelines on living donation are extensively used by donor teams, and these have been important in changing culture. We recognize that guidelines are not, however, necessarily effective by themselves at changing practice- in this regard, the close liaison that one team member (LB) has with donor co-ordinators at all transplant centres, and the living donor forum which she organizes, will be vital.
The support of the BTS Clinical Trials Committee for this study (attached) is indicative of the close involvement and support of the BTS. There is an existing process for developing guidelines by the BTS, through the BTS Standards Committee. We will convene a small group, including NHSBT and BTS representatives, as well as service users, to draft a guideline, which can be sent to the BTS Standards Committee for consideration. Typically, this is opened for public consultation via the BTS website for a short period, revised and then disseminated to all units. The leads for this work will be Prof N Mamode and Ms L Burnapp.

Commissioners' report

The Chief Investigator is a member of the Renal Transplant Clinical Reference Group (CRG) and has been involved in drafting Service Specifications for transplantation. He will send a report, which will be drafted with the help of the study team, including service users, to the CRG for discussion and dissemination to NHSE and counterparts in other constituent countries.

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SF-12v2™ Health Survey. 1992-2002 by Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved. SF-12® is a registered trademark of Medical Outcomes Trust. (IQOLA SF-12v2 Standard, English (United Kingdom) 8/02)

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Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

Appendix 1

Appendix 1. Projected number of unspecified kidney donors to 2020

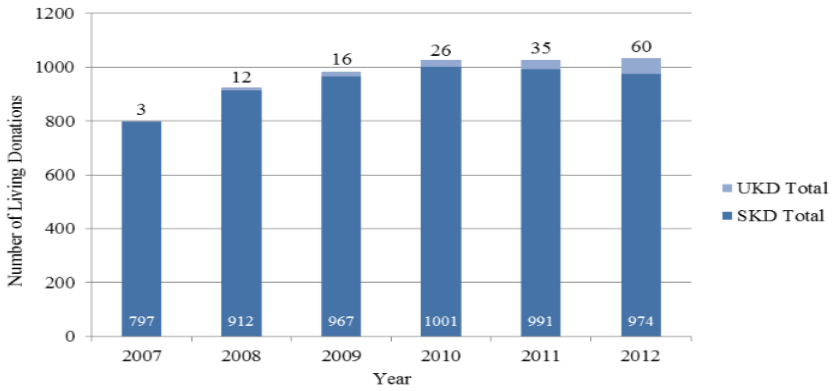

Figure 1. Number of living kidney donations in the UK by unspecified and specified kidney donors

Figure 1 shows the total number of living kidney donations in the UK per year, separated by unspecified and specified type. Over the six year period shown there has been an increase in the total number of living donations. Since 2010, the increase is driven by unspecified donations, with the number of unspecified donations actually falling.

Figure 2 and Table 1 below shows projections for the number of unspecified (altruistic) kidney donors to 2020 by two methods. The first method fits a linear rate of increase based on the past trend. The second method assumes a non-linear (quadratic) rate of change. The quadratic method fits the observed data best but this is no indication it provides a more accurate projection.

With recruitment between March 2015 and Feb 2018 we can expect between 279 (linear = 83+93+103) and 493 (non-linear = 131+163+199) donors based on the projections. The expected sample size will be based on the more conservative linear estimate. An even more conservative estimate would assume rates staying stable at the 2012 figures. This would mean the expected sample size of 180 (60+60+60).

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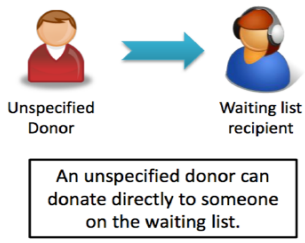
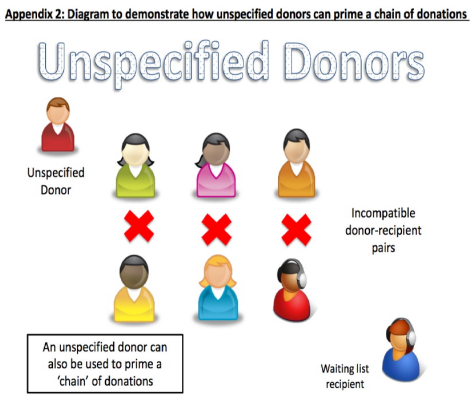
RQ2 Study Protocol V2.1
25.05.2016

Appendix 2a

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



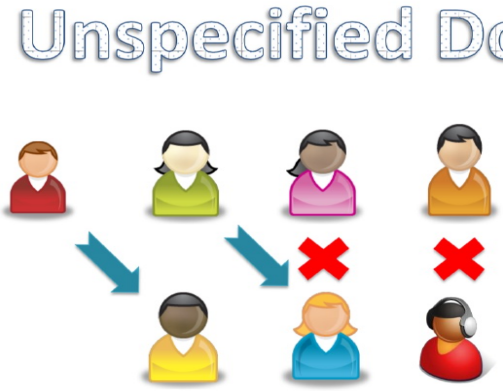
Appendix 2b



Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations

Appendix 2d

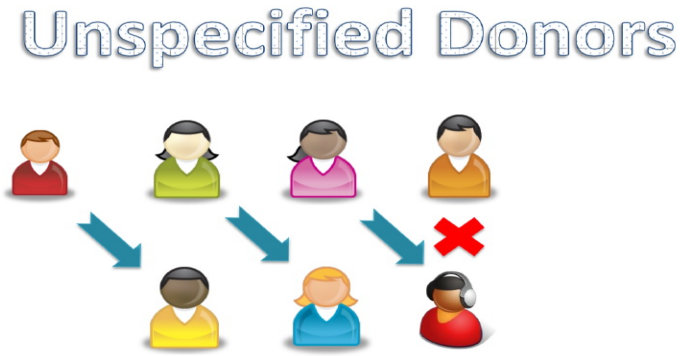
Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



RQ2 Study Protocol V2.1
25.05.2016

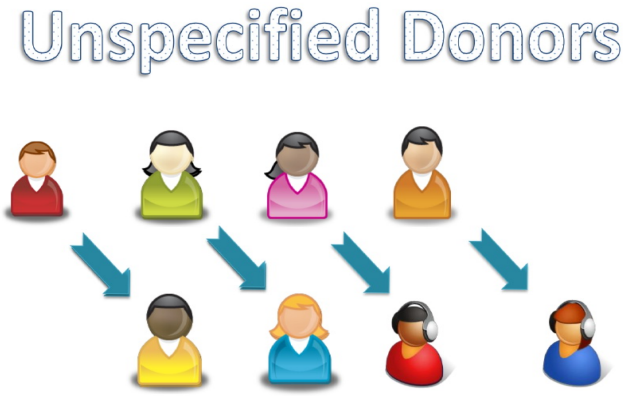
Appendix 2e

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



Appendix 2f

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



Appendix 3

BOUnD

Appendix 3: Topic list: Qualitative interviews

RQ2 Study Protocol V2.1
25.05.2016

Appendix 4:

		Phase 1: Potential donors				Phase 2: Outcomes			
		Recruitment		Pre donation		Donation		Follow-Up	
	Data (source)	Pre-enrolment	Enrolment	Baseline	Pre-op (1 week)	Surgery	Post-op	Follow-up 3 months	Follow-up 12 months
Enrolment	Initial contact (Centre)	X							
	Referral (Centre)	X							
	Eligibility screen (Trial manager)		X						
	Informed Consent (Trial manager)		X						
Assessments	Baseline demographic data			A					
	Personality: TIPI (Questionnaire)			A					
	Social support: MSPSS (Questionnaire)			A	A			A	A
	Peri-operative physical outcome data (NHSBT)				A		D		D
	Surgical procedure data (NHSBT)					D			
	Withdrawal (Questionnaire & Centre data)			W	W				
	Rosenberg (Questionnaire)			A	A			A	A
	SWLS (Questionnaire)			A	A			A	A
	PHQ9 & GAD7 (Questionnaire)			A	A			A	A
	Flourishing Scale			A	A			A	A
	Decision Regret Scale							A	A
	SF12 (Questionnaire)			A	A			A	A
	Client Service Receipt Inventory (Questionnaire)			A	A			A	A
	In-House Questionnaire			A	A			A	A

X= recruitment and centre level data (pre-consent)
A= Data from all potential donors
D= Data for donors only
W= Data for withdrawn only

BMJ Open

Understanding barriers and outcomes of Unspecified (non-directed altruistic) kidney donation from both professional's and patient's perspectives: Research protocol for a national multicentre mixed-methods prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015971.R1
Article Type:	Protocol
Date Submitted by the Author:	24-May-2017
Complete List of Authors:	Gare, Rebecca; Guy's and Saint Thomas' NHS Foundation Trust, Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust/ King's College Londo Gogalniceanu, Petrut; Guy's and Saint Thomas' NHS Foundation Trust, Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust / King's College London Maple, Hannah; Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust / King's College London London, UK Burnapp, Lisa; NHS Blood and Transplant, NHS Blood and Transplant; Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust / King's College Londo Clarke, Alexis; University of Plymouth, School of Psychology, University of Plymouth Williams, Lynsey; University of Plymouth, School of Psychology, University of Plymouth Norton, Sam; King's College London, Institute of Psychiatry, Psychology & Neuroscience, King's College London Chilcot, Joseph; King\'s College London, Institute of Psychiatry, Psychology & Neuroscience, King's College London London Gibbs, Paul; Portsmouth Hospitals NHS Trust, Renal Transplant Department, Portsmouth Hospitals NHS Trust Mitchell, Annie; University of Plymouth, School of Psychology, University of Plymouth McCrone, Paul; King's College London Draper, Heather; The University of Birmingham, Centre for Biomedical Ethics; Warwick Medical School, Division of Health Sciences Mamode, Nizam; Guy's and Saint Thomas' NHS Foundation Trust, Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust / King's College London London, London, UK
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Renal medicine
Keywords:	Renal transplantation < NEPHROLOGY, Chronic renal failure < NEPHROLOGY, kidney, altruistic/ unspecified donation

Understanding barriers and outcomes of Unspecified (non-directed altruistic) kidney donation from both professional's and patient's perspectives: Research protocol for a national multicentre mixed-methods prospective cohort study

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Abstract

Introduction: Living donation accounts for over one third of all kidney transplants taking place in the UK[1]. The concept of anonymously donating a kidney to a stranger (non-directed altruistic or unspecified kidney donation (UKD)) remains uncomfortable for some clinicians, principally due to concerns about the motivations and long-term physical and psychological outcomes in this donor group.

Aims: The research programme aims to provide a comprehensive assessment of the unspecified donor programme in the UK. It aims to identify reasons for variations in practice across centres, explore outcomes for donors, ascertain barriers and facilitators to UKD for those who have expressed a willingness to donate, and assess the economic implications of unspecified donation.

Methods: The research programme will adopt a mixed-methods approach to assessing UKD nationally using focus groups, interviews and questionnaires. Two study populations will be investigated. The first will include transplant professionals involved in unspecified kidney donation. The second will include a five-year prospective cohort of individuals who present to any of the 23 UK transplant centres as a potential unspecified living kidney donor. Physical and psychological outcomes will be followed up one year following donation or withdrawal from the donation process. A matched sample of specified donors (those donating to someone they know) will be recruited as a control group. Further qualitative work consisting of interviews will be performed on a purposive sample of unspecified donors from both groups (those who do and do not donate). **Dissemination:** The findings will be reported to NHS Blood and Transplant and the British Transplant Society with a view to developing national guidelines and a protocol for the management of those presenting for unspecified donation.

The study is registered with the International Standard Randomised Controlled Trial Number (ISCRTN) – 23895878

Strengths and Limitations of this study:

Strengths

- This is a prospective, mixed methods study using both qualitative and quantitative methods to answer complex questions regarding barriers to service delivery
- This is a widely multi professional study drawing experiences from a variety of fields (surgery, medicine, psychology, psychiatry, ethics, NHS Blood and transplant)
- This study will assist in the development of national guidelines and a protocol in conjunction with NHS Blood and Transplant and The British Transplant Society.
- The study method will capture resource utlisation by unspecified donors providing a novel understanding of the economic implications of the unspecified donation process.

Limitations

- There is a risk of not capturing individuals who are disengaged / disappointed in the process of unspecified kidney donation
- The study relies on a large number of individuals participating and is based on the assumption that unspecified donation rates with continue to occur at the same rates as prior years
- This study relies on the referrals of donors from co-ordinators across the country and we may not be able to capture every enquiry or expression of interest.

Introduction

Live donor kidney transplant recipients have the best outcomes in terms of survival and function post transplantation. Currently over one third of all kidney transplants taking place in the UK are from living donors. A growing subset of living donors consists of individuals who choose to donate a kidney to someone that they have not previously met. These are called 'unspecified kidney donors' (UKDs) or 'non-directed altruistic' donors. Over 500 unspecified donations have taken place in the UK since the practice was introduced in 2006 and it currently accounts for approximately 11% of living donations per year[1].

Recipients of living donor kidneys are provided with a long lasting, high quality organ that is usually sufficient to avoid dialysis for an extended period of time[2]. Organs from UKDs can provide this opportunity for those without a living donor, some of whom would have a low chance of receiving a deceased donor organ from the waiting list due to sensitisation challenges. Additionally, UKD's organs can be further utilised by introducing them into the National Kidney Sharing Scheme. This involves kidney exchanges between pairs of donor and recipients who cannot otherwise proceed due to immunological incompatibility. A kidney from a UKD can be used to convert these exchanges into a 'chain' primed by the UKD (figure 1). In this way, the UKD donates to the first recipient, whose donor then subsequently donates to another recipient, and so on. The chain then terminates with donation to an individual on the deceased donor waiting list. In the US this has resulted in 30 transplants occurring from a single UKD[3]. In the UK, 47% of UKDs have been used to prime short chains of two transplants, and the UK Living Donor Strategy aims for 75% to be used for chains, with 3 transplants in each chain, by 2020[4].

Despite the increase in UKD in the United Kingdom the concept remains illegal in many European countries and is uncomfortable for some healthcare professionals, principally due to concerns about the motivations, characteristics and outcomes in this group of donors[5]. We have performed the largest quantitative study of psychosocial and physical outcomes in UKDs, where we sampled a national cohort of all 148 UKDs in the UK over the first five years of the programme and compared them with a regional sample of 148 specified kidney donors (SKDs - those who

donate to someone with whom the donor has an existing emotional relationship)[6]. All donors were sent a questionnaire which included a range of validated psychosocial outcome measures and questions specific to their donation. Physical outcome data were obtained from NHS Blood and Transplant. This study found that both physical and psychosocial outcomes were comparable between UKDs and SKDs, which suggests that clinician concerns may be unfounded. The limitations of this study were in its retrospective design and the inherent bias associated with this. Whilst we were able to analyse physical outcome data for the entire cohort, we were unable to determine whether those with poor psychosocial outcomes were within the non-responders and therefore not captured as part of the study. In addition, this study demonstrated a broad variation in donation rates across the country, with no obvious underlying reason.

A number of potential deterrents to UKD have been highlighted in our previous qualitative work and through consultation with UKDs in the development of this study.[7] For example, we have previously found that barriers to donation may exist within families where there is tension over the decision to donate altruistically and that there may be a role for transplant services to support families in this situation[7]. UKDs have also reported experiencing scepticism and resistance from some of the healthcare professionals they encountered. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also described as a difficult experience for UKDs who felt that they had to prove their sanity[7].

Aims and Objectives

The aim of this research programme is to perform a comprehensive assessment of the unspecified donor programme in the UK. Its objectives are to establish:

1. Whether variation in practice and attitudes across the UK is unnecessarily preventing some unspecified donation

2. Whether psychosocial and physical outcomes after unspecified donation are equal to those in specified donors

3. The economic benefit of unspecified donation

Ethical dimensions and implications of unspecified donation will also be explored. The programme's data will be used to develop national guidelines and inform transplant teams' decisions about potential donors.

Methods and Analysis

Design

This is a mixed methods research programme investigating unspecified kidney donation in the UK over a period of 5 years.

Research Questions

The study will be asking three main questions based on the research objectives listed above:

1. RQ1- Is there variation in transplant professionals' practice and attitudes, which is preventing some unspecified living kidney donations?
2. RQ2 - Are psychosocial and physical outcomes after unspecified donation equivalent to those after specified donation?
3. RQ3 - What is the economic benefit from unspecified donation?

In order to answer these three research questions we will utilise a mixed methods design, incorporating questionnaires to obtain quantitative data and interviews and focus groups to obtain qualitative data (figure 2). The third question, related to health economics, will be answered using embedded data capture elements within the first two research questions.

RQ1 Transplant Professionals' Perspective

This sub-study defines transplant professionals (TP) as any healthcare professional that may come in contact with a potential unspecified donor. These include renal transplant physicians, surgeons, transplant co-ordinators, nurses involved in transplantation, psychologists and independent assessors, as well as administrative staff from all 23 UK centres. Answering this research question will involve three stages. The first stage will involve focus groups, led by qualitative researchers, in which the views of transplant professionals regarding UKD will be ascertained. Focus groups will be undertaken in four centres, chosen according to their volume of

donations. This will allow sampling from two centres with higher donation rates and two centres whose rates are amongst the lowest. The data obtained will undergo thematic analysis and the key themes identified will be extrapolated. This data will be used to inform the subsequent stages. The second stage will involve questionnaire development, from the themes generated by the focus groups. The questionnaires will form the basis of a series of prospective cohort studies which will help ascertain broader, nationwide attitudes towards unspecified kidney donation, as well as current working practices in the different transplant centres. The questionnaires will be disseminated using professional networks to all UK transplant professionals. The third stage will involve in-depth qualitative interviews that will be conducted with transplant professionals selected from six centres, again chosen according to their donation volume. These interviews will not only provide a more detailed understanding of professionals' views, but will additionally help add meaning to the data obtained from the prospective cohort studies (questionnaire based).

RQ2 Donors' Perspective

Two focus groups will be held to assist in informing the development of study-specific questionnaires. The first focus group will involve individuals that have proceeded to donate a kidney as an unspecified kidney donor, whilst the second will involve individuals who presented as potential unspecified kidney donors, but who did not proceed to donate. Themes emerging from the focus groups will again be analysed using thematic analysis and questions specific to UKD will be written and validated by the research team. These questions will subsequently become part of a larger questionnaires, which will include validated psychosocial outcome measures capturing data on a range of different factors [8-17]. Validated psychosocial outcomes measures will include: The Client service receipt inventory[8], Rosenberg self-esteem scale[9], Generalised anxiety disorder 7-item scale (GAD-7)[10], Multi-dimensional scale of perceived social support (MSPSS) [11], Ten-item personality measure[12], Decision regret scale[13], Patient health questionnaire (PHQ-9)[14], Satisfaction with life scale[15], Flourishing scale[16] and the Quality of life health survey (SF-12) [17].

The questionnaires will be used as part of a longitudinal cohort study with four intervention points, as determined by their progress through the donation pathway. All those presenting to a transplant centre as a potential UKD will complete a baseline

questionnaire. The second questionnaire will be given immediately prior to donation, or immediately after the donor is withdrawn from the assessment process. The final two questionnaires will be given at three and twelve months after donation or withdrawal.

The study population will consist of all those individuals approaching a transplant centre with an interest in becoming an unspecified donor, irrespective of whether they subsequently donated or not. Potential specified donors will be used as the control population. Due to the fact that not all those who present as potential donors go on to donate, the study will result in two test groups and two control groups (figure 3):

1. Test group 1: Potential unspecified donors who proceed to donation
2. Test group 2: Potential unspecified donors who do not proceed to donation (either due to personal choice or withdrawal by the clinical assessors)
3. Control group 1: Potential specified donors who proceed to donation
4. Control group 2: Potential specified donors who do not proceed to donation (either due to personal choice or withdrawal by the clinical assessors)

Qualitative interviews will also be completed with a sample of 15 UKDs who completed their donation, 15 UKDs who withdrew and 15 UKDs who were withdrawn from the process by the transplant team. Participants will be asked about their experience of the donation process and services, barriers and enablers to donation and outcomes from either donating or withdrawing from the process. These interviews will take place three months after donation or withdrawal from the donation process.

The data collected will be compared with and supplemented by each donor's NHS Blood and Transplant records. These will be used to provide physiological outcome data as well as information regarding the donation procedure for each participant. Physiological data will be collected before and after donation, as well as at 12-months following donation, as per national donor follow-up protocol. NHSBT data will be collected retrospectively once a participant completes the 12-month questionnaire, or earlier should they choose to withdraw from the study. Consent to

obtain NHSBT data will be obtained through the initial study participation consent form. A formal request for data use has been approved by NHSBT and has been subsequently ratified by the Ethics Committee.

RQ3 Economic outcomes of unspecified kidney donation

The economic effects of living kidney donation will be determined by examining the impact of donation on healthcare and societal costs for specified and unspecified donors, using the Client Service Receipt Inventory (CSRI) questionnaire[8]. The CSRI has been widely used and will be adapted and customised to reflect the healthcare services used in kidney donation. It will be administered in self-reported questionnaires to donors and will aim to determine the type and frequency of specific health services accessed.

Eligibility Criteria

Participants eligible for RQ1 recruitment include any transplant professional that has had contact with unspecified donors.

Participants eligible for RQ2 recruitment include any individual that makes contact with a transplant centre to enquire about unspecified donation and proceeds beyond the initial telephone conversation, as well as being able to give informed consent. Non-English speakers will be included and adequate translation facilities will be provided.

Individuals who have already begun the donation work-up process at the time of study commencement will also be eligible for recruitment provided they are more than 2 weeks away from donation. Control participants will be recruited from those individuals known to a transplant centre for the purposes of donating a kidney to a known individual (specified donors) using the same inclusion criteria.

Enrolment (Figure 4)

Recruitment to the questionnaire for Professionals study (RQ1) will be through professional networks. Local collaborators at specific centres will be established to assist with recruitment for the focus groups and interviews.

For the participant study (RQ2) all 23 centres across the United Kingdom will be set up as participant identification centres (PIC) sites. Any individual who makes contact with a living donor coordinator to enquire about donation will be informed about the study and recruitment options. If they are happy to receive information and provide verbal consent, the coordinator will either pass their contact details to the research team at Guy's Hospital or will provide the individual with the study co-ordinator's details. Aggregated data will be provided by each centre regarding the total number of enquiries made to allow comparison with numbers making additional contact and recruited to the study. Once contact has been made the research team from Guy's Hospital will provide further information to the individual and be responsible for the recruitment and consent of participants.

Sample size calculation

Based on previous retrospective work[6], it is expected that a recruitment rate of 80% will be achieved. The study will aim to recruit 624 participants, of which 224 will go on to donate as unspecified donors. This recruitment rate is higher than is typical for longitudinal studies but justifiable given the population being studied. A sample size of 624 will provide sufficient precision to estimate the 95% confidence interval for proceeding to donation to within ±4% overall, and to within ±18% for each centre. In summary, the study aims to recruit 224 participants who have undergone unspecified donation (Test group 1) and 400 who did not donate (Test group 2).

The control group will recruit 200 individuals who are donating to friend or relative (specified donors - control group 1) and 200 individuals that intend to donate to a friend or relative but do not proceed (specified non-donors - control group 2). Based on our retrospective study we expect a recruitment rate of 80%. Therefore we will need to approach 500 specified donors. Given a stable rate of approximately 1000 specified donations per year across the UK, we anticipate that we will be able to recruit the control group using the same three-year recruitment window as the main cohort. If there is no difference between the unspecified altruistic and specified donors on the physical and psychological variables at 12 months, it will be possible to determine that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of a standardised mean difference of 0.3, which is

deemed to be the smallest acceptable clinically meaningful difference – this allows for 20% missing data due to drop-out, at a significance level of 5% with 90% power[18]. These individuals will be recruited through transplant co-ordinators nationally.

Study Set up

The research programme will be carried out at a national level, with sponsorship and monitoring provided by the Guy's Hospital Research and Development department. It has received funding from the National Institute of Health Research under HS&DR Project number 13/54/54.

Guy and St Thomas' NHS Foundation Trust is the lead site and are collaborating with Plymouth University, The University of Birmingham and King's College London. Twenty-three centres across the United Kingdom have been established as Patient Identification centres with all research activity being conducted centrally at Guy's Hospital.

Analysis plan

Qualitative Data Analysis

Data generated via the focus groups and staff interviews will be analysed using the Framework Approach. The framework approach was developed by the National Centre for Social Research[19]. It is a deductive form of analysis that is increasingly being used in healthcare research where the aim is to develop practical applications and target policy development. It starts deductively from the aims and objectives identified in the study. However, this approach is grounded and inductive, in that it is heavily based in participants' original accounts and the observations of those studied. Framework analysis largely conforms to the thematic analysis approach aiming to describe patterns in the data and provide a description of the data with an emphasis on making the process of identification clear and delineated[20]. The process of framework analysis enables interaction with the data set until a meaningful account is revealed with a conceptual framework, thus allowing the development to an explanatory account. Data will analysed in adherence with the five stages of data analysis using the framework approach as presented in Ritchie and Lewis (2003) and aided by the computer software program NVIVO (version.11).

Cohort Study Analysis

In addressing RQ1 concerning variables relating to an individual proceeding to donate, descriptive analysis will be used to describe the proportion of people who withdraw or proceed to donation, and the reasons for failing to proceed. Survival analysis will be used to identify predictors of proceeding to donation. Specifically we will estimate Cox proportional hazards models where the dependent variable is the number of days between first contact with the unit and the date of donation, with those who where no decision has been made censored at the date of their last known status. The analysis will include all individuals enquiring about donation, with the dependent variable an indicator for each proceeding to donation. Centre-level structural and attitudinal factors identified in the study group's previous work[8] will be included in the models to determine whether these variables explain variation in donation rates. Individual level demographic variables at baseline (e.g. age, sex, education, and ethnicity) and time dependent psychological factors will be included to determine their association with outcome. Power to detect effects for individual level variables will be acceptable but only large effects will be detectable for centre level variables."

To address RQ 2 relating to outcomes after donation, descriptive analysis will be used to compare baseline variables for individuals in each of the specified donor (test) and unspecified donor (control) groups. Linear or logistic mixed-effects models will be used to estimate between group differences in outcome variables at the 3 and 12 months post-donation follow-up assessments. A three-level model will be specified with observations at each time-point (level 1) nested within individuals (level 2), who themselves are nested within centres (level 3). Group membership and follow-up assessment (time) will be included in the models as dummy variables. Interaction terms for group and time will allow for assessments of differences at individual time points. Models will adjust for potential individual level demographic confounders measured at baseline (e.g. age, sex, education, and ethnicity) and the baseline level of the outcome variable. Missing outcome data is under the assumption that data is missing at random. Sensitivity analysis will be performed to assess this assumption.

Economic Outcomes Analysis

The economic benefits of unspecified donation will be examined using decision analytical methods. Decision analytic models use mathematical relationships to define a series of possible consequences that flow from a set of alternative options being evaluated. Here the decision is to accept or not accept unspecified donation. If unspecified donation is accepted and an individual is assessed then there are a series of events that can occur. These include refusal to proceed, being deemed unsuitable, successfully donating, and a recipient benefiting.

There are costs associated with these and the outcomes will be measured in terms of quality-adjusted life years (QALYs) for donors using the SF-12, and for recipients with QALYs derived from previous literature.

Data for the model will draw on a systematic literature review of published economic evaluations of kidney donation, as well as from the costing exercise described above and expert opinion. The model will take a lifetime horizon (with appropriate discounting) and will allow us to estimate the expected costs and QALY gain following the start of the process of unspecified donation. Given uncertainty around the model parameters, we will conduct a series of sensitivity analyses (deterministic and probabilistic) to assess its robustness. Key parameters to vary may include rejection and refusal rates and values placed on future QALY gains. The model will estimate costs and benefits for the donors. It will also estimate QALY gains for recipients and if possible we will incorporate future costs for recipients as well.

Ethics and Dissemination

The number of individuals considering living kidney donation to someone they have not previously met is becoming more common and has a significant potential to reduce the UK waiting list for kidney transplantation. Despite this trend, the concept of unspecified kidney donation (UKD) remains uncomfortable for some clinicians. Furthermore, the assessment and donation process may have scope for improvement from the donor's perspective. This study will provide a comprehensive assessment of the unspecified donor programme in the UK in order to determine the extent and reasons for variation in practice, ascertain barriers to donation, as well as the

economic implications of unspecified donation. The study will also assess clinical outcomes after unspecified donation in order to facilitate evidence-based decision making regarding future unspecified donors, as well as inform the creation of national guidelines.

Acknowledgements

This study is funded by the National Institute of Health Research under Health Services & Delivery Research Programme project number: 13/54/54.

Authors would also like to acknowledge Jan Shorrock and Paul van den Bosch for their expert advice and support. The study team would also like to acknowledge the support of NHS Blood and Transplantation, The British Transplantation Society and all 23 transplant centres across the United Kingdom.

This research was supported in part by the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) based at Guy's and St. Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Footnotes:

Contributors: NM and HM conceived the idea for the project with input from AM and AC regarding the qualitative work and PMcC leading on the economic aspect of the project. RG, PG, HM, LB, AC, LW, SN, JC, PGibbs, AM, PMcC, HD and NM collaboratively contributed to the design of the study and its protocols. RG and PG led the writing of the manuscript. RG, PG, HM, LB, AC, LW, SN, JC, PGibbs, AM, PMcC, HD and NM have reviewed and revised the manuscript critically for important intellectual content.
RG, PG and NM take responsibility of the paper as a whole.

Funding: This project was funded by the National Institute for Health Research [Health Service and Delivery Research programme] (project number 13/54/54).

Competing Interests: None declared

Data sharing statement: We shall make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs

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Figures:

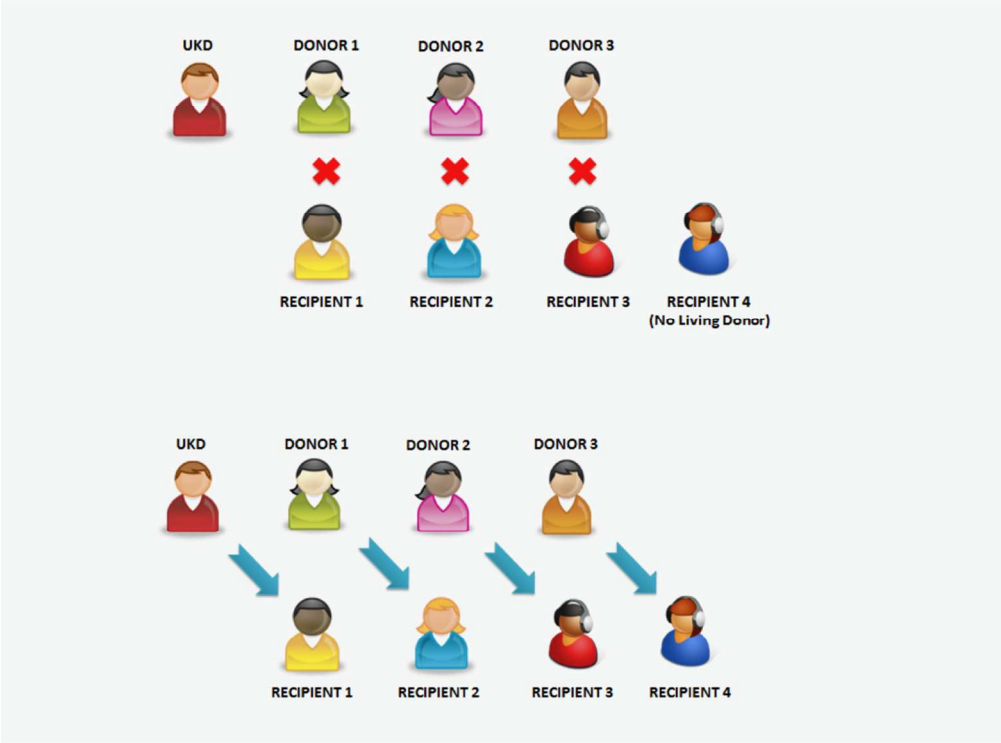

Illustration of an altruistic donor chain, primed by a UKD

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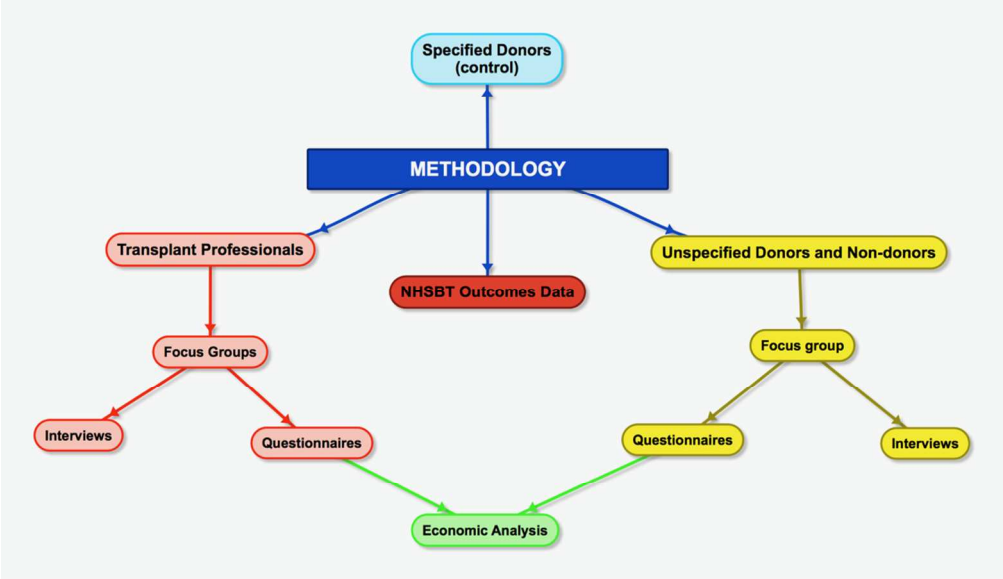

BOUnD Study Methodology

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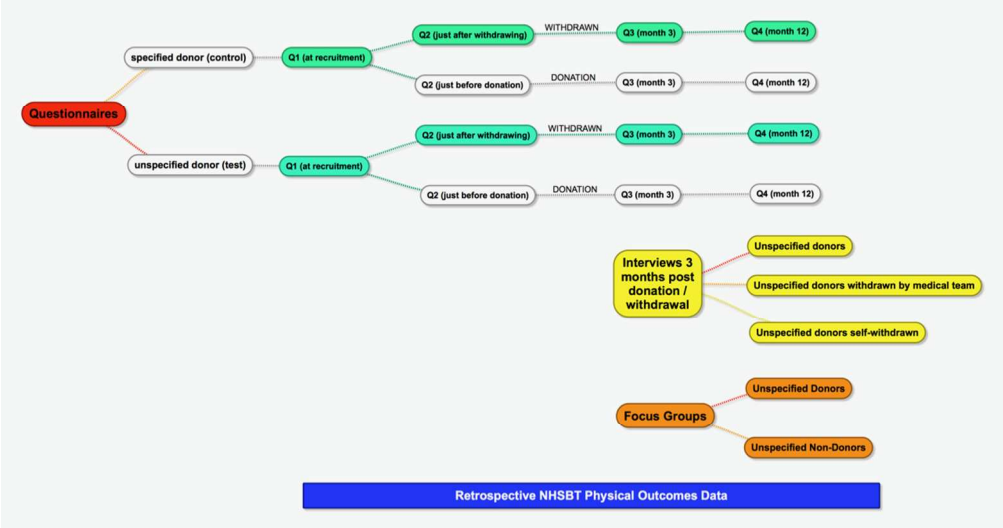

Research Question 2: Participant flow chart

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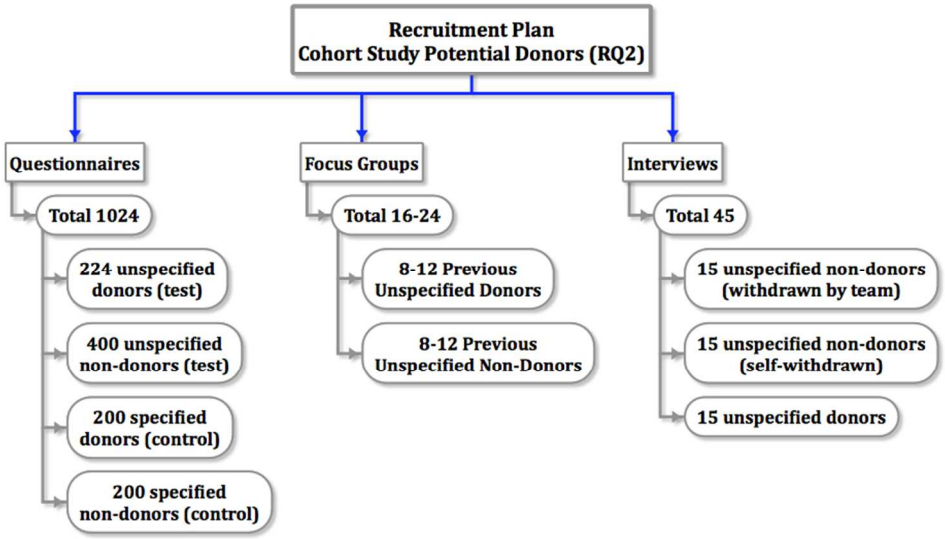

Study recruitment population

342x204mm (72 x 72 DPI)

Unspecified living kidney donation in the UK: barriers to implementation and delivery
- Healthcare Professionals' Perspective -

1. Background

Over one third of all kidney transplants taking place in the UK today are from living donors. A growing subset of living donors are individuals who choose to donate a kidney to someone that they have not previously met; so called 'unspecified' or 'non-directed altruistic' donors. Over 200 unspecified donations have taken place in the UK to date since this was introduced in 2006 and this type of living donation is becoming more routine, currently accounting for approximately 7% of living donations (1).

Despite this increase, the concept of unspecified kidney donation (UKD) remains uncomfortable for some clinicians, principally due to concerns about the motivations, characteristics and outcomes of these donors. In a recent study of clinicians' views', 78% of French physicians were opposed to the practice of unspecified donation (2). In our previous qualitative work, we have found some evidence that this makes donation more difficult or stressful for some potential donors (3-5). Furthermore, we recently performed a large study of a national cohort of all 148 UKDs in the UK over the first five years of the programme, and compared them with a regional sample of 148 specified kidney donors (SKDs - those who donate to someone with whom they have an emotional relationship) (6). This study did not find an excess of poor psychosocial or physical outcomes in UKDs; however the response rate was 74%, with variable retrospective follow-up, and therefore it is impossible to be certain that donors with significant pathology were not missed- indeed, these are the very donors (for example, with depression) that might be expected to fail to respond. The study did highlight broad regional variations in the numbers of UKDs performed and has highlighted differences in the assessment process, which may explain the differences seen across the country. Indeed, 45% of all unspecified donations were performed in 3 centres. There is some evidence from other studies that attitudes from transplant professionals may be a barrier to donation (7-9). Both living donor nurses and psychiatric assessors involved in UKD have expressed concerns about the lack of practice guidance in this area; lack of clear guidance could be a further barrier to donation (4,5).
Through our qualitative work we have also found that barriers to donation may exist within families where there is tension over the decision to donate altruistically and there may be a role for transplant services to support families in this situation (3). We have recently been awarded a grant from the British Renal Society and

British Kidney Patients Association to explore this. This work is due to commence prior to this study and will inform this research.

The UKD participants in our PPI sessions and previous our qualitative study identified a number of issues in the process that they felt acted as deterrents and may have affected the decision by others to donate (3). They found difficulties in knowing how to make initial contact with the transplant centre. The negative attitudes of transplant professionals were also off-putting and this continued whilst donors were in hospital, with some experiencing ignorance and hostility from ward staff, which made them feel guilty for "choosing to become a patient". The length of the workup process was also commonly an issue, which donors found frustrating. Indeed, when considering living donor chains, most donors would have liked to have participated had it been easier and the timing more predictable. Many were working or had other commitments and the unpredictability of when the donation would take place meant that many were not in a position to oblige. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also a difficult experience for donors who felt that they had to prove their sanity (3).

Unspecified kidney donation is apparently more costly than specified donation, as it is resource intensive, with a large number of enquiries and assessments, and a low proportion that proceed to donate. In Portsmouth (the largest centre for unspecified donation), for example, of 149 referrals, 27 have donated and a further 27 are in work-up, giving a drop-put rate of at least 64%. Nevertheless, a kidney from a UKD may be a particularly valuable resource, since it can be used to provide a high quality, long lasting transplant to those who are otherwise difficult to transplant. The National Kidney Sharing Scheme, for example, involves kidney exchanges between pairs of donor and recipients who cannot otherwise proceed due to immunological incompatibility. A kidney from a UKD can be used to convert these exchanges into a 'chain' primed by the UKD; the UKD donates to recipient A, and her donor dates to recipient B, and so on (Appendix 2). In the US this has resulted in 30 transplants occurring from a single UKD (10). In the UK, 47% of UKDs have been used to prime short chains of two transplants, and the UK Living Donor Strategy aims for 75% to be used for chains, with 3 transplants in each chain, by 2020 (11). Thus, assuming UKDs rise to 200 per year, they would result in 450 transplants annually, which is almost half the current annual living donor transplantation rate. Despite this, no economic analysis of unspecified donation has been performed. This is particularly important since, if it is shown to have a significant economic benefit, extra resources could be allocated by NHS Blood and Transplant, as happened with SKDs over the last decade.

We therefore wish to perform an assessment of healthcare professionals' perspectives on the unspecified donor programme in the UK, in order to determine the extent and reasons for variation in practice and ascertain barriers to donation.

2. Aims

The study will specifically explore healthcare professionals' practice and attitudes to unspecified living kidney donation in transplant centres in the UK.

Research Question:

"Is there variation in transplant professionals' practice and attitudes, which is preventing some unspecified living kidney donations?"

3. Methods

The study will include three arms:

i) Focus groups

ii) Qualitative interviews and

iii) A questionnaire study of transplant professionals (surgeons, physicians, co-ordinators and others involved in transplantation in hospital) working with unspecified donors in the UK.

This is a mixed methods study, drawing on both qualitative and quantitative methods:

i) Qualitative information will be obtained by focus groups and individual interviews with transplant professionals in four centres. Sampling is purposive and centres will be chosen according to their numbers of completed donations, allowing us to sample from two centres which have amongst the highest rates of completed donations (Guys and St Thomas and Plymouth) and two centres whose rates are amongst the lowest (Birmingham and Leeds). These focus groups will contain key staff involved in the unspecified donation process (living donor nurses, psychological assessor, surgeons and nephrologists. These groups will be used to inform the approach in subsequent individual interviews with professionals from each discipline (surgeons, physicians, psychological assessors and donor coordinators). The interviews will involve centres chosen according to their number of completed donations. We will interview professionals at three sites which have the highest rates of completed donation (Guys and St Thomas, Plymouth and Manchester) and three centres with lower rates (Birmingham, Leeds and Bristol Southmead). It is anticipated that 60 transplant professionals in total will be interviewed.

ii) Quantitative study: Questionnaires will be sent to all transplant professionals working with unspecified donors across the UK, which will ascertain attitudes

towards unspecified kidney donation and current working practices. Both the focus groups described above and the patient representatives will inform the development of a questionnaire that explores working practices, knowledge of donation and staff attitudes incorporating salient points of interest from the data. This will be supplemented by an existing questionnaire (such as the Organ Donation Attitude [12]), which has been used previously in research to explore the impact of staff attitudes in organ donation.

Participants will be given an information sheet, adequate time to consider the study, and will be asked to give written consent.

If any evidence of distress is elicited in of the different parts of the study, access to a counselor will be offered, an approach we have adopted in a previous study (REC 09-H0804-31). We will ensure that data storage is annonymised and held in a secure fashion, according to Trust SOPs. Trial data will be archived at the end of the study, by our Clinical Trials Office. A trial manager will manage the trial, with help from a research fellow.

The data will be collected by collaborators from the Department of Psychology at Plymouth University. Focus group and individual interviews will be performed at sites most convenient for the healthcare professionals recruited. These may include NHS premises, individuals' homes, or other meeting venues (e.g. professional congresses).

The questionnaire data will be collected by postal or electronic means.

Analysis

Data generated via the focus groups and staff interviews will be analysed via the Framework Approach. The framework approach was developed by the National Centre for Social Research (13). It is a deductive form of analysis that is increasingly being used in healthcare research where the target is to develop practical applications and target policy development. It starts deductively from the aims and objectives identified in the study. However, this approach is grounded and inductive, in that it is heavily based in participants' original accounts and the observations of those studied.

Criteria for acceptance for UKD will be assessed across units in the UK, and requirements for work- up (such as psychiatric assessment) will be compared, in order to determine whether there are significant variations in practice. We will explore this in relation to the number of unspecified donation enquiries and completed donations.

Data from the questionnaire will be analysed using standard statistical tests to compare variations according to demographic factors, individual characteristics and centre effects.

4. Study Steering Committee

There will not be a Data Monitoring Committee, but there will be a Study Steering Committee (SSC), which will have the following responsibilities:
i) To provide advice, through its Chair, to the Chief Investigator, the Project Sponsor, the Project Funder, the Host Institution and the Contractor on all appropriate aspects of the project
ii) To concentrate on progress of the project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question
iii) The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society
iv) To ensure appropriate ethical and other approvals are obtained in line with the project plan
v) To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
vi) To provide advice to the investigators on all aspects of the project

The SSC will be constituted as follows: An independent chairperson, an independent statistician, one member (not directly involved with the study) from within the Trust, one member external to the Trust, and two service users. An observer from the sponsor and from the CLRN will be invited to attend.

The SSC will meet at 4 to 6 monthly intervals, or more frequently if the Chairperson deems this to be necessary.
There will be a Trial Steering Committee which will manage the project on a regular basis, and which will consist of the members of the project team. This will meet at 3 to 6 month intervals.

5. Data storage

A database will be constructed by the Guys and St Thomas Biomedical Research Centre. Online or paper questionnaires and interview transcripts will be transferred to the database, held on a secure server at either Guys Hospital or Plymouth University, in an anonymised fashion, with password protected access, limited to the study team. Back up will be performed automatically by the Trust systems, and data archiving will be undertaken by the Kings Health Partners Joint Clinical Trials Office, according to their standard operating procedures.

6. Outputs

The data collected will be used together with data from a concomitant NIHR study[1] to achieve several specific outputs, in addition to published manuscripts and conference presentations:

a) A report to NHSBT and the BTS, summarising the findings of the study
b) National guidelines, produced in conjunction with NHSBT and the BTS
c) A protocol for management of those presenting for unspecified donation
d) A report to the Renal Transplant Clinical Reference Group, which reports to NHS England (which commissions transplant services in England), and to the Scottish, Welsh and Northern Irish Departments of Health.

The process for developing these outputs (beyond the first, which will be written by the study team) is as follows:

National Guidelines

The transplant community is small, and there is a widespread desire for guidance on unspecified donation. Existing guidelines on living donation are extensively used by donor teams, and these have been important in changing culture. We recognize that guidelines are not, however, necessarily effective by themselves at changing practice- in this regard, the close liaison that one team member (LB) has with donor coordinators at all transplant centres, and the living donor forum which she organizes, will be vital.
The support of the BTS Clinical Trials Committee for this study is indicative of the close involvement and support of the BTS. There is an existing process for developing guidelines by the BTS, through the BTS Standards Committee. We will convene a small group, including NHSBT and BTS representatives, as well as service users, to draft a guideline, which can be sent to the BTS Standards Committee for consideration. Typically, this is opened for public consultation via the BTS website for a short period, revised and then disseminated to all units.

Commissioners' report

The Chief Investigator is a member of the Renal Transplant Clinical Reference Group (CRG) and has bee involved in drafting Service Specifications for transplantation. He will send a report, which will be drafted with the help of the study team, including service users, to the CRG for discussion and dissemination to NHSE and counterparts in other constituent countries.

[1] Unspecified living kidney donation in the UK: barriers to implementation and delivery - *Potential Donors Study*

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Guy's and St Thomas' NHS
NHS Foundation Trust

PROTOCOL TITLE:

Understanding barriers and outcomes of unspecified (altruistic) kidney donation (BOUnD); a multicentre prospective cohort study

BOUnD

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Study Synopsis

Title	**Understanding barriers and outcomes of unspecified (altruistic) kidney donation (BOUnD); a multicentre prospective cohort study.**
Protocol Short Title/Acronym	BOUnD (Barriers and Outcomes in Unspecified kidney Donation)
Protocol Version number and Date	RQ2 Protocol v2.1, 25/05/2016
Is the study a Pilot?	No
Study Hypothesis	(i) Regional differences in unspecified (altruistic) kidney donor rates will be explained by prospective donor experience e.g. depending on donor interaction with staff members, local expertise and resources. (ii) There is no detrimental impact of unspecified donation on mental and physical health.
Study Duration	December 2015 – April 2018
Methodology	Prospective, mixed-method cohort study recruiting unspecified potential donors (and a directed donor control group). Participants will be recruited to a prospective donor phase shortly after first enquiring about donation (hypothesis i). Those that proceed to donation will continue to a second phase focusing on outcomes over 1 year (hypothesis ii). Nested qualitative studies will explore experiences of the process in donors and non-donors using structured interviews. Focus groups will be used to guide questionnaire design and interview topic guide.
Sponsor name	Guy's and St.Thomas' NHS Foundation Trust R&D Office
Chief Investigator	Prof Nizam Mamode
REC number	15/SC/0637
Medical condition or disease under investigation	Unspecified (altruistic) living kidney donation
Purpose of study	To identify methods of improving the process of unspecified (altruistic) donation in the UK and inform the development of national guidelines
Primary objective	Physical and mental-health related quality of life, anxiety, depression, life satisfaction and self-esteem
Secondary objective (s)	1. Barriers to unspecified kidney donation 2. Economic outcomes of unspecified kidney donation
Number of Subjects/Patients	(i) 16 - 24 participants (focus groups); (ii) 1024 participants (questionnaires), as follows: Test group: 224 unspecified donors that proceed to donate and 400 unspecified donors that withdraw. Control group: 200 directed / specified donor controls that proceed to donate and 200 directed / specified potential donors who did not proceed; (iii) 45 participants (interviews),
Study Design	Prospective cohort study
Endpoints	(i) time from enquiry to donation (for those that proceed to donation) (ii) mental and physical health at 3 and 12 months post donation / withdrawal, compared to directed donor controls
Inclusion Criteria	Individuals contacting a UK transplant centre wishing to become specified or unspecified kidney donors or those that have already begun the work-up process
Exclusion Criteria	Foreign nationals that are unable to donate altruistically in their countries of residence or prisoners
Statistical Methodology and Analysis	Quantitative analysis: (i) Time-to-event analysis using Cox regression; (ii) propensity score weighted mean differences at 12 months using

	linear mixed effects models Qualitative analysis: Framework (thematic) approach

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Introduction

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The UKD participants in our PPI sessions and previous qualitative study identified a number of issues in the process that they felt acted as deterrents and may have affected the decision by others to donate (3). They found difficulties in knowing how to make initial contact with the transplant centre. The negative attitudes of transplant professionals were also off-putting and this continued whilst donors were in hospital, with some experiencing ignorance and hostility from ward staff which made them feel guilty for "choosing to become a patient". The length of the workup process was also commonly an issue, which donors found frustrating. Indeed, when considering living donor chains, most donors would have liked to have participated had it been easier and the timing more predictable. Many were working or had other commitments and the unpredictability of when the donation would take place meant that many were not in a position to oblige. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also a difficult experience for donors who felt that they had to prove their sanity (3).

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We therefore wish to perform a comprehensive assessment of the unspecified donor programme in the UK, in order to determine the extent and reasons for variation in practice, ascertain barriers to donation, and determine the economic costs and benefits of an unspecified donation. We will also assess outcomes after unspecified donation, in order to provide detailed evidence for transplant teams' decisions about potential donors.

2 Study Objectives and Design

2.1. Study Objectives

Aims: This study aims to perform a comprehensive assessment of unspecified altruistic donor programme in the UK to explore variation between centres and identify barriers and facilitators to donation for those that have expressed a willingness to do so.

Objectives:
(i) Identify and explain regional variations in unspecified kidney donation (UKD), based on donor interaction with staff members, local expertise and resources, and other economic variables
(ii) Establish prospectively the psychosocial, physical and economic outcomes of individuals undertaking unspecified kidney donation, compared to specified donors.

Outcomes

Primary outcomes: Physical and mental health-related quality of life.
Psychosocial health outcomes:

- quality of life (SF-12)
- anxiety (General Anxiety Disorder-7 (GAD-7)
- depressive symptoms (Patient Health Questionnaire-9 (PHQ-9)
- life satisfaction (Satisfaction With Life Scale)
- self-esteem (Rosenberg Self-Esteem Scale)
- Decision Regret Scale
- Flourishing Scale
- in house questionnaire

Physical health outcomes
NHSBT pre and post donation physiological and clinical outcomes

Secondary outcomes:
- Barriers to donation (qualitative data from interviews and focus groups)
- Healthcare resource utilisation data (Client Service Receipt Inventory (CSRI))

2.2 Recruitment Strategy

The primary study group will comprise all those who approach a transplant team in any UK transplant centre, offering to donate a kidney to a stranger over a three year period (2015 – 2018). Follow-up will take place up to 2020.
The control study group will comprise all those who approach a transplant team across the UK offering to donate a kidney to a family member or friend ("specified donors").
The study will use the same national professional transplantation network to collaborate with transplant co-ordinators and living donor nurses willing to participate in the recruitment process. Participant recruitment will take place subsequent to local R&D approval and transplant centres being identified and approved as participant identification centres (PIC).

UK Transplant co-ordinators will be briefed regarding the aims, objectives and recruitment criteria of the study. Communication and liaison with local transplant co-ordinators will be through Ms Lisa Burnapp (Lead Nurse - Living Donation, Organ Donation and Transplantation, NHSBT), who is a collaborator in the study.

Focus Groups Recruitment.

The Focus Groups represent the smallest aspect of the study and serve to help fine-tune the questionnaire design and interview topic guides. As such, only two focus groups will take place in centres such as Guy's Hospital (London) or Plymouth Derriford Hospital, where the study team has long-standing collaboration links with the donation teams. The local transplant co-ordinator or living donation nurse specialist (living donation team) will approach individuals that have recently donated or have withdrawn from donation and explore whether they would be interested in considering the study. Those that would be interested will be given the contact details of our research team or asked if they would agree to be contacted by us. The research team would then be able to provide further information and lead the consent and recruitment process.

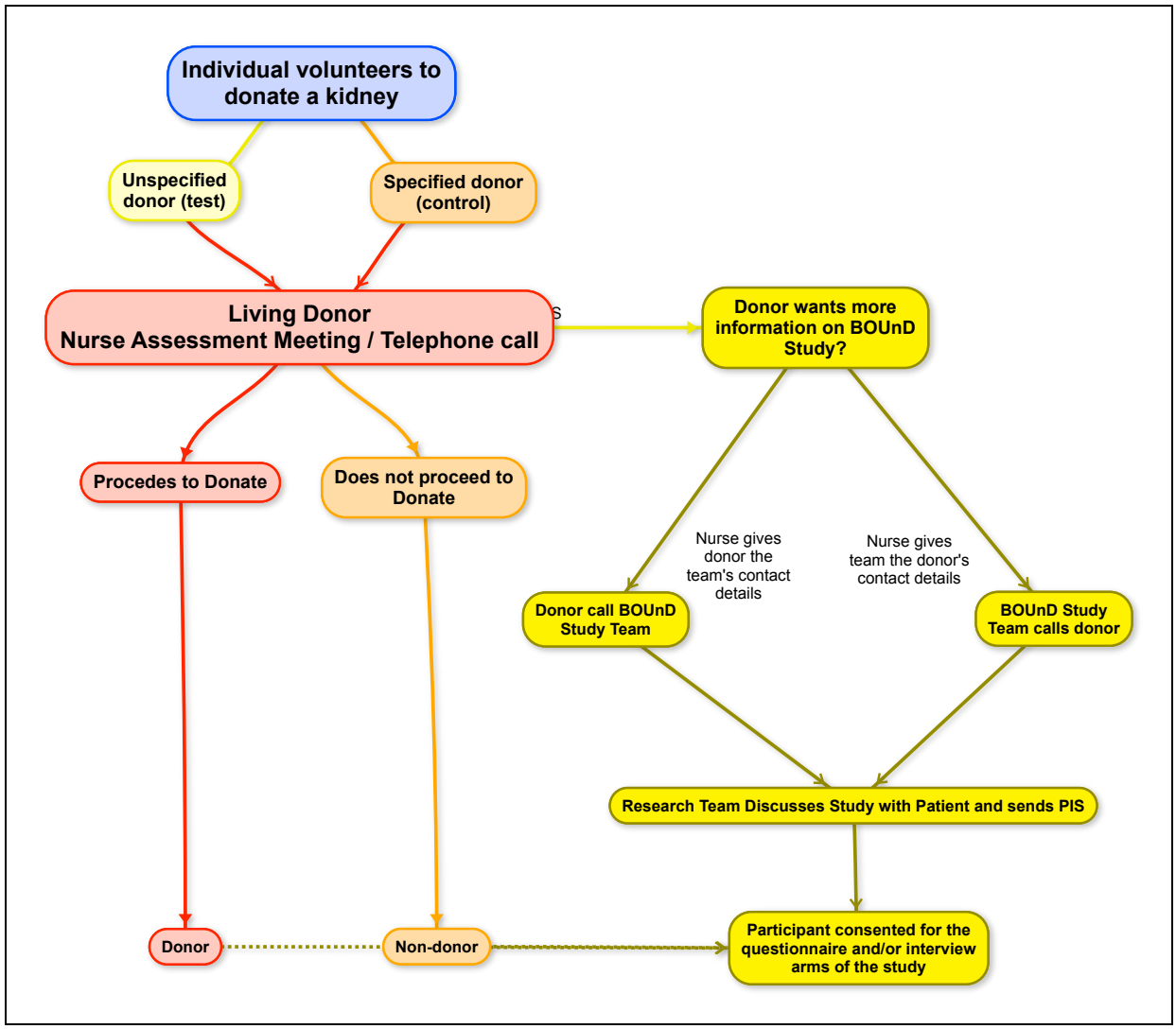
Interview and Questionnaire Recruitment

Transplant co-ordinators at each of the 23 UK transplant centres will ask potential donors approaching their units if they would be interested in participating in the study. This does not equate to being consented into the study, but simply facilitates further information gathering regarding our work. This will occur either at the initial telephone contact between the potential donor and the transplant centre or at the first clinic consultation with the transplant co-ordinator, depending on local practice protocols. Potential donors already being worked-up will also be given the opportunity to contact the study team for recruitment into the study.

Once a potential donor agrees to find out more about the study, the local transplant co-ordinator will facilitate contact with the research team by either giving the team's contact details to the potential donor, or (with the donor's permission) pass on their preferred contact details to the research team. The study's manager will be notified of individuals interested in the study. The research team will contact potential participants by phone, email or post to provide further information, discuss the study and provide participant information sheets. Those that indicate a willingness to participate will be enrolled in the study subsequent to completion of the relevant consent forms. The emphasis of the study is to cause minimal inconvenience to local transplant units and human resources. As such, once a transplant co-ordinator has facilitated the contact between the potential donor and the study team, no further involvement will be needed and all subsequent administrative and research work will be co-ordinated by the study's manager or investigators.

The control group will consist of individuals who are donating to friend or relative (specified donors). Control (specified) donors will be recruited in a similar consecutive manner by transplant co-ordinators. Control donors

that do not procede to specified donation will still be asked to participate in the study in order to provide robust data for comparison.



2.3 Study Design

Focus Groups

Two focus groups with potential donors will be undertaken. One focus group will involve those that have proceeded to donation. The other will involve potential donors that have withdrawn or been withdrawn from the donation process. 8-12 participants will take part in each focus group. The focus groups will not involve control participants. The physical location of the focus groups will be a suitable hospital venue, such as a conference room or a postgraduate centre. Recruitment will be undertaken as described above. The focus group discussion will be audio-recorded and transcribed for future analysis.

Data regarding socio-demographic (including the area postcode), physical, psychological characteristics, and resource use variables will be collected at baseline (shortly after contacting the transplant centre).

Questionnaires

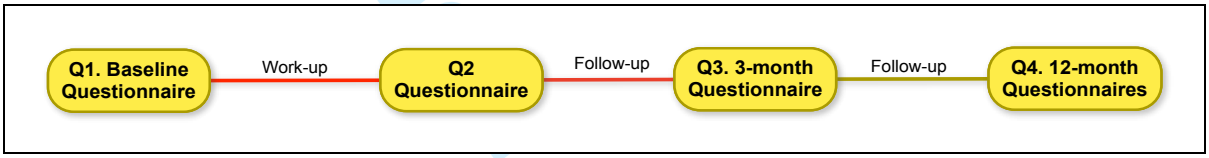
The questionnaire part of the study will have four research populations on which questionnaire data will be collected at four intervention points (Q1-Q4): baseline, preoperatively and at 3 and 12 months post-donation in the form of a study questionnaire bundle. Additional data (such as gender, age or ethnic group) will be collected at the time of recruitment into the study.

Q1. Baseline data will be collected within the first week of recruitment to assess the participant prior to the work-up process.

Q2. Pre-operative data will be collected in the 2 weeks preceding donation surgery (+/- 3 days). This will not be collected on the day of surgery in order to avoid confounding errors. This will mark the end of the work-up period. For those that withdraw from the study a longer period of time may be needed to capture these participants. In this case, the Q2 intervention point will span from the time of withdrawal to 3 weeks post withdrawal.

Q3. 3 months post donation or withdrawal

Q4. 12 months post donation or withdrawal



The four study populations will include:

1. Those that **proceed to donation** ('unspecified donors') – Test 1 population

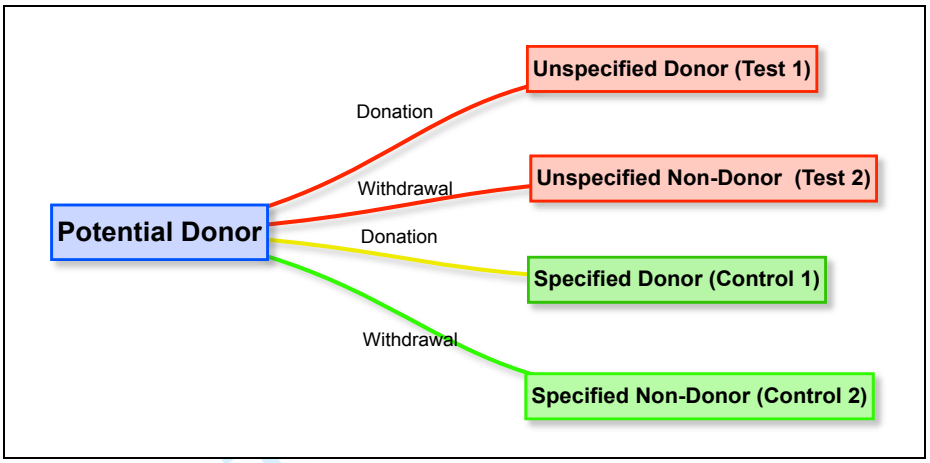
2. Those that **do not to donate** ('unspecified non-donors') due to donor's choice or withdrawal by the clinical assessors – Test 2 population

3. Those that undergo **living donation to a known individua**l ('specified donors'), which will act as **control group 1**

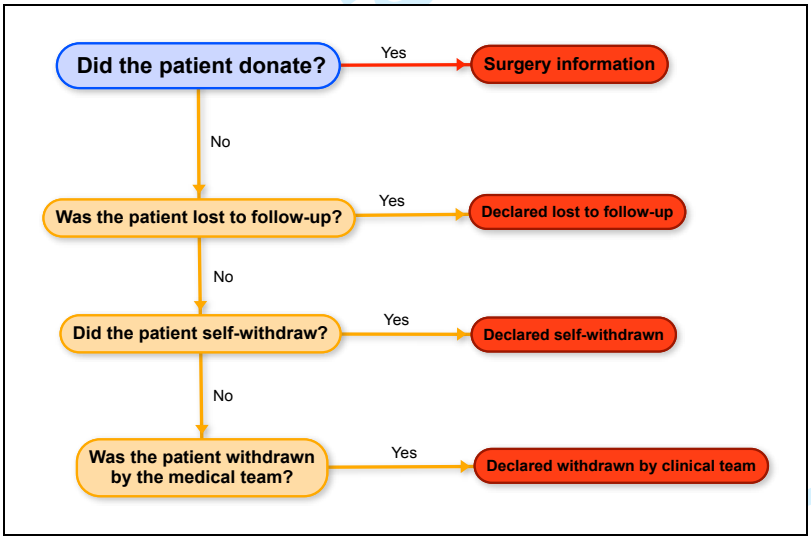
4. Those **intending to donate to a known individual that do not donate** ('specified non-donors'), which will act as control group 2

To ensure feasibility of the study questionnaire burden will be tested and considered in conjunction with the PPI group.

Questionnaire validation will be carried out by asking 20-30 volunteers that are previous kidney donors or future specified donors to review the in-house questionnaires. This will involve a facilitated think-aloud exercise to identify any face validity issues related to the newly developed questions. This exercise will result only in minor changes to the question structure, phrasing or answering methods. The questionnaire content validity will have already been validated by 15 members of the research team who will review the developed questionnaires on at least three occasions.



Participants who do not proceed to donation will be identified either by regularly checking with their local transplant coordinators (every two weeks) or by self-referral to the study team. The study researchers will then ascertain whether the patient self-withdrew or was withdrawn by the clinical team. The following data collection algorithm will be used:



Interviews

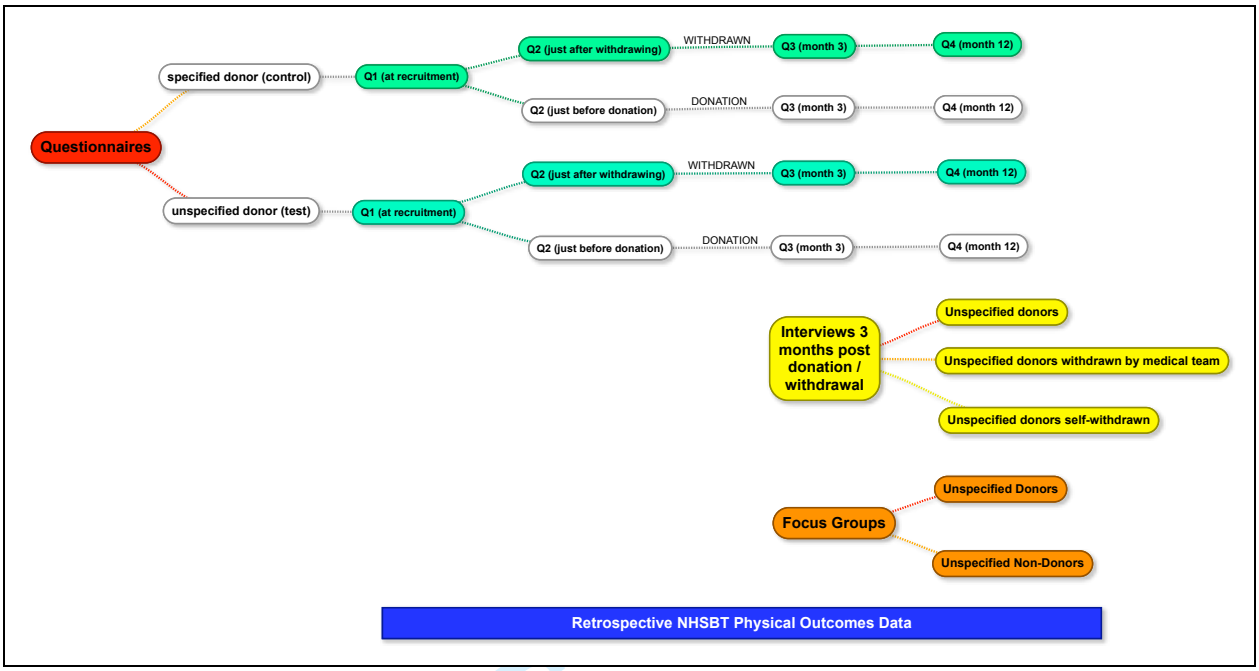
Qualitative interviews will also be completed with a sample of 15 donors who completed their donation, 15 who withdrew and 15 who were withdrawn by the transplant team from the process. Participants will be asked about their experience of the donation process and services, barriers and enablers to donation and outcomes from either donating or withdrawing from the process. The interview questions have been informed by our previous grounded qualitative work, focus groups and current research. Participants will be purposively sampled to ensure a range of demographics and experiences are captured.

Interviews will take place at 3 months following donation or withdrawal from the process.

Other Study Data

Linkage to the NHS Blood and Transplant records will provide physiological outcome data as well as information donation procedure for all donors. Physiological data will be collected pre- and post-donation, as well as at 12-months following donation, as per national donor follow-up protocol. This is described in Appendix 4. NHSBT data will be collected retrospectively once a participant completes the 12-month questionnaire, or earlier should they choose to withdraw from the study. Consent to obtain NHSBT data will be obtained through the initial study participation consent form. Subsequent to this a formal request for data access from the NHSBT will be made.

2.4 Study Outline



2.5 Trial Statistics and Data Analysis

The study endpoints will be:

i) time from enquiry to donation (for those that proceed to donation)

ii) mental and physical health at 3 and 12 months post donation, compared to directed donor controls

All primary analyses will be undertaken by the study statistician and investigator / research fellow in accordance with a predetermined analysis plan.

Descriptive analysis will be used to describe the proportion of people who withdraw or proceed to donation, and the reasons for failing to proceed. The analysis will include all individuals enquiring about donation, with the dependent variable an indicator for each proceeding to donation. Centre-level structural and attitudinal factors identified in our parallel study (IRAS 170483) will be included in the models to determine whether these variables explain variation in donation rates.

Descriptive analysis will be used to compare baseline variables for individuals that express an interest in donation that: i) the transplant team withdraw from donation; ii) those who decide not to proceed; iii) those that proceed to donation; and iv) the specified kidney donor control group, who either proceed or do not proceed to donate. Linear or logistic mixed-effects models will be used to estimate difference in outcome variables at the 3 and 12 months follow-up assessments between the groups at the outcome assessments. Group membership and follow-up assessment (time) will be included in the models as dummy variables. Interaction terms for group and time will allow for assessments of differences at individual time points. Models will adjust for potential demographic confounders measured at baseline (e.g. age, sex, education, ethnicity) and the baseline level of the outcome variable. Missing outcome data is under the assumption that data is missing at random. Sensitivity analysis will be performed to assess this assumption.

The analysis of qualitative data will be performed using the Framework (thematic) approach as described above.

3. Sample Size and Selection

Focus Groups

The two focus groups will recruit 8-12 potential or actual unspecified kidney donors each. These will be volunteers identified by UK transplant co-ordinators.

Questionnaires

Consecutive people contacting each of the transplant centres in the UK between April 2015 and Feb 2018 will be recruited to participate in the study. Based on current trends we conservatively estimate that there will be at least 279 kidney transplants from unspecified altruistic donors during that period. Indeed, there were 107 UKD in the UK in 2013. Assuming that the proportion of individuals contacting transplant centres who go on to donate remains stable (36%, based on data from Portsmouth in 2012), we expect that 780 people considering unspecified altruistic donation will contact transplant centres during that period. Based on our previous retrospective study, we expect at least a 80% recruitment rate- that is, 624 in total, of which 224 will go on to donate). This recruitment rate is higher than is typical for longitudinal studies but justifiable given the population being studied. A sample size of 624 will provide sufficient precision to estimate the 95% confidence interval for proceeding to donation to within ±4% overall, and to within ±18% for each centre. In summary we aim to recruit 224 who have undergone unspecified donation and 400 who failed to donate.

The control group will recruit 200 people who are donating to friend or relative (specified donors) and 200 individuals that intend to donate to a friend or relative but do not (specified non-donors). Based on our retrospective study we expect a recruitment rate of 80%. Therefore we will need to approach 500 specified donors. Given a stable rate of approximately 1000 specified donations per year across the UK, we anticipate that we will be able to recruit the control group using the same three-year recruitment window as the main cohort. If there is no difference between the unspecified altruistic and specified donors on the physical and psychological variables at 12 months, it will be possible to determine that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of a standardised mean difference of 0.3, which is deemed to be the smallest acceptable clinically meaningful difference – this allows for 20% missing data due to drop-out, at a significance level of 5% with 90% power (14). These individuals will be recruited through transplant co-ordinators nationally.

Interviews

Qualitative interviews will also be completed with a sample of 15 donors who completed their donation, 15 who withdrew and 15 who are withdrawn by the transplant team from the process. These individuals will be identified from the initial cohort of patients that approached transplant centres with the intention to donate altruistically.

Recruitment Targets

The following recruitment targets have been set:

Focus Groups: 2 focus groups of 8-12 previous donors and 8-12 non-donors.
Total: 16-24 participants

Questionnaires:
624 potential donors (test population)
224 who have donated
400 who did not donate

200 specified donors (control population 1) and 200 specified non-donors (control population 2)
Total: 1024 participants

Interviews:
15 potential donors that donated
15 potential donors that did not donate (self-withdrawn)
15 potential donors that did not donate (withdrawn by clinical team)
Total: 45 participants

Inclusion criteria

Any individual contacting a transplant centre to enquire about unspecified donation, who proceeds beyond the initial telephone conversation, and is able to give informed consent will be considered as a potential study participant. Non-English speakers will be included and adequate translation facilities will be provided. Individuals who have already begun the donation work-up process at the time of study commencement will also be eligible for recruitment provided they are more than 2 weeks away from donation. Control participants will be recruited from those individuals contacting a centre in order to donate to a known individual.

Exclusion criteria

Any individual who declines to participate at any stage will be excluded from the study. Individuals lacking capacity will also be excluded as will any individual not eligible to donate in UK. This includes foreign nationals who are unable to donate altruistically in their country of residence or prisoners.

4. Study procedures

4.1 Consent

The study research fellow or study manager will be notified of any eligible individuals by UK transplant co-ordinators. Potential participants will be invited to participate in the study by phone or post and will be provided with an information sheet prior to the consent process. Separate consent forms have been designed for each of the three study arms (focus groups, questionnaires and interviews). Where necessary these will be translated or explained by an interpreter. Individuals who agree to participate will be asked to complete a baseline assessment, in either paper or online format. Pre-operative assessments will be completed one week prior to donation.

The following study documents have been created (Appendix 5):

- PIS Unspecified Donors Focus Group
- PIS Unspecified Donors Questionnaire and Interview Group
- PIS Specified (Control) Donors Questionnaire and Interview Group
- Consent Form Unspecified Donors Focus Group
- Consent Form Unspecified Donors Interview Group

- Consent Form Unspecified Donors Questionnaire Group
- Consent Form Specified (Control) Donors Questionnaire Group

4.2 Follow up Procedures

Follow-up assessments will be sent by post (and made available to complete online). To minimise loss to follow up anyone who has failed to return their 12 month follow up assessments within 14 days will be contacted by phone with the aim of collecting information on at least the primary outcome variable.

4.3 Maximizing Response Rates

Unspecified donors are highly motivated individuals, who, in our experience, are enthusiastic about participation in studies that may help other donors. The response rate of 74% in our previous study, whilst too low for definitive conclusions in a retrospective study, is nevertheless higher than expected for a questionnaire survey (6).

However, it is vital that response rates are high enough to accurately capture outcomes, and we aim to achieve this as follows:

I. Participants presenting for donation will be contacted directly by the research fellow or study manager (usually by telephone or email). Non-responders will be contacted on 2 occasions, including using an alternative method (such as a written letter and/or telephone calls outside standard working hours).
II. Participants will be given the opportunity to return documents in a freepost envelope or by completing an online form.
III. The trial manager will contact all 23 transplanting centres on a regular basis to ensure that those who present for unspecified donation have been considered for inclusion in the study.
IV. One team member (LB) already has close and regular contact with donor co-ordinators (who are the first point of contact for any donor presenting at a transplant centre) in all transplanting centres. She will send reminders to all co-ordinators regularly to ensure continued referral of potential participants.

We will monitor the success of this approach using the internal pilot study described in the protocol.

4.4 End of Study Definition

Completion of the final questionnaire (at 12 months) of participants recruited in the 3-year period will mark the end of the study.

5. Laboratories

No laboratory facilities will be used for this study

6. Assessment of Safety

6.1 Emotional or Psychological Distress

If any clinical concern is identified by the research team from the questionnaires or interviews (for example suicidal thoughts, or severe depression) the local clinical team (transplant donor co-ordinator) will be informed with a view to referral to the local psychological or counselling service; we used this approach previously in our retrospective study. The provision of this facility is part of our commitment to good practice and we do not anticipate this will be needed. In the unlikely event that concern is raised about a participant who has withdrawn from the donation process early in the assessment period and has no further contact with their local transplant

unit, we will contact their GP directly. The GP contact details will be collected as part of the recruitment baseline data.

6.2 Impact of study on decision to donate

Focus Groups. The Focus Groups will be with altruistic kidney donors who have already completed or have withdrawn from the donation process. As such, the study will not be able to impact on their decision to donate from the perspective of the focus group alone.

Interviews. The qualitative interviews will be performed prospectively and take place three months after donation or withdrawal from the donation process. This is to avoid any undue influence on the participant's decision to donate. The interviews will be conducted by experienced qualitative researchers who have interviewed both altruistic kidney donors and donors withdrawn from the process. The REC applications associated with these previous projects are: Understanding Barriers and enablers to altruistic kidney donation v1.14/SW/1105 and 10/H0203/11-Understanding the experiences of altruistic kidney donors. (Clarke, A., Mitchell, A., & Abraham, C. 2013. Understanding donation experiences of unspecified (altruistic) kidney donors. British Journal of Health Psychology.)

Questionnaires. The questionnaires which will be used are validated and widely used research tools which are regularly employed in the fields of social science and psychology. We have previously used similar tools in our research with no significant impact on the participants' mental or physical health.

6.3 Sensitive questions

Additional questions that will be formulated as a result of the focus group data (in addition to the already validated questionnaires) will be discussed amongst the study research group that consists of psychologists, transplant surgeons and nurses who are highly aware and sensitive to the process of altruistic donation as a result of their extensive clinical experience. Furthermore, two members of the 'Give a Kidney Charity', who represent the altruistic donor community, will review and be involved in the development of any further questions. Any new questions that would potentially impact on the decision to donate will be excluded from the questionnaire bundle

6.4 Ethics Reporting

Reports of related and unexpected SAEs will be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. The form will be completed in typescript and signed by the chief investigator. The Coordinator of the main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt should be sent to the R&D Directorate.

No SAE are expected for this study.

7. Trial Steering Committee

7.1 Study Steering Committee

The study does not have a Data Monitoring Committee, but there is a Study Steering Committee (SSC), which will have the following responsibilities:

i) To provide advice, through its Chair, to the Chief Investigator, the Project Sponsor, the Project Funder, the Host Institution and the Contractor on all appropriate aspects of the project

ii) To concentrate on progress of the project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question

iii) The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society

iv) To ensure appropriate ethical and other approvals are obtained in line with the project plan

v) To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
vi) To provide advice to the investigators on all aspects of the project

The SSC will be constituted as follows: An independent chairperson, an independent statistician, one member (not directly involved with the study) from within the Trust, one member external to the Trust, and two service users. An observer from the sponsor and from the CLRN will be invited to attend.

The SSC will meet at 4 to 6 monthly intervals, or more frequently if the Chairperson deems this to be necessary.

The study steering committee has the following members:

Chair
Prof Kenneth Farrington
Consultant Renal Physician
ken.farrington@nhs.net

Independent statistician
Dr Matthew Robb
NHBST

One member (not directly involved with the study) from within the Trust
Dr David Game
Consultant Renal Physician

One member external to the Trust:
Dr Sian Griffin
Consultant Renal Physician

Previous Service Users
Mr Peter Cordwell

Mr Nicholas Crace

7.2 Trial Management Committee

The Trial Management Committee manages the project on a regular basis. It consists of members of the project team and meets at 3 to 6 month intervals. Minutes and agendas are issued in the regular manner. The committee has two permanent PPI members representing the 'Give a Kidney' Charity.

8. Ethics & Regulatory Approvals

15/SC/0637
South Central – Berkshire B Research Ethics Committee
Health Research Authority
Bristol HRA Centre, Level 3, Block B,
Whitefriars, Lewins Mead, Bristol BS1 2NT
HRA (Bristol Centre): 0117 342 1382 | www.hra.nhs.uk, nrescommittee.southcentral-berkshireb@nhs.net

9. Data Handling

Confidentiality

A database will be constructed by the Guys and St. Thomas Biomedical Research Centre. Online or paper questionnaires and interview transcripts will be transferred to the database, held on a secure server at either Guys Hospital or Plymouth University, in an anonymous fashion, with password protected access. Access to the database will be limited to the study researchers, Chief investigator and study manager. Participant data will be managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

Each patient will have a unique study identity number which will avoid the use of patients' hospital numbers, NHS numbers, dates of birth or names. The Chief Investigator will have a separate key linking the study identification number with identity of the study participants. The study key information will be kept in a separate password secure and locked environment.

Back-up will be performed automatically by the Trust systems, and data archiving will be undertaken by the Kings Health Partners Joint Clinical Trials Office, according to their standard operating procedures.

Record Retention and Archiving

All records will be kept in secure conditions. When the research trial is complete the records are kept for a further 5 years.

Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

Non-Compliance

The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

10. Finance and Publication Policy

10.1 Funding

The research is funded by the National Institute of Health Research (NIHR) HS&DR Award (13/54/54), with a total value of £872,756.

National Institute of Health Research
University of Southampton
Alpha House
Enterprise Road
Southampton
SO16 7NS

The funds will be managed centrally by the research team at Guy's Hospital and distributed to collaborating units according to a collaboration agreement, which has been negotiated by the relevant academic, financial and legal departments within the collaborating universities and hospitals.

10.2 Outputs

There will be several specific outputs in addition to published manuscripts and conference presentations:

a) A report to NHSBT and the BTS, summarising the findings of the study
b) National guidelines, produced in conjunction with NHSBT and the BTS
c) A protocol for management of those presenting for unspecified donation
d) A report to the Renal Transplant Clinical Reference Group, which reports to NHS England (which commissions transplant services in England), and to the Scottish, Welsh and Northern Irish Departments of Health.

The process for developing these outputs (beyond the first, which will be written by the study team) is as follows:

National Guidelines

The transplant community is small, and there is a widespread desire for guidance on unspecified donation. Existing guidelines on living donation are extensively used by donor teams, and these have been important in changing culture. We recognize that guidelines are not, however, necessarily effective by themselves at changing practice- in this regard, the close liaison that one team member (LB) has with donor co-ordinators at all transplant centres, and the living donor forum which she organizes, will be vital.
The support of the BTS Clinical Trials Committee for this study (attached) is indicative of the close involvement and support of the BTS. There is an existing process for developing guidelines by the BTS, through the BTS Standards Committee. We will convene a small group, including NHSBT and BTS representatives, as well as service users, to draft a guideline, which can be sent to the BTS Standards Committee for consideration. Typically, this is opened for public consultation via the BTS website for a short period, revised and then disseminated to all units. The leads for this work will be Prof N Mamode and Ms L Burnapp.

Commissioners' report

The Chief Investigator is a member of the Renal Transplant Clinical Reference Group (CRG) and has been involved in drafting Service Specifications for transplantation. He will send a report, which will be drafted with the help of the study team, including service users, to the CRG for discussion and dissemination to NHSE and counterparts in other constituent countries.

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SF-12v2™ Health Survey. 1992-2002 by Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved. SF-12® is a registered trademark of Medical Outcomes Trust. (IQOLA SF-12v2 Standard, English (United Kingdom) 8/02)

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Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

RQ2 Study Protocol V2.1
25.05.2016

Appendix 1

Appendix 1. Projected number of unspecified kidney donors to 2020

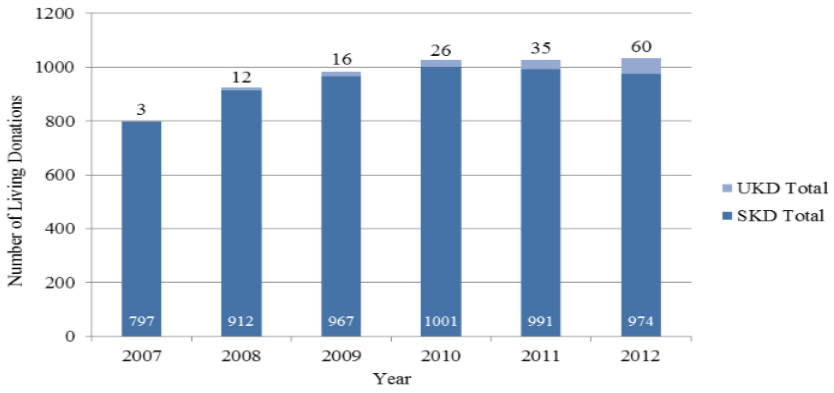

Figure 1. Number of living kidney donations in the UK by unspecified and specified kidney donors

Figure 1 shows the total number of living kidney donations in the UK per year, separated by unspecified and specified type. Over the six year period shown there has been an increase in the total number of living donations. Since 2010, the increase is driven by unspecified donations, with the number of unspecified donations actually falling.

Figure 2 and Table 1 below shows projections for the number of unspecified (altruistic) kidney donors to 2020 by two methods. The first method fits a linear rate of increase based on the past trend. The second method assumes a non-linear (quadratic) rate of change. The quadratic method fits the observed data best but this is no indication it provides a more accurate projection.

With recruitment between March 2015 and Feb 2018 we can expect between 279 (linear = 83+93+103) and 493 (non-linear = 131+163+199) donors based on the projections. The expected sample size will be based on the more conservative linear estimate. An even more conservative estimate would assume rates staying stable at the 2012 figures. This would mean the expected sample size of 180 (60+60+60).

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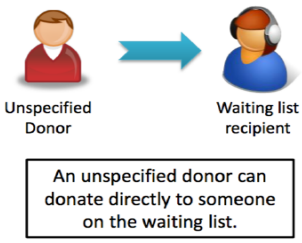
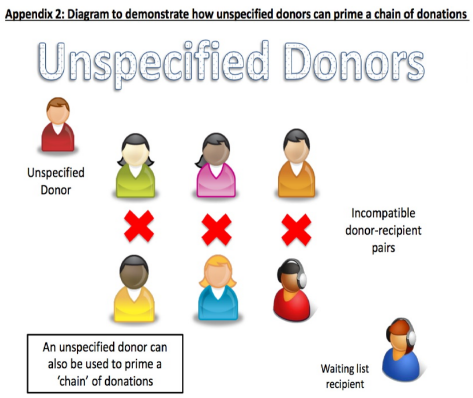
Appendix 2a

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



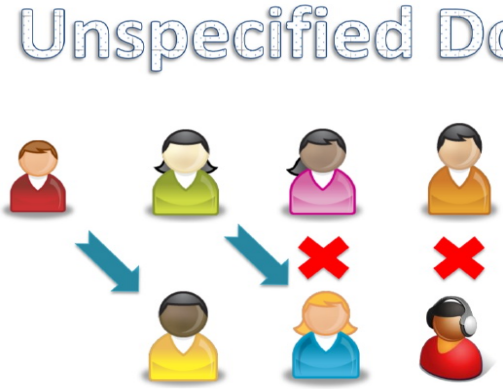
Appendix 2b



Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations

Appendix 2d

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



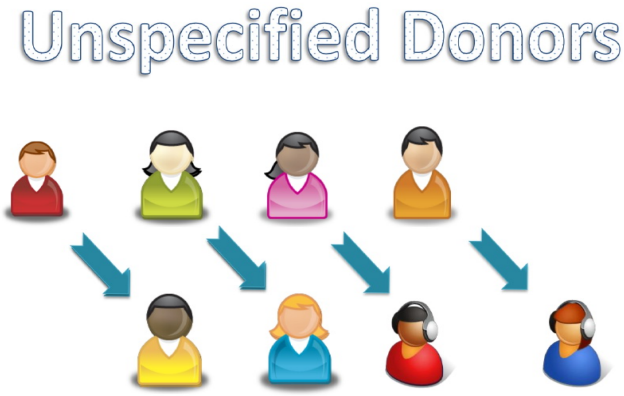
RQ2 Study Protocol V2.1
25.05.2016

Appendix 2e

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations

Appendix 2f

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



Appendix 3

BOUnD

Appendix 3: Topic list: Qualitative interviews

RQ2 Study Protocol V2.1
25.05.2016

Appendix 4:

		Phase 1: Potential donors				Phase 2: Outcomes			
		Recruitment		Pre donation		Donation		Follow-Up	
	Data (source)	Pre-enrolment	Enrolment	Baseline	Pre-op (1 week)	Surgery	Post-op	Follow-up 3 months	Follow-up 12 months
Enrolment	Initial contact (Centre)	X							
	Referral (Centre)	X							
	Eligibility screen (Trial manager)		X						
	Informed Consent (Trial manager)		X						
Assessments	Baseline demographic data			A					
	Personality: TIPI (Questionnaire)			A					
	Social support: MSPSS (Questionnaire)			A	A			A	A
	Peri-operative physical outcome data (NHSBT)				A		D		D
	Surgical procedure data (NHSBT)					D			
	Withdrawal (Questionnaire & Centre data)			W	W				
	Rosenberg (Questionnaire)			A	A			A	A
	SWLS (Questionnaire)			A	A			A	A
	PHQ9 & GAD7 (Questionnaire)			A	A			A	A
	Flourishing Scale			A	A			A	A
	Decision Regret Scale							A	A
	SF12 (Questionnaire)			A	A			A	A
	Client Service Receipt Inventory (Questionnaire)			A	A			A	A
	In-House Questionnaire			A	A			A	A

X= recruitment and centre level data (pre-consent)
A= Data from all potential donors
D= Data for donors only
W= Data for withdrawn only

BMJ Open

Understanding barriers and outcomes of Unspecified (non-directed altruistic) kidney donation from both professional's and patient's perspectives: Research protocol for a national multicentre mixed-methods prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015971.R2
Article Type:	Protocol
Date Submitted by the Author:	28-Jun-2017
Complete List of Authors:	Gare, Rebecca; Guy's and Saint Thomas' NHS Foundation Trust, Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust/ King's College Londo Gogalniceanu, Petrut; Guy's and Saint Thomas' NHS Foundation Trust, Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust / King's College London Maple, Hannah; Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust / King's College London London, UK Burnapp, Lisa; NHS Blood and Transplant, NHS Blood and Transplant; Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust / King's College Londo Clarke, Alexis; University of Plymouth, School of Psychology, University of Plymouth Williams, Lynsey; University of Plymouth, School of Psychology, University of Plymouth Norton, Sam; King's College London, Institute of Psychiatry, Psychology & Neuroscience, King's College London Chilcot, Joseph; King\'s College London, Institute of Psychiatry, Psychology & Neuroscience, King's College London London Gibbs, Paul; Portsmouth Hospitals NHS Trust, Renal Transplant Department, Portsmouth Hospitals NHS Trust Mitchell, Annie; University of Plymouth, School of Psychology, University of Plymouth McCrone, Paul; King's College London Draper, Heather; The University of Birmingham, Centre for Biomedical Ethics; Warwick Medical School, Division of Health Sciences Mamode, Nizam; Guy's and Saint Thomas' NHS Foundation Trust, Department of Renal Transplantation, Guy's and St Thomas' NHS Foundation Trust / King's College London London, London, UK
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Renal medicine
Keywords:	Renal transplantation < NEPHROLOGY, Chronic renal failure < NEPHROLOGY, kidney, altruistic/ unspecified donation

Understanding barriers and outcomes of Unspecified (non-directed altruistic) kidney donation from both professional's and patient's perspectives: Research protocol for a national multicentre mixed-methods prospective cohort study

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Abstract

Introduction: Living donation accounts for over one third of all kidney transplants taking place in the UK[1]. The concept of anonymously donating a kidney to a stranger (non-directed altruistic or unspecified kidney donation (UKD)) remains uncomfortable for some clinicians, principally due to concerns about the motivations and long-term physical and psychological outcomes in this donor group.

Aims: The research programme aims to provide a comprehensive assessment of the unspecified donor programme in the UK. It aims to identify reasons for variations in practice across centres, explore outcomes for donors, ascertain barriers and facilitators to UKD for those who have expressed a willingness to donate, and assess the economic implications of unspecified donation.

Methods: The research programme will adopt a mixed-methods approach to assessing UKD nationally using focus groups, interviews and questionnaires. Two study populations will be investigated. The first will include transplant professionals involved in unspecified kidney donation. The second will include a five-year prospective cohort of individuals who present to any of the 23 UK transplant centres as a potential unspecified living kidney donor. Physical and psychological outcomes will be followed up one year following donation or withdrawal from the donation process. A matched sample of specified donors (those donating to someone they know) will be recruited as a control group. Further qualitative work consisting of interviews will be performed on a purposive sample of unspecified donors from both groups (those who do and do not donate). **Dissemination:** The findings will be reported to NHS Blood and Transplant and the British Transplant Society with a view to developing national guidelines and a protocol for the management of those presenting for unspecified donation.

The study is registered with the International Standard Randomised Controlled Trial Number (ISCRTN) – 23895878

Strengths and Limitations of this study:

Strengths

- This is a prospective, mixed methods study using both qualitative and quantitative methods to answer complex questions regarding barriers to service delivery
- This is a widely multi professional study drawing experiences from a variety of fields (surgery, medicine, psychology, psychiatry, ethics, NHS Blood and transplant)
- This study will assist in the development of national guidelines and a protocol in conjunction with NHS Blood and Transplant and The British Transplant Society.
- The study method will capture resource utlisation by unspecified donors providing a novel understanding of the economic implications of the unspecified donation process.

Limitations

- There is a risk of not capturing individuals who are disengaged / disappointed in the process of unspecified kidney donation
- The study relies on a large number of individuals participating and is based on the assumption that unspecified donation rates with continue to occur at the same rates as prior years
- This study relies on the referrals of donors from co-ordinators across the country and we may not be able to capture every enquiry or expression of interest.

Introduction

Live donor kidney transplant recipients have the best outcomes in terms of survival and function post transplantation. Currently over one third of all kidney transplants taking place in the UK are from living donors. A growing subset of living donors consists of individuals who choose to donate a kidney to someone that they have not previously met. These are called 'unspecified kidney donors' (UKDs) or 'non-directed altruistic' donors. Over 500 unspecified donations have taken place in the UK since the practice was introduced in 2006 and it currently accounts for approximately 11% of living donations per year[1].

Recipients of living donor kidneys are provided with a long lasting, high quality organ that is usually sufficient to avoid dialysis for an extended period of time[2]. Organs from UKDs can provide this opportunity for those without a living donor, some of whom would have a low chance of receiving a deceased donor organ from the waiting list due to sensitisation challenges. Additionally, UKD's organs can be further utilised by introducing them into the National Kidney Sharing Scheme. This involves kidney exchanges between pairs of donor and recipients who cannot otherwise proceed due to immunological incompatibility. A kidney from a UKD can be used to convert these exchanges into a 'chain' primed by the UKD (figure 1). In this way, the UKD donates to the first recipient, whose donor then subsequently donates to another recipient, and so on. The chain then terminates with donation to an individual on the deceased donor waiting list. In the US this has resulted in 30 transplants occurring from a single UKD[3]. In the UK, 47% of UKDs have been used to prime short chains of two transplants, and the UK Living Donor Strategy aims for 75% to be used for chains, with 3 transplants in each chain, by 2020[4].

Despite the increase in UKD in the United Kingdom the concept remains illegal in many European countries and is uncomfortable for some healthcare professionals, principally due to concerns about the motivations, characteristics and outcomes in this group of donors[5]. We have performed the largest quantitative study of psychosocial and physical outcomes in UKDs, where we sampled a national cohort of all 148 UKDs in the UK over the first five years of the programme and compared them with a regional sample of 148 specified kidney donors (SKDs - those who

donate to someone with whom the donor has an existing emotional relationship)[6]. All donors were sent a questionnaire which included a range of validated psychosocial outcome measures and questions specific to their donation. Physical outcome data were obtained from NHS Blood and Transplant. This study found that both physical and psychosocial outcomes were comparable between UKDs and SKDs, which suggests that clinician concerns may be unfounded. The limitations of this study were in its retrospective design and the inherent bias associated with this. Whilst we were able to analyse physical outcome data for the entire cohort, we were unable to determine whether those with poor psychosocial outcomes were within the non-responders and therefore not captured as part of the study. In addition, this study demonstrated a broad variation in donation rates across the country, with no obvious underlying reason.

A number of potential deterrents to UKD have been highlighted in our previous qualitative work and through consultation with UKDs in the development of this study.[7] For example, we have previously found that barriers to donation may exist within families where there is tension over the decision to donate altruistically and that there may be a role for transplant services to support families in this situation[7]. UKDs have also reported experiencing scepticism and resistance from some of the healthcare professionals they encountered. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also described as a difficult experience for UKDs who felt that they had to prove their sanity[7].

Aims and Objectives

The aim of this research programme is to perform a comprehensive assessment of the unspecified donor programme in the UK. Its objectives are to establish:

1. Whether variation in practice and attitudes across the UK is unnecessarily preventing some unspecified donation

2. Whether psychosocial and physical outcomes after unspecified donation are equal to those in specified donors

3. The economic benefit of unspecified donation

Ethical dimensions and implications of unspecified donation will also be explored. The programme's data will be used to develop national guidelines and inform transplant teams' decisions about potential donors.

Methods and Analysis

Design

This is a mixed methods research programme investigating unspecified kidney donation in the UK over a period of 5 years.

Research Questions

The study will be asking three main questions based on the research objectives listed above:

1. RQ1- Is there variation in transplant professionals' practice and attitudes, which is preventing some unspecified living kidney donations? (Protocol in supplementary file 1)
2. RQ2 - Are psychosocial and physical outcomes after unspecified donation equivalent to those after specified donation? (Protocol in supplementary file 2)
3. RQ3 - What is the economic benefit from unspecified donation?

In order to answer these three research questions we will utilise a mixed methods design, incorporating questionnaires to obtain quantitative data and interviews and focus groups to obtain qualitative data (figure 2). The third question, related to health economics, will be answered using embedded data capture elements within the first two research questions.

RQ1 Transplant Professionals' Perspective

This sub-study defines transplant professionals (TP) as any healthcare professional that may come in contact with a potential unspecified donor. These include renal transplant physicians, surgeons, transplant co-ordinators, nurses involved in transplantation, psychologists and independent assessors, as well as administrative staff from all 23 UK centres. Answering this research question will involve three stages. The first stage will involve focus groups, led by qualitative researchers, in which the views of transplant professionals regarding UKD will be ascertained. Focus

groups will be undertaken in four centres, chosen according to their volume of donations. This will allow sampling from two centres with higher donation rates and two centres whose rates are amongst the lowest. The data obtained will undergo thematic analysis and the key themes identified will be extrapolated. This data will be used to inform the subsequent stages. The second stage will involve questionnaire development, from the themes generated by the focus groups. The questionnaires will form the basis of a series of prospective cohort studies which will help ascertain broader, nationwide attitudes towards unspecified kidney donation, as well as current working practices in the different transplant centres. The questionnaires will be disseminated using professional networks to all UK transplant professionals. The third stage will involve in-depth qualitative interviews that will be conducted with transplant professionals selected from six centres, again chosen according to their donation volume. These interviews will not only provide a more detailed understanding of professionals' views, but will additionally help add meaning to the data obtained from the prospective cohort studies (questionnaire based).

RQ2 Donors' Perspective

Two focus groups will be held to assist in informing the development of study-specific questionnaires. The first focus group will involve individuals that have proceeded to donate a kidney as an unspecified kidney donor, whilst the second will involve individuals who presented as potential unspecified kidney donors, but who did not proceed to donate. Themes emerging from the focus groups will again be analysed using thematic analysis and questions specific to UKD will be written and validated by the research team. These questions will subsequently become part of a larger questionnaires, which will include validated psychosocial outcome measures capturing data on a range of different factors [8-17]. Validated psychosocial outcomes measures will include: The Client service receipt inventory[8], Rosenberg self-esteem scale[9], Generalised anxiety disorder 7-item scale (GAD-7)[10], Multi-dimensional scale of perceived social support (MSPSS) [11], Ten-item personality measure[12], Decision regret scale[13], Patient health questionnaire (PHQ-9)[14], Satisfaction with life scale[15], Flourishing scale[16] and the Quality of life health survey (SF-12) [17].

The questionnaires will be used as part of a longitudinal cohort study with four intervention points, as determined by their progress through the donation pathway. All

those presenting to a transplant centre as a potential UKD will complete a baseline questionnaire. The second questionnaire will be given immediately prior to donation, or immediately after the donor is withdrawn from the assessment process. The final two questionnaires will be given at three and twelve months after donation or withdrawal.

The study population will consist of all those individuals approaching a transplant centre with an interest in becoming an unspecified donor, irrespective of whether they subsequently donated or not. Potential specified donors will be used as the control population. Due to the fact that not all those who present as potential donors go on to donate, the study will result in two test groups and two control groups (figure 3):

1. Test group 1: Potential unspecified donors who proceed to donation
2. Test group 2: Potential unspecified donors who do not proceed to donation (either due to personal choice or withdrawal by the clinical assessors)
3. Control group 1: Potential specified donors who proceed to donation
4. Control group 2: Potential specified donors who do not proceed to donation (either due to personal choice or withdrawal by the clinical assessors)

Qualitative interviews will also be completed with a sample of 15 UKDs who completed their donation, 15 UKDs who withdrew and 15 UKDs who were withdrawn from the process by the transplant team. Participants will be asked about their experience of the donation process and services, barriers and enablers to donation and outcomes from either donating or withdrawing from the process. These interviews will take place three months after donation or withdrawal from the donation process.

The data collected will be compared with and supplemented by each donor's NHS Blood and Transplant records. These will be used to provide physiological outcome data as well as information regarding the donation procedure for each participant. Physiological data will be collected before and after donation, as well as at 12-months following donation, as per national donor follow-up protocol. NHSBT data will be collected retrospectively once a participant completes the 12-month

questionnaire, or earlier should they choose to withdraw from the study. Consent to obtain NHSBT data will be obtained through the initial study participation consent form. A formal request for data use has been approved by NHSBT and has been subsequently ratified by the Ethics Committee.

RQ3 Economic outcomes of unspecified kidney donation

The economic effects of living kidney donation will be determined by examining the impact of donation on healthcare and societal costs for specified and unspecified donors, using the Client Service Receipt Inventory (CSRI) questionnaire[8]. The CSRI has been widely used and will be adapted and customised to reflect the healthcare services used in kidney donation. It will be administered in self-reported questionnaires to donors and will aim to determine the type and frequency of specific health services accessed.

Eligibility Criteria

Participants eligible for RQ1 recruitment include any transplant professional that has had contact with unspecified donors.

Participants eligible for RQ2 recruitment include any individual that makes contact with a transplant centre to enquire about unspecified donation and proceeds beyond the initial telephone conversation, as well as being able to give informed consent. Non-English speakers will be included and adequate translation facilities will be provided.

Individuals who have already begun the donation work-up process at the time of study commencement will also be eligible for recruitment provided they are more than 2 weeks away from donation. Control participants will be recruited from those individuals known to a transplant centre for the purposes of donating a kidney to a known individual (specified donors) using the same inclusion criteria.

Enrolment (Figure 4)

Recruitment to the questionnaire for Professionals study (RQ1) will be through professional networks. Local collaborators at specific centres will be established to assist with recruitment for the focus groups and interviews.

For the participant study (RQ2) all 23 centres across the United Kingdom will be set up as participant identification centres (PIC) sites. Any individual who makes contact with a living donor coordinator to enquire about donation will be informed about the study and recruitment options. If they are happy to receive information and provide verbal consent, the coordinator will either pass their contact details to the research team at Guy's Hospital or will provide the individual with the study co-ordinator's details. Aggregated data will be provided by each centre regarding the total number of enquiries made to allow comparison with numbers making additional contact and recruited to the study. Once contact has been made the research team from Guy's Hospital will provide further information to the individual and be responsible for the recruitment and consent of participants.

Sample size calculation

Based on previous retrospective work[6], it is expected that a recruitment rate of 80% will be achieved. The study will aim to recruit 624 participants, of which 224 will go on to donate as unspecified donors. This recruitment rate is higher than is typical for longitudinal studies but justifiable given the population being studied. A sample size of 624 will provide sufficient precision to estimate the 95% confidence interval for proceeding to donation to within ±4% overall, and to within ±18% for each centre. In summary, the study aims to recruit 224 participants who have undergone unspecified donation (Test group 1) and 400 who did not donate (Test group 2).

The control group will recruit 200 individuals who are donating to friend or relative (specified donors - control group 1) and 200 individuals that intend to donate to a friend or relative but do not proceed (specified non-donors - control group 2). Based on our retrospective study we expect a recruitment rate of 80%. Therefore we will need to approach 500 specified donors. Given a stable rate of approximately 1000 specified donations per year across the UK, we anticipate that we will be able to recruit the control group using the same three-year recruitment window as the main cohort. If there is no difference between the unspecified altruistic and specified

donors on the physical and psychological variables at 12 months, it will be possible to determine that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of a standardised mean difference of 0.3, which is deemed to be the smallest acceptable clinically meaningful difference – this allows for 20% missing data due to drop-out, at a significance level of 5% with 90% power[18]. These individuals will be recruited through transplant co-ordinators nationally.

Study Set up

The research programme will be carried out at a national level, with sponsorship and monitoring provided by the Guy's Hospital Research and Development department. It has received funding from the National Institute of Health Research under HS&DR Project number 13/54/54.

Guy and St Thomas' NHS Foundation Trust is the lead site and are collaborating with Plymouth University, The University of Birmingham and King's College London. Twenty-three centres across the United Kingdom have been established as Patient Identification centres with all research activity being conducted centrally at Guy's Hospital.

Analysis plan

Qualitative Data Analysis

Data generated via the focus groups and staff interviews will be analysed using the Framework Approach. The framework approach was developed by the National Centre for Social Research[19]. It is a deductive form of analysis that is increasingly being used in healthcare research where the aim is to develop practical applications and target policy development. It starts deductively from the aims and objectives identified in the study. However, this approach is grounded and inductive, in that it is heavily based in participants' original accounts and the observations of those studied. Framework analysis largely conforms to the thematic analysis approach aiming to describe patterns in the data and provide a description of the data with an emphasis on making the process of identification clear and delineated[20]. The process of framework analysis enables interaction with the data set until a meaningful account is revealed with a conceptual framework, thus allowing the development to an explanatory

account. Data will analysed in adherence with the five stages of data analysis using the framework approach as presented in Ritchie and Lewis (2003) and aided by the computer software program NVIVO (version.11).

Cohort Study Analysis

In addressing RQ1 concerning variables relating to an individual proceeding to donate, descriptive analysis will be used to describe the proportion of people who withdraw or proceed to donation, and the reasons for failing to proceed. Survival analysis will be used to identify predictors of proceeding to donation. Specifically we will estimate Cox proportional hazards models where the dependent variable is the number of days between first contact with the unit and the date of donation, with those who where no decision has been made censored at the date of their last known status. The analysis will include all individuals enquiring about donation, with the dependent variable an indicator for each proceeding to donation. Centre-level structural and attitudinal factors identified in the study group's previous work[8] will be included in the models to determine whether these variables explain variation in donation rates. Individual level demographic variables at baseline (e.g. age, sex, education, and ethnicity) and time dependent psychological factors will be included to determine their association with outcome. Power to detect effects for individual level variables will be acceptable but only large effects will be detectable for centre level variables."

To address RQ 2 relating to outcomes after donation, descriptive analysis will be used to compare baseline variables for individuals in each of the specified donor (test) and unspecified donor (control) groups. Linear or logistic mixed-effects models will be used to estimate between group differences in outcome variables at the 3 and 12 months post-donation follow-up assessments. A three-level model will be specified with observations at each time-point (level 1) nested within individuals (level 2), who themselves are nested within centres (level 3). Group membership and follow-up assessment (time) will be included in the models as dummy variables. Interaction terms for group and time will allow for assessments of differences at individual time points. Models will adjust for potential individual level demographic confounders measured at baseline (e.g. age, sex, education, and ethnicity) and the baseline level of the outcome variable. Missing outcome data is

under the assumption that data is missing at random. Sensitivity analysis will be performed to assess this assumption.

Economic Outcomes Analysis

The economic benefits of unspecified donation will be examined using decision analytical methods. Decision analytic models use mathematical relationships to define a series of possible consequences that flow from a set of alternative options being evaluated. Here the decision is to accept or not accept unspecified donation. If unspecified donation is accepted and an individual is assessed then there are a series of events that can occur. These include refusal to proceed, being deemed unsuitable, successfully donating, and a recipient benefiting.

There are costs associated with these and the outcomes will be measured in terms of quality-adjusted life years (QALYs) for donors using the SF-12, and for recipients with QALYs derived from previous literature.

Data for the model will draw on a systematic literature review of published economic evaluations of kidney donation, as well as from the costing exercise described above and expert opinion. The model will take a lifetime horizon (with appropriate discounting) and will allow us to estimate the expected costs and QALY gain following the start of the process of unspecified donation. Given uncertainty around the model parameters, we will conduct a series of sensitivity analyses (deterministic and probabilistic) to assess its robustness. Key parameters to vary may include rejection and refusal rates and values placed on future QALY gains. The model will estimate costs and benefits for the donors. It will also estimate QALY gains for recipients and if possible we will incorporate future costs for recipients as well.

Ethics and Dissemination

The number of individuals considering living kidney donation to someone they have not previously met is becoming more common and has a significant potential to reduce the UK waiting list for kidney transplantation. Despite this trend, the concept of unspecified kidney donation (UKD) remains uncomfortable for some clinicians. Furthermore, the assessment and donation process may have scope for improvement

from the donor's perspective. This study will provide a comprehensive assessment of the unspecified donor programme in the UK in order to determine the extent and reasons for variation in practice, ascertain barriers to donation, as well as the economic implications of unspecified donation. The study will also assess clinical outcomes after unspecified donation in order to facilitate evidence-based decision making regarding future unspecified donors, as well as inform the creation of national guidelines.

Acknowledgements

This study is funded by the National Institute of Health Research under Health Services & Delivery Research Programme project number: 13/54/54.

Authors would also like to acknowledge Jan Shorrock and Paul van den Bosch for their expert advice and support. The study team would also like to acknowledge the support of NHS Blood and Transplantation, The British Transplantation Society and all 23 transplant centres across the United Kingdom.

This research was supported in part by the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) based at Guy's and St. Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Footnotes:

Contributors: NM and HM conceived the idea for the project with input from AM and AC regarding the qualitative work and PMcC leading on the economic aspect of the project. RG, PG, HM, LB, AC, LW, SN, JC, PGibbs, AM, PMcC, HD and NM collaboratively contributed to the design of the study and its protocols. RG and PG led the writing of the manuscript. RG, PG, HM, LB, AC, LW, SN, JC, PGibbs, AM, PMcC, HD and NM have reviewed and revised the manuscript critically for important intellectual content.
RG, PG and NM take responsibility of the paper as a whole.

Funding: This project was funded by the National Institute for Health Research [Health Service and Delivery Research programme] (project number 13/54/54).

Competing Interests: None declared

Data sharing statement: We shall make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs

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Figures:

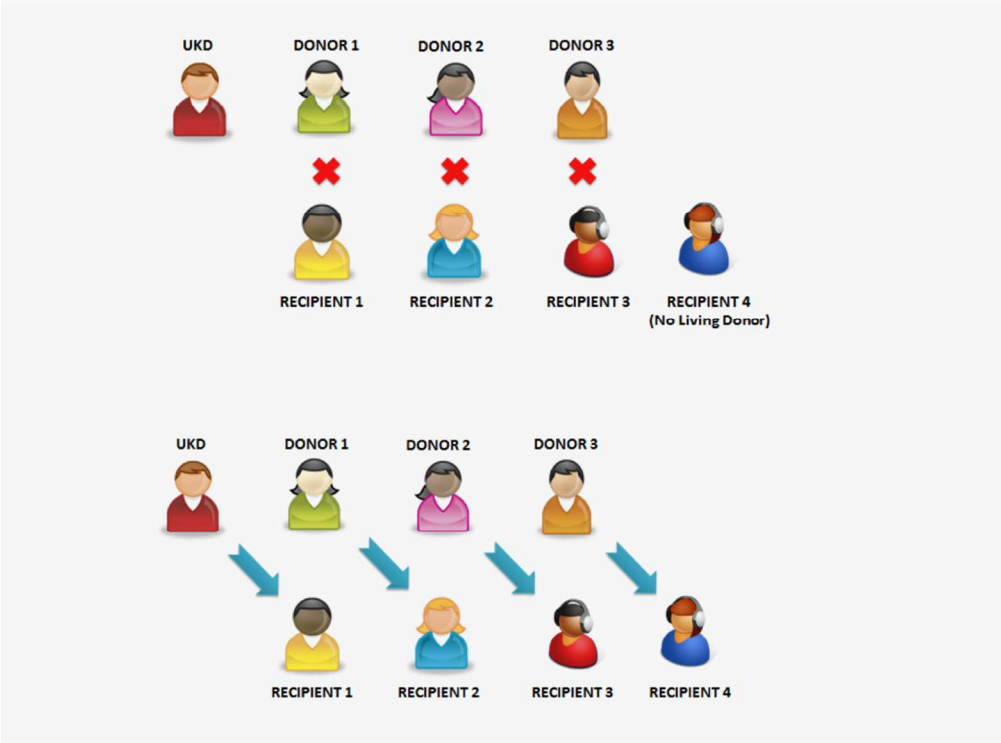

Figure 1

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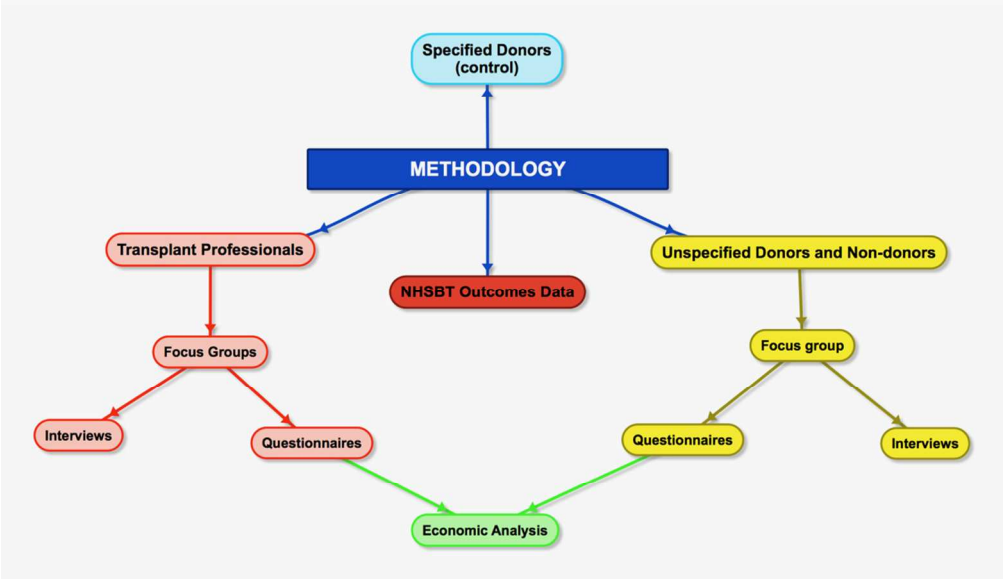

Figure 2

108x62mm (300 x 300 DPI)

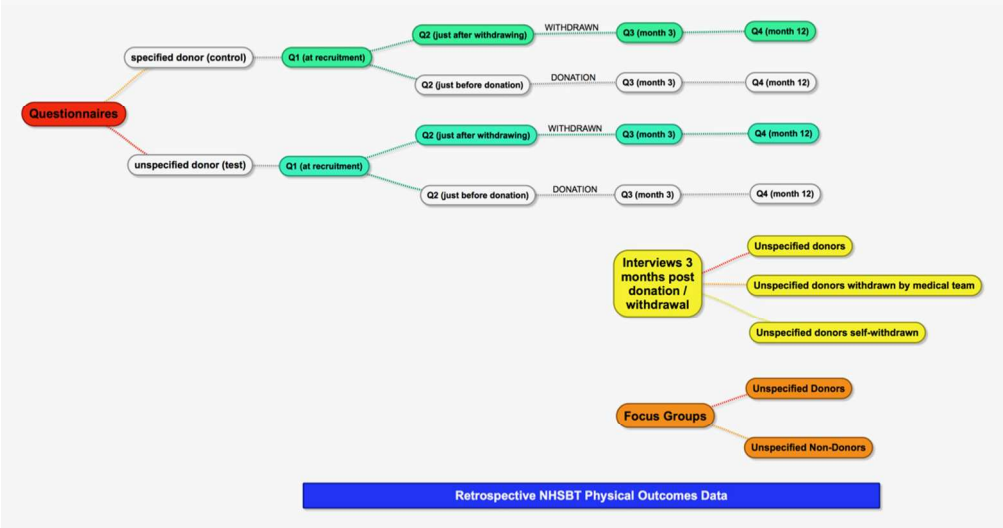

Figure 3

108x57mm (300 x 300 DPI)

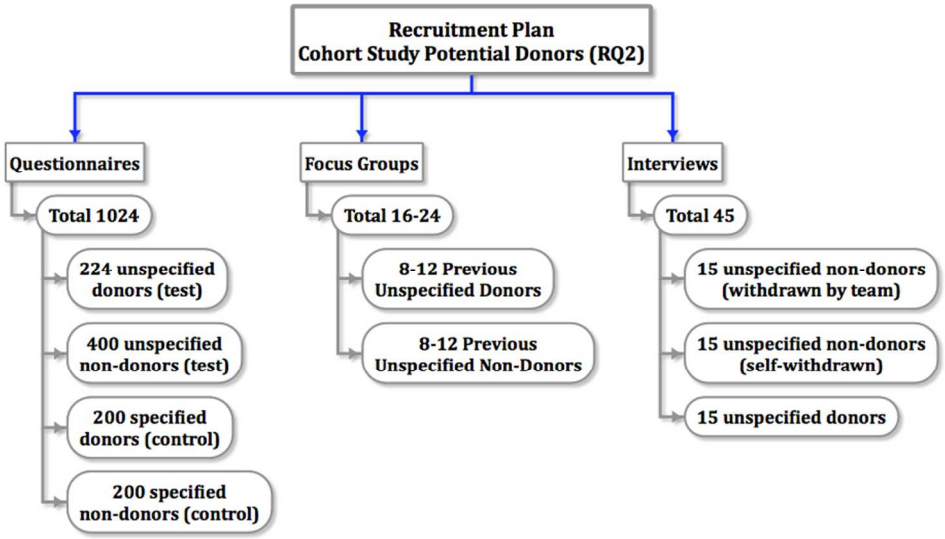

Figure 4

83x49mm (297 x 297 DPI)

Unspecified living kidney donation in the UK: barriers to implementation and delivery
- Healthcare Professionals' Perspective -

1. Background

Over one third of all kidney transplants taking place in the UK today are from living donors. A growing subset of living donors are individuals who choose to donate a kidney to someone that they have not previously met; so called 'unspecified' or 'non-directed altruistic' donors. Over 200 unspecified donations have taken place in the UK to date since this was introduced in 2006 and this type of living donation is becoming more routine, currently accounting for approximately 7% of living donations (1).

Despite this increase, the concept of unspecified kidney donation (UKD) remains uncomfortable for some clinicians, principally due to concerns about the motivations, characteristics and outcomes of these donors. In a recent study of clinicians' views', 78% of French physicians were opposed to the practice of unspecified donation (2). In our previous qualitative work, we have found some evidence that this makes donation more difficult or stressful for some potential donors (3-5). Furthermore, we recently performed a large study of a national cohort of all 148 UKDs in the UK over the first five years of the programme, and compared them with a regional sample of 148 specified kidney donors (SKDs - those who donate to someone with whom they have an emotional relationship) (6). This study did not find an excess of poor psychosocial or physical outcomes in UKDs; however the response rate was 74%, with variable retrospective follow-up, and therefore it is impossible to be certain that donors with significant pathology were not missed- indeed, these are the very donors (for example, with depression) that might be expected to fail to respond. The study did highlight broad regional variations in the numbers of UKDs performed and has highlighted differences in the assessment process, which may explain the differences seen across the country. Indeed, 45% of all unspecified donations were performed in 3 centres. There is some evidence from other studies that attitudes from transplant professionals may be a barrier to donation (7-9). Both living donor nurses and psychiatric assessors involved in UKD have expressed concerns about the lack of practice guidance in this area; lack of clear guidance could be a further barrier to donation (4,5).
Through our qualitative work we have also found that barriers to donation may exist within families where there is tension over the decision to donate altruistically and there may be a role for transplant services to support families in this situation (3). We have recently been awarded a grant from the British Renal Society and

British Kidney Patients Association to explore this. This work is due to commence prior to this study and will inform this research.

The UKD participants in our PPI sessions and previous our qualitative study identified a number of issues in the process that they felt acted as deterrents and may have affected the decision by others to donate (3). They found difficulties in knowing how to make initial contact with the transplant centre. The negative attitudes of transplant professionals were also off-putting and this continued whilst donors were in hospital, with some experiencing ignorance and hostility from ward staff, which made them feel guilty for "choosing to become a patient". The length of the workup process was also commonly an issue, which donors found frustrating. Indeed, when considering living donor chains, most donors would have liked to have participated had it been easier and the timing more predictable. Many were working or had other commitments and the unpredictability of when the donation would take place meant that many were not in a position to oblige. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also a difficult experience for donors who felt that they had to prove their sanity (3).

Unspecified kidney donation is apparently more costly than specified donation, as it is resource intensive, with a large number of enquiries and assessments, and a low proportion that proceed to donate. In Portsmouth (the largest centre for unspecified donation), for example, of 149 referrals, 27 have donated and a further 27 are in work-up, giving a drop-put rate of at least 64%. Nevertheless, a kidney from a UKD may be a particularly valuable resource, since it can be used to provide a high quality, long lasting transplant to those who are otherwise difficult to transplant. The National Kidney Sharing Scheme, for example, involves kidney exchanges between pairs of donor and recipients who cannot otherwise proceed due to immunological incompatibility. A kidney from a UKD can be used to convert these exchanges into a 'chain' primed by the UKD; the UKD donates to recipient A, and her donor dates to recipient B, and so on (Appendix 2). In the US this has resulted in 30 transplants occurring from a single UKD (10). In the UK, 47% of UKDs have been used to prime short chains of two transplants, and the UK Living Donor Strategy aims for 75% to be used for chains, with 3 transplants in each chain, by 2020 (11). Thus, assuming UKDs rise to 200 per year, they would result in 450 transplants annually, which is almost half the current annual living donor transplantation rate. Despite this, no economic analysis of unspecified donation has been performed. This is particularly important since, if it is shown to have a significant economic benefit, extra resources could be allocated by NHS Blood and Transplant, as happened with SKDs over the last decade.

We therefore wish to perform an assessment of healthcare professionals' perspectives on the unspecified donor programme in the UK, in order to determine the extent and reasons for variation in practice and ascertain barriers to donation.

2. Aims

The study will specifically explore healthcare professionals' practice and attitudes to unspecified living kidney donation in transplant centres in the UK.

Research Question:

"Is there variation in transplant professionals' practice and attitudes, which is preventing some unspecified living kidney donations?"

3. Methods

The study will include three arms:

i) Focus groups

ii) Qualitative interviews and

iii) A questionnaire study of transplant professionals (surgeons, physicians, co-ordinators and others involved in transplantation in hospital) working with unspecified donors in the UK.

This is a mixed methods study, drawing on both qualitative and quantitative methods:

i) Qualitative information will be obtained by focus groups and individual interviews with transplant professionals in four centres. Sampling is purposive and centres will be chosen according to their numbers of completed donations, allowing us to sample from two centres which have amongst the highest rates of completed donations (Guys and St Thomas and Plymouth) and two centres whose rates are amongst the lowest (Birmingham and Leeds). These focus groups will contain key staff involved in the unspecified donation process (living donor nurses, psychological assessor, surgeons and nephrologists. These groups will be used to inform the approach in subsequent individual interviews with professionals from each discipline (surgeons, physicians, psychological assessors and donor coordinators). The interviews will involve centres chosen according to their number of completed donations. We will interview professionals at three sites which have the highest rates of completed donation (Guys and St Thomas, Plymouth and Manchester) and three centres with lower rates (Birmingham, Leeds and Bristol Southmead). It is anticipated that 60 transplant professionals in total will be interviewed.

ii) Quantitative study: Questionnaires will be sent to all transplant professionals working with unspecified donors across the UK, which will ascertain attitudes

towards unspecified kidney donation and current working practices. Both the focus groups described above and the patient representatives will inform the development of a questionnaire that explores working practices, knowledge of donation and staff attitudes incorporating salient points of interest from the data. This will be supplemented by an existing questionnaire (such as the Organ Donation Attitude [12]), which has been used previously in research to explore the impact of staff attitudes in organ donation.

Participants will be given an information sheet, adequate time to consider the study, and will be asked to give written consent.

If any evidence of distress is elicited in of the different parts of the study, access to a counselor will be offered, an approach we have adopted in a previous study (REC 09-H0804-31). We will ensure that data storage is annonymised and held in a secure fashion, according to Trust SOPs. Trial data will be archived at the end of the study, by our Clinical Trials Office. A trial manager will manage the trial, with help from a research fellow.

The data will be collected by collaborators from the Department of Psychology at Plymouth University. Focus group and individual interviews will be performed at sites most convenient for the healthcare professionals recruited. These may include NHS premises, individuals' homes, or other meeting venues (e.g. professional congresses).

The questionnaire data will be collected by postal or electronic means.

Analysis

Data generated via the focus groups and staff interviews will be analysed via the Framework Approach. The framework approach was developed by the National Centre for Social Research (13). It is a deductive form of analysis that is increasingly being used in healthcare research where the target is to develop practical applications and target policy development. It starts deductively from the aims and objectives identified in the study. However, this approach is grounded and inductive, in that it is heavily based in participants' original accounts and the observations of those studied.

Criteria for acceptance for UKD will be assessed across units in the UK, and requirements for work- up (such as psychiatric assessment) will be compared, in order to determine whether there are significant variations in practice. We will explore this in relation to the number of unspecified donation enquiries and completed donations.

Data from the questionnaire will be analysed using standard statistical tests to compare variations according to demographic factors, individual characteristics and centre effects.

4. Study Steering Committee

There will not be a Data Monitoring Committee, but there will be a Study Steering Committee (SSC), which will have the following responsibilities:
i) To provide advice, through its Chair, to the Chief Investigator, the Project Sponsor, the Project Funder, the Host Institution and the Contractor on all appropriate aspects of the project
ii) To concentrate on progress of the project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question
iii) The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society
iv) To ensure appropriate ethical and other approvals are obtained in line with the project plan
v) To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
vi) To provide advice to the investigators on all aspects of the project

The SSC will be constituted as follows: An independent chairperson, an independent statistician, one member (not directly involved with the study) from within the Trust, one member external to the Trust, and two service users. An observer from the sponsor and from the CLRN will be invited to attend.

The SSC will meet at 4 to 6 monthly intervals, or more frequently if the Chairperson deems this to be necessary.
There will be a Trial Steering Committee which will manage the project on a regular basis, and which will consist of the members of the project team. This will meet at 3 to 6 month intervals.

5. Data storage

A database will be constructed by the Guys and St Thomas Biomedical Research Centre. Online or paper questionnaires and interview transcripts will be transferred to the database, held on a secure server at either Guys Hospital or Plymouth University, in an anonymised fashion, with password protected access, limited to the study team. Back up will be performed automatically by the Trust systems, and data archiving will be undertaken by the Kings Health Partners Joint Clinical Trials Office, according to their standard operating procedures.

6. Outputs

The data collected will be used together with data from a concomitant NIHR study[1] to achieve several specific outputs, in addition to published manuscripts and conference presentations:

a) A report to NHSBT and the BTS, summarising the findings of the study
b) National guidelines, produced in conjunction with NHSBT and the BTS
c) A protocol for management of those presenting for unspecified donation
d) A report to the Renal Transplant Clinical Reference Group, which reports to NHS England (which commissions transplant services in England), and to the Scottish, Welsh and Northern Irish Departments of Health.

The process for developing these outputs (beyond the first, which will be written by the study team) is as follows:

National Guidelines

The transplant community is small, and there is a widespread desire for guidance on unspecified donation. Existing guidelines on living donation are extensively used by donor teams, and these have been important in changing culture. We recognize that guidelines are not, however, necessarily effective by themselves at changing practice- in this regard, the close liaison that one team member (LB) has with donor coordinators at all transplant centres, and the living donor forum which she organizes, will be vital.
The support of the BTS Clinical Trials Committee for this study is indicative of the close involvement and support of the BTS. There is an existing process for developing guidelines by the BTS, through the BTS Standards Committee. We will convene a small group, including NHSBT and BTS representatives, as well as service users, to draft a guideline, which can be sent to the BTS Standards Committee for consideration. Typically, this is opened for public consultation via the BTS website for a short period, revised and then disseminated to all units.

Commissioners' report

The Chief Investigator is a member of the Renal Transplant Clinical Reference Group (CRG) and has bee involved in drafting Service Specifications for transplantation. He will send a report, which will be drafted with the help of the study team, including service users, to the CRG for discussion and dissemination to NHSE and counterparts in other constituent countries.

[1] Unspecified living kidney donation in the UK: barriers to implementation and delivery - *Potential Donors Study*

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Guy's and St Thomas' NHS
NHS Foundation Trust

PROTOCOL TITLE:

Understanding barriers and outcomes of unspecified (altruistic) kidney donation (BOUnD); a multicentre prospective cohort study

BOUnD

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Study Synopsis

Title	**Understanding barriers and outcomes of unspecified (altruistic) kidney donation (BOUnD); a multicentre prospective cohort study.**
Protocol Short Title/Acronym	BOUnD (Barriers and Outcomes in Unspecified kidney Donation)
Protocol Version number and Date	RQ2 Protocol v2.1, 25/05/2016
Is the study a Pilot?	No
Study Hypothesis	(i) Regional differences in unspecified (altruistic) kidney donor rates will be explained by prospective donor experience e.g. depending on donor interaction with staff members, local expertise and resources. (ii) There is no detrimental impact of unspecified donation on mental and physical health.
Study Duration	December 2015 – April 2018
Methodology	Prospective, mixed-method cohort study recruiting unspecified potential donors (and a directed donor control group). Participants will be recruited to a prospective donor phase shortly after first enquiring about donation (hypothesis i). Those that proceed to donation will continue to a second phase focusing on outcomes over 1 year (hypothesis ii). Nested qualitative studies will explore experiences of the process in donors and non-donors using structured interviews. Focus groups will be used to guide questionnaire design and interview topic guide.
Sponsor name	Guy's and St.Thomas' NHS Foundation Trust R&D Office
Chief Investigator	Prof Nizam Mamode
REC number	15/SC/0637
Medical condition or disease under investigation	Unspecified (altruistic) living kidney donation
Purpose of study	To identify methods of improving the process of unspecified (altruistic) donation in the UK and inform the development of national guidelines
Primary objective	Physical and mental-health related quality of life, anxiety, depression, life satisfaction and self-esteem
Secondary objective (s)	1. Barriers to unspecified kidney donation 2. Economic outcomes of unspecified kidney donation
Number of Subjects/Patients	(i) 16 - 24 participants (focus groups); (ii) 1024 participants (questionnaires), as follows: Test group: 224 unspecified donors that proceed to donate and 400 unspecified donors that withdraw. Control group: 200 directed / specified donor controls that proceed to donate and 200 directed / specified potential donors who did not proceed; (iii) 45 participants (interviews),
Study Design	Prospective cohort study
Endpoints	(i) time from enquiry to donation (for those that proceed to donation) (ii) mental and physical health at 3 and 12 months post donation / withdrawal, compared to directed donor controls
Inclusion Criteria	Individuals contacting a UK transplant centre wishing to become specified or unspecified kidney donors or those that have already begun the work-up process
Exclusion Criteria	Foreign nationals that are unable to donate altruistically in their countries of residence or prisoners
Statistical Methodology and Analysis	Quantitative analysis: (i) Time-to-event analysis using Cox regression; (ii) propensity score weighted mean differences at 12 months using

	linear mixed effects models Qualitative analysis: Framework (thematic) approach

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Introduction

Over one third of all kidney transplants taking place in the UK today are from living donors. A growing subset of living donors are individuals who choose to donate a kidney to someone that they have not previously met; so called 'unspecified' or 'non-directed altruistic' donors. Over 200 unspecified donations have taken place in the UK to date since this was introduced in 2006 and this type of living donation is becoming more routine, currently accounting for approximately 7% of living donations (1).

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Through our qualitative work we have also found that barriers to donation may exist within families where there is tension over the decision to donate altruistically and there may be a role for transplant services to support families in this situation (3). We have recently been awarded a grant from the British Renal Society and British Kidney Patients Association to explore this. This work is due to commence prior to this study and will inform this research.

The UKD participants in our PPI sessions and previous qualitative study identified a number of issues in the process that they felt acted as deterrents and may have affected the decision by others to donate (3). They found difficulties in knowing how to make initial contact with the transplant centre. The negative attitudes of transplant professionals were also off-putting and this continued whilst donors were in hospital, with some experiencing ignorance and hostility from ward staff which made them feel guilty for "choosing to become a patient". The length of the workup process was also commonly an issue, which donors found frustrating. Indeed, when considering living donor chains, most donors would have liked to have participated had it been easier and the timing more predictable. Many were working or had other commitments and the unpredictability of when the donation would take place meant that many were not in a position to oblige. The psychiatric assessment (which is no longer legally mandatory but is considered current best practice) was also a difficult experience for donors who felt that they had to prove their sanity (3).

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We therefore wish to perform a comprehensive assessment of the unspecified donor programme in the UK, in order to determine the extent and reasons for variation in practice, ascertain barriers to donation, and determine the economic costs and benefits of an unspecified donation. We will also assess outcomes after unspecified donation, in order to provide detailed evidence for transplant teams' decisions about potential donors.

2 Study Objectives and Design

2.1. Study Objectives

Aims: This study aims to perform a comprehensive assessment of unspecified altruistic donor programme in the UK to explore variation between centres and identify barriers and facilitators to donation for those that have expressed a willingness to do so.

Objectives:
(i) Identify and explain regional variations in unspecified kidney donation (UKD), based on donor interaction with staff members, local expertise and resources, and other economic variables
(ii) Establish prospectively the psychosocial, physical and economic outcomes of individuals undertaking unspecified kidney donation, compared to specified donors.

Outcomes

Primary outcomes: Physical and mental health-related quality of life.
Psychosocial health outcomes:

- quality of life (SF-12)
- anxiety (General Anxiety Disorder-7 (GAD-7)
- depressive symptoms (Patient Health Questionnaire-9 (PHQ-9)
- life satisfaction (Satisfaction With Life Scale)
- self-esteem (Rosenberg Self-Esteem Scale)
- Decision Regret Scale
- Flourishing Scale
- in house questionnaire

Physical health outcomes
NHSBT pre and post donation physiological and clinical outcomes

Secondary outcomes:
- Barriers to donation (qualitative data from interviews and focus groups)
- Healthcare resource utilisation data (Client Service Receipt Inventory (CSRI))

2.2 Recruitment Strategy

The primary study group will comprise all those who approach a transplant team in any UK transplant centre, offering to donate a kidney to a stranger over a three year period (2015 – 2018). Follow-up will take place up to 2020.
The control study group will comprise all those who approach a transplant team across the UK offering to donate a kidney to a family member or friend ("specified donors").
The study will use the same national professional transplantation network to collaborate with transplant co-ordinators and living donor nurses willing to participate in the recruitment process. Participant recruitment will take place subsequent to local R&D approval and transplant centres being identified and approved as participant identification centres (PIC).

UK Transplant co-ordinators will be briefed regarding the aims, objectives and recruitment criteria of the study. Communication and liaison with local transplant co-ordinators will be through Ms Lisa Burnapp (Lead Nurse - Living Donation, Organ Donation and Transplantation, NHSBT), who is a collaborator in the study.

Focus Groups Recruitment.

The Focus Groups represent the smallest aspect of the study and serve to help fine-tune the questionnaire design and interview topic guides. As such, only two focus groups will take place in centres such as Guy's Hospital (London) or Plymouth Derriford Hospital, where the study team has long-standing collaboration links with the donation teams. The local transplant co-ordinator or living donation nurse specialist (living donation team) will approach individuals that have recently donated or have withdrawn from donation and explore whether they would be interested in considering the study. Those that would be interested will be given the contact details of our research team or asked if they would agree to be contacted by us. The research team would then be able to provide further information and lead the consent and recruitment process.

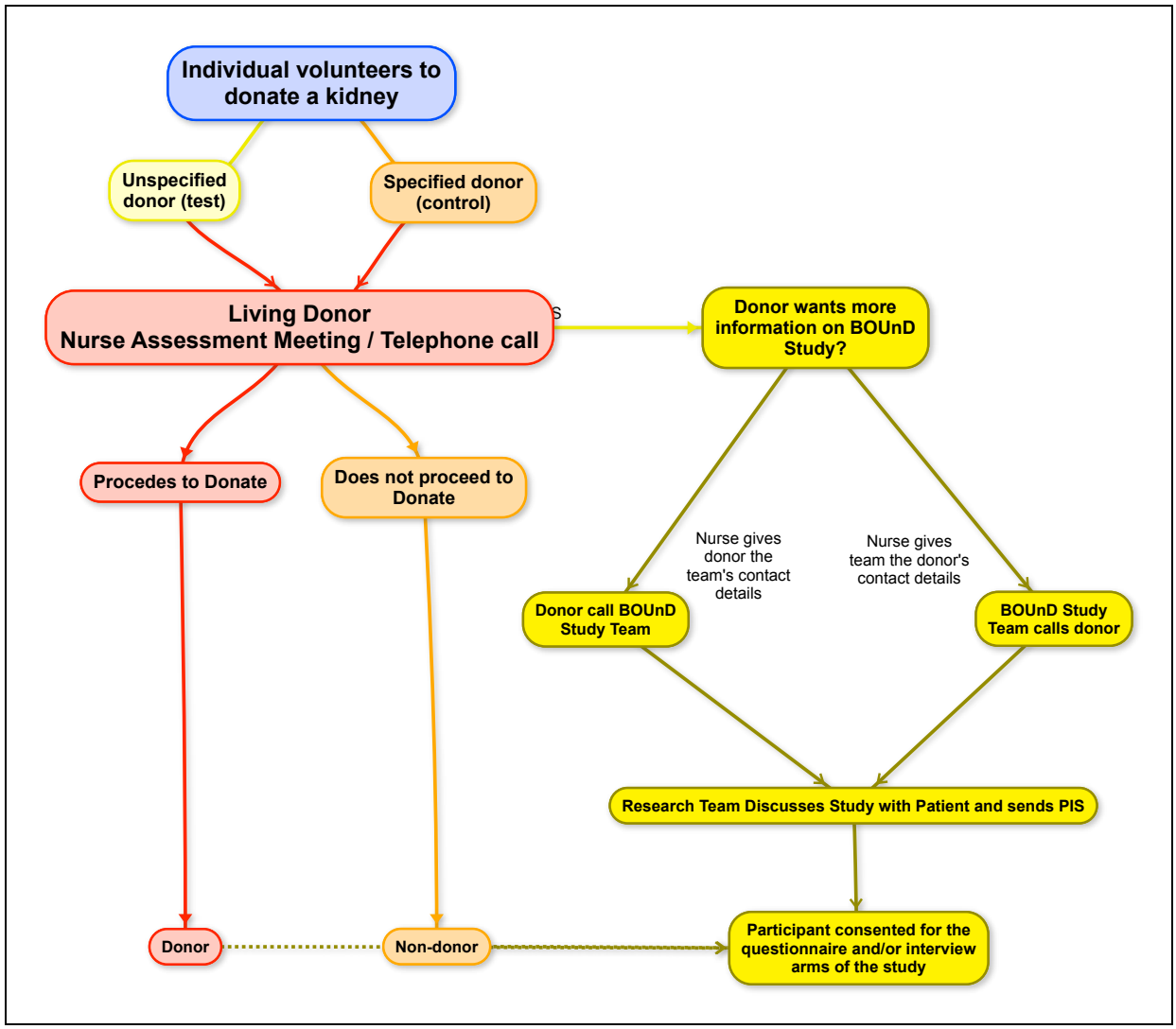
Interview and Questionnaire Recruitment

Transplant co-ordinators at each of the 23 UK transplant centres will ask potential donors approaching their units if they would be interested in participating in the study. This does not equate to being consented into the study, but simply facilitates further information gathering regarding our work. This will occur either at the initial telephone contact between the potential donor and the transplant centre or at the first clinic consultation with the transplant co-ordinator, depending on local practice protocols. Potential donors already being worked-up will also be given the opportunity to contact the study team for recruitment into the study.

Once a potential donor agrees to find out more about the study, the local transplant co-ordinator will facilitate contact with the research team by either giving the team's contact details to the potential donor, or (with the donor's permission) pass on their preferred contact details to the research team. The study's manager will be notified of individuals interested in the study. The research team will contact potential participants by phone, email or post to provide further information, discuss the study and provide participant information sheets. Those that indicate a willingness to participate will be enrolled in the study subsequent to completion of the relevant consent forms. The emphasis of the study is to cause minimal inconvenience to local transplant units and human resources. As such, once a transplant co-ordinator has facilitated the contact between the potential donor and the study team, no further involvement will be needed and all subsequent administrative and research work will be co-ordinated by the study's manager or investigators.

The control group will consist of individuals who are donating to friend or relative (specified donors). Control (specified) donors will be recruited in a similar consecutive manner by transplant co-ordinators. Control donors

that do not procede to specified donation will still be asked to participate in the study in order to provide robust data for comparison.



2.3 Study Design

Focus Groups

Two focus groups with potential donors will be undertaken. One focus group will involve those that have proceeded to donation. The other will involve potential donors that have withdrawn or been withdrawn from the donation process. 8-12 participants will take part in each focus group. The focus groups will not involve control participants. The physical location of the focus groups will be a suitable hospital venue, such as a conference room or a postgraduate centre. Recruitment will be undertaken as described above. The focus group discussion will be audio-recorded and transcribed for future analysis.

Data regarding socio-demographic (including the area postcode), physical, psychological characteristics, and resource use variables will be collected at baseline (shortly after contacting the transplant centre).

Questionnaires

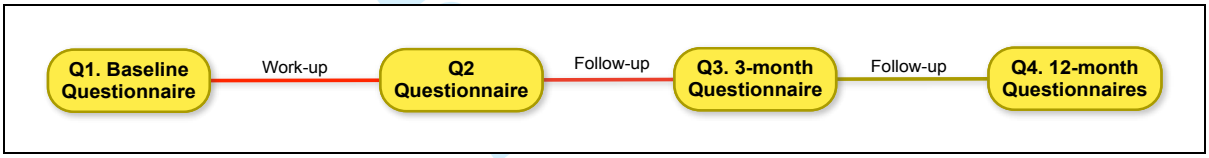
The questionnaire part of the study will have four research populations on which questionnaire data will be collected at four intervention points (Q1-Q4): baseline, preoperatively and at 3 and 12 months post-donation in the form of a study questionnaire bundle. Additional data (such as gender, age or ethnic group) will be collected at the time of recruitment into the study.

Q1. Baseline data will be collected within the first week of recruitment to assess the participant prior to the work-up process.

Q2. Pre-operative data will be collected in the 2 weeks preceding donation surgery (+/- 3 days). This will not be collected on the day of surgery in order to avoid confounding errors. This will mark the end of the work-up period. For those that withdraw from the study a longer period of time may be needed to capture these participants. In this case, the Q2 intervention point will span from the time of withdrawal to 3 weeks post withdrawal.

Q3. 3 months post donation or withdrawal

Q4. 12 months post donation or withdrawal



The four study populations will include:

1. Those that **proceed to donation** ('unspecified donors') – Test 1 population

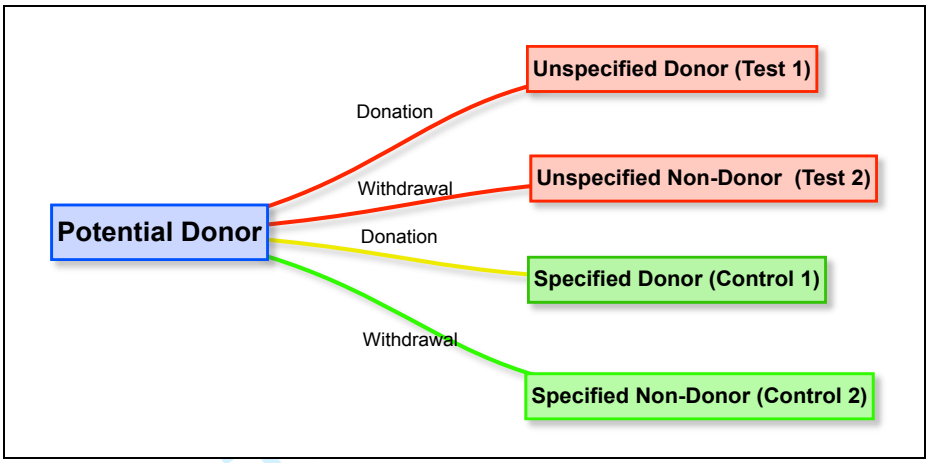
2. Those that **do not to donate** ('unspecified non-donors') due to donor's choice or withdrawal by the clinical assessors – Test 2 population

3. Those that undergo **living donation to a known individual** ('specified donors'), which will act as **control group 1**

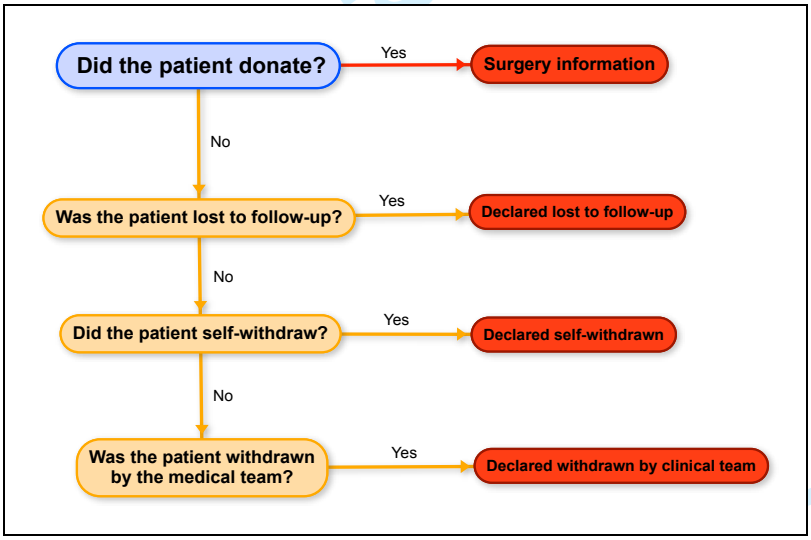
4. Those **intending to donate to a known individual that do not donate** ('specified non-donors'), which will act as control group 2

To ensure feasibility of the study questionnaire burden will be tested and considered in conjunction with the PPI group.

Questionnaire validation will be carried out by asking 20-30 volunteers that are previous kidney donors or future specified donors to review the in-house questionnaires. This will involve a facilitated think-aloud exercise to identify any face validity issues related to the newly developed questions. This exercise will result only in minor changes to the question structure, phrasing or answering methods. The questionnaire content validity will have already been validated by 15 members of the research team who will review the developed questionnaires on at least three occasions.



Participants who do not proceed to donation will be identified either by regularly checking with their local transplant coordinators (every two weeks) or by self-referral to the study team. The study researchers will then ascertain whether the patient self-withdrew or was withdrawn by the clinical team. The following data collection algorithm will be used:



Interviews

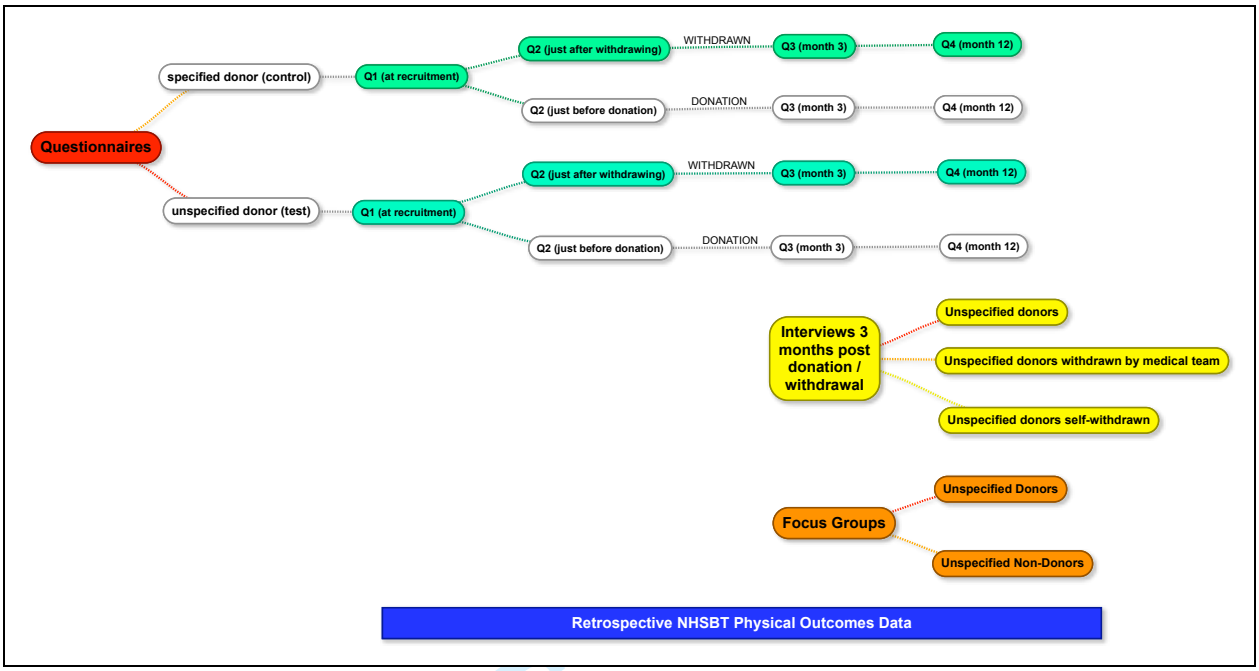
Qualitative interviews will also be completed with a sample of 15 donors who completed their donation, 15 who withdrew and 15 who were withdrawn by the transplant team from the process. Participants will be asked about their experience of the donation process and services, barriers and enablers to donation and outcomes from either donating or withdrawing from the process. The interview questions have been informed by our previous grounded qualitative work, focus groups and current research. Participants will be purposively sampled to ensure a range of demographics and experiences are captured.

Interviews will take place at 3 months following donation or withdrawal from the process.

Other Study Data

Linkage to the NHS Blood and Transplant records will provide physiological outcome data as well as information donation procedure for all donors. Physiological data will be collected pre- and post-donation, as well as at 12-months following donation, as per national donor follow-up protocol. This is described in Appendix 4. NHSBT data will be collected retrospectively once a participant completes the 12-month questionnaire, or earlier should they choose to withdraw from the study. Consent to obtain NHSBT data will be obtained through the initial study participation consent form. Subsequent to this a formal request for data access from the NHSBT will be made.

2.4 Study Outline



2.5 Trial Statistics and Data Analysis

The study endpoints will be:

i) time from enquiry to donation (for those that proceed to donation)

ii) mental and physical health at 3 and 12 months post donation, compared to directed donor controls

All primary analyses will be undertaken by the study statistician and investigator / research fellow in accordance with a predetermined analysis plan.

Descriptive analysis will be used to describe the proportion of people who withdraw or proceed to donation, and the reasons for failing to proceed. The analysis will include all individuals enquiring about donation, with the dependent variable an indicator for each proceeding to donation. Centre-level structural and attitudinal factors identified in our parallel study (IRAS 170483) will be included in the models to determine whether these variables explain variation in donation rates.

Descriptive analysis will be used to compare baseline variables for individuals that express an interest in donation that: i) the transplant team withdraw from donation; ii) those who decide not to proceed; iii) those that proceed to donation; and iv) the specified kidney donor control group, who either proceed or do not proceed to donate. Linear or logistic mixed-effects models will be used to estimate difference in outcome variables at the 3 and 12 months follow-up assessments between the groups at the outcome assessments. Group membership and follow-up assessment (time) will be included in the models as dummy variables. Interaction terms for group and time will allow for assessments of differences at individual time points. Models will adjust for potential demographic confounders measured at baseline (e.g. age, sex, education, ethnicity) and the baseline level of the outcome variable. Missing outcome data is under the assumption that data is missing at random. Sensitivity analysis will be performed to assess this assumption.

The analysis of qualitative data will be performed using the Framework (thematic) approach as described above.

3. Sample Size and Selection

Focus Groups

The two focus groups will recruit 8-12 potential or actual unspecified kidney donors each. These will be volunteers identified by UK transplant co-ordinators.

Questionnaires

Consecutive people contacting each of the transplant centres in the UK between April 2015 and Feb 2018 will be recruited to participate in the study. Based on current trends we conservatively estimate that there will be at least 279 kidney transplants from unspecified altruistic donors during that period. Indeed, there were 107 UKD in the UK in 2013. Assuming that the proportion of individuals contacting transplant centres who go on to donate remains stable (36%, based on data from Portsmouth in 2012), we expect that 780 people considering unspecified altruistic donation will contact transplant centres during that period. Based on our previous retrospective study, we expect at least a 80% recruitment rate- that is, 624 in total, of which 224 will go on to donate). This recruitment rate is higher than is typical for longitudinal studies but justifiable given the population being studied. A sample size of 624 will provide sufficient precision to estimate the 95% confidence interval for proceeding to donation to within ±4% overall, and to within ±18% for each centre. In summary we aim to recruit 224 who have undergone unspecified donation and 400 who failed to donate.

The control group will recruit 200 people who are donating to friend or relative (specified donors) and 200 individuals that intend to donate to a friend or relative but do not (specified non-donors). Based on our retrospective study we expect a recruitment rate of 80%. Therefore we will need to approach 500 specified donors. Given a stable rate of approximately 1000 specified donations per year across the UK, we anticipate that we will be able to recruit the control group using the same three-year recruitment window as the main cohort. If there is no difference between the unspecified altruistic and specified donors on the physical and psychological variables at 12 months, it will be possible to determine that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of a standardised mean difference of 0.3, which is deemed to be the smallest acceptable clinically meaningful difference – this allows for 20% missing data due to drop-out, at a significance level of 5% with 90% power (14). These individuals will be recruited through transplant co-ordinators nationally.

Interviews

Qualitative interviews will also be completed with a sample of 15 donors who completed their donation, 15 who withdrew and 15 who are withdrawn by the transplant team from the process. These individuals will be identified from the initial cohort of patients that approached transplant centres with the intention to donate altruistically.

Recruitment Targets

The following recruitment targets have been set:

Focus Groups: 2 focus groups of 8-12 previous donors and 8-12 non-donors.
Total: 16-24 participants

Questionnaires:
624 potential donors (test population)
224 who have donated
400 who did not donate

200 specified donors (control population 1) and 200 specified non-donors (control population 2)
Total: 1024 participants

Interviews:
15 potential donors that donated
15 potential donors that did not donate (self-withdrawn)
15 potential donors that did not donate (withdrawn by clinical team)
Total: 45 participants

Inclusion criteria

Any individual contacting a transplant centre to enquire about unspecified donation, who proceeds beyond the initial telephone conversation, and is able to give informed consent will be considered as a potential study participant. Non-English speakers will be included and adequate translation facilities will be provided. Individuals who have already begun the donation work-up process at the time of study commencement will also be eligible for recruitment provided they are more than 2 weeks away from donation. Control participants will be recruited from those individuals contacting a centre in order to donate to a known individual.

Exclusion criteria

Any individual who declines to participate at any stage will be excluded from the study. Individuals lacking capacity will also be excluded as will any individual not eligible to donate in UK. This includes foreign nationals who are unable to donate altruistically in their country of residence or prisoners.

4. Study procedures

4.1 Consent

The study research fellow or study manager will be notified of any eligible individuals by UK transplant co-ordinators. Potential participants will be invited to participate in the study by phone or post and will be provided with an information sheet prior to the consent process. Separate consent forms have been designed for each of the three study arms (focus groups, questionnaires and interviews). Where necessary these will be translated or explained by an interpreter. Individuals who agree to participate will be asked to complete a baseline assessment, in either paper or online format. Pre-operative assessments will be completed one week prior to donation.

The following study documents have been created (Appendix 5):

- PIS Unspecified Donors Focus Group
- PIS Unspecified Donors Questionnaire and Interview Group
- PIS Specified (Control) Donors Questionnaire and Interview Group
- Consent Form Unspecified Donors Focus Group
- Consent Form Unspecified Donors Interview Group

- Consent Form Unspecified Donors Questionnaire Group
- Consent Form Specified (Control) Donors Questionnaire Group

4.2 Follow up Procedures

Follow-up assessments will be sent by post (and made available to complete online). To minimise loss to follow up anyone who has failed to return their 12 month follow up assessments within 14 days will be contacted by phone with the aim of collecting information on at least the primary outcome variable.

4.3 Maximizing Response Rates

Unspecified donors are highly motivated individuals, who, in our experience, are enthusiastic about participation in studies that may help other donors. The response rate of 74% in our previous study, whilst too low for definitive conclusions in a retrospective study, is nevertheless higher than expected for a questionnaire survey (6).

However, it is vital that response rates are high enough to accurately capture outcomes, and we aim to achieve this as follows:

I. Participants presenting for donation will be contacted directly by the research fellow or study manager (usually by telephone or email). Non-responders will be contacted on 2 occasions, including using an alternative method (such as a written letter and/or telephone calls outside standard working hours).
II. Participants will be given the opportunity to return documents in a freepost envelope or by completing an online form.
III. The trial manager will contact all 23 transplanting centres on a regular basis to ensure that those who present for unspecified donation have been considered for inclusion in the study.
IV. One team member (LB) already has close and regular contact with donor co-ordinators (who are the first point of contact for any donor presenting at a transplant centre) in all transplanting centres. She will send reminders to all co-ordinators regularly to ensure continued referral of potential participants.

We will monitor the success of this approach using the internal pilot study described in the protocol.

4.4 End of Study Definition

Completion of the final questionnaire (at 12 months) of participants recruited in the 3-year period will mark the end of the study.

5. Laboratories

No laboratory facilities will be used for this study

6. Assessment of Safety

6.1 Emotional or Psychological Distress

If any clinical concern is identified by the research team from the questionnaires or interviews (for example suicidal thoughts, or severe depression) the local clinical team (transplant donor co-ordinator) will be informed with a view to referral to the local psychological or counselling service; we used this approach previously in our retrospective study. The provision of this facility is part of our commitment to good practice and we do not anticipate this will be needed. In the unlikely event that concern is raised about a participant who has withdrawn from the donation process early in the assessment period and has no further contact with their local transplant

unit, we will contact their GP directly. The GP contact details will be collected as part of the recruitment baseline data.

6.2 Impact of study on decision to donate

Focus Groups. The Focus Groups will be with altruistic kidney donors who have already completed or have withdrawn from the donation process. As such, the study will not be able to impact on their decision to donate from the perspective of the focus group alone.

Interviews. The qualitative interviews will be performed prospectively and take place three months after donation or withdrawal from the donation process. This is to avoid any undue influence on the participant's decision to donate. The interviews will be conducted by experienced qualitative researchers who have interviewed both altruistic kidney donors and donors withdrawn from the process. The REC applications associated with these previous projects are: Understanding Barriers and enablers to altruistic kidney donation v1.14/SW/1105 and 10/H0203/11-Understanding the experiences of altruistic kidney donors. (Clarke, A., Mitchell, A., & Abraham, C. 2013. Understanding donation experiences of unspecified (altruistic) kidney donors. British Journal of Health Psychology.)

Questionnaires. The questionnaires which will be used are validated and widely used research tools which are regularly employed in the fields of social science and psychology. We have previously used similar tools in our research with no significant impact on the participants' mental or physical health.

6.3 Sensitive questions

Additional questions that will be formulated as a result of the focus group data (in addition to the already validated questionnaires) will be discussed amongst the study research group that consists of psychologists, transplant surgeons and nurses who are highly aware and sensitive to the process of altruistic donation as a result of their extensive clinical experience. Furthermore, two members of the 'Give a Kidney Charity', who represent the altruistic donor community, will review and be involved in the development of any further questions. Any new questions that would potentially impact on the decision to donate will be excluded from the questionnaire bundle

6.4 Ethics Reporting

Reports of related and unexpected SAEs will be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. The form will be completed in typescript and signed by the chief investigator. The Coordinator of the main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt should be sent to the R&D Directorate.

No SAE are expected for this study.

7. Trial Steering Committee

7.1 Study Steering Committee

The study does not have a Data Monitoring Committee, but there is a Study Steering Committee (SSC), which will have the following responsibilities:

i) To provide advice, through its Chair, to the Chief Investigator, the Project Sponsor, the Project Funder, the Host Institution and the Contractor on all appropriate aspects of the project

ii) To concentrate on progress of the project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question

iii) The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society

iv) To ensure appropriate ethical and other approvals are obtained in line with the project plan

v) To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
vi) To provide advice to the investigators on all aspects of the project

The SSC will be constituted as follows: An independent chairperson, an independent statistician, one member (not directly involved with the study) from within the Trust, one member external to the Trust, and two service users. An observer from the sponsor and from the CLRN will be invited to attend.

The SSC will meet at 4 to 6 monthly intervals, or more frequently if the Chairperson deems this to be necessary.

The study steering committee has the following members:

Chair
Prof Kenneth Farrington
Consultant Renal Physician
ken.farrington@nhs.net

Independent statistician
Dr Matthew Robb
NHBST

One member (not directly involved with the study) from within the Trust
Dr David Game
Consultant Renal Physician

One member external to the Trust:
Dr Sian Griffin
Consultant Renal Physician

Previous Service Users
Mr Peter Cordwell

Mr Nicholas Crace

7.2 Trial Management Committee

The Trial Management Committee manages the project on a regular basis. It consists of members of the project team and meets at 3 to 6 month intervals. Minutes and agendas are issued in the regular manner. The committee has two permanent PPI members representing the 'Give a Kidney' Charity.

8. Ethics & Regulatory Approvals

15/SC/0637
South Central – Berkshire B Research Ethics Committee
Health Research Authority
Bristol HRA Centre, Level 3, Block B,
Whitefriars, Lewins Mead, Bristol BS1 2NT
HRA (Bristol Centre): 0117 342 1382 | www.hra.nhs.uk, nrescommittee.southcentral-berkshireb@nhs.net

9. Data Handling

Confidentiality

A database will be constructed by the Guys and St. Thomas Biomedical Research Centre. Online or paper questionnaires and interview transcripts will be transferred to the database, held on a secure server at either Guys Hospital or Plymouth University, in an anonymous fashion, with password protected access. Access to the database will be limited to the study researchers, Chief investigator and study manager. Participant data will be managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

Each patient will have a unique study identity number which will avoid the use of patients' hospital numbers, NHS numbers, dates of birth or names. The Chief Investigator will have a separate key linking the study identification number with identity of the study participants. The study key information will be kept in a separate password secure and locked environment.

Back-up will be performed automatically by the Trust systems, and data archiving will be undertaken by the Kings Health Partners Joint Clinical Trials Office, according to their standard operating procedures.

Record Retention and Archiving

All records will be kept in secure conditions. When the research trial is complete the records are kept for a further 5 years.

Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

Non-Compliance

The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

10. Finance and Publication Policy

10.1 Funding

The research is funded by the National Institute of Health Research (NIHR) HS&DR Award (13/54/54), with a total value of £872,756.

National Institute of Health Research
University of Southampton
Alpha House
Enterprise Road
Southampton
SO16 7NS

The funds will be managed centrally by the research team at Guy's Hospital and distributed to collaborating units according to a collaboration agreement, which has been negotiated by the relevant academic, financial and legal departments within the collaborating universities and hospitals.

10.2 Outputs

There will be several specific outputs in addition to published manuscripts and conference presentations:

a) A report to NHSBT and the BTS, summarising the findings of the study
b) National guidelines, produced in conjunction with NHSBT and the BTS
c) A protocol for management of those presenting for unspecified donation
d) A report to the Renal Transplant Clinical Reference Group, which reports to NHS England (which commissions transplant services in England), and to the Scottish, Welsh and Northern Irish Departments of Health.

The process for developing these outputs (beyond the first, which will be written by the study team) is as follows:

National Guidelines

The transplant community is small, and there is a widespread desire for guidance on unspecified donation. Existing guidelines on living donation are extensively used by donor teams, and these have been important in changing culture. We recognize that guidelines are not, however, necessarily effective by themselves at changing practice- in this regard, the close liaison that one team member (LB) has with donor co-ordinators at all transplant centres, and the living donor forum which she organizes, will be vital.
The support of the BTS Clinical Trials Committee for this study (attached) is indicative of the close involvement and support of the BTS. There is an existing process for developing guidelines by the BTS, through the BTS Standards Committee. We will convene a small group, including NHSBT and BTS representatives, as well as service users, to draft a guideline, which can be sent to the BTS Standards Committee for consideration. Typically, this is opened for public consultation via the BTS website for a short period, revised and then disseminated to all units. The leads for this work will be Prof N Mamode and Ms L Burnapp.

Commissioners' report

The Chief Investigator is a member of the Renal Transplant Clinical Reference Group (CRG) and has been involved in drafting Service Specifications for transplantation. He will send a report, which will be drafted with the help of the study team, including service users, to the CRG for discussion and dissemination to NHSE and counterparts in other constituent countries.

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SF-12v2™ Health Survey. 1992-2002 by Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved. SF-12® is a registered trademark of Medical Outcomes Trust. (IQOLA SF-12v2 Standard, English (United Kingdom) 8/02)

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Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

Appendix 1

Appendix 1. Projected number of unspecified kidney donors to 2020

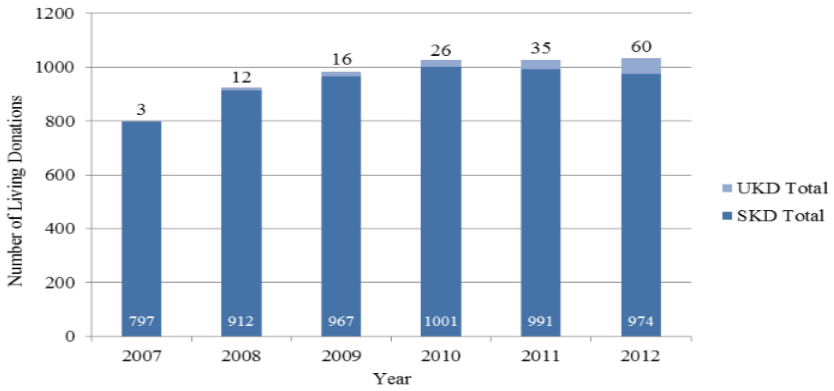

Figure 1. Number of living kidney donations in the UK by unspecified and specified kidney donors

Figure 1 shows the total number of living kidney donations in the UK per year, separated by unspecified and specified type. Over the six year period shown there has been an increase in the total number of living donations. Since 2010, the increase is driven by unspecified donations, with the number of unspecified donations actually falling.

Figure 2 and Table 1 below shows projections for the number of unspecified (altruistic) kidney donors to 2020 by two methods. The first method fits a linear rate of increase based on the past trend. The second method assumes a non-linear (quadratic) rate of change. The quadratic method fits the observed data best but this is no indication it provides a more accurate projection.

With recruitment between March 2015 and Feb 2018 we can expect between 279 (linear = 83+93+103) and 493 (non-linear = 131+163+199) donors based on the projections. The expected sample size will be based on the more conservative linear estimate. An even more conservative estimate would assume rates staying stable at the 2012 figures. This would mean the expected sample size of 180 (60+60+60).

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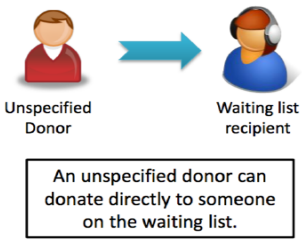
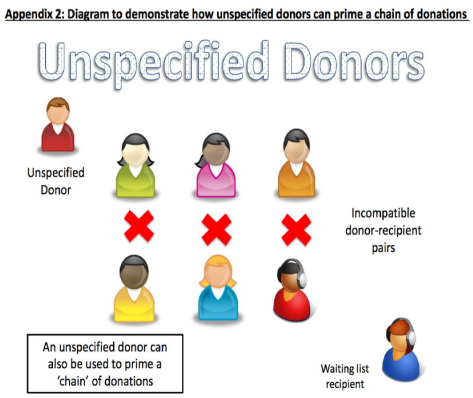
RQ2 Study Protocol V2.1
25.05.2016

Appendix 2a

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



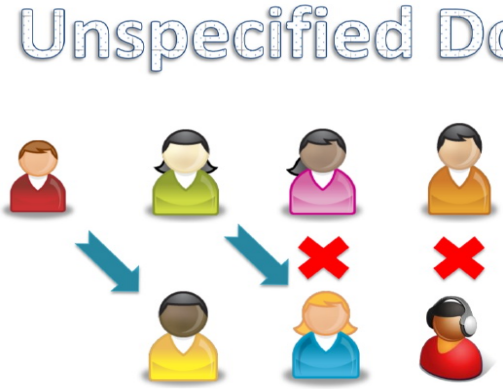
Appendix 2b



Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations

Appendix 2d

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



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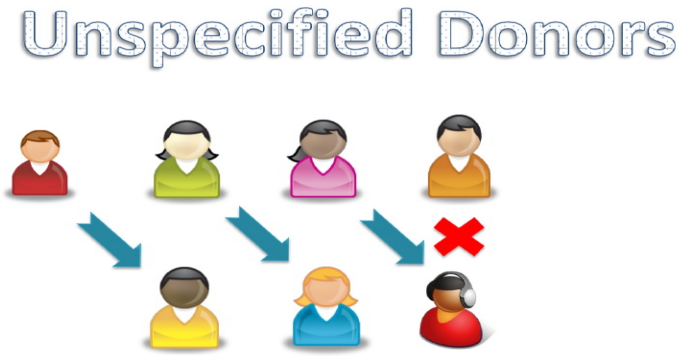
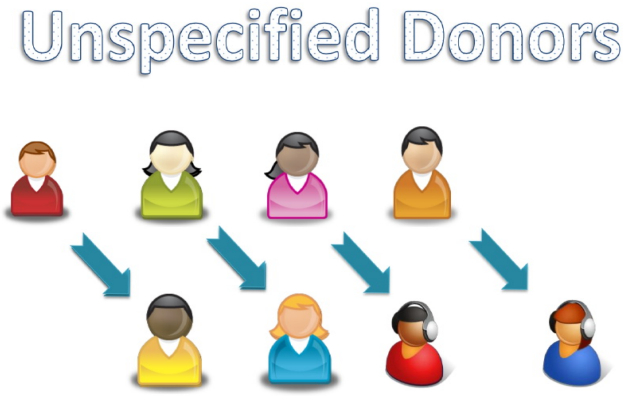
Appendix 2e

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



Appendix 2f

Appendix 2: Diagram to demonstrate how unspecified donors can prime a chain of donations



Appendix 3

BOUnD

Appendix 3: Topic list: Qualitative interviews

Appendix 4:

		Phase 1: Potential donors				Phase 2: Outcomes			
		Recruitment		Pre donation		Donation		Follow-Up	
	Data (source)	Pre-enrolment	Enrolment	Baseline	Pre-op (1 week)	Surgery	Post-op	Follow-up 3 months	Follow-up 12 months
Enrolment	Initial contact (Centre)	X							
	Referral (Centre)	X							
	Eligibility screen (Trial manager)		X						
	Informed Consent (Trial manager)		X						
Assessments	Baseline demographic data			A					
	Personality: TIPI (Questionnaire)			A					
	Social support: MSPSS (Questionnaire)			A	A			A	A
	Peri-operative physical outcome data (NHSBT)				A		D		D
	Surgical procedure data (NHSBT)					D			
	Withdrawal (Questionnaire & Centre data)			W	W				
	Rosenberg (Questionnaire)			A	A			A	A
	SWLS (Questionnaire)			A	A			A	A
	PHQ9 & GAD7 (Questionnaire)			A	A			A	A
	Flourishing Scale			A	A			A	A
	Decision Regret Scale							A	A
	SF12 (Questionnaire)			A	A			A	A
	Client Service Receipt Inventory (Questionnaire)			A	A			A	A
	In-House Questionnaire			A	A			A	A

X= recruitment and centre level data (pre-consent)
A= Data from all potential donors
D= Data for donors only
W= Data for withdrawn only