Assessing the outcome and benefit of the unspecified living kidney donor programme in the UK

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 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 (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 if 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. Aims

This study aims to provide a comprehensive assessment of the unspecified kidney donation programme in the UK. There are three specific research questions (RQs):

RQ 1) Is there variation in transplant professionals' practice and attitudes, which is preventing some unspecified donations?

RQ 2) Are psychosocial and physical outcomes after unspecified donation equivalent to those after specified donation?

RQ3) What is the economic benefit from unspecified donation?

3. Methods

The research project involves three interlinked studies delivered over a period of five years. These are detailed in the flow chart attached.

1) Mixed methods study

There are two parts to this work drawing on both qualitative and quantitative methods (RQ1):

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 (please see appendix 3 for topic list). There will also be a focus group including patients in two centres. These groups will be used to inform the approach in subsequent individual interviews with professionals from each discipline (surgeons, physicians, psychological assessors and donor co-ordinators). It is anticipated that 60 transplant professionals in total will be interviewed (please see appendix 3 for topic list).

ii) 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.

Analysis

Leads for analysis: For the qualitative work: Dr Annie Mitchell. For the quantitative work: Dr Joe Chilcot.

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.

2) Prospective cohort study

The primary study group will comprise all those who approach a transplant team in any UK centre, offering to donate a kidney to a stranger over a three year period (RQ2).

a) Design

Data regarding sociodemographic, physical, psychological, and resource use variables will be collected at baseline (shortly after contacting the transplant centre). For those that proceed to donation, follow-up data will be collected pre-operatively, and at 3 and 12 months post-donation. For those that decide not to donate, or in whom the transplant team decline to proceed, data will be collected at baseline, and at 3 and 12 months after the decision has been made. Two focus groups with donors that have completed their donation will be conducted to inform the questionnaire selection.

To ensure feasibility of the study questionnaire burden will be tested and considered in conjunction with the PPI group. The first year of the recruitment will form an internal pilot study to ensure recruitment/retention rates and data completeness is acceptable.

b) Recruitment & sample size

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 (Appendix 1). 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 (RQ1). 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). Based on our retrospective study we expect a recruitment rate of 80%. Therefore we will need to approach 250 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 (RQ2), 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).
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 (RQ1). 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 (please see appendix 3 for topic list). 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.

c) Inclusion criteria

Any individual contacting a transplant centre to enquire about unspecified donation, who proceeds beyond the initial phone conversation, and is able to give informed consent. Non-English speakers will be included.

d) Exclusion criteria

Any individual who declines to participate.

e) Study procedures

Eligible individuals will be notified to the trial research fellow and invited to participate in the study. Participants will be given an information sheet and asked to sign a written consent form. Where necessary this 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. 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. Linkage to the NHS Blood and Transplant records will provide physiological outcome data physiological outcomes of all for all donors, even if self-reported follow-up outcome data is not available.

Physical and psychosocial outcome data will be collected from case records at individual centres.

If any clinical concern is identified by the research team from the questionnaires or interviews (for example suicidal thoughts, or severe depression), the clinical team will be informed, with a view to referral to the local psychological or counseling service; this approach was used by us previously in our retrospective study.

f) Measures

Primary outcomes: Physical and mental health-related quality of life will be assessed using the SF12, collected at all assessments. This 12 item questionnaire provides estimates of an individual physical and mental quality of life (normed against the general population).

Secondary outcomes: Other outcome variables collected at all assessments will include symptoms of anxiety (General Anxiety Disorder-7 (GAD-7)) and depressive symptoms (Patient Health Questionnaire-9 (PHQ-9)), life satisfaction (Satisfaction

With Life Scale) and self-esteem (Rosenberg Self-Esteem Scale). For the economic analysis, service use information will be collected using the Client Service Receipt Inventory (CSRI). At the follow-up assessments we will additionally ask donors if they regret their decision to donate. Linkage to the NHSBT database will provide physiological variables.

Baseline only variables: Demographic information, personality (Ten Item Personality Inventory), social support (Multidimensional Scale of Perceived Social Support), social comparison (Social Comparison Scale), motivations and other altruistic behaviours will be collected at baseline. Items to measure motivation and altruistic behaviour have been developed as part of our previous retrospective study.

We anticipate the baseline questionnaire will take 30-40 minutes to complete. All subsequent questionnaires, which will include just 5 measures, will take 15-20 minutes to complete. Additional psychosocial factors may be added following the qualitative interviews if additional themes emerge from the qualitative interview data.

g) Maximising response rates

Unspecified donors are highly motivated individuals, who, in our experience, are enthusiastic about participation in studies which 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 (usually by telephone or email). Non-responders will be contacted on repeated 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 below.

Analysis

Leads for analysis. For the quantitative work, Dr H Maple. For qualitative study, Dr A Clarke

All primary analyses will be undertaken by the study statistician SN in accordance with a predetermined analysis plan. Further analysis will be undertaken by HM.
Descriptive analysis will be used to describe the proportion of people who withdraw or proceed to donation, and the reasons for failure to proceed (RQ1). Variation in donation rates between centres will be explored using mixed effects logistic regression models incorporating centre as a random effect (RQ1). 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 mixed methods study will be included in the models to determine whether these variables explain variation in donation rates (RQ1).
Descriptive analysis will be used to compare baseline variables for individuals that express an interest in donation that: i) the transplant team decline to proceed with donation; ii) those who decide not to proceed; iii) those that proceed to donation; and iv) the specified kidney donor control group (RQ2). 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 (RQ2). 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 approach as described above.

<u>3) Economic benefit</u>

Lead for analysis: Prof Paul McCrone.

Two key questions will be asked in the economic evaluation. First, does unspecified kidney donation result in extra costs compared to specified donation? Second, what is the economic benefit of unspecified donation?

The impact on healthcare and societal costs for donors in both groups will be examined. This will involve the use of the Client Service Receipt Inventory (CSRI) (15). The CSRI has been widely used and will be adapted for this study. It will be administered in self-reported questionnaires to donors (3 and 12 months after donation) and will ask for information on whether specific services have been used and how often. This will include those services directly related to the donation process (assessments, tests, counseling etc) and also other services that may be affected. To address societal costs, information on extra time spent providing care by family/friends in specific areas (e.g. personal care, child care, help in the home, accompanying patient to use services) will be elicited as well as time taken off work by donors. Costs will subsequently be calculated by combining the service use data with appropriate unit cost information (16), NHS Reference Costs, BNF). The costs of care from family/friends and the cost of lost employment will be valued using average wage rates. Costs will be compared between the two groups controlling for baseline differences in a regression model and using bootstrap methods to address the likely non-normal distribution of regression residuals.

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, refusing to proceed, being deemed unsuitable, successfully donating, and a recipient benefiting. There are costs associated with these and outcomes associated with successful donation or failure to achieve this. These outcomes will be measured in terms of quality-adjusted life years (QALYs) for recipients using the SF-12. Data for the model will draw on a systematic literature review of published economic evaluations of kidney donation and also from the costing exercise described above and from 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.

4. Internal pilot study

It is important that we ensure both recruitment rates and data capture is adequate, particularly for the prospective cohort study. We therefore propose that during the first year, we will conduct an internal pilot study to assess these. The first 30 UKDs and 30 SKDs will be included (as recommended [17]), along with 3 month follow-up

data. This will be analysed and presented to the study steering committee, which will make an assessment according to pre-determined stop/go criteria.

5. 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.

6. 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.

7. 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 liason 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 Mr N Mamode and Ms L Burnapp.

Protocol

The protocol for management may differ in some respects from the guideline, since it will deal with practical issues which need to be considered when a potential donor presents. For example, it may be that a central telephone hotline would be the first contact point for any potential unspecified donor. Currently, no protocol exists.
The protocol will be developed by a small team including service users and donor co-ordinators, and will be sent to NHSBT for ratification. It will then be sent to all transplant centres. The lead for the development of the protocol will be Ms L Burnapp.

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.

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