

PROTOCOL TITLE:

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

BOUnD

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RQ2 Study Protocol V3.1

06/12/2017

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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 v3.1 06/12/2017
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 2020
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) 758 participants (questionnaires), as follows: Test group: 137 unspecified donors that proceed to donate and 243 unspecified donors that withdraw. Control group: 189 directed / specified donor

	controls that proceed to donate and 189 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 3 and 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

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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-out 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 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 (September 2016-1st October 2019). 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.

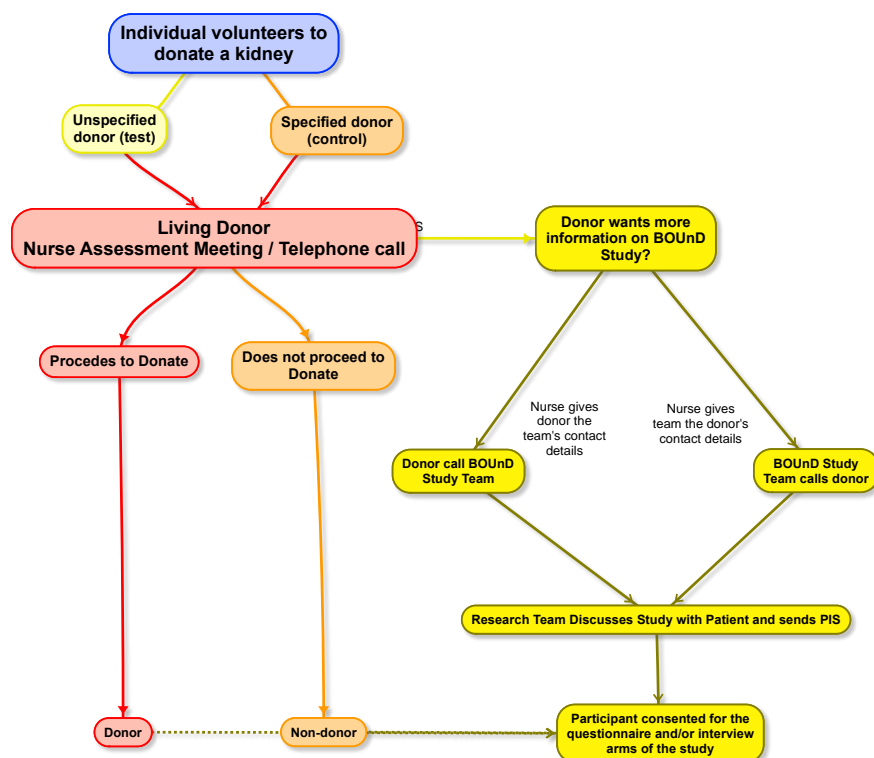
The Focus Groups represent the smallest aspect of the study and serve to help fine-tune the questionnaire design and interview topic guides. As such, only two focus groups will take place in centres such as Guy’s Hospital (London) or Plymouth Derriford Hospital, where the study team has long-standing 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 proceed 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

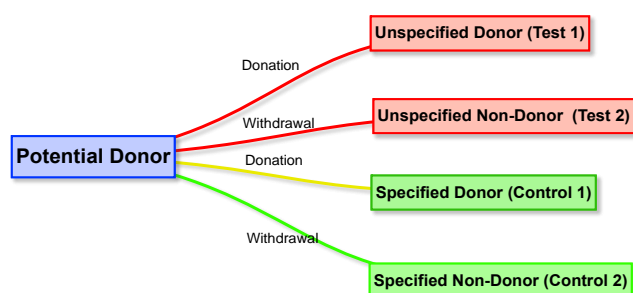


The four study populations will include:

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

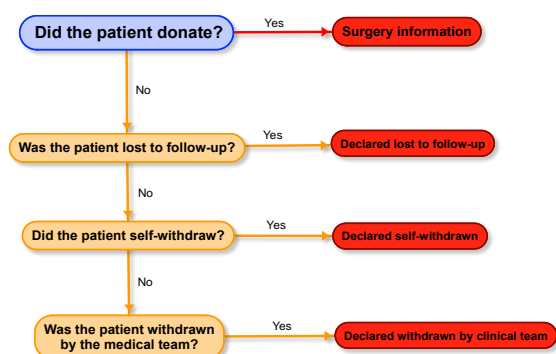
To ensure feasibility of the study questionnaire burden will be tested and considered in conjunction with the PPI group.

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

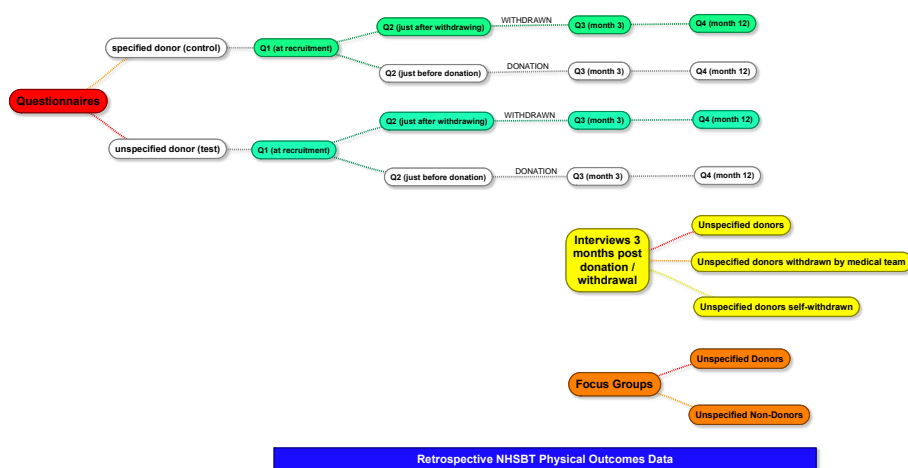
Qualitative interviews will also be completed with a sample of 15 donors who completed their donation, 15 who withdrew and 15 who were withdrawn by the transplant team from the process. Participants will be asked about their experience of the donation process and services, barriers and enablers to donation 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 regarding the donation procedure for all donors. Physiological data will be collected pre- and post-donation (Appendix 4). NHSBT data will be collected retrospectively at 3-months (discharge data) and at 12-months (1-year data), as per national donor follow-up protocol. NHSBT data will be collected earlier should the donor 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:

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

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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 September 2016 and October 2019 will be recruited to participate in the study.

Initial Recruitment Plan

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 $\pm 4\%$ overall, and to within $\pm 18\%$ for each centre. In summary, we aim to recruit 224 who have undergone unspecified donation and 400 who failed to donate.

Commented [GR1]: This needs amending based on new power calculation

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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.

Amended Recruitment Plan

An amendment was added to the protocol in December 2017, at the request of the Study' Steering Committee and with the permission of the funder (NIHR). This was based on recruitment data to June 2017, and driven by a delayed study start and lower than expected recruitment rate.

Amendment

The original target was to recruit 624 prospective unspecified donors between April 2015 and February 2018 (27/month), with an anticipated 224 proceeding to donation. This was based on trends between 2006 and 2012 that indicated a fairly conservative estimate of the likely number of unspecified donations during the recruitment period would be 280. The number of prospective donors was unknown and estimated based on a 36% conversion rate from pilot data and assuming an 80% recruitment rate consistent with previous studies of this population. Given delays in the start of recruitment (late September 2016) and a lower number of unspecified donors, recruiting to the target of 624 prospective unspecified donors is extremely unlikely. Therefore, it is necessary to reconsider the likely sample size and the power and precision available for the analysis of the main objectives.

As of June 2017, 109 prospective unspecified donors have been recruited in the 8 months since recruitment started – equating to a recruitment rate of approximately 14/month. Based on this rate it is anticipated that the actual number of potential donors recruited by the end of February 2018 will be 241. Of these, 87 are expected to proceed to donation based on the 36% conversion rate from pilot data. Statistical precision and power is dependent on this figure, where a lower conversion rate would negatively impact the study. The assumed rate of 36% appears tenable given current data. To date, 26 (24%) of those recruited have proceeded to donation with an upper estimate of 49 (45%) who will donate unless there are unforeseen circumstances (e.g. change of mind or incident health complication).

In addition to the prospective unspecified donors, a comparison group of specified donors is also being recruited to enable comparison of post-donation outcomes. The target sample size for this cohort was 200. Given the delayed start, based on current recruitment (7/month) we anticipate a sample size of 119 by February 2018.

A revised target sample size of 380 prospective unspecified donors is proposed based on current recruitment figures, with 137 expected to proceed to donation. The recruitment rate has increased during the period of recruitment and further initiatives are being implemented to maintain and perhaps increase this rate are underway. As such, this target appears to be feasible. Extending the period of recruitment for the for the directed donor comparison cohort to December 2018 leads to a revised target sample size of 189. This is close to the original target. Extending the period of recruitment naturally has an impact on the time available for analysis prior to the end of the study in April 2020.

Precision and power with respect to donation rates

The original power calculation indicated that the study, with 624 potential donors, would have sufficient precision to estimate the 95% confidence interval for proceeding to donation to within $\pm 4\%$ overall assuming the donation rate is 35%. Based on the expected 241 prospective unspecified donors to February 2018, precision for the overall donation rate will be approximately $\pm 6\%$, which is still acceptable. Based on the revised estimate of 380, overall precision for the overall donation rate will be approximately $\pm 5\%$.

Precision per centre will be affected to a greater degree. Originally 95% confidence intervals for the donation rate would have been estimated to within $\pm 18\%$ for each centre assuming a donation rate of 36% for each centre. Based on the expected figure by February 2018 and the revised target to December 2018, precision will be approximately $\pm 26\%$ and $\pm 22\%$ for each centre, respectively. This figure is based on a binomial exact confidence interval for the proportion. In the analysis we will use an empirical Bayes estimate, which will provide additional precision since centre level estimates draw on information across centres. A simulation study indicates that using this approach the average precision per centre will be approximately $\pm 13\%$ and $\pm 9\%$ at the centre level, respectively for the expected sample size to February and the revised target to December 2018, respectively. The revised target sample size provides acceptable precision to estimate donation rates. While it will not be possible (or indeed reasonable) to rank centres in terms of donation rates, it will be possible to identify case-mix adjusted rates highlighting centres that are particularly under or over-performing with respect to the average donation rate.

Individual and centre level predictors of time to donation will be based on cox regression models. Based on the expected sample size of 241 to February 2018 and a donation rate of 36%, it is anticipated that, accounting for the clustered nature of the data, the study will have 80% power to detect effects equivalent to a hazard ratio of 1.48 for a standardised continuous variable. Clustering is accounted for by a design effect assuming 12 observations per centre on average and intra-cluster correlation of .1. This compares with 80% power to detect a hazard ratio of approximately 1.33 based on the original target sample size and 1.40 based on the revised target. For all estimates the detectable hazard ratio is in the range considered 'small' when converting to Cohen's rules of thumb for interpretation. Increases in the overall sample size provide only negligible improvements in the detectable hazard ratio since the

increasing number of observations per centre leads to diminishing returns beyond around 10 to 12 observations per centre.

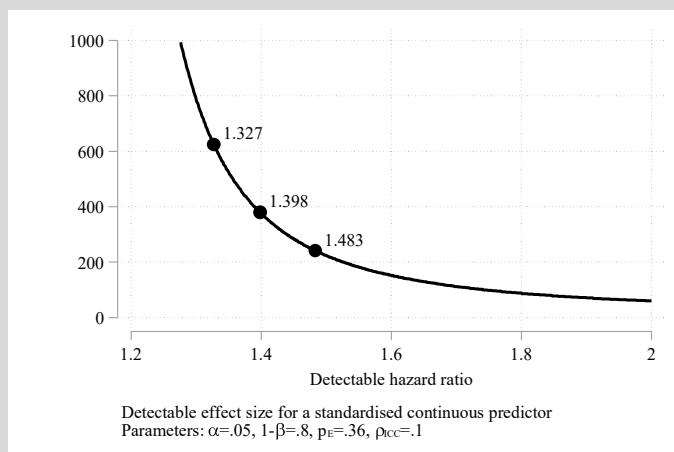


Figure 1. Detectable hazard ratio given sample size (adjusted for the clustered nature of the data) assuming a 36% donation rate

Power with respect to outcomes compared to directed donors

Outcomes over time for undirected donors will be compared to directed donors. The hypothesis is that undirected donors do no worse than directed donors 12 months after follow-up in terms of mental and physical health. The original target sample size of 224 undirected donors and 200 directed donors provided 80% power to determine non-inferiority of outcomes with a non-inferiority limit equal to a standardised mean difference of no more than .27, which was rounded to .3 in the application and protocol. This allowed for 20% missing data at the 12-month follow up. Given the expected sample size of 87 undirected and 119 directed donors based on recruitment to February 2018, power for a non-inferiority test with the same limit is reduced to 68% assuming 20% missing data. The expected sample size has 80% power when the non-inferiority limit is set at a standardised mean difference of .38. The revised target of 137 prospective unspecified donors and 187 specified donors leads to has 80% power when the non-inferiority limit is set at a standardised mean difference of .32. The non-inferiority limit for the revised target sample size is more acceptable given that it is closer to the minimum important difference for the outcomes considered range between a standardised mean difference of between .3 to .4.

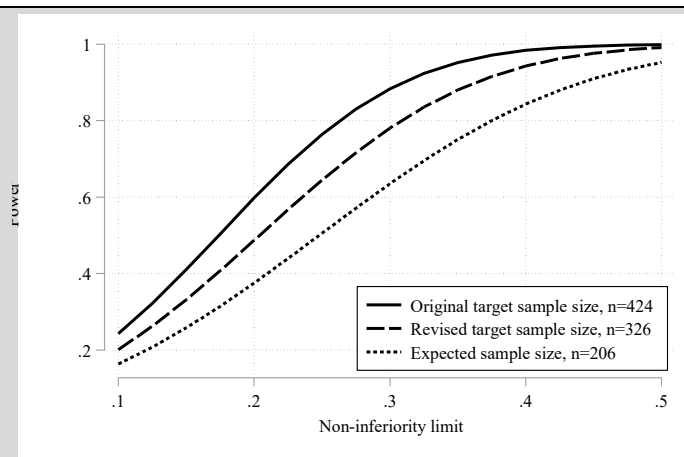


Figure 2. Power by non-inferiority limit (standardised mean difference) for original target sample size and expected sample size, accounting for 20% missing data at 12 months.

The revised power calculation with respect to outcomes for undirected compared to directed donors indicated revised target sample size would have 80% power to detect non-inferiority where the bound was a standardised mean difference of $d=.38$, as opposed the original bound of $d=.3$. For the SF12 physical component score (PCS) in undirected donors this relates to a difference of 3.3 units as opposed to 2.6 units; based on the standard deviation of the PCS for unspecified donors in the UK being 8.72 (Maple, H., et al., 2014. *Transplantation*, 98(11), pp.1182-1189.)

Amendment outcomes:

In summary, three main changes resulted from the amendment:

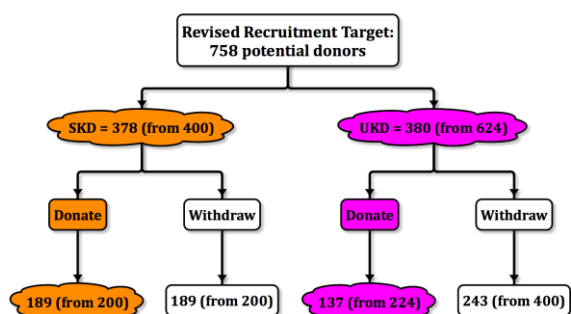
1. A reduction in the total recruitment and donation targets across all study populations
2. An extension to the recruitment period (to October 2019)
3. A change in primary focus from the 12-month to the 3-month outcomes data

To address the issue of potential prolonged work-up time period for UKDs, donors will be asked to provide an estimate of the date of first contact with the transplant services. This will take place at the pre-transplant (Q2) time point. A second supplementary question will be asked at the first post-donation questionnaire (Q3, 3-months) asking donors to describe potential reasons for delays in their work-up process.

RQ2 Study Protocol V3.1

06/12/2017

Consequently, the study's recruitment targets were changed as follows:



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

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

The following revised minimum recruitment targets have been set:

Questionnaires:

380 potential unspecified donors (test population)

- 137 who have donated
- 243 who did not donate

378 potential specified donors (control population)

- 189 specified donors (control population 1)
- 189 specified non-donors (control population 2)

Total: 758 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 months 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

06/12/2017

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 Nicholas Palmer

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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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	Main REC and Sponsor

			Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
<u>Progress Reports</u>	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
<u>Declaration of the conclusion or early termination of the study</u>	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) <i>The end of study should be defined in the protocol</i>	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
<u>Summary of final Report</u>	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

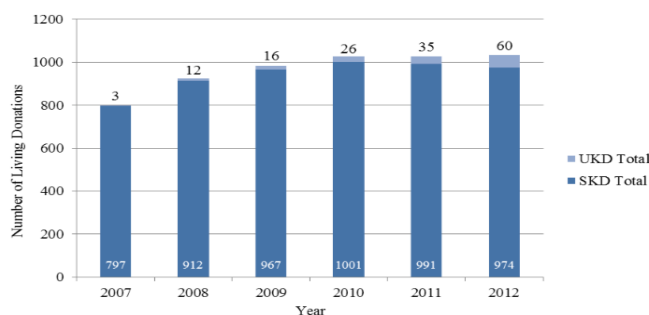
*Appendix 1***Appendix 1. Projected number of unspecified kidney donors to 2020****Figure 1. Number of living kidney donations in the UK by unspecified and specified kidney donors**

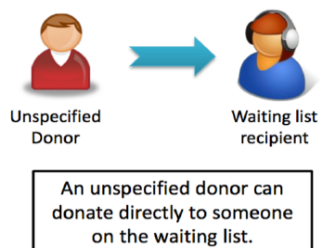
Figure 1 shows the total number of living kidney donations in the UK per year, separated by unspecified and specified type. Over the six year period shown there has been an increase in the total number of living donations. Since 2010, the increase is driven by unspecified donations, with the number of 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 ($60+60+60$).

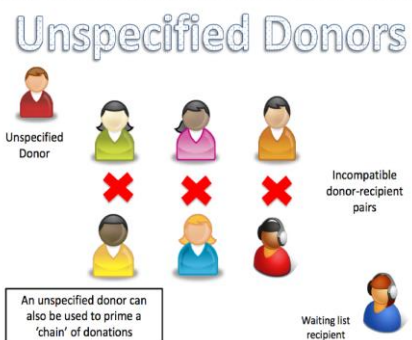
Appendix 2a

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

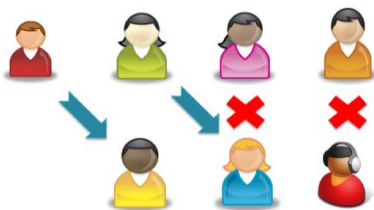
Unspecified Donors



Appendix 2d

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

Unspecified Donors



Appendix 2e

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

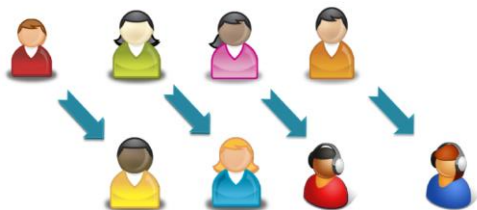
Unspecified Donors



Appendix 2f

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

Unspecified Donors



Appendix 3

BOUnD

Appendix 3: Topic list: Qualitative interviews

Donor Individual Interviews

Interview Questions

(NB: interviews are semi-structured which means the interviewer will use their skills to follow up any salient/interesting points with further questioning).

1. Can you tell me the story of your donation /choosing not to or being told that you were unable to donate. How did it all start?
2. No doubt you have been asked this before, but what led you to consider being an altruistic donor?
3. How have other people responded to your decision/idea to donate your kidney altruistically (professionals, peers, family)?
4. Can you tell me about how you have found the donation team; how did they respond?
5. Can you tell me about when you found out that you would/would not be able to donate your kidney ?
Or: can you tell me about your decision not to proceed with your donation ?
6. What have been the outcomes (donating or not), firstly for you personally (prompts- health/financial/psychological) and have you noticed any broader ripples (prompts- social impact)?
7. Could you suggest how the altruistic kidney donation service could be improved for the future?

Version 1.0, 07/10/2015

Appendix 4:

		Phase 1: Potential donors				Phase 2: Outcomes			
	Data (source)	Recruitment		Pre donation		Donation		Follow-Up	
		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						
	Baseline demographic data			A					
Assessments	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