University Hospitals of Derby and Burton
NHS Foundation Trust

Clinical Evaluation of an Antimicrobial Impregnated Catheter Against Peritonitis	
The CAP Study	
Version and Date of Protocol:	v1.0 09/Oct/2023
Sponsor:	University Hospitals of Derby & Burton NHS Foundation Trust
Chief Investigator:	Professor Maarten Taal
Local Reference:	UHDB/2021/021
IRAS Number:	333587
ISRCTN number:	TBC
Funder(s):	National Institute for Health Research
This protocol has regard for the HRA guidance	

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities, and members of the Research Ethics Committee.

SIGNATURE PAGE

The undersigned confirm that the following clinical investigation plan has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved clinical investigation plan and will adhere to the principles outlined in the Declaration of Helsinki, Medical Devices Regulations 2002, ISO 14155:2020, the Sponsor's SOPs, and other regulatory requirement.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this clinical investigation plan will be explained.

Clinical Investigation Plan Version 1.0 09/Oct/2023 authorisation signatures:

Chief Investigator:

Signature:  Date: 12 / 10 / 2023

Name (please print): Maarten Taal

For and on behalf of the Trial Sponsor (if required):

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

KEY TRIAL CONTACTS

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Trial Manager/ Co-ordinator:	To Be Arranged
Sponsor:	University Hospitals of Derby & Burton NHS Foundation Trust Royal Derby Hospital Uttoxeter Road Derby, DE22 3NE 01332 724639 UHDB.sponsor@nhs.net
Funder(s):	National Institute for Health Research (Invention for Innovation)
Trial Statistician:	Laura Nellums, Assistant Professor, School of Medicine, University of Nottingham, mszlbn@exmail.nottingham.ac.uk

TRIAL SUMMARY

Trial Title:	Clinical Evaluation of an Antimicrobial Impregnated Catheter Against Peritonitis (The CAP Study)	
Local Study Reference:	UHDB/2021/021	
Trial Design:	Non Randomised Feasibility study	
Trial Participants:	Adults requiring peritoneal dialysis who require a peritoneal dialysis catheter insertion	
Planner Number of Sites:	1	
Planned Sample Size:	40	
Treatment Duration:	6 months	
Follow Up Duration:	6 months as per protocol then routine care	
Planned Start Date:	1st March 2024	
Planned Recruitment End Date:	30th September 2025	
Planned Study End Date:	31st March 2026	
	Objectives	**Outcome Measures**
Primary:	To test the safety and tolerability of an antimicrobial impregnated catheter in 40 PD patients.	Adverse events
Secondary:	To assess patient acceptability. To record peritoneal dialysis related infections and compare the incidence with locally and nationally reported rates. To assess the impact of the antimicrobial impregnation on bacterial colonisation	IPOS Renal questionnaire Patient acceptability questionnaire PD Peritonitis (identified and defined using local protocols and International Society for Peritoneal Dialysis Guidelines) Exit site/tunnel infection (identified and defined using local protocols and International Society for Peritoneal Dialysis Guidelines) Technique failure (transfer from PD to HD) Microorganism colonisation of PD catheters removed within the study period Antibiotic resistance profile of organisms causing catheter-related infections
Investigational Device:	The novel antimicrobial catheter will be manufactured by impregnating commercially available PD catheters with the antimicrobials rifampicin, sparfloxacin, and triclosan.	

Eligibility Criteria:	**Inclusion Criteria** Aged 18 years or older End stage kidney disease (ESKD) of any cause Elective PD catheter insertion **Exclusion Criteria** Documented allergy to rifampicin, sparfloxacin (or any fluoroquinolone), triclosan, or silicone Pregnant, likely to become pregnant, or breastfeeding Emergency PD catheter insertion

FUNDING AND SUPPORT IN KIND

Funder(s)	**Financial and Non-Financial Support Given**
National Institute for Health Research (Invention for Innovation) https://www.nihr.ac.uk/about-us/contact-us/contact-us.htm	Research Grant
Kimal, Sherwood Rd, Bromsgrove B60 3DR	Support in Kind by providing the untreated catheters

ROLES & RESPONSIBILITIES

Sponsor

The Sponsor, University Hospitals of Derby & Burton NHS Foundation Trust, take on overall responsibility for appropriate arrangements being in place to set up, run and report the research project. The sponsor is not providing funds for this study, but has taken on responsibility for ensuring finances are in place to support the research.

Funder

The study is funded by NIHR.

Study Management Committees

Study Management Group

The study management group will meet regularly to oversee the day-to-day management of the study, including all aspects of the conduct of the study. Any problems with study conduct will be raised and addressed during SMG meetings.

The SMG will comprise of chief investigator and all members co investigators; at least 3 members should be present to hold a valid meeting of the SMG. The SMG will meet at least every 3 months.

Clinical Investigation Plan Contributors

A number of contributors have been involved in the development of the CIP, these include; Professor Taal, Dr Pittman, Dr Dukka, Katie Belfield, Roger Bayston, Roy Harris, Niall Buntain. Contributors are responsible for inputting into the design of the study, ensuring that it is designed transparently and efficiently.

Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
APDC	antimicrobial PD catheter
CI	Chief Investigator
CIP	Clinical Investigation Plan
CKD	Chronic Kidney Disease
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
ESRD	End Stage Renal Disease
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HD	Haemodialysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IR	Interventional Radiology
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
NHS R&D	National Health Service Research & Development
PD	Peritoneal Dialysis
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
RCT	Randomised Control Trial
REC	Research Ethics Committee
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SMG	Study Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
UHDB	University Hospitals of Derby and Burton

STUDY FLOW CHART

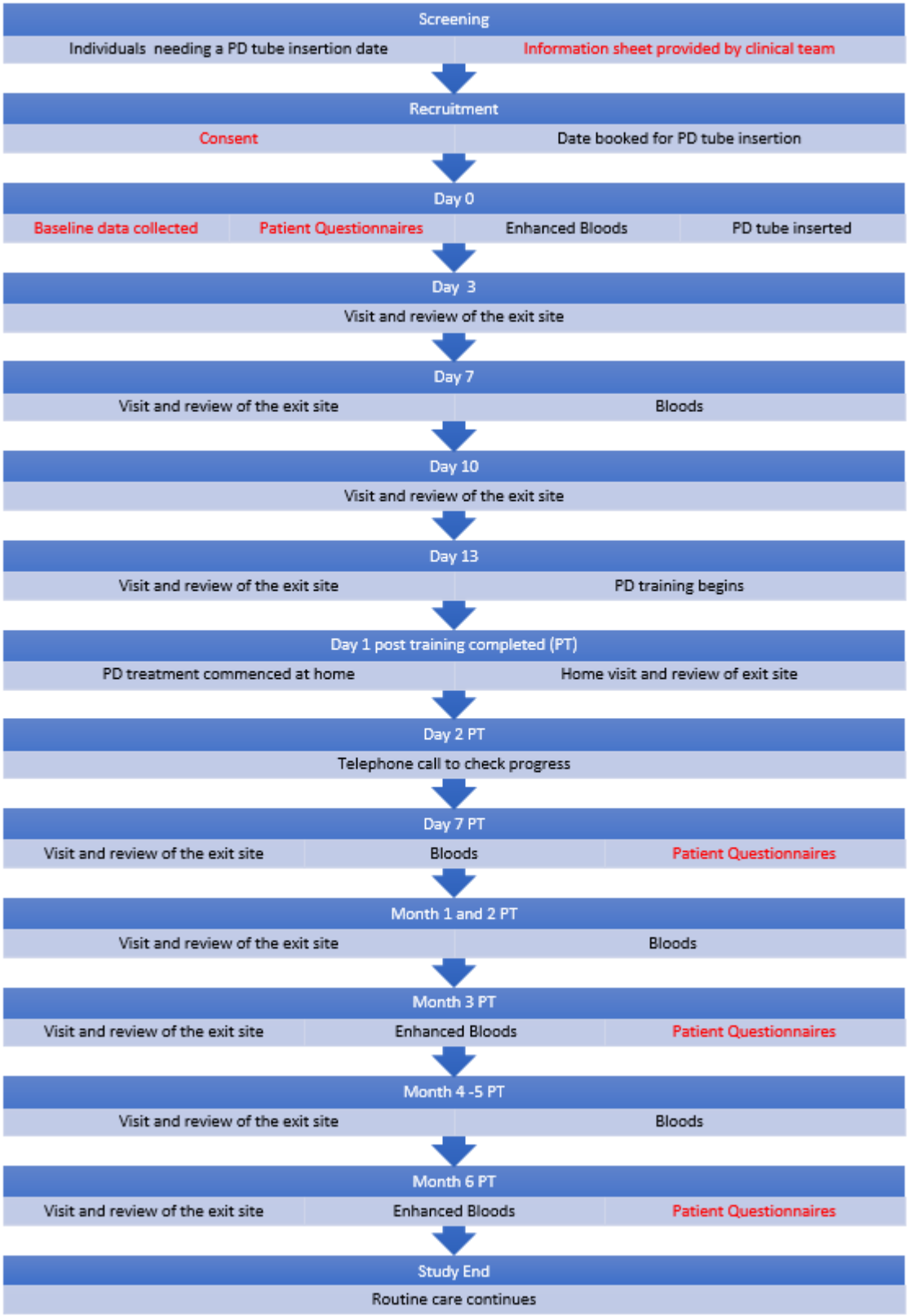

Figure 1 Flow diagram of routine study visits, Items highlighted in red are additional to routine care.

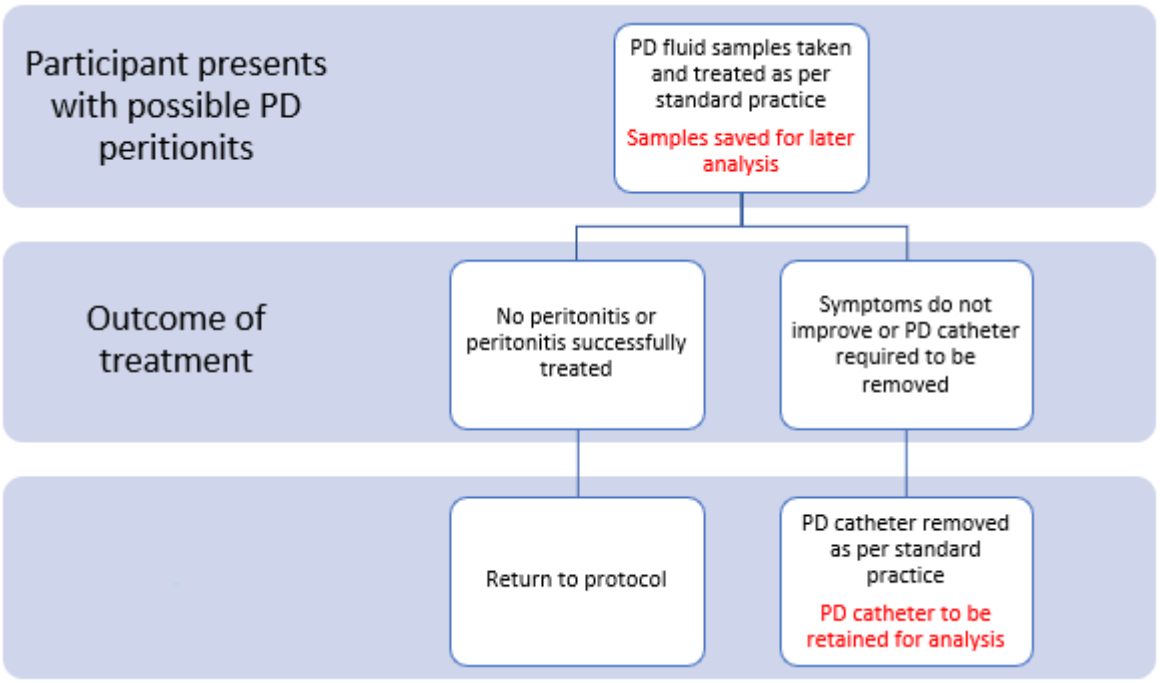

Figure 2 Flow diagram of additional study procedures for PD peritonitis Items highlighted in Red are additional to routine care

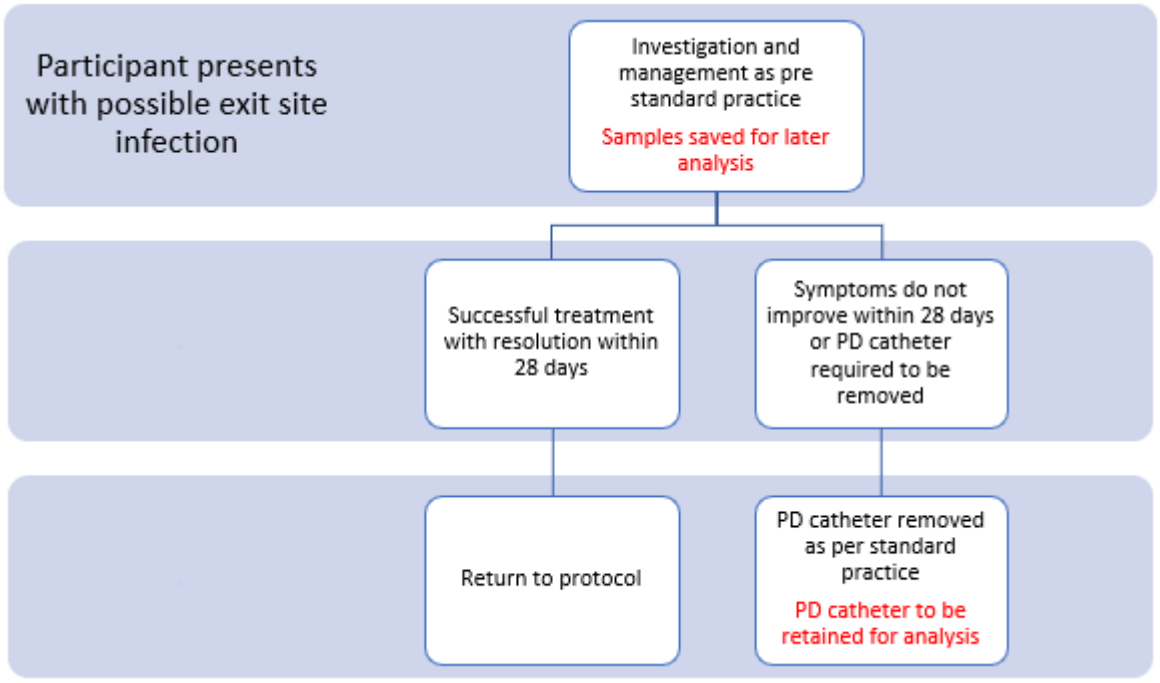

Figure 3 Flow diagram for additional study procedures for exit site infections, Items highlighted in Red are additional to routine care

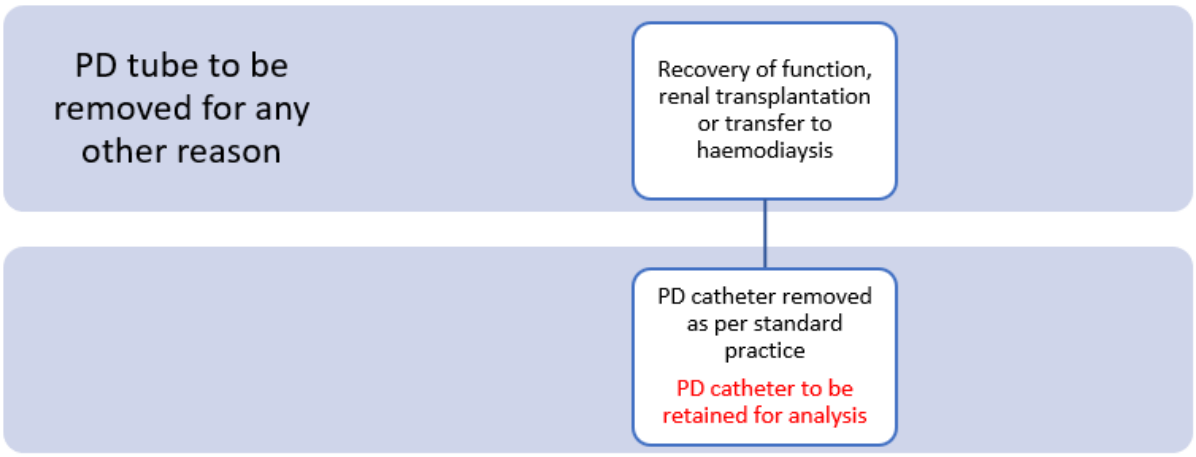

Figure 4 Flow diagram for additional study procedures if PD catheter to be removed as no longer required, Items highlighted in Red are additional to routine care

CLINICAL INVESTIGATION PLAN

BACKGROUND

Chronic Kidney Disease (CKD) affects approximately 10% of the adult population. In a minority of people, CKD progresses to end-stage kidney disease (ESKD) that requires treatment with renal replacement therapy (RRT). At the end of 2017 just under 65,000 patients in the UK were receiving RRT: 55.2% had a renal transplant, 39.3% were receiving haemodialysis (HD) and 5.4% were undertaking peritoneal dialysis (PD) (1). Peritoneal dialysis (PD) is a type of dialysis used to treat people with kidney failure. To perform PD, a silicone tube is placed with one end in the abdominal cavity and the other end exiting through the skin. Fluid is run into the abdomen via the tube and then drained out again after 1-4 hours. While in the abdomen, toxins and other waste chemicals move from the body into the fluid and are then removed when it is drained out. In this way, PD partially replaces kidney function. The choice of RRT is dependent on many factors including individual preference. Recently there has been a growing appreciation of the advantages offered by forms of dialysis that can be performed in patients' own homes (home HD and PD) and the National Institute for Health and Care Excellence (NICE) recommends that all patients should be offered the opportunity to receive home dialysis (2). Home HD and PD offer the advantage of people being in control of their own therapy but are currently under-utilised. The COVID pandemic has highlighted an additional advantage of home therapies because patients who have dialysis at home are able to shield to reduce their risk of infection. Consequently, recent NICE guidelines recommended increased use of home dialysis during the pandemic (3).

The number of people performing PD in the UK is still small, with approximately 3500 prevalent PD patients and about 1700 incident patients annually (1). One of the biggest problems limiting PD use is PD catheter-related infection, classified by the site affected (exit site, catheter tunnel or peritonitis). Peritonitis can be severe, requiring hospital admission and urgent removal of the infected catheter. Infections are the major cause of hospital admissions, morbidity and mortality in PD patients and are the most common cause of PD catheter access failure within the first year (1). In 2016-17 the rate of PD related peritonitis averaged 40-50 episodes per 100 patient years across units in England and infections accounted for 20.3% of all deaths in people performing PD (1).

PD catheter infections are caused mainly by Staphylococcus aureus (including methicillin-resistant S. aureus), Staphylococcus epidermidis and Escherichia coli. A number of different approaches have been tried to reduce PD catheter infections with varying degrees of success (4). No anti-infective PD devices currently exist on the market. University of Nottingham (UoN) has developed and patented a method of impregnating, not coating, medical devices with antimicrobials to give extended protection from microbial colonisation (5). Pre-clinical studies show that PD catheters can be impregnated with the antimicrobials rifampicin, triclosan, and sparfloxacin to give long-term protection against the main causative agents of PD-associated infections. Bacteria accessing the catheter are killed and biofilm development is prevented (6).

1. RATIONALE

This proposal seeks to address the clinically important and costly problem of infections associated with PD through the use of an antimicrobial-impregnated catheter, whose baseline technology has already been demonstrated to be safe and cost-effective in other clinical applications.

RRT is expensive and consumes over half of the £1.45 billion NHS England budget for CKD (2009-2010 data) (7). The approximate cost for treatment of PD-associated peritonitis is £3,103 per episode (8). In addition, peritonitis causes acute distress to patients and its management may require hospital admission and removal of the PD catheter. Recurrent peritonitis contributes to loss of peritoneal membrane function and reduced dialysis adequacy. Catheter related infections are therefore an important contributor to patients having to transfer from PD to HD. Furthermore, serial courses of antibiotics are associated with development of antibiotic resistance and other adverse events such as Clostridium difficile disease (9). Any reduction in PD infection would therefore likely improve patient experience and quality of life as well as reducing hospital admissions, technique failure, antibiotic use, antibiotic resistance and cost.

Additionally, there is a gap in anti-infective technology available to PD catheter users. Strategies for preventing PD catheter infections and peritonitis include rigorous training in the use of aseptic technique when connecting the catheter to PD fluid bags, daily application of mupirocin or gentamicin cream at the exit site and prophylactic antibiotics immediately prior to PD catheter placement. However, guidelines note that use of prophylactic antibiotics increases risk of resistance and colonisation by more unusual organisms (10).

1.1. Assessment and Management of Risk

The antimicrobial PD catheter and its technology have been previously developed and validated (6,11,12). Clinical and pre-clinical studies of other medical devices using the antimicrobial impregnation technology support its effectiveness. Neurosurgical shunt devices impregnated with rifampicin and clindamycin are currently sold world-wide (67 countries) as Codman® Bactiseal® (Integra Life Sciences). In a randomised controlled trial of antimicrobial-impregnated shunts and silver-treated shunts versus standard shunts in 1605 adult and paediatric patients, shunt infection rates were 60% lower for patients receiving the antimicrobial-impregnated shunt compared to standard shunt (hazard ratio 0.38, 97.5% CI 0.18 to 0.80; P=0.004) but infections were not lower with silver-treated shunts (hazard ratio 0·99, 97.5% CI 0·56 to 1·74, p=0·96). The study concluded that antimicrobial– impregnated shunts should be adopted for all patients undergoing their first ventriculo-peritoneal shunt insertion (13).

The formulation of the antimicrobial-impregnated PD catheters is the same as the antimicrobial–impregnated urinary catheters that we have tested for patient acceptability and tolerability in long-term catheter users. Results from a study of the antimicrobial urinary catheter suggest that the formulation is biocompatible following human exposure for up to 84 days (14). The antimicrobial PD catheter is also likely to be biocompatible within the delicate peritoneum. Silicone material impregnated with rifampicin, triclosan, and trimethoprim using the same technology, and implanted into the peritoneum of male rats did not show any difference in the peritoneal membrane at 7 or 31 days after implantation compared to controls. There was no evidence of peritonitis or local inflammation macroscopically or histologically (6).

One of the advantages of the antimicrobial-impregnation technology over coated devices is that the antimicrobials are embedded throughout the silicone, rather than on the surface. The formulation is such that the antimicrobial molecules migrate freely within the silicone matrix, and are able to move to the catheter surface to replenish antimicrobials rinsed away to maintain a constant and high-level of antimicrobial activity at the surface, the site of microorganism colonisation (11). Both inner and outer surfaces are protected. A second advantage is that antimicrobials are released locally so that, based on known drug release profiles, they are very unlikely to cause antibiotic-associated side effects, interact with concomitant medicines, or contribute to the development of antibiotic resistance at distant sites. The antimicrobial PD catheter contains three antimicrobials from different drug classes, optimising its design according to the Dual Drug Principle. This states that the use of two antibiotics from different classes prevents emergence of resistance, as the likelihood of bacteria developing two simultaneous mutations is low (15). We have previously shown in laboratory studies that this approach prevents the generation of resistance over long periods. Specifically, catheter segments impregnated with these three antimicrobials were serially passaged daily on a bacterial lawn for 280 days and no resistance was observed. There was carryover of bacteria on the impregnated segments from one plate to the next so that the same bacterial population was exposed repeatedly to the antimicrobials (11). These three antimicrobials were selected so that at least two antimicrobials would be active against the majority of PD infection causative organisms. The third advantage of the antimicrobial-impregnated PD catheter is its long duration of protective activity. In studies that involve the flow of fluid through catheters causing elution of the antimicrobials, the antimicrobial PD catheters were able to prevent bacterial colonisation for 84 days by clinically relevant microorganisms, including those that are multi-drug resistant (6,12).

2. OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

Is a PD catheter impregnated with the antimicrobials rifampicin, sparfloxacin, and triclosan well-tolerated by patients and do these data support future studies of efficacy and commercial adoption?

2.1. Primary Objectives

For this feasibility study we will assess the safety and tolerability of the antimicrobial PD catheter, defined as the rate of adverse events attributable to the antimicrobials or the impregnation process encountered by PD patients.

2.2. Secondary Objectives

Assessment of Patient acceptability
PD Peritonitis Rates
Exit site/tunnel infection rates
Technique failure (transfer from PD to HD)
Microorganism colonisation of PD catheters removed within the study period
Antibiotic resistance profile of organisms causing catheter-related infections

2.3. Primary Endpoint/ Outcome

The rate of adverse events attributable to the antimicrobials or the impregnation process encountered by PD patients.

2.4. Secondary Endpoints/ Outcomes

Patient acceptability determined by modified IPOS Renal questionnaire and patient acceptability questionnaire
PD Peritonitis (identified and defined using local protocols and International Society for Peritoneal Dialysis Guidelines)
Exit site/tunnel infection (identified and defined using local protocols and International Society for Peritoneal Dialysis Guidelines)
Technique failure (transfer from PD to HD)
Microorganism colonisation of PD catheters removed within the study period
Antibiotic resistance profile of organisms causing catheter-related infections

3. TRIAL DESIGN

Non-randomised feasibility study to gather preliminary information on the antimicrobial impregnated PD catheter to inform the design and the feasibility of conducting a randomised trial.

4. STUDY SETTING

This study will be undertaken at University Hospitals of Derby & Burton NHS Foundation Trust (UHDB) and participants will be recruited from patients already known under the care of the renal team at UHDB.

5. ELIGIBILITY CRITERIA

All patients who opt for peritoneal dialysis (PD) will be invited to participate, subject to the following inclusion and exclusion criteria.

5.1. Inclusion Criteria

Aged 18 years or older
End stage kidney disease (ESKD) of any cause
Elective PD catheter insertion

5.2. Exclusion Criteria

Documented allergy to rifampicin, sparfloxacin (or any fluoroquinolone), triclosan, or silicone
Pregnant, likely to become pregnant, or breastfeeding
Emergency PD catheter insertion

6. TRIAL PROCEDURES

6.1. Recruitment

6.1.1. Patient Identification

Patients will be provided with information regarding the study once they have made a decision to have PD. This may be several months prior to starting dialysis. Once the decision is made to commence PD, patients will be asked whether they wish to participate and approached for consent to enter the study. They will be offered a date for PD catheter insertion, normally within 1-3 weeks.

6.1.2. Screening

Patients are provided with extensive counselling in the months and weeks leading up to the need for renal replacement therapy and when choosing to have PD treatment and are provided with a separate patient information sheet relating to the insertion procedure and consent as part of routine care.

All patients who opt for PD at UHDB will be approached at a clinic visit by their clinical team and given information regarding the trial. For individuals already or previously on PD who are transferring back and require a new PD catheter they will be approached by the PD team.

There will be no payments to participants and no visits additional to routine care.

6.2. Consent

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial (including the collection of identifiable participant data, unless the trial has prior approval from the Confidentiality Advisory Group (CAG) and the REC.

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent according to the REC approved CIP, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Once individuals have been identified as eligible for inclusion they will be provided with a patient information sheet (PIS) and given time to consider the information. If they indicate that they are willing to participate they will then have a meeting with a member of the study team who will take consent for the study after answering any questions that they may have. Participants will still need to be consented separately by the clinical team for the PD catheter insertion procedure.

Only individuals who have capacity to consent are eligible to be recruited to this study. If they lose capacity at a later point they will continue within the study unless they have withdrawn consent prior to losing capacity. Any potential participant has the right to refuse participation without giving reasons

and this will not alter their care in any way. If required a trained interpreter will be provided. The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

If a participant wishes to withdraw from the study then no further data (aside from safety data) will be collected with regards to that individual. The PD catheter will remain in situ until such time as it is decided by the clinical team that it should be removed for clinical reasons.

6.3. Baseline Data

To be collected from the participants and medical notes

- Demographic information (Age, Sex, Height, Weight, Ethnicity)
- Previous renal replacement therapy (RRT), (modality, duration, complications)
- Past medical history (Angina, Previous MI, Previous CABG or coronary angioplasty, Heart disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, liver disease, malignancy, claudication, ischaemic/neuropathic ulcers, other (non-coronary) angioplasty, amputation for peripheral vascular disease
- Smoking history
- Current drug therapy and allergies
- Blood Results (enhanced set (see below))

6.4. Trial Assessments

Outline of visit schedule; See **Error! Reference source not found.**

PD catheters at UHDB are inserted in interventional radiology (IR) with real-time x-ray screening (fluoroscopy) as standard care and the same will be the case for the research participants. Whenever there are concerns over the position of functioning of a PD catheter this is also assessed with a plain abdominal X-Ray. We do not anticipate any additional Radiation exposure as a result of this trial design or the use of the Antibiotic impregnated PD catheter.

PD catheter insertion counts as day 0 and will be undertaken in interventional radiology as per our standard of care for PD catheter insertions. A small number of PD catheters will require surgical insertion for patient related factors. For IR inserted catheters we have consulted a medical physics expert and IRMER (Ionising Radiation Medical Exposure Regulations) practitioner who have provided the following assessment.

Trial radiation procedures
A participant in this trial would undergo an insertion of a peritoneal dialysis catheter impregnated with antimicrobial treatment. Fluoroscopy imaging is used to guide the insertion. If there are concerns about catheter placement, a plain film abdominal x-ray may be carried out. The participant would have a catheter insertion whether in the trial or not, so the radiation in the study is consistent with standard care.

Estimated effective dose

Local dose audit for peritoneal dialysis catheter insertion resulted in a dose-area product of 0.2Gycm2 (n=39). Using conversion factor for abdominal examination from CRCE028 [1], this results in approximately 0.04mSv effective dose.
The NDRL for abdominal plain film x-ray is 2.5Gycm2 [2]. This results in approximately 0.45mSv effective dose [1].

Estimated risk
The estimated total research protocol dose is set at 0.5mSv. This is the equivalent of less than three months of UK background radiation. It would increase the individual's risk of cancer by 0.0025% (compared to our natural risk of cancer, of 50%) [1].
This exposure would take place as part of routine clinical care: participants taking part in this study will therefore not be exposed to any additional radiation through participation.

Details of assessments to be undertaken

1. Bloods tests:
    a. All visits requiring bloods, electrolytes, urea, creatinine, calcium, phosphate, liver function tests, c reactive protein, full blood count,
    b. Enhanced bloods as per routine care at 0, 3 and 6 months (ferritin, transferrin saturation, folic acid, vitamin B12, parathyroid hormone)

2. Exit site review: Exit sites will be examined by the PD nurse and a photograph will be taken and stored as part of the electronic patient record. This procedure is already a standard of care in the unit. Exit sites will be scored by the PD nurse and a PD consultant according to the scale developed by Schaefer et al Figure 5.

Exit-Site Scoring System

Parameter	Score[a] 0	1	2
Swelling	No	Exit only (<0.5 cm)	>0.5 cm or tunnel or both
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain	No	Slight	Severe
Drainage	No	Serous	Purulent

[a] Infection should be assumed with a score of 4 or higher. Purulent drainage, even by itself, is sufficient to indicate infection. A score of less than 4 may or may not represent infection.

Figure 5 Modified version of Schaefer F et al(14) as presented in the ISPD guidelines

3. Questionnaires:
   IPOS Renal: To be completed at baseline, 3 weeks post PD catheter insertion and at 3 and 6 months post insertion (see Appendix 3 - IPOS Renal Questionnaire). IPOS Renal is a QOL measure for repeated measures in renal patients.

   Acceptability questionnaire: to be completed at 3 months post catheter insertion.

   Patient acceptability

How would you rate the tolerability of your PD catheter? (10 no problems, 1 intolerable)

How much do you value having antibiotics added to the catheter? (10 very much, 1 not at all)

Did you experience any specific problems related to the catheter? (Yes/No)

If yes, please describe any problems you experienced.

Any other comments about the catheter?

4. PD prescription details will be recorded and the reason for any change in prescription will be logged.

All blood and PD fluid tests will be part of routine care. All study visits will coincide with routine clinical visits. The IPOS Renal questionnaire is in addition to routine care. At 24 weeks after PD catheter insertion the study will be considered completed and individuals will continue with routine clinical care. Additional visits will be arranged if there are any concerns raised between routine visits.

Additional visits for foreseeable adverse events related to treatment with a PD catheter : See Figure 2,Figure 3, and Figure 4 for the flow diagrams of participant care leading to additional study visits

Any episode of PD related infection (exit site, tunnel or Peritonitis) will result in an extra visit and investigation/ treatment as per existing guidelines (Appendix 4 - PD Peritonitis Guideline). The results of these investigations and the clinical outcome will be recorded. If any microorganisms are isolated during the routine clinical processing of samples this isolate will be stored.

If a PD catheter is removed for any reason during the study period the catheter will be retained for further analysis by the study team.

All adverse events reported by participants will be recorded. Individuals transferring off PD will be recorded but individuals who stop PD due to a functioning kidney transplant or recovery of independent kidney function will not be recorded as adverse events.

In the event that a participant moves away for the area the receiving team will be informed of the fact that they are participating in a study and no further data will be collected. Due to the nature of the treatment and the relatively short duration of the study it is very unlikely that participants will otherwise be “lost to follow up” but every effort will be made to contact them and ensure appropriate follow up.

6.5. Withdrawal Criteria

If a participant wishes to withdraw from the study then no further data (aside from safety data) will be collected with regards to that individual. The PD catheter will remain in situ until such time as it is decided by the clinical team that it should be removed for clinical reasons.

Participants will be withdrawn from the study if they have the PD catheter removed for any reason. The study may be stopped early if there is a concern about safety/tolerability of the novel PD catheter.

6.6. Storage and Analysis of Samples

Stored samples will consist of:

Positive Microbiology Isolates

After incubation of culture plates from PD fluid (undertaken as standard of care in the microbiology lab at UHDB) , the plates should be secured by means of adhesive tape to ensure that the lids remain in place, and placed in a secure transit container (available from either UoN or Derby clinical laboratory). They should then be transmitted promptly (within 24hr) to the laboratory at UoN. Films prepared for microscopy examination of the PD fluid should be placed in a slide carrier and this placed in a secure container for transit with the plates, and accompanied by the initial request form and any notes and observations from the Derby clinical laboratory.

On arrival at the research laboratory at UoN, the plates will be allotted a serial number and this entered in a register. They will then be examined by a microbiology-trained person for any bacterial or fungal growth. Microscopy slides will be re-examined and a report prepared.

- Any bacterial growth will be identified by conventional methods (eg API and where appropriate, MALDI-ToF). Fungal growth will be identified to genus level. All isolated will be subcultured and stored as frozen.
- Bacterial isolates will be tested for susceptibility to the three drugs in the antimicrobial catheter. A disk test is available to rifampicin susceptibility. For sparfloxacin and triclosan susceptibility, agar-incorporation assays will be used.
- All data will be recorded and securely stored, with reference to the sample serial number allotted to them on receipt in the laboratory.

Removed PD Catheters:

Sample Collection

Removed PD catheters will be removed by the direct care team at University Hospitals of Derby and Burton NHS Foundation Trust. Any connectors, valves or accessories should be removed and discarded. The removed PD catheters will be packaged and labelled for transportation according to the World Health Organisation basic triple packaging system.

- The removed PD catheters and their attached cuffs should be placed in a specimen collection bag. This is its primary packaging.
    - If any of the cuffs were excised during removal, any detached cuffs should be placed in a sterile Universal container. There should be only 1 cuff per sterile Universal container. Therefore, if both cuffs were excised from the catheter, 2 sterile Universal containers will be required: one for each cuff

- The specimen collection bag should be labelled with the date the PD catheter was removed and the participant's study identifier.
- The specimen collection bag containing the PD catheter and any Universal containers should then be placed into a second sterile clear zip-lock bag containing an absorbent pad. This is the secondary packaging.
- The PD catheter and cuffs in their primary and secondary packaging should be then placed in an opaque, hard-side container for transportation. This is their transportation packaging. Transportation packaging should be labelled with 'UN3373 Biological Substance Category B' for transportation to the University of Nottingham.
- If the removed PD catheter and cuffs are not sent for transportation within one hour of removal, they should then be stored in their transportation packaging at 4-8□C.
- Once arriving at the laboratory, PD catheter and cuffs should be stored at 4-8□C until it they are processed, which should be within 24 hours of collection.

Sample Analysis

The PD catheters and their cuffs will be analysed for any microorganisms attached to the PD catheter or cuff material. Microorganisms will be isolated from the catheter and cuffs by sonication in a method similar to previously published methods for isolating microorganisms from urinary catheters (16,17)Any isolated microorganisms will then be identified and tested for antimicrobial resistance to the three antimicrobials of the PD catheter; rifampicin, sparfloxacin, and triclosan.

Storage

Microorganisms isolated from PD catheters and/or their cuffs may be stored for future reference and these will be stored at the University of Nottingham. Any microorganism isolates from PD catheters and/or their cuffs will not be linked to any patient identifiable information and will not contain any relevant material. Individual microorganism isolates will be stored in cryogenic vials at -20□C.

Destruction

Removed PD catheters and their cuffs will not be retained for more than 2 weeks beyond the end of the study . Once analysis is complete they will be neutralised by incineration as part of clinical waste disposal. The laboratory records and CRF will be updated to demonstrate that the sample is no longer under the custodianship of the University of Nottingham.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

6.7. End of Trial

The end of trial will be defined as last patient, last visit. The Sponsor will notify the participating sites and REC within 90 days of the end of trial. The clinical trial report will be written within 12 months of the end of trial.

7. INVESTIGATIONAL DEVICE

7.1. Name and Description of Investigational Device(s)

Device description

The device under investigation is the antimicrobial PD catheter (APDC) which is an all-silicone PD catheter that is impregnated with three antimicrobials: 0.922% w/w triclosan (CAS 3380-34-5), 0..509% w/w sparfloxacin (CAS 110871-86-8), and 0.057% w/w rifampicin (CAS 13292-46-1). The APDC consists of a base CE-marked all-silicone PD catheter that is then modified by the antimicrobial impregnation process described in the patent entitled 'Medical devices and methods of making medical devices' (Publication No WO2006/032904).

The antimicrobial PD catheters will be manufactured in two sizes: Table 1

Catheter description	Catheter length	Catheter outer diameter	Catheter inner diameter
Adult, Coiled Tenckhoff 2 cuff PD catheter	575 mm	4.9 mm	2.6 mm
Adult, Coiled Tenckhoff 2 cuff PD catheter	630 mm	4.9 mm	2.6 mm

Table 1 Size and specification of PD catheters

The APDC is terminally sterilised by ethylene oxide and supplied as sterile to the direct care team. It should not be re-used or re-sterilised.

The materials used in the APDC and its manufacturing and their contact with the body can be found in Table 2below. According to ISO 10993-1 the APDC is an externally communicating medical device and the device is in contact with the patient's peritoneum and skin at the exit site.

Function / Process	Component	Materials	Body Contact
Base silicone PD catheter	Shaft	Medical grade silicone rubber tubing	Yes
		Radiopaque X-ray stripe	Yes
	Cuffs (2)	Dacron (polyethylene terephthalate)	Yes
	Connector (part 6175)	*<need info from base PD catheter supplier>*	No
Impregnation	Antimicrobials	Rifampicin (0.057% w/w)	Yes
		Sparfloxacin (0.509% w/w)	Yes
		Triclosan (0.922% w/w)	Yes
Solvent	Impregnation reagents	Chloroform (Reduced to nil)	Yes, if any residues
Rinsing		0.1N Sodium hydroxide (Reduced to nil)	Yes, if any residues
Sterilisation	Residuals	Ethylene oxide	Yes, if any residues

Table 2 Summary of Materials and Body contact

All three antimicrobials used in the manufacture of APDCs meet the pharmaceutical standards for manufacturing and have the accreditations and supporting documentation in Table 3to support their safe use.

Active ingredient	Name of manufacturer	GMP certifying body	DMF	WC	COA	CTD access
Rifampicin	*Name redacted* (commercially sensitive, can provide is requested)	China Food and Drug Administration China	Yes	Yes	BP2019	Yes
Sparfloxacin	*Name redacted* (commercially sensitive, can provide is requested)	Drugs Control Administration - Telangana	No	No	Inhouse	No
Triclosan	*Name redacted* (commercially sensitive, can provide is requested)	Central Drugs Standard Control Organisation-India, Food and Drug Administration -USA	No	Yes	USP	No

Table 3 Supplier of antimicrobials for APDC manufacture with accompanying accreditation and documentation. GMP: Good Manufacturing Practice, DMF: Drug Master File, WC: Written Confirmation, COA: Certificate of Analysis, CTD: Common Technical Document, USP: United States Pharmacopoeia,

Intended purpose

The primary purpose of the APDC is for access to the peritoneal cavity through which dialysis fluid is administered for acute and chronic peritoneal dialysis therapies. The antimicrobials are present in the catheter secondarily to protect the catheter from bacterial attachment which could lead to infection.

Neither the APDC nor the antimicrobials contained in it are intended for therapeutic application to treat infection.

Intended user

Antimicrobial Peritoneal Dialysis Catheters should be implanted and/or explanted by a physician experienced with percutaneous and/or surgical placement and familiar with the complications of their use.

Intended populations

The antimicrobial PD catheter is intended for use in adults. Contraindications include:

Absolute

- Allergy to rifampicin, sparfloxacin or any other fluoroquinolone antibiotic, and / or triclosan
- Presence of stoma
- Presence of large inoperable hernia
- Known peritoneal fibrosis
- Severe obesity

Relative

- Previous major abdominal surgery
- Abdominal aortic aneurysm
- Multiple previous abdominal hernias

Packaging and labelling

All APDCs will be individually packaged in a primary packaging sterile barrier and packing will be carried out in a Class ISO 14644 Class 8 Cleanroom.

Each catheter will be individually labelled with a Primary Product Label in accordance with ISO 15223-1: 2016. The Primary Product Label will include a catheter sizing diagram, harmonised symbols and information that the catheter is 'exclusively for clinical evaluation'.

Description of the specifical medical or surgical procedures involved in the use of the investigational device.

The use and insertion of the antimicrobial PD catheter is no different from the use and insertion of a standard PD catheter.

PD catheters are manufactured from silicone tubing. One end has several perforations in the silicone to assist drainage and this end is also curled ("pig-tailed") to assist placement in the pelvis. The other end is left "plain" and is designed to receive a sterile plastic connector with a screw thread for connection to a further silicone tube that has an opening/closing device which in turn connects to a bag of PD fluid. When not in use, a sterile cap is applied to the end of the catheter to prevent contamination. PD catheters are produced in different lengths to suit the body size of different patients.

PD catheters are placed, either percutaneously (with local anaesthetic) employing a Seldinger technique (guidewire) assisted by real-time x-ray imaging to facilitate correct positioning or surgically via laparoscopy requiring general anaesthetic. The perforated (proximal) end of the catheter is placed in the pelvis. The distal end is externalised below the umbilicus and then tunnelled laterally through the subcutaneous fat to an exit site 10-15 cm lateral to the midline on the left or right, depending on patient preference and or anatomical considerations.

The subcutaneous portion of the catheter has two Dacron cuffs attached to secure the catheter in the subcutanous tissues After several weeks, fibrosis around the Dacron cuffs fixes the catheter in the subcutaneous tissue. A surgical dressing is applied to the exit site and changed regularly to protect in from infection. Patients are thoroughly trained in the use of aseptic technique to be applied when PD fluid exchanges are performed.

Risk assessment summary

The risks associated with the APDC are either well-understood in that they are risks of all PD catheters or are unique to antimicrobial impregnation process. Firstly, those risks associated with all PD catheters are accepted risks that are well-characterised and understood as PD catheters are currently in use world-wide. The base CE-marked catheter (which is subsequently modified by antimicrobial impregnation) has achieved the CE-mark because the risks associated its manufacture and with PD catheterisation are understood and are mitigated as far as possible.

Secondly, the process of antimicrobial impregnation does introduce additional risks that are relatively unique. However, these risks are controlled for using in-process controls and finished product testing before the AMUCs are available for clinical use. The risks associated with antimicrobial impregnation can be mitigated with the current processes and controls in place. The risks are likely to be outweighed by the potential prevention of peritonitis and exit site infections, which are significant adverse events that can potentially lead to serious consequences such as hospitalisation, sepsis, and potentially death.

Medical device classification

The APDC is a Class III Medical Device in accordance with the UK Medical Devices Regulations 2002, SI 618 (UK MDR 2002). The APDC is defined as a medical device in accordance with Part I, Regulation 2 of the UK MDR 2002 which includes in its definition of a medical device "....devices intended to administer a medicinal product or which incorporate as an integral part a substance which, if used separately, would be a medicinal product and which is liable to act upon the body with action ancillary to that of the device". The APDC is classified as a Class III medical device in agreement with UK MDR 2002 Part II, Regulation 7 which is in accordance with Rule 13 of Annex IX of Directive 93/42,which states "All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III."

Comparator
There is no comparator device in this study.

7.2. Traceability of the Device

The antimicrobial PD catheters will not be loaned or gifted to participants. They will be inserted by the direct care team at UHDB. Each catheter has a unique reference number that is recorded both in the patient record and in the CRF.

7.3. Investigator Brochure (IB)

An Investigator Brochure is available for the APDC.
All antimicrobial peritoneal dialysis catheters will come supplied with instructions for use (IFU) in each package.

7.4. Device Storage, Supply and Accountability

The APDC should be stored at controlled room temperature (protected from excessive heat) and protected from light and humidity. The devices will be stored in a locked cupboard at UHDB separate to any routine clinical supplies.

If a PD catheter is removed for any reason during the study period the PD catheter will be retained for further analysis by the study team. The PD catheter and its components will be destroyed by incineration after the laboratory analyses are completed.

There will be no post-trial access to the device.

7.5. Assessment of Compliance

This is an implanted device, the use and functioning of the device will be monitored at a minimum frequency of monthly once established on therapy and more frequently if there are any concerns.

8. PHARMACOVIGILANCE

8.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, where or not related to the investigational medical device and whether anticipated or unanticipated.
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. *NOTE: this definition includes:* • *AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.* • *Any event resulting from use error or from intentional misuse of the investigational medical device.* • *'Comparator' if the comparator is a medical device.*

Serious Adverse Event (SAE)	An adverse event that led to any of the following:
	• death
	• serious deterioration in the health of the subject, users, or other persons as defined by one of more of the following
	  ○ a life-threatening illness or injury, or
	  ○ a permanent impairment of a body structure or a body function including chronic diseases, or
	  ○ in-patient of prolonged hospitalisation, or
	  ○ medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure of a body function,
	• foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.
	
	NOTE: Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP without a serious deterioration in health, is not considered a SAE.

Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. *NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.*

Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. *NOTE: This definition includes:* • *Malfunctions, use errors, and inadequacy in the information supplies by the manufacturer including labelling.* • *Device deficiencies related to the investigational medical device or the comparator.*
Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. *NOTE: this would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.*

8.2. Operational Definitions for (S)AEs

(S)AEs that require reporting to the Sponsor will include;
Any episode of hospital admission or attendance related to a suspected reaction to the PD catheter
Any episode of infection where resistance to any of the antibiotics used in this catheter is identified.
Any incidence of the catheter migration/falling out.

The following events will not be considered (s)AE's;
Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
Any admission to hospital or other institution for general care where there was no deterioration in condition.
Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

Foreseeable adverse events and the management of these are described in section 7.7 Trial assessments and associated appendices and do not need to be reported to the sponsor but will be recorded in the participants medical records. Episodes of PD related peritonitis infection occur at a rate of around 0.37 infections per patient year in our current population. A rate of peritonitis above this in our study population will require review at the trial management committee.

8.3. Recording and Reporting SAEs and USADEs

All AEs, SAEs and device deficiencies must be recorded from the time of written informed consent until 26 weeks after the insertion date.

All AEs and device deficiencies occurring during the duration of the study must be reported by the investigator within the CRF. The PI is responsible for checking for AEs and SADEs when participants attend for treatment and follow-up.

The following events are considered reportable:

- Any SAE (whether initially considered device related or not)
- Any device deficiency that might have led to a SAE if:
    - Suitable action had not been taken or
    - Intervention had not been made or
    - If circumstances had been less fortunate.
- New findings/updates in relation to already reported events

All reportable events must be recorded by the investigator using the Sponsor's SAE reporting form and emailed to UHDB within 3 calendar days of the research team becoming aware of the event; even if not all information is available at the time (further information should be provided on the Sponsor's SAE Follow Up Report Form). Any change of condition or other follow-up information should be sent to the Sponsor as soon as it is available, or at least within 3 working days of the information becoming available. Events will be followed up until the event has been resolved or a final outcome has been reached. Safety information will be reviewed during trial management group meetings.

UHDB contact information:

Email: uhdb.randdsae@nhs.net.
Telephone: 01332 724639 or 01332 789339 (must be followed up with a written report).

For each reportable event the following information will be collected:

- Full details of the event, including a diagnosis
- MedDRA coding (system organ class and preferred term)
- Duration (start and end dates)
- Seriousness criteria
- Outcome.
- Action taken.
- Causality (i.e. related to investigational medical device)
- Expectedness

Safety information will be reviewed for ongoing assessment of the risk/ benefit during study management group meetings as per the trial monitoring plan.

8.3.1. Assessment of AEs and SAEs

8.3.1.1 Severity

The investigator should determine the severity of the AE;

- Mild: no interference with daily activities.
- Moderate: moderate interference with daily activities.

- Severe: considerable interference with daily activities (e.g. inability to work).

NOTE: to avoid confusion or misunderstanding the term "severe" is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as "serious" which is described in the safety definitions.

8.3.1.2 Causality

Clinical judgement should be used to determine the relationship between use of the investigational medical device (including the medical-surgical procedure) and the occurrence of each AE;

- Not-related: relationship to the device or procedures can be excluded when:
    - The event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
    - The event has no temporal relationship with the use of the investigational device or the procedures;
    - The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
    - The discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
    - The event involves a body-site or an organ not expected to be affected by the device or procedure;
    - The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
    - The event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
    - Harms to the subject are not clearly due to use error;
    - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
- Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
    - The event is a known side effect of the product category the device belongs to or of similar devices and procedures;
    - The event has a temporal relationship with investigational device use/application or

procedures;
- The event involves a body-site or organ that
  - The investigational device or procedures are applied to;
  - The investigational device or procedures have an effect on;
- The serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- Other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- Harm to the subject is due to error in use;
- The event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Assessment of causality must be made by a medically qualified doctor (usually the principal investigator). If a doctor is unavailable, initial reports should be submitted to UHDB without the causality assessment but they must be followed up with a medical assessment as soon as possible.

8.3.1.3 Expectedness

The assessment of expectedness is only required if the event is deemed to be related to use of the investigational medical device as per the clinical investigation plan.

- Expected: Reaction previously identified and described in the investigator brochure/ clinical investigation plan.
- Unexpected: Reaction not previously described in the investigator brochure/ clinical investigation plan.

The expectedness assessment is delegated to the CI.

8.3.2. Expedited reporting

For trials of investigational medical devices that are non CE-marked or CE marked but being used outside of their intended use(s) covered by the CI mark all reportable events must be reported to the MHRA (aic@mhra.gov.uk) using the MEDDEV 2.7/3 SAE reporting table and the manufacturer. In addition all USADEs must be reported to the REC.

8.4. Pregnancy reporting

If a participant, or the partner of a participant, becomes pregnant or is suspected to be pregnant from the time of consent up to 6 months following the fitting of the investigational medical device the

investigator must notify the Sponsor within 14 days of becoming aware of the pregnancy using the Sponsor's pregnancy notification form. All pregnancies will be followed up until the outcome of the pregnancy; if at any stage an event occurs that meets the criterion for an SAE then it must be reported as such.

8.5. Reporting Urgent Safety Measures

If any urgent safety measure is taken the research team should inform the Sponsor with 24 hours using the Sponsors safety incident reporting form. The Sponsor will inform the REC and participating sites of the measures taken and the circumstances giving rise to those measures within 3 days on implementation of the urgent safety measure.

9. DATA HANDLING

9.1. System and Compliance

All data will be collected on a paper CRF for each participant where each participant will be assigned a unique trial ID. Each participant will be assigned a trial identity code number, for use on CRFs, other trial documents and the electronic database. The key linking participant identifiable data to the trial ID will be stored in a password protected file on a secure server (University Hospitals of Derby and Burton NHS Foundation Trust). The electronic results system will be the source document for haematological, biochemical and microbiology laboratory test results.

Only study staff shall have access to study documentation other than the regulatory requirements listed below. The investigators will keep records of all participating patients, all original signed informed consent forms and copies of the CRF pages in the Investigator Site File. Data will be added into the CRF directly and therefore it will act as a source document.

Patent reported outcome measures will be recorded on paper and filed in the CRF on Completion

Any data used for dissemination purposes will be anonymised, ensuring participants cannot be identified from data.

9.2. Source Data

See section 10.1

9.3. Data Workflow

The CRF will be managed by the investigatory team and data from the CRF will be entered into an electronic database (excel) by trial ID which will be held securely and password protected. All data will be stored on a secure web server (University Hospitals of Derby and Burton NHS Foundation Trust). Access will be restricted by user identifiers and passwords (encrypted using a one way encryption

method). Information about the study in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format as per the standard server backup process.

9.4. Data Access and Security

Only the chief investigator and co-investigators will have access to the anonymised data.
Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

9.5. Archiving

At the end of the trial, following completion of the end of trial report, UHDB will securely archive all centrally held trial related documentation for a minimum of 5 years. At the end of the defined archive period arrangements for confidential destruction will be made. It is the responsibility of each PI to ensure that data and all essential documents relating to the trial are retained securely for a minimum of 5 years after the end of trial, and in accordance with national legislation.
UHDB will notify sites when trial documentation held at sites may be archived, and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request.

10. STATISTICS AND DATA ANALYSIS

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10.1. Sample Size Calculation

This is a feasibility study and a sample size calculation is therefore not required. The sample size is based on the number of PD catheters anticipated to be inserted during the recruitment period. Observation of 40 participants for 6 months with yield a total observation period of 240 patient months which should provide adequate data for comparison with nationally reported PD peritonitis rates and international quality standards (International Society of Peritoneal Dialysis recommends the rate should be below 0.4 episodes per patient year).

10.2. Planned Recruitment Rate

We aim to recruit 40 participants in 18 months. Based on data from the past 3 years, our clinical team places approximately 50 PD catheters per year. We therefore expect 75 catheters to be placed during the recruitment period of 18 months and will require a recruitment rate of 40/75 (53%). Based on our discussions with PPI representatives we believe that this is achievable.

10.3. Statistical Analysis

Statistical analysis will be performed by Dr Laura Nellums.

10.3.1. Summary of Demographic/Baseline Data and Flow of Patients

Descriptive statistics will be presented to summarize the distribution of baseline variables. Baseline variables will include comprehensive demographic and clinical variables. The continuous baseline variables will be reported with means and 95% confidence intervals (95% CI), if shown to be normally distributed, using a normality plot, otherwise will be reported with medians and interquartile ranges (IQR). The categorical variables will be reported with frequencies and percentages.

10.3.2. Primary Outcome Analysis

The primary outcome is adverse events. We will report the total number of each category of adverse event as well as the adverse event rate per participant observation month.

10.3.3. Secondary Outcome Analysis

Secondary outcomes will be analysed as follows:

1. IPOS Renal questionnaire: responses will be analysed using the methodology specified for this questionnaire. (see Appendix 5 - IPOS AnalysisFor details
2. Patient acceptability questionnaire: scores will be summarised using descriptive statistics. Patient comments will be collated and used to inform future study design.
3. PD Peritonitis (identified and defined using local protocols and International Society for Peritoneal Dialysis Guidelines)
    a. Rate will be calculated per patient year
    b. Causative organisms will be reported and summarised using descriptive statistics.
4. Exit site/tunnel infection (identified and defined using local protocols and International Society for Peritoneal Dialysis Guidelines)
    a. Rate will be calculated per patient year
    b. Causative organisms will be reported and summarised using descriptive statistics.
5. Technique failure (transfer from PD to HD) – rate will be reported per patient year
6. Microorganism colonisation of PD catheters removed - organisms will be reported and summarised using descriptive statistics
7. Antibiotic resistance profile of organisms causing catheter-related infections - will be reported and summarised using descriptive statistics

10.4. Interim analysis and criteria for the premature termination of the trial

No interim analyses are planned but we will monitor all adverse events as described in this protocol.

The Sponsor may suspend or prematurely terminate either the entire study, or the study at an individual site, for significant reasons that must be documented (e.g. an unacceptable risk to participants or serious repeated deviations from the clinical investigation plan/ regulations). If this occurs the Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e. participants, investigators, participating sites, REC, regulatory bodies).

10.5. Analysis Groups

This is an observational study with a single study arm, so all participants will be included on a single group.

10.6. Procedure(s) to Account for Missing or Spurious Data

Data will be collected using a case report form (CRF). Research nurses will be asked to complete all data fields and CRFs will be checked by the project manager upon completion. Missing data items will be obtained from the participants' clinical records. Research nurses will be asked to provide a reason for any data item that is missing.
We will not impute missing data.

10.7. Other Statistical Considerations

Not applicable

10.8. Health Economic Evaluation

Not applicable

11. MONITORING, AUDIT & INSPECTION

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor and competent authority may visit the participating sites to conduct audits/ inspections.
Monitoring and source data verification will be conducted by the Sponsor according to the study monitoring plan. The extent and nature of monitoring will be determined by the study objectives, purpose, design, complexity, blinding, number of patients and sites, and endpoints.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Peer review

This study has been peer reviewed as part of the National Institute for Health Research (Invention for Innovation) application process.

12.2. Public and Patient Involvement

Our PPI group consists of 1 patient co applicant to the Grant who sits on the SMG and a further 2 current PD patients. They have been or will be involved in study design and dissemination of findings. This will include advice and invlovement in any materials or events informing participants of the results.

12.3. Research Ethics Committee (REC) & Regulatory Compliance

The investigation will be conducted in compliance with the approved clinical investigation plan, the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) Medical Devices Regulations 2002 and ISO 14155:2020.

The clinical investigation plan and all related documentation (e.g. informed consent form, participant information sheet, questionnaires) have been reviewed and received approval by a Research Ethics Committee (REC). The trial has been classified as a clinical investigation for a medical device but does not require a notice of no objection from the UK competent authority, the Medicines and Healthcare Regulatory Agency (MHRA) During the development of this protocol as a team we have communicated extensively with the MHRA regarding the legal requirements and have email confirmation that "In reference to your application I have reviewed the annotated flow chart and can confirm that no MHRA approval is required for your intended study and this email will suffice for any ethics review. "

The investigator will not begin any participant activities until approval from the HRA and REC has been obtained and documented. Any additional requirements imposed by the REC, HRA and regulatory authority shall be followed. All documentation and correspondence must be retained in the trial master file/ investigator site file. Substantial amendments that require HRA and REC review will not be implemented until the HRA, REC grants a favourable opinion (with the exception of those necessary to reduce immediate risk to participants.

It is the responsibility of the Chief Investigator to ensure that an annual progress report (APR) is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, annually until the study is declared ended. The CI is also responsible for notifying the REC of the end of trial (see Section 7.10) within 90 days, however if the study ends prematurely, the notification must be submitted within 15 days. Within one year of the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

Before any site can enroll a patient into the trial confirmation of capacity must be sought from the site's research and development (R&D) department. In addition for any amendment that will potentially affect the site's permission, the research team must confirm with the site's R&D department that permission is ongoing.

For IR inserted catheters we have consulted a medical physics expert and IRMER (Ionising Radiation Medical Exposure Regulations) practitioner who have provided the following assessment. Please see section 7.4 for details.

12.4. Clinical Investigation Plan Compliance/ Non-Compliance Reporting

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures described in this clinical investigation plan. Prospective, planned deviations and/or waivers to the clinical investigation plan are not acceptable, however accidental deviations (non-compliances) may happen and as such these must be recorded. Non-compliances should be recorded in the CRF and/or a non-compliance log kept in the ISF. All non-compliances should be reviewed and assessed by the PI (or appropriately delegated individual) to determine if they meet the criteria of a "serious breach" (Section 12.6). Non-compliances which are found to frequently recur are not acceptable, will require immediate action, and could potentially be classified as a serious breach. Corrective and preventative actions should be documented in line with Sponsor procedures.
Principal investigators may be disqualified for the following:

- Fraud & misconduct
- Severe lack of PI oversight
- Lack of response to findings arising from monitoring and/or audits
- Constant non-compliance and a lack of action once identified.

12.5. Notification of Serious Breaches to GCP and/or the Clinical Investigation Plan

A "serious breach" is a departure from the clinical investigation plan, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the trial; or
(b) The scientific value of the trial.

If the PI (or delegate) is unsure if a non-compliance meets these criteria, they should consult the Sponsor for further guidance. If a serious breach is identified the investigator should notify the Sponsor immediately (i.e. within 1 working day) using the 'Non-CTIMP Notification of a Serious Breach' form . The report will be reviewed by the Sponsor and CI, and where appropriate, the Sponsor will notify the REC within 7 calendar days of being made aware of the breach.

12.6. Data Protection and Patient Confidentiality

The trial will be conducted in accordance with the Data Protection Act 2018. The investigator must ensure that participant's anonymity is maintained throughout the study and following completion of the study. Participants will be identified on all trial specific documents (except for the informed consent form and enrolment log) only by the participants study specific identifier (and initials if deemed necessary). This identifier will be recorded on documents, biological samples and the

database. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study.
All documents will be stored securely with access restricted to trial staff and authorised personnel.

Maarten Taal will act as the **custodian** of the data generated in the trial.

12.7. Financial and Other Competing Interests for the Chief Investigator, Principal Investigators at Each Site and Committee Members for the Overall Trial Management

No Financial interests.
Roger Bayston is the original holder of the IP via the University of Nottingham (UON). The UoN own the rights to the technology.

12.8. Indemnity

As UHDB is acting as the research Sponsor for this study, NHS indemnity applies. NHS indemnity provides cover for legal liabilities where the NHS has a duty of care. Non-negligent harm is not covered by the NHS indemnity scheme. UHDB, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

12.9. Amendments

If changes to the study are requested, these must be discussed with the sponsor, who is responsible for deciding if an amendment is required and if it should be deemed substantial or non-substantial. Substantial amendments will be submitted to the relevant regulatory bodies (REC, HRA) for review and approval. The amendments will only be implemented after approval and a favorable opinion from REC has been obtained. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgment. Amendments will not be implemented until all relevant approvals are in place.

12.10. Post Trial Care

On completion of the study participants will revert to standard clinical care and follow up.

12.11. Access to Final Trial Dataset

The final dataset will be limited to the Chief Investigator and co-investigators as well as well as authorised sponsor personal and statisticians from the DRS. External investigators will be required to submit a formal request to the sponsor for access to data.

13. DISSEMINATION POLICY

The clinical investigation will be registered on a publicly accessible database and the results of the investigation will be made publicly available. The UK medical devices regulations require that a written report of a clinical investigation must be produced. This must contain a critical evaluation of all the data collected during the clinical investigation.

13.1. Dissemination Policy

Upon completion of the study and End of Study report will be generated and submitted to REC within 12 months of the end of the study.

As sponsor, UHDB will own all data arising from the study.

A report of the study will also be submitted to the NIHR as funder and as a requirement of the award funding the study. Support for the study from the NIHR will be acknowledged in publications and all publications need to be authorised by the funder prior to release.

The results of this study will be submitted to peer-reviewed journals for publication, including an open access journal as soon as data analysis is completed. The results will also be presented at conferences. Participants will not be identified in any publications. However, participants will be informed of the results of the study via a departmental research newsletter, which is made available to all patients. Patient representatives will be encouraged to be involved in conference presentations and publications.

13.2. Authorship Eligibility Guidelines and any Intended Use of Professional Writers

Authorship will be in line with international committee of medical journal editors guidelines (ICMJE) section II.A.2 and based on the following criteria;

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

We are not planning to use professional writers.

14. REFERENCES

1. UK Renal Registry (2019). UK Renal Registry 21st Annual Report - data to 31/12/2017. Bristol, UK. Available from https://www.renalreg.org/publications-reports/
2. National Institute for Health and Care Excellence. Renal replacement therapy and conservative management, NICE Guideline (NG107) 2018. Available from https://www.nice.org.uk/guidance/ng107
3. National Institute for Health and Care Excellence. COVID-19 rapid guideline: dialysis service delivery NICE Guideline (NG160) 2020. Available from www.nice.org.uk/guidance/ng160
4. Bender FH, Bernardini J, Piraino B. Prevention of infectious complications in peritoneal dialysis: best demonstrated practices. Kidney Int Suppl. 2006:S44-54.
5. Bayston R. Medical devices and methods of making medical devices. United States US2007022423A1: University of Nottingham; 2007.
6. Bayston R, Fisher L, Weber K. An antimicrobial modified silicone peritoneal catheter with activity against both Gram-positive and Gram-negative bacteria. Biomaterials. 2009; 30:3167- 3173.
7. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transplant. 2012; Suppl 3:iii73-80.
8. National Institute for Health and Care Excellence. Kidney disease: peritoneal dialysis in the treatment of stage 5 chronic kidney disease: Appendix B. 2011. Available from https://www.nice.org.uk/guidance/cg125/documents/appendix-b-cost-effectiveness-analysis2
9. Wolfgram DF, Foster D, Astor BC, Chan MR. Development of Clostridium difficile colitis in peritoneal dialysis patients treated for peritonitis. Peritoneal Dialysis International. 2012; 32 (6): 666 – 668.
10. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. Perit Dial Int. 2016; 36:481-508.
11. Fisher LE, Hook AL, Ashraf W, et al. Biomaterial modification of urinary catheters with antimicrobials to give long-term broadspectrum antibiofilm activity. J Control Release. 2015; 202:57-64.
12. Belfield K, Chen X, Smith EF, Ashraf W, Bayston R. An antimicrobial impregnated urinary catheter that reduces mineral encrustation and prevents colonisation by multi-drug resistant organisms for up to 12 weeks. Acta Biomater. 2019; 90:157-168.
13. Mallucci CL, Jenkinson MD, Conroy EJ, et al. Antibiotic or silver versus standard ventriculoperitoneal shunts (BASICS): a multicentre, single-blinded, randomised trial and economic evaluation. The Lancet. 2019; 394:1530-1539.
14. Belfield K, Betts H, Parkinson R, Bayston R. A tolerability and patient acceptability pilot study of a novel antimicrobial urinary catheter for long-term use. Neurourol Urodyn. 2019; 38: 338- 345.
15. Zhao X, Drlica K. Restricting the selection of antibiotic-resistant mutants: a general strategy derived from fluoroquinolone studies. Clin Infect Dis. 2001; 33:S147-S156.
16. Belfield K, Kalith S, Aimar K, Parkinson R, Bayston R. Micro-organisms attached to the lumens and balloons of indwelling urinary catheters and correlation with symptoms, antibiotic use and catheter specimen of urine results. J Med Microbiol. 2019 Apr;68(4):549-554. doi: 10.1099/jmm.0.000946. Epub 2019 Feb 26. PMID: 30806614.
17. Belfield K. Characterisation and clinical studies of an antimicrobial urinary catheter for longterm use, PhD Thesis, University of Nottingham; 2018.

15. **APPENDICES**

15.1. Appendix 1 – Schedule of Assessments

See Also Figure 1

Procedures	Visit Number															
	Consent	Baseline	3	4	5	6	7	8	9	10	11	12	13	14	15	Additional
Informed consent	✓															
Demographics		✓														
Medical history		✓														
Physical examination of exit site			✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications		✓										✓			✓	
Assessment 1 (IPOS Renal and acceptability Questions)		✓							✓			✓			✓	
Assessment 2 (Basic bloods)				✓					✓	✓	✓		✓	✓		✓
Assessment 3, Enhanced Bloods		✓										✓			✓	
Adverse event assessments			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Foreseeable adverse events																Additional visit with treatment as per standard care, samples saved for Microbiology and or PD catheter assessment (if removed)

15.2. Appendix 2 – Amendment History

Amendment No.	Clinical investigation plan version no.	Date issued	Author(s) of changes	Details of changes made

15.3. Appendix 3 - IPOS Renal Questionnaire

15.4. Appendix 4 - PD Peritonitis Guideline

15.5. Appendix 5 - IPOS Analysis