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:

Dr Ramnath Elaswarapu
Programme Manager for the West Midlands region
Ramnath.elaswarapu@nihr.ac.uk
Telephone number: 0208 843 8066
NIHR CCF help line: 0208 843 8057

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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-0711-25081

Region West Midlands

Date submitted

For office use

1. Project Details

Project Title*:	A prospective, randomised controlled trial to determine the safety and efficacy of steroid impregnated tape compared to standard therapy with silver nitrate in the treatment of over-granulating peritoneal dialysis catheter exit sites		
NHS Contracting Organisation*:	University Hospitals Birmingham NHS Foundation Trust		
Project Duration*: (months)	36 months	Grant Value:	£211,042.00
Start Date:	01 December 2013	Agreed Extension (months):	4 months
End Date:	30 November 2016	Revised End Date:	31 March 2017

2. Grant Holder's Details

Title*:	Dr		
Surname*:	Foggensteiner	Forename*:	Lukas
Department*:	Renal Medicine		
Role in Project*:	Chief Investigator		
Institution*:	University Hospitals Birmingham NHS Fdn Trust		
Street*:	QEHB		
Town/City*:	Birmingham	County*:	West Mids
Post Code*:	B15 2WB		
Telephone*:	0121 471 5841	Extension:	15841
Email Address*:	lukas.foggensteiner@uhb.nhs.uk		

3. Details of the Research Team

Co-applicant 1

Title:	Prof Surname: Davies	Forename: Simon
Post held:	Consultant Nephrologist, Professor of Nephrology	
Department:	Renal Medicine	
Organisation:	University Hospitals of North Midlands NHS Trust	
Telephone:	01782 554164	Extension:
e-mail address:	simondavies1@compuserve.com	
Role in project:	Involved in grant application and protocol development	

Co-applicant 2

Title:	Mrs Surname: Dutton	Forename: Mary
Post held:	Senior Renal Research Sister	
Department:	Research and Development	
Organisation:	University Hospitals Birmingham NHS Fdn Trust	
Telephone:	0121 371 2000	Extension: 3287
e-mail address:	mary.dutton@uhb.nhs.uk	
Role in project:	Steering Group/Trial Management Group member	

Co-applicant 3

Title:	Dr Surname: Kamesh	Forename: Lavanya
Post held:	Consultant Nephrologist	
Department:	Renal Medicine	
Organisation:	University Hospitals Birmingham NHS Fdn Trust	
Telephone:	0121 371 5839	Extension:
e-mail address:	lavanya.kamesh@uhb.nhs.uk	
Role in project:	Principal Investigator, steering committee member	

Co-applicant 4

Title:	Mrs Surname: McEntee	Forename: Siobhan
Post held:	PD Sister	
Department:	Renal Medicine, CAPD Unit	
Organisation:	University Hospitals Birmingham NHS Fdn Trust	
Telephone:	0121 627 2515	Extension:
e-mail address:	siobhan.mcentee@uhb.nhs.uk	
Role in project:	PD Sister, steering committee member	

Co-applicant 5

Title: Please select.. Surname: Forename:

Post held:

Department:

Organisation:

Telephone: Extension:

e-mail address:

Role in project:

Co-applicant 6

Title: Please select.. Surname: Forename:

Post held:

Department:

Organisation:

Telephone: Extension:

e-mail address:

Role in project:

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.

Nicola Anderson was appointed study co-ordinator July2013.

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)

Kidney failure is a chronic illness requiring treatment with haemodialysis (HD), peritoneal dialysis (PD) or transplantation to preserve life. PD is the preferred option for many because it is a home-based therapy which preserves patient's independence and is associated with superior quality of life compared to HD. PD involves instilling dialysis fluid into the abdominal cavity via a catheter. Occasionally, where the catheter exits the skin, a reaction can occur resulting in lumpy red tissue known as overgranulation tissue. This tissue can be unsightly, bleed, become painful and if infected, can lead to serious complications including dialysis failure, sepsis and death. There is no agreement on treatment for overgranulation of the PD exit site, but traditionally PD staff have removed the tissue through the application of silver nitrate solution to chemically burn the tissue away. This treatment can be associated with complications including burns to surrounding skin and discolouration. It is also inconvenient requiring multiple hospital visits over several weeks. Steroid impregnated occlusive tape (Haelan, Typharm Ltd) is licensed for use in over-granulating wounds and can be self applied at home but may increase the risk of infection. The aim of this project was to compare the treatment of over-granulating PD exit sites with standard therapy using silver nitrate or steroid impregnated tape, in terms of safety and effectiveness. 8 PD Units took part and a total of 32 patients were recruited, from an initial target of 80. 16 patients were allocated treatment with silver nitrate and 16 patients treated with steroid tape. Recruitment rates were lower than anticipated and a data monitoring committee reviewed the response rate scores from 2 independent observers who assessed photographic sequences taken at study visits. In terms of a complete response rate at 14 days, the data was unable to demonstrate whether either treatment was significantly more effective than the other. This assessment also showed no likelihood of the study showing a significant difference between treatments if current recruitment and response rates continued to study end.Therefore the study was halted. Due to the fact that we did not recruit to target, we were unable to demonstrate statistically that either treatment was better than the other. However, valuable learning was gained through the conduct of this randomised controlled trial within the PD environment.

6. Keywords*

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

Peritoneal Dialysis
Exit site care
Over-granulation
Randomised Controlled Trial
Steroid impregnated tape
Cautery with silver nitrate

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: According to the UK Renal Registry, in 2014, Peritoneal dialysis (PD) was the modality of renal replacement therapy used by 20% of individuals with end stage renal disease (ESRD). PD requires the placement of a silicone rubber catheter to obtain access to the peritoneal cavity. The commonest form of PD catheter has a coiled end which sits in the peritoneal cavity and two Dacron cuffs which anchor the catheter into the abdominal wall; the catheter exiting the body through a subcutaneous tunnel. Catheter exit sites are susceptible to complications including trauma, infection, allergy and over-granulation. Maintaining catheter function is important to allow uninterrupted dialysis and is associated with improved outcomes. It is therefore important to have proven strategies to manage catheter complications including over-granulation. Granulation tissue consists of a highly vascular matrix of fibroblasts and is an important part of normal wound healing. Over-granulation consists of excessive and disorganised granulation tissue, which stands proud of the rest of the skin. The phenomenon of over-granulation is commonly seen at exit sites of medical devices such as PD catheters, tracheostomy tubes and supra-pubic catheters and may be related to repeated skin trauma from the device. It poses a problem as it prevents epithelial cells from migrating across the wound surface leaving a moist and delicate surface over the exit site. The incidence and prevalence of over-granulation of PD exit sites is not reported in the literature but local experience suggested it may affected up to 10% of the PD population per year. Over-granulating exit sites can be uncomfortable for patients, harbour infection or bleed. Associated infection may then be difficult to treat and lead to removal of the catheter and interruption of the therapy, severe complications could include sepsis and death. Current treatment for over-granulating exit sites includes cautery with silver nitrate, topical steroid ointments or a variety of proprietary dressings. No literature exists comparing treatments for over-granulating PD exit sites but cautery with silver nitrate has been recommended by Gokhal and others and is the most widely used treatment. Steroid ointments may be effective but there are concerns that this might increase exit site infection rates.
In 2010 the PD unit at University Hospitals Birmingham NHS Trust (UHBFT) undertook a pilot study of a steroid (Fludroxycortide) impregnated tape (Haelan tape, Typharm Ltd) in the treatment of over-granulating exit sites. This prospective, uncontrolled and non randomised study suggested that the tape was safe, effective and superior to the previous standard therapy of silver nitrate. 15 patients were recruited over a 6 months from a prevalent PD population of 153 patients. Steroid impregnated occlusive tape is licensed for use in over-granulating wounds, however, no prospective trials of any treatment in this condition have been conducted. Silver nitrate is known to be associated with side effects that include skin irritation, ulceration and bleeding and steroid treatment may be associated with increased risk of infection. Therefore a randomised controlled trial (RCT) comparing the treatments was proposed.
Aims and Objectives: To conduct a RCT to determine the safety and efficacy of steroid impregnated tape compared to standard therapy with silver nitrate in the treatment of over-granulating peritoneal dialysis catheter exit sites.
Methods: A multi-centre, prospective, RCT of Haelan tape versus silver nitrate therapy. Particpants who met study inclusion/exclusion criteria requirements and who had an over-granulating exit site judged to require treatment according to protocol and who provided valid informed consent, were randomised to either study arm using an internet based randomisation service. Block randomisation was used to ensure even distribution of allocation across the 8 active UK sites. Upon recruitment, assigned treatment was administered according to standard operating procedures for 2 weeks followed by an additional 2 weeks if clinically indicated. If after 14 days the over-granulation was worse than at day 0, then a

medical decision to continue treatment could be taken. A further 2 weeks of the designated treatment could then be administered although this could be discontinued at any point if a satisfactory clinical response was observed. Patients requiring further treatment after 28 days could have treatment according to original randomisation at the discretion of the local investigator. The protocol did not allow for crossover of treatment. Cautery with silver nitrate was undertaken by nursing staff either at the PD unit or a home visit, up to twice weekly. Patients were taught to self apply the haelan tape on a daily basis. Study visits were undertaken at Day 0, 7, 14, 21, 28 and day 56 (with +/- 24 hour time allowance). At each study visit the following data was collected: a patient questionnaire recording pain, discomfort and convenience; assessment of the exit site by PD staff using a standardised exit site assessment tool. A swab for microscopy, culture and senstitivity was taken and adverse events recorded. At each visit a sequence of standardised photographs were taken according to study specific guidelines using equipment provided by the co-ordinating centre (camera, colour calibration card, distance bar and scale labels). Patients, PD and research staff and local investigators were unblinded to treatment allocation.

The primary outcome measure was complete response rate at 14 days. Secondary outcomes included overall (partial or complete) response rate and recurrence of over-granulation within the 56 day study period. Additional secondary outcomes included the exit site infection rate, patient reported pain, discomfort and satisfaction scores and exit site assessment by PD staff using a standardised exit site assessment tool.

Assessment of over-granulation is necessarily subjective and made by visual inspection of the exit site. Assessment was made by the local therapy administrator by direct inspection of the exit site to determine the treatment schedule. However, assessment for the trial endpoint was undertaken by two, independent observers, blinded to the treatment received, following review of the sequential photographs. Each independent observer scored the exit sites according to a standardised response rate developed specifically for the study.

Data, including photographs, were recorded electronically onto a study specific data base based within an NHS server that was accessible via the N3 network by all sites. Thus allowing remote monitoring of all study data.

In order to detect a 30% difference in complete response rates between treatments the sample size of 80 participants was set (40 patients in each treatment arm). This was to be achieved recruiting across 8 PD Units. However, recruitment rates were much lower than anticipated. and a total of 32 particpants were recruited. All sites reported lower rates of overgranulation than were anticipated by the QE pilot study. 16 patients were allocated to each arm, 30 patients received treatment with 2 withdrawals prior to treatment commencement but post randomisation, before the decision to halt the study was made by the Trial Steering Group, upon recommendation by the Data Monitoring Committee and study statistician. Various initiatives were taken to combat the reduced rate of recruitment, from the introduction of reasonable travel expenses for patients, closure of non-recruiting sites, addition of new sites, use of poster aides advertising the study and the request for a no-cost extension to increase the total period of recruitment.

Results: 32 particpants were recruited, 16 participants in each arm. Data was made available for 30 participants: 2 patients withdrew before treatment commenced but post randomisation as their over-granulation had resolved. Statistical analysis of response rates were based on 'intention to treat'. with primary outcome defined as complete response (CR) at 14 days. For analysis purposes, CR was considered achieved if at least one of the blinded assessors graded the response as complete and the other assessor graded at least a partial response (PR).

Following preliminary analysis 3/16 patients were assessed as demonstrating a CR at 14 days in the Haelan tape arm and 1/14 patients treated with silver nitrate. Applying a Chi-squared test (0.8705, p-value .350807 $p < 0.05$) there was no observed significant difference in CR at 14 days between the two treatment arms. When rates of PR were analysed, there was no significant difference between the two groups at 14 days (chi square test).Furthermore, no significant differences in AE's or satisfaction rates were observed. Therefore, whilst unable to demonstrate a significant difference in the primary outcome measures between the two treatment arms, it has been possible to gather safety, compliance

and satisfaction data. Further analysis will compare exit site assessment made by unblinded clinical staff with the response rate scores from the blinded independent assessors. Additionally, valuable information has been gathered in terms of methodology and the experience of undertaking a nurse-led multi-centre interventional study within the PD clinical environment.

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 were made to the overall aims and objectives as outlined in the original proposal. The study team successfully opened 9 sites to recruitment undertaking site initiation visits and teaching sessions following staff turnover. A study specific case report form and associated database was developed and access arranged via the N3 pathway for all recruiting sites. All sites undertook study activities according to study specific standard operating procedures following on site training and review. All sites were required to return screening, adverse event and protocol deviation logs on a regular basis. On site and remote monitoring of the bespoke electronic database ensured the data set is as complete as possible.

Research Plan and Methodology:
The recruitment target and associated sample size (80 participants, 40 in each arm) was originally set following review of the pilot study data. However, it soon became clear that the overall incidence rate of over-granulation at all sites was lower than anticipated.
We have observed static recruitment of approximately 10 patients per year. Whilst it was always expected that there could be peaks and troughs in the incidence of over-granulation at individual sites, one of the factors leading to a multi-centre design, it has been observed that a lower than expected incidence of over-granulation has been reported at all sites. In the reporting period, 50% of sites have experienced staff capacity issues; in the form of staff leaving, going on maternity leave or dealing with sickness within the team. These issues have impacted on the study, requiring further training. To combat this lower than forecasted recruitment rate, the following measures were taken: 1. Screening logs were analysed to identify the main reasons for non-participation and assess whether changes needed to be made to the inclusion/exclusion criteria. Whilst it was agreed that such changes i.e. to allow the use of low dose oral steroids, might increase recruitment, it would affect the overall reliability and validity of the results. Therefore, the inclusion/exclusion criteria were unaltered. 2. Payment of reasonable travel expenses for study visits associated with standard clinical care were offered, this assisted in recruiting at sites covering large geographical areas. 3. A non-recruiting site was closed and an alternative site opened. 4. The study profile within PD departments was maintained through close contact between coordinating centre and site staff. 5. A patient poster for display in all participating PD Units was designed and utilised with PPI input. 6. A request for a 12 month no cost extension was agreed with the commissioners. 7. The project was discussed at a national PD Research Meetings. In May 2016, with most PI's present, leading members of the PD research community and patient/public representation, the meeting highlighted the importance of PPI engagement. However, this meeting did not highlight any other actions which could be taken and attendees recognised the lower incidence rate of over-granulation nationally. 8. Finally, we have undertaken an interim review of data with our blinded independent assessors and statistician leading to the decision to close the study.

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 Queen Elizabeth Hospital Kidney Patients Association has been consulted about the type of research that patients wish to see happening locally. They have stated they are keen to support in terms of both finance and experience, research projects that have relevance to the patient experience of their chronic disease

Peritoneal dialysis is a home based and self administered modality of renal replacement therapy. Therefore patients are intimately involved in managing their therapy, identifying and dealing with complications and liasing with medical and nursing staff. The problem of overgranulating PD exit sites was identified by patients as a concern and alternatives to standard therapy were sought since it required additional clinic attendance to be treated with silver nitrate. Patients were involved in designing the pilot project, particularly with regard to practical considerations of how to administer the trial treatment, which is self-administered by patients. This input in study design was reflected in the final study protocol and associated patient relevant documentation, which was reviewed by patients undergoing PD for ease of understanding and relevant content. This review of study documentation by PD patients continued thoughout the study, when amendments were made.

Members of the STOP study team were invited to attend a national PD Research study day in Sheffield on 6 May 2016. The aim of this meeting was not only to reflect on PD Research in the UK but also to look at how PPI could influence PD research programmes. Several PPI representatives were speakers at this event, and members of the audience included local PPI representatives of R & D departments and local kidney groups as well as national representatives from kidney charities and research organisations. This representation proved invaluable when discussing ways in which to increase recruitment to the STOP study, and whilst most suggestions had already been implemented or considered by the STOP steering committee it was agreed that a patient poster for use in participating PD units would be designed. The initial draft of the poster was then sent to PPI representatives from the May meeting who were instrumental in refining the poster design.

The Sponsor Trust website carries a dedicated research section which lists all the research studies active within the Trust, including the STOP study. This disseminates details of the study including recruitment figures and targets to members of the public. The Sponsor Trust supports an annual Research Showcase during which researchers are offered the opportunity to share their research projects with members of the public attending the hospital. STOP team members have been present at the Showcase for the last 3 years.

A challenge faced is the continued clinic and hospital attendance burden faced by the PD population, this means that they do not always want to attend for additional events. Therefore, it important that PPI be linked to current clinic visits and training.

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)**

The PD community is relatively small within the UK and information sharing is well established through meetings and special interest group study days therefore research findings and changes to practice are quickly disseminated. The outputs of this study will be presented at local, national and international nephrology meetings and will be submitted for publication in a peer review journal. The Editor of Pertioneal Dialysis International has accepted a request to publish the study and associated findings, in principal. Whilst the results did not indicate a positive outcome, the UK Renal Association's Peritoneal Dialysis Guideline Group and the International Society of Peritoneal Dialysis will be advised in order that study findings can be disseminated to PD professionals.

Whilst it has not been possible to demonstrate superiority in terms of efficacy of either arm, and the study was not powered to show equivalence of either study treatment, it seems on preliminary analysis that there were no significant differences regarding pain, satisfaction and adverse event rates. Further detailed analysis is being undertaken on recurrence rates, partial resolution of over-granulation and the usage of the standardised exit site assessment tool.

The findings confirm that both treatments can be used safely, as per the Summary of Product Characteristics, but we have been unable to demonstrate either statistical superiority or equivalence of either intervention.Therefore, without a clear evidence base for the treatment of over-granulating PD exit sites, PD staff and patients will continue to decide on a treatment option which meets the individualised patient needs. Some patients will prefer self administering steroid tape whilst other patients will prefer attending the PD Unit for nurse led care. As many PD units serve large geographical areas, the option of using a self administered therapy for over-granulation could offer time and cost savings. Any findings that can benefit the patient by reducing the frequency or amount of time spent visiting their renal unit and minimises discomfort associated with the treatment of over-granulation of PD exit site, thus reducing overall service costs, are likely to be quickly adopted.

There are no plans to pursue a further study on the treatment of overgranulation of PD exit sites. Observed incidence rates during the study period which much lower than those observied during the pilot study. Reasons for this are unknown. Clinical audit of the treatment of over-granulating exit sites at all UK PD Units would provide useful data on this aspect of care.

Valuable information has been gathered in terms of methodology and the experience of undertaking a nurse-led multi-centre interventional study within the PD clinical environment. This CTIMP study across 9 sites in the UK was conducted without input from a clinical trials unit, demonstrating that it is possible to design and undertake such a study without a CTU and associated costs. It is hoped that some of the experiences gained in conducting research within UK PD units in terms of site set up , training, monitoring and data collection can be shared wuth the wider research and nephrology community.

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
McEntee S, Anderson N, Foggensteiner L	Pilot study for the use of steroid impregnated tape in the treatment of over-granulating PD catheter exit sites	Sep 2014 Poster presentation Conference: International Society of Peritoneal Dialysis, Madrid, Spain
Anderson N, Foggensteiner L	Steroid impregnated tape in the treatment of over-granulating PD exit sites	May 2014 Oral presentation National PD research study day, SheffieldTeaching Hospitals NHS Foundation Trust
Anderson N, Foggensteiner L	Steroid impregnated tape in the treatment of over-granulating PD exit sites	May 2015 Oral presentation National PD research study day, SheffieldTeaching Hospitals NHS Foundation Trust
Anderson N, Foggensteiner L	Steroid impregnated tape in the treatment of over-granulating PD exit sites	May 2016 Oral presentation National PD research study day, SheffieldTeaching Hospitals NHS Foundation Trust
Anderson N, Dutton M, Foggensteiner L	The STOP study: A prospective, RCT to determine the safety and efficacy of steroid impregnated tape compared to standard therapy with silver nitrate in the treatment of over-granulating PD exit sites	Jun 2017 Poster presentation National Conference UK Kidney Week, Liverpool
Anderson N, Dutton M, McEntee S Foggensteiner L	The challenges of conducting an RCT in UK Peritoneal Dialysis units:The STOP study - A prospective, randomised controlled trial to determine the safety and efficacy of steroid impregnated tape compar	April 2018 Poster presentation RCN International Nursing Research Conference -submission accepted