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# Testing the ability to reduce immunosuppression in older renal transplant recipients

**Submission date**
17/05/2022

**Recruitment status**
Stopped

**Registration date**
29/09/2022

**Overall study status**
Stopped

**Last Edited**
11/08/2026

**Condition category**
Urological and Genital Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

## Plain English summary of protocol

Background and study aims
Older kidney transplant recipients are at increased risk of infection and death from infection-related complications compared to younger transplant recipients. Despite knowledge of age-related immunological changes, immunosuppressive treatment plans have remained the same for both young and older kidney transplant recipients. Our provisional knowledge suggests that standard dose of immunosuppression (anti-rejection) medication in older patients can result in more infections but fewer episodes of rejection (known as acute rejection [AR]) compared to younger recipients. Acute rejection occurs when the body's immune system attacks the donated kidney and can limit the long-term lifespan of the transplant.

Achieving a better balance by reducing the risk of infections, without increasing the risk of AR, would be highly desirable. This trial will help us define how much immunosuppressive medicine is ideal for transplant recipients of different ages.

One type of infection transplant recipients are prone to is cytomegalovirus (CMV). In the transplant population, CMV infection can affect the bone marrow, lung, stomach and intestine, brain and eyes (causing inflammation such as bone marrow suppression, pneumonitis, colitis, retinitis and encephalitis), which can lead to higher possibility of loss of life. In this trial we will measure the amount of CMV in the blood regularly after transplantation to help us check that you are not receiving too much immunosuppression medicine in the study. This will possibly help us define this process as a marker for over-immunosuppression in transplant recipients.

There are no current recommendations regarding the average dose or recommended levels of immunosuppression (IS) treatment, and importantly, no age-specific standards. Our research could provide a better understanding of what these should be.

A rapidly emerging area of research has been assays that can detect genetic material (DNA; deoxyribonucleic acid) circulating in the blood, whereby it is possible to measure how much DNA from the donor organ ends up in the recipient. If there is acute rejection, cells from the donor kidney get injured and break off, as a consequence, pieces of DNA can get released from the

donated kidney into the blood of the recipient. This is known as donor-derived cell-free DNA or “dd-cfDNA”. Elevated levels of dd-cfDNA detected in the blood of transplant recipients have been increasingly reported as a potential reliable indicator for AR. This means the measure of dd-cfDNA could be used as a marker for AR.

Measuring the stability of this marker (i.e., a lack of rise of dd-cfDNA) in the blood after transplantation, may make it possible to personalise the amount/dosage of IS treatment we give to transplant recipients. Our study will provide information that will justify this strategy.

Who can participate?
Kidney transplant recipients over 60 years old

What does the study involve?
Participants who are about to undergo a kidney transplant will be randomised to either the normal doses or the reduced doses of our standard drugs used to keep the kidney from rejecting. The participants will be treated just like they would be if they were not in the trial , except for a few additional blood tests and some assessments of their physical strength. During their follow up in the clinic we will check the levels of the drugs they are taking , which is again standard of care and adjust the doses according to the trial protocol.
There will not be any extra visits to the clinic over and above what is usual for the new transplant patients.

What are the possible benefits and risks of participating?
Benefits:
We don’t really know how little of the drugs we use to stop rejection of the kidney we can use. So the benefit here is that individuals will help us define what is a safe level to use and what the side effects are like compared to standard doses. For an individual this might mean fewer infections or long term complications if they are on the lower doses of drugs. The participants on standard doses will be no better or worse off than if they had not enrolled in the trial.
Risks:
Venesection- potential for bruising and discomfort from venepuncture site- this will be coordinated with standard of care bloods to minimise Venesection- potential for bruising and discomfort from venepuncture site- this will be coordinated with standard of care bloods to minimise venepuncture required
Increased risk of rejection or development of anti-donor antibodies: this is mitigated by excluding higher risk patients and by careful monitoring or all transplant parameters. Early signs of graft dysfunction will be picked up as we normally do in our routine clinics.
No other significant risks or intrusions or changes to lifestyle.

Where is the study run from?
University College London (UK)

When is the study starting and how long is it expected to run for?
May 2022 to July 2027

Who is funding the study?
Natera (USA)

Who is the main contact?
Dr Alan Salama, a.salama@ucl.ac.uk

# Contact information

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Scientific


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# Additional identifiers

### ClinicalTrials.gov (NCT)
NCT05073822

### Clinical Trials Information System (CTIS)
2022-000051-36

### Integrated Research Application System (IRAS)
1005447

### Protocol serial number
140986

# Study information

### Scientific Title

A randomised feasibility trial on the minimisation of immunosuppression in elderly renal transplant recipients

## Study objectives

Kidney transplantation provides the optimal form of kidney replacement therapy. We are increasingly using older donor kidneys, transplanted into increasingly older recipients with greater comorbidities. Increasing age remains a major risk factor for death after kidney transplantation, with the commonest causes of death being cardiovascular disease, infection, and malignancies. Immunosuppressant drugs, critical for the maintenance of the transplanted organ can contribute to increased morbidity and mortality, by direct effects or through lowered immunity predisposing to infection. Cytomegalovirus (CMV) is a common opportunistic infections that affects kidney transplant patient outcome and can be monitored prospectively. We wish to test lower vs standard doses of immunosuppressants in older kidney transplant recipients, using CMV viraemia as one main outcome measure, and investigate if cell free donor derived DNA is a means to further stratify doses of immunosuppression given.

To assess the willingness of patients to be randomised
Our main aims are:
1. To assess the willingness of clinicians to randomise patients
2. To determine adequate separation of immunosuppressive burden between study arms:
2.1. Characterise the time accumulated difference in immunosuppression exposure between arms.
2.2. Assess intermediate markers of overimmunosuppression.
Secondary aims:
1.Impact of lower immunosuppression on:
1.1. Kidney function
1.2. Other infections
1.3. Quality of life
1.4. Development of new DSA
1.5. Development of diabetes after transplantation and major cardiovascular events
1.6. Transplant failure (return to dialysis)
1.7. Incidence of malignancy
1.8. Intensity of antihypertensive and lipid lowering therapy
1.9. Variation in tacrolimus levels
2. Can donor derived cell free DNA(dd-cfDNA) be used in older recipients to customise immunosuppressive therapy?
3. Does physical frailty mirror immunological senescence and can it help predict need for immunosuppression targets

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Approval pending, London - Hampstead (United Kingdom), ref: 22/LO/0389

## Primary study design

Interventional

## Study design

Interventional randomized controlled trial

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Kidney transplant recipients

## Interventions
In Arm 1: standard of care Immunosuppression (SOC-IS) therapy
serum tacrolimus level: target tacrolimus levels 8-12ng/ml in the first 3 months target tacrolimus levels 6-8ng/ml in months 4-12 target tacrolimus level 4-8ng/ml after the 1st year
Mycophenolate mofetil dose:
2g/day for 1 month
1.5mg/day between months 2-12
1g/day after the 1st year

In Arm 2: minimised immunosuppression (Min-IS) therapy
serum tacrolimus level : target tacrolimus levels 6-8ng/ml for first 3 months target tacrolimus levels 4-8ng/ml in months 4-12.
Mycophenolate mofetil dose:
1.5g/day in the first month
1g/day until 1year post-transplantation

*The intervention/treatment is reduction of both standard Tacrolimus & Mycophenolate mofetil doses.

## Intervention Type
Drug

## Phase
Not Applicable

## Drug/device/biological/vaccine name(s)
mycophenolate mofetil, tacrolimus (tacrolimus monohydrate)

## Primary outcome(s)
1. The willingness of patients to be randomised measured by the proportion of participants approached who consent to take part during Recruitment Period
2. The willingness of clinicians to randomise patients measured by the Proportion of primary transplant clinicians recruiting to the trial during Recruitment Period
3. To determine adequate separation of immunosuppressive burden between study arms:
3.1. Characterise the time accumulated difference in immunosuppression exposure between arms measured using Time-accumulated 1 year mycophenolate dose and Time-accumulated 1 year tacrolimus levels within 12 months of receipt of treatment
3.2. Assess intermediate markers of overimmunosuppression by Incidence of CMV viraemia as defined as any detectable virus by (PCR) above the threshold of 200 copies/ml in 1st year within 12 months of receipt of treatment

## Key secondary outcome(s)
Exploratory analyses:
Assess impact of lower immunosuppression by 12 months within 12- 18 months post randomisation:

1. Kidney function by median kidney transplant function as determined by the MDRD-derived estimated Glomerular Filtration Rate (eGFR) by 12 months after randomisation
2. Other infections measured by incidence of post-transplant bacterial and non-CMV viral and bacterial infections up to by 12 months after randomisation. Infectious complications will include, but not be limited to, urinary tract infections (defined as a positive urine culture [>50, 000 CFUs/ml] from mid-stream urine, and categorised as asymptomatic bacteriuria [no symptoms], cystitis [lower urinary tract symptoms without systemic features] or pyelonephritis [systemic features, graft dysfunction, C-Reactive Protein >50]), BK viremia, and respiratory tract (RV) infections, Torque teno virus (TTV) and respiratory tract (RT) infections.
3. Quality of life measured by median health-related quality of life (EQ-5D) scores will be assessed pre- and post-randomisation.
4. Development of new DSA measured by proportion of patients who develop antibodies to human leukocyte antigens (HLA)
5. Development of diabetes after transplantation and major cardiovascular events measured by incidence of new-onset diabetes after transplant (NODAT) and cardiovascular disease (myocardial infarction or stroke)
6. Transplant failure (return to dialysis) measured by incidence of biopsy-proven acute rejection (BPAR) as per Banff classification (1, 2) by 12 months after randomisation
7. New onset malignancy
8. Intensity of antihypertensive and lipid lowering therapy
9. Variation in tacrolimus levels

### Completion date
01/07/2027

### Reason abandoned (if study stopped)
Undisclosed

## Eligibility

### Key inclusion criteria
1. First time adult recipients of either a deceased or living donor kidney transplant
2. Recipient of a single organ transplant only
3. Age above 60 years
4. Negative screen for donor-specific antibody prior to transplantation (MFI<2000)

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Mixed

### Lower age limit
60 Years

### Upper age limit
120 Years

**Sex**
All

**Total final enrolment**
0

**Key exclusion criteria**
1. Recipients that are highly sensitised (cRF >85%)
2. Inability to participate in frequent monitoring of renal transplant function and clinical visits (every 4 weeks) during dd-cfDNA monitoring and IS minimisation.
3. Immune-mediated renal disease in which IS minimisation is inadvisable
4. EBV IgG negative recipient (as IS minimisation is part of standard protocol)
5. Inability to comply with study directed treatment

**Date of first enrolment**
30/06/2022

**Date of final enrolment**
30/08/2026

# Locations

**Countries of recruitment**
United Kingdom

England

**Study participating centre**
**Renal Clinic - Royal Free Hospital**
Royal Free Hospital
Pond Street
London
England
NW3 2QG

# Sponsor information

**Organisation**
University of London

**ROR**
https://ror.org/04cw6st05

# Funder(s)

**Funder type**
Industry

**Funder Name**
Natera

# Results and Publications

**Individual participant data (IPD) sharing plan**
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof Alan Salama, a.salama@ucl.ac.uk. Fully anonymised data, based on reasonable requests and in fully consented patients.

**IPD sharing plan summary**
Available on request

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |