

# Optimized Tacrolimus and MMF for HLA Antibodies after Renal Transplantation

|                                        |                                                                       |                                                                                                              |
|----------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>Submission date</b><br>26/03/2013   | <b>Recruitment status</b><br>No longer recruiting                     | <input checked="" type="checkbox"/> Prospectively registered<br><input checked="" type="checkbox"/> Protocol |
| <b>Registration date</b><br>26/03/2013 | <b>Overall study status</b><br>Completed                              | <input type="checkbox"/> Statistical analysis plan<br><input checked="" type="checkbox"/> Results            |
| <b>Last Edited</b><br>24/01/2023       | <b>Condition category</b><br>Injury, Occupational Diseases, Poisoning | <input type="checkbox"/> Individual participant data                                                         |

## Plain English summary of protocol

### Background and study aims

Treatment of kidney disease accounts for a significant proportion of NHS spending. Transplantation is the best treatment for kidney failure, in terms of length and quality of life. It is also more cost-effective than dialysis. However, most transplants fail after 10-12 years and patients have to go back onto dialysis, placing a considerable burden on the NHS. Damage by the immune system, called 'chronic rejection' accounts for 50% of failing transplants and it is now possible to identify patients at risk by screening for a biomarker of chronic rejection called HLA antibodies (found in the blood). All transplant units in the UK can do this, but routine screening of patients has not been adopted because it is not clear how best to treat patients with antibodies. This study will test a screening and treatment protocol for HLA antibodies. The aim is to reduce transplant failure rates over 3 years.

### Who can participate?

The trial is open to all kidney transplant recipients aged 18-70 years who have had their transplant for 12 months or more and currently have good kidney function.

### What does the study involve?

Participants with antibodies will be randomly allocated to one of two groups: the biomarker-led (BLC) group or the standard care (SC) group. In the BLC group, test results are revealed and recruits will have their anti-rejection drugs changed to a regime of three drugs, prednisone, tacrolimus and MMF, each already licensed for use in transplant recipients. We have evidence that this treatment will be effective at preventing dysfunction and expect this to feed through to improvements in graft survival. In the SC group, screening results are not made available and participants will remain on their current treatments. Participants without antibodies will be randomly allocated to one of two groups: a group called blinded screening where results will not be given or a group called unblinded screening where results will be given. They will remain on standard treatment. Testing will continue every 8 months. Recruits in the SC group will move into the BLC group if they become antibody positive.

### What are the possible benefits and risks of participating?

As well as the potential impact on transplant failure, the drugs used here are associated with better cholesterol profiles and lower blood pressures than others in common usage. There are

potential risks. Tacrolimus is associated with an increased risk of diabetes mellitus and enhanced immunosuppression in general is associated with an increased incidence of infection, especially viral and with an increased risk of malignancy. It is difficult to predict such risks in this study. The incidence of diabetes, infection and malignancy will be monitored carefully on this trial.

Where is the study run from?

The study is run and coordinated by a team from King's College London, based at Guy's Hospital (UK).

When is the study starting and how long is it expected to run for?

June 2013 to September 2020 (updated 12/05/2020, previously: Recruitment will begin in June 2013 and finish by May 2016. The study is scheduled to finish in May 2019.)

Who is funding the study?

National Institute for Health Research through an EME programme grant (UK)

Who is the main contact?

Professor Anthony Dorling

anthony.dorling@kcl.ac.uk

added 12/05/2020: Senior Trial Manager

Dr Leanne Gardner

leanne.gardner@kcl.ac.uk

## Contact information

### Type(s)

Scientific

### Contact name

Prof Anthony Dorling

### Contact details

MRC Centre for Transplantation

Dept. of Nephrology and Transplantation

Guy's Hospital Great Maze Pond

London

United Kingdom

SE1 9RT

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## Additional identifiers

Clinical Trials Information System (CTIS)

2012-004308-36

Protocol serial number

13990

## Study information

## Scientific Title

A randomized controlled clinical trial to determine if a combined screening /treatment programme can prevent premature failure of renal transplants due to chronic rejection in patients with HLA antibodies

## Acronym

OuTSMART

## Study objectives

Current study hypothesis as of 12/05/2020:

Treatment of kidney disease accounts for a significant proportion of NHS spending. Although transplantation is the best treatment for kidney failure, most transplants do not survive for the recipient's natural lifespan, but instead fail after 10-12 years. Damage by the immune system, called 'chronic rejection' accounts for 50% of failing transplants and it is now possible to identify patients at risk by screening for 'HLA antibodies' in the blood. This application is to test a screening and treatment protocol for antibodies in a randomised controlled trial. Those with antibodies will be randomised into biomarker-led (BLC) or standard care (SC) groups. In the former, test results are revealed and recruits will have their anti-rejection drugs changed to a regime of prednisone, tacrolimus and MMF, each already licensed for use in transplant recipients. We have evidence that this regime is effective at preventing graft dysfunction and expect this to double blinded and recruits will remain on their current therapies. In those without antibodies, recruits will be randomised to either blinded or unblinded screening and remain on standard treatment. Testing will continue every 8 months; recruits in the unblinded screening group will move into the BLC group if they become antibody positive. The primary outcome is to determine the time to graft

failure in patients testing positive for HLA Ab at baseline or within 32 months of randomization who receive an optimized anti-rejection medication intervention with prednisone, Tac and MMF ('treatment'), compared to a control group who test positive for HLA Ab at baseline or within 32 months post-randomization who remain on their established immunotherapy and whose clinicians are not aware of their Ab status. The primary endpoint will be assessed remotely when a minimum of 43 months post-randomisation has been achieved by all. Secondary outcomes include rates of deterioration, the incidence of infections, cancers and diabetes, an analysis of the role of non-adherence with medication, and a scientific study to identify new biomarkers associated with outcomes. A cost analysis will confirm whether the screening programme and treatment protocol can save money by keeping kidney transplants functioning for longer. The recruitment target is to enroll 1900 HLA antibody-negative patients. This should allow recruitment of sufficient numbers of HLA antibody-positive patients.

More details can be found at: <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=13990>

Previous study hypothesis:

Treatment of kidney disease accounts for a significant proportion of NHS spending. Although transplantation is the best treatment for kidney failure, most transplants do not survive for the recipient's natural lifespan, but instead fail after 10-12 years. Damage by the immune system, called 'chronic rejection' accounts for 50% of failing transplants and it is now possible to identify patients at risk by screening for 'HLA antibodies' in the blood. This application is to test a screening and treatment protocol for antibodies in a randomised controlled trial. Those with antibodies will be randomised into biomarker-led (BLC) or standard care (SC) groups. In the former, test results are revealed and recruits will have their anti-rejection drugs changed to a regime of prednisone, tacrolimus and MMF, each already licensed for use in transplant recipients. We have evidence that this regime is effective at preventing graft dysfunction and expect this to feed through to improvements in survival. In the SC group, screening results are

double blinded and recruits will remain on their current therapies. In those without antibodies, recruits will be randomised to either blinded or unblinded screening and remain on standard treatment. Testing will continue every 8 months; recruits in the unblinded screening group will move into the BLC group if they become antibody positive. The primary outcome is kidney failure rates within 3 years of randomisation in HLA antibody+ recruits, predicted to be approximately 20% in the SC but <10% in the BLC groups. Secondary outcomes include rates of deterioration, the incidence of infections, cancers and diabetes, an analysis of the role of non-adherence with medication, and a scientific study to identify new biomarkers associated with outcomes. A cost analysis will confirm whether the screening programme and treatment protocol can save money by keeping kidney transplants functioning for longer.

The recruitment target is to enroll 1900 HLA antibody-negative patients. This should allow recruitment of sufficient numbers of HLA antibody-positive patients.

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### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

NRES Committee London - Hampstead, 14/01/2013, ref: 12/LO/1759

### **Primary study design**

Interventional

### **Study design**

Randomised; Interventional; Design type: Screening, Treatment

### **Study type(s)**

Treatment

### **Health condition(s) or problem(s) studied**

Topic: Renal and Urogenital; Subtopic: Renal and Urogenital (all Subtopics); Disease: Renal

### **Interventions**

Optimized Treatment protocol, The 'optimized treatment' protocol in the recruits with HLA Ab in unblinded group will be:

1. Mycophenolate mofetil bd, tds or qds, or enteric coated mycophenolic acid bd, with daily dose determined according to local unit guidelines. The patient will be stabilized on the maximum tolerated dose.
2. Tacrolimus od or bd, according to local unit preference, with dose titrated to achieve 12-hour post-dose levels of 4g/L to 8g/L (4-8 ng/ml). The patient will be stabilized on the maximum tolerated dose that achieves these levels.
3. Prednisolone od. Starting at 20mg for two weeks, then reducing by 5 mg od every two weeks down to a maintenance dose of 5mg od.

Screening for HLA antibodies, Serum prepared from 10mls of blood will be used in the commercially available 'LABScreen' tests, containing fluorescently tagged beads coated with purified HLA antigens. All participating centres have 'Luminex' equipment for analysis of these tests and the skills to process samples and interpret results. Therefore, the tests will be performed in each of the centres.

Follow-Up Length: 36 month(s)

## **Intervention Type**

Drug

## **Phase**

Not Applicable

## **Drug/device/biological/vaccine name(s)**

Mycophenolate mofetil, tacrolimus, prednisolone

## **Primary outcome(s)**

Current primary outcome measure as of 12/05/2020:

Determine the time to graft failure in patients testing positive for HLA Ab at baseline or within 32 months of randomization who receive an optimized anti-rejection medication intervention with prednisone, Tac and MMF ('treatment'), compared to a control group who test positive for HLA Ab at baseline or within 32 months post-randomization who remain on their established immunotherapy and whose clinicians are not aware of their Ab status. The primary endpoint will be assessed remotely when a minimum of 43 months post-randomisation has been achieved by all.

Previous primary outcome measure:

Renal Transplant Failure Rates; Timepoint(s): 3 Years post-recruitment

## **Key secondary outcome(s)**

Current secondary outcome measures as of 12/05/2020:

1. Analysis of adherence and perceptions of risk; Timepoint(s): 32 months
2. Change in estimated Glomerular Filtration Rate; Timepoint(s): 32 months
3. Patient Survival; Timepoint(s): 32 months
4. Proteinuria; Timepoint(s): 32 months
5. Rate of acute rejection; Timepoint(s): 32 months
6. Rates of biopsy proven malignancy; Timepoint(s): 32 months
7. Rates of Culture-positive infection; Timepoint(s): 32 months
8. Rates of Diabetes Mellitus; Timepoint(s): 32 months
9. Scientific analyses of humoral & cellular immunity and CD34+ cells; Timepoint(s): 32 months

Previous secondary outcome measures:

1. Analysis of adherence and perceptions of risk; Timepoint(s): 3 years
2. Change in estimated Glomerular Filtration Rate; Timepoint(s): 3 years
3. Patient Survival; Timepoint(s): 3 years
4. Proteinuria; Timepoint(s): 3 years
5. Rate of acute rejection; Timepoint(s): 3 years
6. Rates of biopsy proven malignancy; Timepoint(s): 3 years
7. Rates of Culture-positive infection; Timepoint(s): 3 years
8. Rates of Diabetes Mellitus; Timepoint(s): 3 years
9. Scientific analyses of humoral & cellular immunity and CD34+ cells; Timepoint(s): 3 year

## **Completion date**

30/09/2020

## **Eligibility**

**Key inclusion criteria**

1. Renal transplant recipients >1 year post transplantation
2. Aged 18-70 years, male and female
3. Estimated glomerular filtration rate (eGFR) of  $\geq 30$

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 Years

**Upper age limit**

70 Years

**Sex**

All

**Total final enrolment**

2037

**Key exclusion criteria**

1. Recipient requiring HLA desensitisation to remove antibody for a positive XM transplant
2. Recipient known already to have HLA antibody who has received specific intervention for that antibody or for CAMR / chronic rejection
3. Recipient of additional solid organ transplants (e.g. pancreas, heart, etc).
4. History of malignancy in previous 5 years (excluding non-melanomatous tumours limited to skin)
5. HBsAg+, HBcAb+, HepC+ or HIV+ recipient (on test performed within previous 5 years)
6. History of acute rejection requiring escalation of immunosuppression in the 6 months prior to screening.
7. History of an ongoing or previous infection (no time limit) that would prevent optimization of immunosuppression, including ocular Herpes simplex.
8. Known hypersensitivity to any of the IMPs
9. Known hereditary disorders of carbohydrate metabolism
10. Patient enrolled in any other studies involving administration of another IMP at time of recruitment
11. Pregnancy or breastfeeding females (based on verbal history of recipient)
12. Pre-menopausal females who refuse to consent to using suitable methods of contraception throughout the trial.

**Date of first enrolment**

01/09/2013

**Date of final enrolment**

30/09/2016

## **Locations**

### **Countries of recruitment**

United Kingdom

England

### **Study participating centre**

#### **Guy's and St Thomas' Hospital**

Great Maze Pond

London

United Kingdom

SE1 9RT

### **Study participating centre**

#### **Royal Free Hospital**

Pond Street

London

United Kingdom

NW3 2QG

### **Study participating centre**

#### **The Royal London Hospital**

Whitechapel Road

London

United Kingdom

E1 1FR

### **Study participating centre**

#### **St Helier Hospital**

Epsom

United Kingdom

KT18 7EG

### **Study participating centre**

#### **Bradford Royal Infirmary**

Duckworth Lane

Bradford  
United Kingdom  
BD9 6RJ

**Study participating centre**  
**Manchester Royal Infirmary**  
North Road  
Manchester  
United Kingdom  
M13 9WL

**Study participating centre**  
**St James Hospital**  
Beckett St.  
Leeds  
United Kingdom  
LS9 7TF

**Study participating centre**  
**Salford Royal Hospital**  
Stott Lane  
Salford  
United Kingdom  
M6 8HD

**Study participating centre**  
**York Hospital**  
Wigginton Road  
York  
United Kingdom  
YO31 8HE

**Study participating centre**  
**University Hospitals Birmingham**  
Mindelsohn Way  
Edgbaston  
Birmingham  
United Kingdom  
B15 2GW



**Study participating centre**  
**Royal Preston Hospital**  
Sharoe Green Lane North  
Fulwood  
Preston  
United Kingdom  
PR2 9HT

**Study participating centre**  
**University Hospitals Coventry and Warwickshire**  
Clifford Bridge Road  
Coventry  
United Kingdom  
CV2 2DX

## **Sponsor information**

**Organisation**  
King's College London (UK)

**ROR**  
<https://ror.org/0220mzb33>

## **Funder(s)**

**Funder type**  
Government

**Funder Name**  
NIHR (UK) - Efficacy and Mechanism Evaluation; Grant Codes: 11/100/34

## **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. Anthony Dorling ([Anthony.dorling@kcl.ac.uk](mailto:Anthony.dorling@kcl.ac.uk)).

**IPD sharing plan summary**  
Available on request

## Study outputs

| Output type                          | Details                                        | Date created | Date added | Peer reviewed? | Patient-facing? |
|--------------------------------------|------------------------------------------------|--------------|------------|----------------|-----------------|
| <a href="#">Results article</a>      | protocol                                       | 12/01/2023   | 24/01/2023 | Yes            | No              |
| <a href="#">Protocol article</a>     |                                                | 21/01/2014   |            | Yes            | No              |
| <a href="#">Protocol article</a>     | updated protocol and statistical analysis plan | 05/08/2019   | 07/08/2019 | Yes            | No              |
| <a href="#">Abstract results</a>     |                                                | 24/02/2016   | 18/11/2021 | No             | No              |
| <a href="#">HRA research summary</a> |                                                |              | 28/06/2023 | No             | No              |