NHS
National Institute for Health Research

NIHR Research for Patient Benefit (RfPB) Programme

Final Report Form

IMPORTANT

Final reports are required from all projects funded through the NIHR Research for Patient Benefit Programme. The RfPB Programme requires a final report in order to:

- ensure accountability
- aid in appropriate dissemination of project results
- encourage quality assurance of project outputs
- assess the impact of the research supported by the Programme
- demonstrate the achievements of the Programme

Please keep these aims in mind while completing your final report.

The report needs to offer:

a) a clear summary of the project for practitioners and users of research
b) a record of challenges faced and modifications made to the study
c) a description of experience with patient and public involvement that might help identify lessons for future research
d) an impact assessment both locally and for the NHS more broadly
e) a summary of any outputs, such as publications, from the research (which should be updated as outputs occur). Completion of this report should not pre-empt any publications that have been prepared or are in preparation detailing project results.

The views expressed in this report should reflect those of the entire research team.

Following submission and assessment of this form, the final version of the scientific and lay summaries will be displayed on the NIHR CCF website and will be accessible to a wide range of interested parties.

You will be required to submit a final statement of expenditure at the same time as your final report. Please note that the completed final report along with a final statement of expenditure is required prior to release of the final project payment.

For further guidance or information on completion of your final report, please contact the regional Programme Manager at NIHR CCF, using the details below:

Emily Toon
Programme Manager for the London region
Emily.toon@nihr.ac.uk
Telephone number: 0208 843 8047
NIHR CCF help line: 0208 843 8057

NHS National Institute for Health Research

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Note the maximum field sizes shown include both printing and non-printing characters such as spaces and carriage returns.

Reference Number PB-PG-1010-23108

Region London

Date submitted

For office use

1. Project Details

Project Title*:	Are prophylactic antibiotics necessary before laparoscopic living kindey donation? A randomised, controlled trial		
NHS Contracting Organisation*:	Guy's and St Thomas' NHS Foundation Trust		
Project Duration*: (months)	32 months	Grant Value:	£ 319,051
Start Date:	01/09/2012	Agreed Extension (months):	16 months
End Date:	30/04/2015	Revised End Date:	31/08/2016

2. Grant Holder's Details

Title*:	Prof		
Surname*:	Mamode	Forename*:	Nizam
Department*:	Renal transplantation		
Role in Project*:	Chief investigator		
Institution*:	Guy's & St Thomas' Foundation NHS Trust		
Street*:	Great Maze Pond		
Town/City*:	London	County*:	London
Post Code*:	SE19RT		
Telephone*:	02071887188	Extension:	81543
Email Address*:	nizam.mamode@gstt.nhs.uk		

3. Details of the Research Team

Co-applicant 1

Title:	Dr Surname: Hemsley	Forename: Carolyn
Post held:	Consultant and Clinical Lead for Microbiology and Infectious Diseases	
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Organisation:	Guy's & St Thomas' Foundation NHS Trust	
Telephone:	02071883148	Extension:
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Role in project:	Co-investigator	

Co-applicant 2

Title:	Dr Surname: Rebollo-Mesa	Forename: Irene
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Organisation:	Guy's & St Thomas' Foundation NHS Trust	
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Role in project:	Statistician	

Co-applicant 3

Title:	Mr Surname: Olsburgh	Forename: Jonathon
Post held:	Consultant Transplant & Urological Surgeon	
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Role in project:	Co-investigator	

Co-applicant 4

Title:	Mr Surname: Kessaris	Forename: Nicos
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Role in project:	Co-investigator	

Co-applicant 5

Title:	Mr Surname: Cacciola	Forename: Roberto
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Role in project:	Co-investigator	

Co-applicant 6

Title:	Mr Surname: Ahmed	Forename: Zubir
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e-mail address:	zubir.ahmed@gstt.nhs.uk	
Role in project:	Sub-investigator	

Co-applicant 7

Title:	Please select.. Surname:	Forename:
Post held:		
Department:		
Organisation:		
Telephone:		Extension:
e-mail address:		
Role in project:		

4. Changes to the Research Team

Please outline any changes that have been made to the research team, including an explanation of why these changes were required.

Dr Irene Rebollo-Mesa left the organisation.
Dr Keith Sullivan of the University of Hertfordshire was appointed as study statistician to replace IRM.
Mr Roberto Cacciola left the study team.
Mr Ravi Pararajasingam joined the study team as principal investigator for the Manchester site in 2014.
Mr Jamie Barwell joined the study team as principal investigator for the Plymouth site in 2014.
Miss Sarah Heap joined the study team as principal investigator for the St Georges's site in 2015.
Mr Raphael Uwechue was appointed as research fellow and sub-investigator in 2015 to replace Zubir Ahmed who left the organisation.

Mr Laszlo Szabo joined the study team as principal investigator for the Cardiff site in 2016.

5. Lay/Plain English Summary*

Please provide a summary of the project, including background, findings and conclusions. It is essential that you make the content of your summary and the implications of your research evident to the lay public. It should avoid technical terms and should be written in an accessible style and emphasise in particular the potential for patient benefit arising from the study.
(Maximum 2,500 characters)

Background
Kidney transplantation from a living donor is the best way to treat kidney failure for most patients. Donors face risks from this surgery such as infections, which can cause multiple problems. The use of antibiotics just before surgery has been shown to offer some reduction in the risk of infection in other operations but it is not known if it will also be of benefit in kidney donation surgery. We conducted a clinical trial with the aim of establishing if a single dose of antibiotics given just before the kidney donation operation would reduce the risk of infection.
Methods
Patients were allocated to one of two possible treatments: an antibiotic or a placebo before surgery. The patients and study team were both unaware of which treatment was given. Both groups of patients underwent the same operation and had the same care otherwise. The main effect measured in the study was the rate of infection in both groups of patients. Infections included wound infections, chest infections as well as other infections. We also measured the rate of complications that could have been caused by the use of antibiotics. We aimed to recruit a minimum of 284 patients to be able to show a statistical difference between the groups.
Results
A total of 285 patients were recruited and completed the study. 144 patients received antibiotic and 141 received a placebo before surgery. The overall infection rate was 34% taking both groups into account. The infection rate in the antibiotic group was 27% and it was 41% in the placebo group. This difference of 14% between the groups was shown to be statistically significant. The commonest type of infection was skin infections at the surgical incision which were almost double in the placebo group at 21.3% when compared with the antibiotic group at 11.8%. There was no significant difference in the rate of adverse events in either group.
Conclusion
The use of a single dose of antibiotics before kidney donation surgery reduces the rate of infection in patients compared with not using antibiotics. There appears to be no increase in the risk of antibiotic related complications between the groups. There are currently no guidelines suggesting the use of antibiotics prior to kidney donation surgery in the United Kingdom and practice varies widely between transplant centres. The results of this study will inform the British Transplant Society guidelines for kidney donation, and will change practice in the UK and beyond.

6. Keywords*

Please provide up to 8 keywords that relate to the research undertaken in this study.

Living donor nephrectomy
Infection
Randomized controlled trial
Prophylactic antibiotics

7. Summary of Research and Findings*

Please provide a structured summary of the research including background, aims and objectives, methods, key findings, expected impact on the relevant field and conclusions.
(Maximum 10,000 characters)

Background.

Living donor nephrectomy is a routine operation which is becoming more common. It is performed in a group of patients who are otherwise extremely fit and healthy for no apparent physical benefit to themselves. It is safe, with a low death rate and low risk of major complications. However, infections constitute the biggest challenge for these patients and can cause major morbidity. Infections can present in several ways including at the surgical site, in the chest or in the urinary system. They can prolong hospital stay, require re-operation and leave patients in discomfort or with unsightly scars.

The value of pre-operative antibiotics in preventing or reducing infection after living donor nephrectomy is not known. This is reflected in the lack of randomised clinical trials on this topic in living kidney donation and in the current guidelines on living donation from the British Transplant Society. The unnecessary use of antibiotics is costly and presents potentially serious risks to the patient including diarrhoea, serious allergic reactions and antibiotic resistance.

There is limited evidence for the use of prophylactic antibiotics in laparoscopic surgery in general nor for their safety profile. Therefore, it is not clear if the use of prophylactic antibiotics is of benefit to patients undergoing laparoscopic donor nephrectomy.

Trial objectives.

We aimed to assess whether prophylactic antibiotics are beneficial when given prior to laparoscopic donor nephrectomy. The main hypothesis tested was that a single dose of prophylactic antibiotic before donation results in fewer infectious complications.

Methods.

The trial was a multi-centre, double-blinded, randomised, controlled trial of patients undergoing laparoscopic donor nephrectomy in hospitals in England and Wales. After enrolment in the study, patients were randomised using a web-based computer allocation system to receive an intravenous dose of either the study drug or a placebo. This was given at the induction of anaesthesia, just before the start of surgery. Patients were discharged from hospital as usual, 3 or 4 days after surgery. The study period ended at 30 days. The primary outcome was any infection that occurred in the 30-day study period. A statistical power of 90% was pre-determined to detect a 5% or greater reduction in the 30-day infection rate with a maximum of 200 patients required in each arm of the trial and a minimum of 142 patients in each arm.

The primary outcome was a composite endpoint of any infection including surgical site infections, urinary tract, respiratory and any other infections within 30 days of surgery. Specifically, infection was defined with the presence of any of the following criteria: purulent drainage from the incision site confirmed on microbiological testing (significant bacterial growth and pus cells present), positive culture of any fluid aspirated from the surgical site, at least two signs of inflammation at the incision site (pain, swelling, redness, heat) with either a clinician diagnosed infection or the wound opened by a surgeon, dehiscence of the surgical wound, evidence of deep infection radiologically or at reoperation, symptoms of a urinary tract infection with a positive urine culture, symptoms of a respiratory tract infection with positive sputum cultures or a clinician diagnosis of infection and finally any other infection confirmed on microbiological testing. In addition, surgical site infection (SSI) was classified with the Centres for Disease Control criteria into superficial pertaining to the skin and subcutaneous tissues, deep affecting the fascia and muscle and organ space infections in the abdomen or pelvis.

The inclusion criteria were male and female patients over the age of 18 years undergoing

hand-assisted laparoscopic donor nephrectomy. Patients whose first language is not English were also included and a translation service was used to obtain informed consent. Exclusion criteria were patients with a known allergy to penicillin, a hypersensitivity to another beta-lactam agent, or a history of jaundice or hepatic impairment due to amoxicillin or clavulanic acid. Patients with MRSA colonisation, pregnant or breast-feeding women or those who had participated in another investigational study in the preceding 90 days were also excluded.

The study drug was the penicillin based antibiotic co-amoxiclav which was given intravenously in a dose of 1.2g which is a standard dose used in routine clinical care. The placebo was 0.9% normal saline. These investigational medicinal products (IMPs) were dispensed in a blinded manner by either the local pharmacy or a designated and qualified member of nursing or medical personnel (not involved in the study or direct clinical care of the patient) in each of the participating centres.

Follow-up was conducted at day 10 via a telephone call and at day 30 at a scheduled post-operative clinical review. Data was recorded at the time of enrolment, at randomisation, on the day of surgery and during the inpatient hospital stay, at Days 10 and 30 post-operatively. Data was recorded on a web-based electronic case report form which was password protected and patient data anonymised.

Results

Study sites
Five hospitals in England and Wales participated in the study with eligible patients enrolled in the study between January 2013 and August 2016. The centres participating in the study were Guy's hospital in London, Manchester Royal Infirmary in Manchester from March 2014, Derriford hospital in Plymouth from July 2014, St George's hospital in London from August 2015 and The University of Wales Hospital Cardiff from March 2016.

Patient recruitment
A total of 299 patients were enrolled into the study, 14 patients were withdrawn or excluded from the study leaving 285 patients that completed the study. There were 144 patients in the treatment arm and 141 patients in the placebo arm.

Patient demographics
The mean age of the cohort was 45.4 years (standard deviation 12.5 years) with 58% male and 42% with a mean body mass index (BMI) of 26.7 kg/m2 (s.d. 7 kg/m2).

Primary outcome.
The primary endpoint of any infections within 30 days occurred in 97 out of 285 patients with an overall infection rate of 34%. Infections were detected in 39 patients out of 144 (27.1%) in the antibiotic group and in 58 out of 141 patients (41.1%) in the placebo group (p=0.009).

Superficial surgical site infections occurred in 17 patients (11.8%) in the antibiotic group and in 30 patients (21.3%) in the placebo group (p=0.023). Deep surgical site infections occurred in 1.4% in the antibiotic group and 2.1% in the placebo group (p=0.490), urinary tract infections in 6.9% of the antibiotic group and in 7.0% of the placebo group (p=0.590). Lower respiratory tract infections occurred in 5 patients (3.5%) in the antibiotic group and 12 patients (8.5%) in the placebo group (p=0.06) and other infections were detected in 4 patients (2.8%) in the antibiotic group and in 9 patients (6.4%) of the placebo group (p=0.103).

The overall infection rate at each centre was as follows: Guy's 32%, Manchester 42.6%, St George's 41%, Plymouth 26.7% and Cardiff 0%. There was no statistically significant difference between the centres.

Safety and adverse events.

Adverse events occurred in 154 of 285 patients (54%) overall with 72 (50%) in the antibiotic group and in 82 (58%) of the placebo group (p=0.113). Serious adverse events (SAEs) occurred in 14% and 15.6% of the antibiotic and placebo groups respectively (p=0.470). SAEs included abdominal pains, bleeding associated with surgery, infections and other causes of prolonged hospitalisation or unscheduled hospital attendance.

Conclusions

This study has demonstrated in a large group of patients that the rate of all infections is significantly reduced in first 30 days after a laparoscopic donor nephrectomy when antibiotics are administered pre-operatively compared to when they are not used. The main reduction in infections is seen in the superficial surgical site infections. The other types of infections were not significantly reduced with the use of prophylactic antibiotics.

Superficial surgical site infections are a common complication of surgery in general and have been shown to have a high rate of occurrence in laparoscopic donor nephrectomy in this study. They may cause prolonged hospitalisation with extra medical interventions and increased costs, as well as negatively affecting the patient experience of a group who have offered a kidney for the benefit of another person. This study has shown that these infections can be reduced by a third with the use of a simple intervention: administering antibiotics before surgery with any significant impact on the associated adverse effects of using antibiotics.

There are no significant differences in the occurrences of adverse or serious adverse events in either arm of the study. There were no events that resulted in death, life-threatening complications nor in persistent or significant disability or incapacity that could be associated with the use of antibiotics.

There are no guidelines regarding the use of prophylactic antibiotics in laparoscopic donor nephrectomy and variation between hospitals in the use of antibiotics in this setting. These findings provide a robust evidence base to strongly support the use of prophylactic antibiotics in donor nephrectomy surgery, and have been included in the latest edition of the British Transplant Society Guidelines.

8. Changes in the project since initial approval*

Please summarise any changes made to the project as outlined in the original proposal and outline the reasons for these changes. If there were no changes to the original plans, write ‘not applicable’. **(Maximum 2,500 characters)**

Aims and objectives:
No changes to the trial aims and objectives were made.

Research Plan and Methodology:
The protocol was amended on five occasions:
1. (December 2012) Changes to trial personnel and flow chart to allow for urine sample collection and storage.
2. (March 2013) Allow flexibity for taking patient samples and to do so when clinically indicated.
3. (December 2013) To allow other suitably qualified and blinded personnel to prepare study drug other than pharmacy.
4. (May 2014) To allow for local procedures and protocols to be devised for emergency unblinding at other trial centres.
5. (May 2015) To allow for the extension of patient recruitment for 6 months.

9. Patient and Public Involvement*

The RfPB Programme is particularly keen to learn from the experiences of research teams regarding patient and public involvement (PPI) and contribution from PPI members involved in the research is encouraged when completing this form. Please provide comment on your experiences with PPI, any changes made and lessons drawn. Please include detail of PPI with dissemination and with trajectory into practice both in the project and beyond. **(Maximum 5,000 characters)**

The research team involved patients and the public from an early stage of the study.A focus group of previous donors considered the design of the study, suggesting a modification of the endpoints, and the data collection forms were piloted on a group of donors. Patient representatives also particpated in the Trial Steering Committee and the Data Monitoring Committee.
Our experience of patient participation was positive overall. Specifically, patients contributed to practical considerations that might help to facilitate more involvement in the processes of clinical trials, such as in recruiting participants. The time and expense of attending administrative meetings such as the Trial Steering Committee or the Data Monitoring Committee was raised as an issue and a system to help with expenses was suggested and implemented.

10. Next Steps to Patient Benefit*

Please provide comment on the likely implications for practice which may result from the outcomes of this project and the next steps to be taken to ensure patient benefit both locally and more broadly. Steps already taken and planned for the future should be included. While in funding research, RfPB emphasises a 3-5 year trajectory into practice, it is important not to 'overclaim' and care should be taken to cover the limitations of the study and any risks associated with implementation. Where the project is a pilot, include details of plans for a definitive study, including the likely funder and timetable for its submission. Please give reasons if there is no plan to go forward to a trial at this stage. **(Maximum 5,000 characters)**

This study has demonstrated a high overall infection rate in patients undergoing donor nephrectomy at 34% with surgical site infection accounting for most of these. This is higher than anticipated from local experience (10%) and from the literature on donor nephrectomy which reports significantly lower rates of infection of around 5%. There is currently no consensus on the use of prophylactic antibiotics, with some centres not using them. With about one thousand living donor nephrectomies performed anually in the UK alone, this implies that there is a significant number of patients who are suffering from unnecessary infections.

The next steps for this study are for the dissemination of the findings. The study results have been accepted at the Association of Surgeons of Great Britain and Ireland annual meeting and at the American Transplant Congress meeting for presentation. A manuscript is currently being prepared for publication in a peer reviewed journal with the aim for submission by the end of April 2018. The Kidney Patients Association will also be given a summary of the findings, and these will also be circulated to study participants.The study findings will also be presented at the British Transplant Society annual meeting in 2019, the European Society of Transplantation, the Renal Association, and the British Association of Urological Surgeons, and will be submitted to NICE, NHS Blood and Transplant and the HPA Surgical Site Infection Surveillance Study.

The greatest potential for impact on practice is through the Guidelines for Living Donor Kidney Transplantation by the British Transplantation Society (BTS). Currently these state that there is no evidence for the use of prophylactic antibiotics in living donation. This is because there are no published randomised controlled trials or other studies that definitively address this issue. A new (4th) edition has been prepared, and we have included the results of this study, recommending the use of a single pre-operative dose of antibiotics prior to donor nephrectomy. These guidelines are used as a standard by the transplant community in the UK, and indeed in a number of other countries, and their recommendations usually inform practice in individual transplant centres. This study provides a high level of evidence to support a strong recommendation to use prophylactic antibiotics that could prevent dozens of needless infections anually in the UK. The guidelines will be published in 2018.

11. Key Presentations and Publications*

Please list here any presentations and publications which have resulted from the work. This should include journal articles, conference proceedings, press releases and all publications in the lay and scientific press, including website links to published articles if appropriate. Items that are forthcoming should also be included. **Please note you are contractually obliged to provide 28 days notification prior to any publication.**

Author (s)	Title	Reference/Further Details
Z Ahmed, R Uwechue, N Kessaris, N Mamode.	Prophylaxis Of Wound infections- Antibiotics in Renal donation (POWAR): A multicentre UK double blinded placebo controlled randomised controlled trial.	Accepted as a poster at the American Transplant Congress June 2018
Z Ahmed, R Uwechue, N Kessaris, N Mamode.	Prophylaxis Of Wound infections- Antibiotics in Renal donation (POWAR): A multicentre UK double blinded placebo controlled randomised controlled trial.	Accepted at the Association of surgeons of Great Britain and Ireland annual congress 2018 as an oral presentation for the Moynihan Prize.