The CATHETER II Study: Randomised Controlled Trial CompAring THE Clinical And CosT-Effectiveness Of VaRious Washout Policies Versus No Washout Policy In Preventing Catheter Associated Complications In Adults Living With Long-Term Catheters

PROTOCOL

A UK Collaborative Trial funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number 17/30/02)

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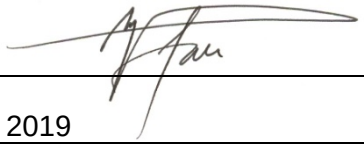
Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above trial.

CI [Mohamed Abdel-Fattah]:  signature

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VERSION HISTORY

Amendment no.	**Protocol version no.**	**Description of changes (*incl. author(s) of changes*)**	**Date of protocol**
n/a	Version 1	New protocol	26/09/2018
n/a	Version 2	Addition of informed consent of participant's carer, removal of the term 'aphasia'	12/02/2019
n/a	Version 3	Addition of increased washout frequency where indicated*;* removal of recruitment of participants who lack capacity to consent, removal of Scottish REC approval, definition of designated person added	12/03/2019
AM02	Version 4	Add email verification; delete 7.3.1 "or their proxy"; define hospitalisation for purposes of SAE; add eCRF source data statement; append authorship policy (Appendix 1); update volume of citric and saline washout; clarification of protocol if change of type and/or frequency of washout is indicated; clarification of protocol if prophylactic washouts indicated in control arm; addition of secondary outcome measure – discontinuation of catheter use; addition of secondary outcome measure – events of changing type and/or frequency (or cessation) of catheter washouts in arms B and C and rates of commencing on prophylactic washouts in arm A; prevalence of LTC use clarified in section 1.1; addition of IRAS number to footer; clarification of catheter *in situ* as a catheter in use for 28 days or more (sections protocol summary, 4.2, 5.2 6.3, 6.5); addition of subgroup analysis recumbent vs non-recumbent; addition of expected adverse events	08/08/2019

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PROTOCOL SUMMARY

Question addressed	What is the clinical and cost-effectiveness, patient acceptability and satisfaction, and safety of weekly prophylactic catheter washout policies in addition to standard long-term catheter (LTC) care compared to standard LTC care only in adults living with LTC?
Considered for entry	Adult men and women, who have been using a catheter for ≥ 28 days and for whom there is no plan for discontinuation of catheter use at the time of recruitment
Inclusion/Exclusion criteria	***Inclusion criteria:*** i. aged ≥18 years ii. able to undertake catheter washouts or has a designated person (relative, friend, other informal carer or paid/NHS healthcare worker) able to perform washouts iii. able to complete the trial documentation or has a designated person able to assist with trial documentation iv. any type and route of LTC can be included ***Exclusion criteria:*** i. intermittent self-catheterisation ii. pregnant or contemplating pregnancy iii. spinal cord injury at or above the sixth thoracic vertebra (T6) (risk of Autonomic Dysreflexia - AD) iv. ongoing S-CAUTI (until treatment is complete) v. visible hematuria (unless investigated/ treated) vi. known allergies to either of the catheter washout solutions vii. current bladder cancer (until treatment is complete) viii. known bladder stones (until treatment is complete) ix. unable to provide consent due to incapacity x. any other clinical and social reasons that would be deemed by the recruitment team to be unsuitable for the study
Interventions	1) **Intervention arm (A):** Saline washouts. A policy of weekly prophylactic normal saline (NaCl 0.9%) catheter washouts plus standard LTC care. 2) **Intervention arm (B):** Acidic washouts. A policy of weekly prophylactic acidic (Citric acid) catheter washouts plus standard LTC care. 3) **Control arm (C):** Standard LTC care only (i.e. no prophylactic catheter washouts)
Outcomes	The primary clinical outcome is catheter blockage requiring intervention up to 24 months post randomisation expressed as number per 1000 catheter days. The primary economic outcome is the incremental cost per quality adjusted life year (QALY) gained for each washout policy compared to standard LTC care only.
Co-ordination	**Local**: by local research teams **Central**: by Trial Office in Aberdeen (Telephone 01224 43xxxx). **Overall**: by the Project Management Group, and overseen by the Trial Steering Committee and the Data Monitoring Committee.

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
CDC	Centre for Disease Control and Prevention
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
EQ-5D- 5L	EuroQol Group's 5 dimension health status questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
GSE	General Self-Efficacy Scale
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ICIQ-LTCqol	International Consultation on Incontinence Modular Questionnaire – Long Term Catheter quality of life
ISD	Information Statistics Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
LTC	Long-term catheters
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NHSG	National Health Service Grampian
NICE	National Institute for Health and Care Excellence
NIHR	National Institute Health Research
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Patient Information Leaflet
PMG	Project Management Group
PPI	Patient and Public Involvement
PQ	Participant Questionnaire
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S-CAUTI	Symptomatic catheter associated urinary tract infections
SD	Standard Deviation
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
UC	Urinary Catheter
UI	Urinary Incontinence
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen

TRIAL PERSONNEL

Chief Investigator

1 Mohamed Abdel-Fattah

Trial Office Team

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2	CHaRT Director	8	
3	Trial Managers	9	
4	Data Co-ordinators	10	
5	Senior Trials Manager	11	
6	Senior IT Manager	12	

Project Management Group (PMG)

This Group is comprised of the grant holders along with representatives from the Trial Office team. The CI may invite experts in the field to serve as advisors for the PMG and attend relevant meetings as required.

Trial Steering Committee (TSC) Members

The membership of this Committee comprises independent members along with the Chief Investigator (CI) or a nominated delegate. The other CATHETER II grant-holders and key members of the Trial Office team (e.g. the trial manager) may attend TSC meetings.

Data Monitoring Committee (DMC) Members

This Committee is comprised of independent members, and the trial statistician contributes as appropriate. The CI and/or a delegate may contribute to the open session of the meetings as appropriate.

1. INTRODUCTION

1.1 Background

Transurethral indwelling catheterisation is defined as passage of a catheter into the urinary bladder for drainage of urine via the urethra (urethral catheter). In suprapubic catheterisation, a surgical operation creates an opening through the anterior abdominal wall directly into the urinary bladder, through which a catheter is inserted. Long-term catheters (LTC) are used by patients with conditions such as intractable urinary incontinence (UI) or chronic urinary retention. The latter can be secondary to variety of conditions such as: enlarged prostate, underactive bladder, neurological conditions such as spinal cord injury and multiple sclerosis[1, 2]. National Institute for Health and Care Excellence (NICE) CG139 recommends indwelling catheter for those who are unable to perform intermittent catheterisation or amenable to toileting[3].

There is no robust evidence to support a definition for the duration of catheter stay that constitutes a "long-term" catheter use. Evidence from the Cochrane review[2], indicate that the majority of studies defined LTC use as urethral or supra-pubic catheter in situ for >28 days and predicted use over 6-12 months. This definition was also used in the NICE CG139 [3]. LTC use may be for many years, Wilde et al[4] reported a mean duration of 6 years (SD 7) in 202 participants (median 3.25 years).

The exact prevalence of LTC use is not known[5]. A study of 11 European countries showed that in the UK, 3.8% of those aged ≥65 and receiving home care routinely use a LTC[6]. Kohler-Ockmore[7] surveyed three UK community districts and found LTC prevalence of 0.07% in adults >18 years, rising to 0.5% for those ≥75 years. 87% of the patients with a LTC had some form of chronic illness: cerebrovascular accident (26%), dementia (12%) and multiple sclerosis (11%); 26% of the patients were resident in nursing homes. The indication for catheterisation was UI in 59% and of these, 91% received a urethral catheter (UC)[7]. In 2013, the European Centre for Disease Prevention and Control conducted a point prevalence survey of healthcare-associated infections and antimicrobial use in 1181 European long-term care facilities. The mean prevalence of LTC use was 8.8%; the prevalence in England was 1.35%; Wales 5.27% and Northern Ireland 4.86%. Most recently, in May-July 2017 at the request of the trial team, colleagues in 6 English CRNs and from the Scottish Primary Care Research Network ran searches of primary care records which suggested a prevalence of 0.2-0.5% of the general population in the UK living with LTC, with approximately 20% living in care/ nursing homes. A more recent audit in Grampian showed 1045 patients with LTC on the caseload of District nurses teams i.e. prevalence of 0.26%.

LTC can be associated with several adverse events[4, 8] which affect the daily life of patients and can consume substantial NHS resources. Wilde et al reported typical adverse events of: LTC blockage (34%), symptomatic catheter associated urinary tract infections (S-CAUTI) (57%); accidental dislodgment (28%), urinary leakage (67%), bladder spasms (59%), kinks/twists (42%), and pain 49%[1]. LTC blockage and S-CAUTI in particular are physically and psychologically traumatic to patients and pose a substantial burden to NHS resources:

- **LTC Blockage** often occur secondary to the formation of encrustations on the luminal and outer surfaces of the catheter; with a prevalence of 40-50% in most studies[7, 9-11]. Wilde et al in 2017[1] assessed 202 patients with LTC over 12 months and showed blockage prevalence of 34% and rate of 8.54/1000 days of catheter-use.
  Current practice for the prevention and/ or management of LTC blockage is predominately two-fold: more frequent change of the catheter and/or the use of washout solutions (saline or acidic) to irrigate/ flush the catheter. The former imposes substantial workload on nursing staff and can be associated with higher risk of S-CAUTI, while the Cochrane review concluded that there is insufficient evidence to determine if prophylactic washout policies were beneficial or harmful[2].
- **S-CAUTI** secondary to bacteriuria or candiduria is another common problem in LTC users (57%)[1]. There are a number of definitions for S-CAUTI: the British Infection Association definition relies on clinical diagnosis only while the Centre for Disease Control and Prevention (CDC) definition incorporates systemic and localising clinical findings with laboratory-based criteria.[12] Pickard et al[13] in the CATHETER study defined S-CAUTI based on the development of symptoms and signs of UTI and prescription of antibiotics by the responsible clinician. This

is a modification of the CDC definition that is more pragmatic and relevant to patients and practice in the UK. In CATHETER II we opted to use the latter definition for SCAUTI.

Muncie et al[14] compared saline washouts versus no washouts policy over 24 weeks in a limited population and showed no significant differences in S-CAUTI/ 100 days of catheter-use. Concerns exist that use of washouts can damage the bladder mucosa and possibly increase risk of S-CAUTI. NICE CG139 recommend that "Catheter washouts must not be used to prevent catheter associated infections"[3]

1.2 Rationale for the trial

Several catheter washouts policies are used in clinical practice for prevention and/ or management of LTC blockage. Washouts used are of different types (normal saline, acidic, antimicrobial); volumes (50ml, 2 x 30mls and 100mls) and frequency of administration. The recent Cochrane review (2017) assessed the best available evidence and found insufficient evidence to determine whether prophylactic catheter washout policies had a beneficial or harmful effect on any of the outcomes in patients with LTC. The authors recommended a rigorous and methodologically robust RCT to assess the clinical and cost effectiveness of washout policies in patients with LTC.

2. TRIAL AIM AND OBJECTIVES

The aim of the study is to determine whether the addition of a policy of prophylactic catheter washouts on a weekly basis to the current standard LTC care improves the outcome of care for people living with a LTC in the UK.

Research question: What is the clinical and cost-effectiveness, patient acceptability and satisfaction, and safety of weekly prophylactic catheter washout policies in addition to standard LTC care compared to standard LTC care only, in adults living with LTC?

The hypotheses being tested are:

1) Does a policy of weekly prophylactic normal saline catheter washouts plus standard LTC care result in a relative reduction of 25% (or more) in catheter blockage requiring intervention compared to standard LTC care alone?
2) Does a policy of weekly prophylactic acidic catheter washouts plus standard LTC care result in a relative reduction of 25% (or more) in catheter blockage requiring intervention compared to standard LTC care alone?

3. TRIAL DESIGN

A pragmatic three-arm open multicentre superiority RCT comparing the clinical and cost-effectiveness, patient acceptability and satisfaction, and safety of weekly prophylactic catheter washouts policies in addition to standard LTC care compared to standard LTC care only, in adults living with LTC.

3.1 Interventions

The interventions being compared are:

- **Intervention arm (A):** Saline washouts. A policy of weekly prophylactic normal saline (NaCl 0.9%) catheter washouts plus standard LTC care.
- **Intervention arm (B):** Acidic washouts. A policy of weekly prophylactic acidic (citric) catheter washouts plus standard LTC care.
- **Control arm (C):** Standard LTC care only (i.e. no prophylactic catheter washouts)

4. TRIAL RECRUITMENT

4.1 Trial population

This trial is taking place in approximately 70 sites: GP practices, care homes, secondary and tertiary care units in England, Wales and Scotland. We are recruiting six hundred men and women living with LTC and meeting the following criteria:

4.2 Inclusion and exclusion criteria

Inclusion criteria:

- aged ≥18 years
- catheter has been in use for ≥28 days
- no plan for discontinuation of LTC at the time of recruitment
- able to undertake catheter washouts or has a designated person (relative, friend, other informal carer or paid/NHS healthcare worker) able to perform washouts
- able to complete the trial documentation or has a designated person able to assist with trial documentation
- any type and route of LTC can be included

***Exclusion criteria*:**

- intermittent self-catheterisation
- pregnant or contemplating pregnancy
- spinal cord injury at or above the sixth thoracic vertebra (T6) (risk of Autonomic Dysreflexia - AD)
- ongoing S-CAUTI (until treatment is complete)
- visible hematuria (unless investigated/ treated)
- known allergies to either of the catheter washout solutions
- current bladder cancer (until treatment is complete and patient discharged from cancer surveillance program)
- known bladder stones (until treatment is complete)
- unable to provide consent due to incapacity
- any other clinical and social reasons that would be deemed by the recruitment team to be unsuitable for the study.

4.3 Identifying and approaching participants

We are recruiting participants from primary care (GP practices), secondary and tertiary care hospitals, community hospitals and care homes including nursing homes. Recruitment strategies differ between sites depending on local geographic and NHS organisational factors.

4.3.1 Primary care

In England, recruitment from primary care may be conducted in conjunction with the appropriate division of the Local Clinical Research Networks (LCRN).

General Practice (GPs) can act as an independent site or as Participant Identification Centres (PICs) for a recruiting GP site. For GPs or GP Federations acting as independent study sites and GP acting as PICs; the LCRN/collaborating centre liaises directly with GP practice managers/GPs/community nursing team/district nurses (DN)/ local DN nursing team leaders who undertake a database search (based on eligibility criteria described above) to identify potential participants. Potentially suitable participants are sent an invitation letter on practice headed paper and a short PIL, as a brief introduction to the study, informing them of the trial aims and level of participation required. A member of the GP practice/ LCRN team may follow with a phone call in few days to answer any questions and see if the potential participant is interested and arrange a recruitment visit. The letter will also provide a range of methods for interested potential participants to contact the trial team (telephone, text, e-mail, reply paid envelope depending on local arrangements) for more information and to arrange a recruitment visit if the potential participant is interested in taking part in the trial.

In Scotland the Scottish Primary Care Research Network mirrors the role undertaken by the LCRN by identifying potential participants in primary care.

Other potential avenues for identifying eligible patients include general practitioners; DNs, community nursing teams and continence teams approaching potentially eligible individuals within a consultation. As above, potentially eligible patients are provided with an invitation letter on headed paper and short PIL.

All potential participants who express an interest in taking part will receive the fully comprehensive CATHETER II PIL as per section 4.4.1

4.3.2 Care homes

A member of the trial team makes the initial approach to local care homes to determine whether they are willing to be involved in the study. The care home is provided with a CATHETER II study information pack, if they are interested in taking part, a visit to discuss the study can be arranged. If the care home agrees to take part the care home manager identifies potentially eligible individuals. These individuals are approached to see if they are interested in participating in the study. If they are interested, the research team provides a study information leaflet (PIL) to consider study participation and follow the same process described above.

4.3.3 Secondary/tertiary care and community hospitals

A large number of patients are seen in Accident and Emergency departments with blocked catheters or catheter bypassing. The CRN and collaborating centres can liaise with research-active departments and A&E teams to approach eligible patients who will be provided with an invitation letter on headed paper and PIL. Similarly, Urology specialist nurses are a port of call for district nurses and GPs for advice and help on community patients with blocked catheters. Such patients are also seen in Urology and Care of the Elderly outpatient clinics and wards. Eligible patients identified will be provided with an invitation letter on headed paper and PIL.

Participants identified within secondary/tertiary care are recruited either in secondary/tertiary care or within primary care.

In both primary and secondary care, docmail (http://www.docmail.co.uk/) can be used to mail invitation letters and study information to potential participants. Docmail is an online hybrid mail toolkit that it is used in the NHS to mail letters and other documents to patients.

Across all settings potential participants are asked whether they need the help of a relative, friend or other informal carer, who is not a paid healthcare worker or NHS staff, to take part in the CATHETER II study. If they indicate that they need or have help with their catheter care and/ or will need help completing the trial documentation then the study team approaches the identified person to take part also. The relative, friend or other informal carer is given a comprehensive PIL so that they can consider participation.

4.4 Informed consent

Informed consent to participate in the trial will be sought and obtained according to Good Clinical Practice (GCP) guidelines. Procedures to seek and gain informed consent from eligible potential participants and their relative, friend or other informal carer are agreed and confirmed by Research Ethics Committees with responsibility for reviewing applications for research. The application for approval is made via the National Research Ethics Service in England/Wales.

4.4.1 Potential participants

Potential participants are given ample time to read and understand the fully comprehensive CATHETER II PIL. A pictorial and simple text information are also available to help explain the study. All potential participants are given opportunity to ask questions and have these answered before giving their informed decision on whether to join the study and sign the study consent form.

Signed consent forms are obtained in all centres by an appropriately trained member of the local research team who is listed on the delegation log. The participant's permission is sought to inform

their GP that they are taking part in this trial. Potential participants are also informed in the patient information leaflet that their contact details will be used to send them the washout solutions (if they are randomised to one of these arms), and that contact details will be shared with the courier company or Royal Mail who will deliver the washout solutions.

Consent forms that are returned by post are checked, signed and dated with the date of receipt. No study specific activities take place before consent is given.

4.5 Baseline assessment

All interested potential participants receive an initial contact by the local research team who assesses the participant's eligibility including the participant's and/or relative's, friend's or informal carer's capabilities of self-administered care. Eligibility can be confirmed by a medically trained individual, member of the immediate care team or care-home team.

Following consent, the local research team and participants with or without the assistance of their relative, friend or informal carer will complete the baseline information and measures, and participants will provide a urine sample for pH testing (full details section 6.2). Consented participants are randomised as per the procedure.

4.6 Randomisation and allocation

Participants are allocated to one of the three trial arms using a centralised computerised randomisation system created by CHaRT.

Random allocation uses the minimisation covariates: Region; gender; age (< 45year, 45-64 years and ≥65 years); residential status (care home vs community); previous blockages requiring intervention in last 6 months (0 vs ≥ 1); previous S-CAUTI requiring antibiotics in last 6 months (0 vs ≥ 1); Urine pH (normal vs acidic vs alkaline).

Participants will be randomised 1:1:1 to one of the following:

- **Intervention arm (A):** Saline washouts. A policy of weekly prophylactic normal saline (NaCl 0.9%) catheter washouts plus standard LTC care.
- **Intervention arm (B):** Acidic washouts. A policy of weekly prophylactic acidic (Citric acid) catheter washouts plus standard LTC care.
- **Control arm (C):** Standard LTC care only (i.e. no prophylactic catheter washouts)

Where deemed clinically necessary by the doctor / nurse in charge, the pragmatic design of the study permits the following changes to the washout policies:

- An increase in the frequency of the LTC washouts, at the onset of the study or following regular review during the course of the study
- A change in the type of washout, at the onset of the study or following regular review during the course of the study
- The use of prophylactic washouts in the control arm, following regular review during the course of the study (but not at the onset of the study)

These changes will be implemented and any reasons for the change recorded in the medical notes and study records. The participant will remain in the study and be followed up as per protocol.

Participants are randomised only after eligibility is confirmed and following consent.

The Principal Investigator (PI) at site, or member of the local research team (with delegated authority), accesses the web based system. Minimisation characteristics are entered into the web-based system, which returns the allocation status. Participants are informed of their allocated pathway following randomisation. If the participants are not present at the time of randomisation,

they are contacted by the research team to inform them of the allocated pathway after randomisation.

4.7 Delivery of the intervention

There are no restrictions on the type or route of LTC used. All participants receive their written standard LTC care plan from their local health team as per standard care – this may differ according to region/ country e.g. Catheter Passports are used in Scotland. If a participant does not have a written standard LTC care plan, the research team inform the local healthcare team and recommend that such plan should be in place as soon as practical. The research team also sign post the local healthcare team to the current guidelines from the government, national bodies and NICE[3]. Its best practice for the standard LTC care plan to include advice on: adequate hydration, securing the catheter position, avoidance of catheter kinking, how often the catheter and the catheter bag/valve need to be changed, advice on how to prevent and manage complications and the contact details of the participant's healthcare team (nurse in charge) in case they need to contact for catheter related complications.

All participants continue their ongoing regular review by their local healthcare team as per standard NHS care.

Study arms A (Saline washouts) and B (Acidic washouts):
In addition to standard LTC care described above, participants/ designated persons are asked to use catheter washout on weekly basis using 100 mls of normal saline (NaCL 0.9%) solution (study arm A) or 2 x 30ml of acidic solution (citric acid 3%; study arm B). Participants and/or their relative, friend or other informal carer are provided with a leaflet explaining the best practice technique in performing LTC washouts with special attention to minimise the breakage of the closed drainage system integrity.

Participants and/or their relative, friend or other informal carer receive additional training to enable them to self-administer the LTC washout. Training is delivered by their DN or an appropriately trained member of the local study team (1-2 hours) at the participant's home, GP practice, other appropriate setting (whichever is most suitable). This may be repeated to ensure mastery of the best practice technique described below. LTC washout is a simple procedure undertaken at the same time as the LTC bag/ valve change. Previous research has shown that this technique is rarely a barrier to participation [15, 16]. Our survey of community and urology nurses indicated that the technique can be mastered after 1-3 hours of training for the majority of participants. Participants or relatives, friends or other informal carers having difficulties with the washout technique can be offered more training. The need for more is monitored in the pilot study.

If a health professional (nurse or health care assistant) usually changes the LTC bag/ valve for a specific participant (for special medical or social indications especially those in care homes) then they will be asked to undertake the above training and perform the washouts within the study.

Participants will receive the catheter washouts free of charge on regular intervals (up to 6 deliveries over 24 months) through a courier or Royal Mail.

4.8 Administration arrangements post-recruitment

Following trial entry, the trial office:

- Informs the participant's GP of the randomised allocation (by letter enclosing information about CATHETER II and Study Office contact details) if the participant consents for this
- Informs the participant and relative, friend or informal carer (if applicable) of the randomised allocation

The local research team:

- Give a copy of the consent form to the participant and relative, friend or informal carer (if applicable)

- File a copy of the consent form/s in the relevant medical notes (primary care or secondary care or care home, depending where the patient is recruited) along with information about the trial
- Enter trial data regarding the participant into the bespoke trial website
- Maintain trial documentation at site
- Return a copy of the signed consent form/s to the Trial Office in Aberdeen.

5. OUTCOME MEASURES

5.1 Primary outcome measure

The primary clinical outcome is catheter blockage requiring intervention up to 24 months post randomisation expressed as number per 1000 catheter days.

- Intervention is defined as any of the following: unplanned catheter removal or change or washout performed by the participant/ designated person or required unplanned visits to/from any healthcare provider, or hospital admission.

The primary economic outcome is the incremental cost per quality adjusted life year (QALY) gained for each washout policy compared to standard LTC care only.

5.2 Secondary outcome measures

Secondary outcomes include:

- S-CAUTI requiring antibiotics use (as defined by Pickard et al[16])
- Duration of LTC in use, catheter change due to other reasons than blockage
- Adverse events
- Hospital admissions, GP/ nurse outpatient visits for catheter related complications
- Generic quality of life as assessed by EQ-5D-5L[17] (EuroQol questionnaire – 5 dimensions – 5 levels)
- Condition specific quality of life assessed by ICIQ-LTCqol[18] (International Consultation on Incontinence Modular Questionnaire – Long Term Catheter quality of life)
- Adherence to allocated interventions
- Patients' convenience and satisfaction assessed by an adapted version of the abbreviated Treatment Satisfaction Questionnaire for medication[19]
- Impact on day to day activities using The General Self-Efficacy Scale (GSE)[20] and ICECAP-A (ICEpop CAPability measure for Adults) (≤ 65 years) or ICECAP-O[21] (ICEpop CAPability measure for Older people) > 65 years
- Time and travel costs for patients and their relatives, friends or informal carers
- Discontinuation of catheter use
- Events changing type and/or frequency (or cessation) of catheter washouts in arms B and C and rates of commencing on prophylactic washouts in arm A.

Qualitative study outcomes:

- Participants' experience of LTC-related AEs such as blockage, S-CAUTI, urinary incontinence, bladder pain
- Participants' attitudes/ preferences to washout versus no washout policies and expected outcomes (prior to randomisation or knowing their allocated study group) (acceptability);
- Participants' experience with washout/ no washout policies and evaluation of outcomes (satisfaction)
- Clinicians attitudes towards influence of washout policies on outcomes
- Participants' and clinicians' experience of training provided and enactment of the treatment skill. This would clarify the fidelity of the intervention.

6. DATA COLLECTION AND PROCESSING

6.1 Measuring outcomes

Table 1 summarises what outcomes are assessed at the time points of assessments. Further details about collection of outcome data are provided elsewhere in this section.

Table 1: Source and timing of measures

Measure	**Source**	**Randomisation**				
		Pre*	**Post**			
Catheter blockage requiring intervention S-CAUTI requiring antibiotics Catheter change Adverse events NHS/Healthcare use	D & CRF		Monthly completion for 24 months			
			Months			
			6	**12**	**18**	**24**
EQ-5D-5L	PQ	✓	✓	✓	✓	✓
ICIQ-LTCqol	PQ	✓	✓	✓	✓	✓
GSE Scale	PQ	✓	✓	✓	✓	✓
ICECAP-A or O	PQ	✓	✓	✓	✓	✓
Satisfaction with treatment	PQ	✓	✓	✓	✓	✓
Participant/ relative, friend or informal carer's time and travel	PQ				✓	

CRF = Case Report Form, D = LTC Diary/Calendar; PQ = participant/ relative, friend or informal carer completed questionnaire. *Pre randomisation is after informed consent has been given but prior to randomisation

6.2 Baseline data (data collected prior to random allocation to treatment)

Participants with or without the assistance of their relative, friend or informal carer complete the baseline questionnaire prior to randomisation. The baseline questionnaire includes the EQ-5D-5L, the ICIQ-LTCqol, GSE Scale and the ICECAP-A or ICECAP-O. A catheter urine sample for pH testing will obtained from all participants and tested immediately using the simple urine dipstick test.

The local research team completes the baseline CRF which includes the following information: gender; age, residential status, neuropathic bladder; previous blockages requiring intervention in last 6 months; previous S-CAUTI requiring antibiotics in last 6 months and other catheter-related history.

6.3 Follow-up

Participants (or the relative, friend or informal carer carrying out the washout) record LTC related events on their LTC calendar/diary including: LTC blockage requiring intervention (as defined in section 5.1); LTC change and the reason; adverse events such as S-CAUTI; antibiotics use for S-CAUTI; emergency catheter washout and its indication; treatments in primary or secondary care. The CATHETER II LTC diary is adapted from a purpose built diary that has been successfully used in an RCT in this field (permission already obtained from Wilde et al 2017[1])

The primary outcome, a number of the secondary outcomes, adverse events, and adherence are collected approximately monthly for 24 months from the participant and/or the relative, friend or informal carer carrying out the washout. A member of the research team, as delegated, completes the CRF over the phone or by agreed methods e.g. post/ email. A face to face interview will be arranged by the research team if/ when appropriate e.g. significant missing data from the monthly

contact. Where local site teams capture follow up information directly to the CATHETER II electronic CRF, the electronic record is the source data.

The EQ-5D-5L, the ICIQ-LTCqol, GSE Scale and the ICECAP-A/ or ICECAP-O and satisfaction with treatment are completed by participants with or without assistance from their relative, friend or informal carer at 6, 12, 18, and 24 months after randomisation.

Participants and their relative, friend or informal carer, if applicable, are asked to complete a time and travel questionnaire at 18 months after randomisation. This is to be used to estimate costs to participants.

We offer and use all methods of delivery and collection of questionnaires and reminders including use of research teams, telephone, post, e-mail (e-mail verification is used to validate e-mail addresses), and web based taking into account each participant and/or their relative, friend or informal carer(if applicable) stated preferred means of receiving and completing the measures (recorded on the contact preference form). One reminder for the questionnaire is sent to participants and their relative, friend or informal carer, if applicable, by post, email, or phone taking into account any preferences they may have for mode of communication.

A small token of appreciation (shopping voucher(s)) is sent to participants on receiving their completed follow up questionnaires, unless they opt out on the study consent form.

If a participant stops using a long-term catheter (no catheter in use) >=28 days, all data collected up to the point of stopping long term catheter use are retained and used in the analysis. We will ask these participants with or without the assistance of their relative, friend or informal carer, if applicable, to complete one further (exit) EQ-5D-5L with one reminder.

6.4 Future research, including long term follow-up

We plan to seek funding and the necessary approvals for future research or to follow up CATHETER II participants. We will ask for their permission to be contacted about such studies. The PIL informs the participants of this (and that we would hold their details for 10 years after the end of the study to facilitate this).

6.5 Change of Status/Withdrawal procedures

Participants are free to withdraw their consent to participate at any time.

Participants are followed up for the trial outcomes wherever possible. If a participant does not receive or continue with their allocated intervention, either because of participant preference or change of circumstance, they continue to participate as per trial data collection schedule unless the participant declines to participate in the data collection schedule.

All data collected up to the point of complete withdrawal are retained and used in the analysis. Participants who do not complete their trial follow up but for whom any outcome data are available are included in the study analysis.

If a participant stops using a long-term catheter (no catheter in use >=28 days), all data collected up to the point of stopping long term catheter use are retained and used in the analysis. We will ask these participants with or without the assistance of their relative, friend or informal carer, if applicable, to complete one further (exit) EQ-5D-5L with one reminder.

6.6 Data processing

Local study team members as listed on the delegation log can enter locally collected data. Staff in the Trial Office work closely with local study team to ensure the data is as complete and accurate as possible.

7. SAFETY

7.1 Standard definitions

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE is considered for severity, causality or expectedness and may be reclassified as a serious adverse event based on prevailing circumstances.

A **serious adverse event** (SAE), is any AE, that:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation*;
- results in persistent or significant disability or incapacity;
- is otherwise considered medically significant by the investigator.

*Hospitalisation is defined as an overnight hospital admission.

7.2 Trial specific considerations

In this trial, the following events are expected and are reported as SAEs:

- Bacteraemia/ urosepsis
- Pyelonephritis
- Allergic reactions
- Erosion (tearing) of the urethra, primarily the urinary meatus
- Creation of a false passage/ urethral fistula
- Autonomic dysreflexia
- Damage to rectum/ peritonitis
- Urethritis
- Epididymitis.

In this trial, the following events are anticipated and are captured as primary or secondary outcomes rather than being captured through adverse event or serious adverse event reporting processes.

- Catheter blockage
- S-CAUTI
- Urinary retention
- Catheter change due to other reasons such as S-CAUTI, Urinary Leakage
- Catheter twists/ kinking/ dislodgement
- Bladder pain/ spasm
- Haematuria/ pyuria
- Urethral trauma/ bleeding
- Urinary bypass/ urinary leakage/ urinary incontinence
- Bladder stones
- Urethral stricture/ narrowing
- Irritation.

Hospitalisations or prolongations of an existing hospitalisation due to any of the LTC related events listed within the primary or secondary outcomes will not be considered or recorded or reported as an SAE. They are recorded as outcomes and regularly reviewed/ monitored by the DMC.

Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered or recorded or reported as an SAE. Complications occurring during such hospitalisation will also not be considered, recorded or reported as an SAE.

In this trial, all other SAEs that are related to the catheter and associated washout procedures are recorded. In addition, all deaths (any cause) are also recorded as SAEs. Events that are serious but are not related to the catheter or associated washouts will not be recorded as SAEs.

7.3 Procedures for detecting, recording, evaluating & reporting AEs, SAEs

7.3.1 Detecting AEs and SAEs

All SAEs meeting the criteria for recording within the CATHETER II study (see section 7.2) are recorded from the time a participant consents to join the CATHETER II study until their last trial follow-up. The Investigator asks about the occurrence of relevant SAEs (i.e. those that meet the criteria for recording within the CATHETER trial) at every contact with the participant or the designated person carrying out the washout.

7.3.2 Recording AEs and SAEs

When an SAE meeting the criteria for recording within the Catheter II trial occurs, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. If an SAE is recorded on a participant questionnaire, the Trial office liaises with primary/secondary care to obtain further information if appropriate.

The Investigator (or delegate) will then record all relevant information about SAEs in the relevant form.

7.3.3 Evaluating AEs and SAEs

Seriousness, relatedness (causality), and expectedness is evaluated by a medically qualified individual either at the recruitment site or the Chief Investigator or delegate).

Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined above.

Assessment of Relatedness (causality)

The Investigator will make an assessment of whether the SAE is likely to be related to research procedures according to the following definitions:

- **Related**: resulted from administration of a procedure required by the protocol, whether or not it is either a) the specific intervention under investigation or b) it is administered outside the study as part of normal care.
- **Unrelated**: where an event is not considered to have resulted from any of the research procedures.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment are considered.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 7.2).

7.3.4 Notification and reporting AEs and SAEs

Site staff are responsible for notifying the trial office of SAEs meeting the criteria for recording within the CATHETER II trial.

When an SAE form is uploaded onto the trial website, the Trial Manager is automatically notified. If, in the opinion of the local PI and/or the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager notifies the Sponsor within 24 hours of receiving the signed SAE notification. The Sponsor provides an assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity is resolved by further discussion between these parties.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

7.3.5 Regulatory reporting requirements

The CI or delegate reports any SAEs that are related to any of the research procedures and unexpected to the REC within 15 days of the CI becoming aware of it using the HRA SAE form. The CI or delegate is responsible for submitting annual reports to the REC on the anniversary of the approval.

All SAEs recorded within the study are summarised and reported to the Ethics Committee, the Funder, the Trial Steering Committee and the Data Monitoring Committee in their regular reports. In addition, adverse events captured as secondary outcomes (in particular S-CAUTI) will be regularly summarised and reported to the Data Monitoring Committee in their regular reports or earlier if indicated.

8. SAMPLE SIZE AND PROPOSED RECRUITMENT RATE

8.1 Sample size

We have used information from a survey of experts and patients and also from available literature to decide that for washouts to be worthwhile there must be a reduction in LTC blockage of 25%.[1] (and personal communication). In our case this would be a reduction in the rate of blockage from 11.8 per 1000 days to 8.9 per 1000 days. Participants will be followed up for 2 years. The trial has 90% power and significance level 2.5%. The number of blockages has a negative binomial distribution with dispersion parameter 0.6. Recruiting 200 participants per arm allows for approximately 50 out of 730 loss to follow-up days. All available days of follow-up are to be used. The formula from Zhu and Lakkis[26] was used to calculate the sample size for comparing two negative binomial rates.

8.2 Recruitment rates

Our recruitment projection is based upon estimates of expected number of eligible participants from electronic primary care records provided by our 6 supporting CRNs in May-July 2017 (North & Cumbria; South West Peninsula; North West; Eastern; North East, & West of Scotland). We expect to recruit a mix of small and large primary care (GP) practices (n=46-50) from which the majority of participants (60-70%) are recruited. From the results of our survey and data from Kohler-Ockmore et al[7], we anticipate recruiting 15-20% of our population from care homes (n=10-12 care homes), and 15-20% participants from 10-12 secondary and tertiary care units (urology, care of the elderly and neurology wards).

Our recruitment projection is based upon estimates of 70 sites, each recruiting 10-11 per centre for 6-8 months to achieve our target of 600 participants over the 18 month recruitment period. The 18 month recruitment period allows for a staggered site set up and 50% lower recruitment during peak holiday times (Christmas, and summer).

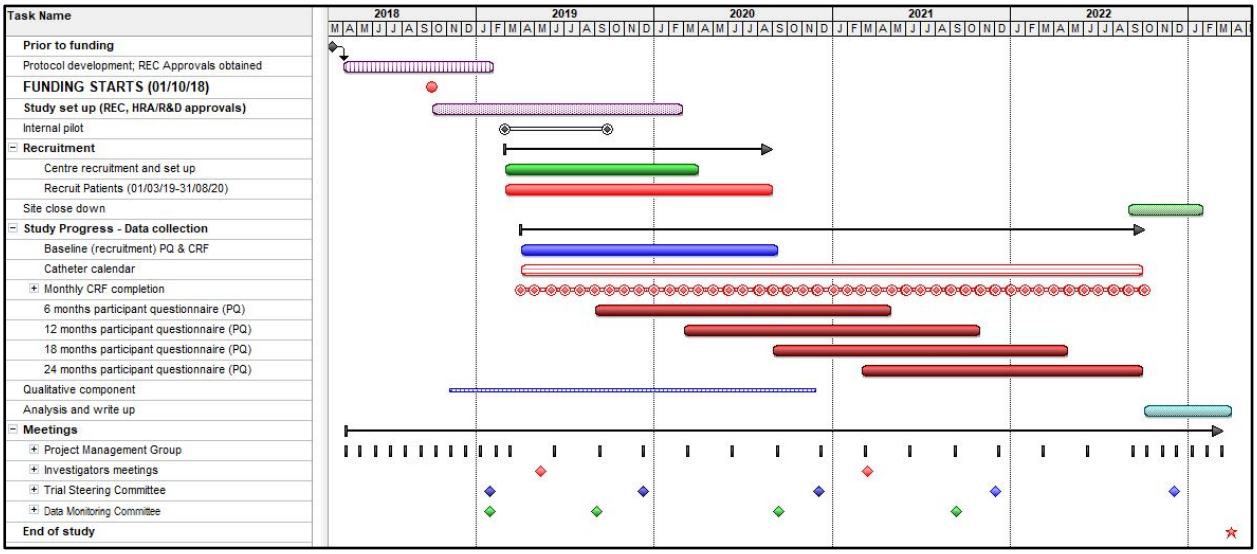
Figure 2: Projected participant recruitment and centre start up

8.3 Project timetable and milestones

The study duration is 54 months including an internal pilot phase.

Study Milestones
Months: 1-5: study initiation, NHS approvals; start site set up;
Months: 6-18: staggered site start up; establish study in 70 centres;
Months: 5-23: identify and recruit participants;
Months: 24-48: complete 24 months follow up;
Months: 49-54: close down, analysis, report writing.

Figure 3: Gantt chart of trial progress:



8.4 Internal pilot study

The internal pilot study (with stop/go criteria) is designed to establish whether the projected recruitment rate is achievable. We aim to set up the first 3 sites in calendar month 6, and then over the following 5 months open a further 28 sites, with a total of 31 site by the end of study month 11. By this time we aim to have recruited 100 participants. Considering the number randomised per month from each site as following independent Poisson distributions with mean and variance 0.9; then we can say:

1) If we recruit at least 80 within the 111 centre months; we are within 2 standard deviations (SD) of the expected 100 and recruitment can continue without modification;
2) If we recruit between 60 and 80; we are between 4 and 2 SD of the expected 100. We would need to modify the recruitment approach – for example, recruiting more centres, or allowing for more recruitment time at a centre, (setting up centres more quickly and/ or adding some extra months to lengthen the recruitment at the best recruiting centres). We would continue to monitor recruitment carefully to ensure that these recovery manoeuvres had worked.
3) If we recruit less than 60 we would be >4 SD from our target and we would enter discussions with the funder to determine whether the RCT is feasible.

During the pilot phase we are measuring the adherence to the intervention policies. That is the frequency of prophylactic washout in arms A and B. We would expect at least 80% of participants to be undertaking 60% of their washouts. If this threshold is not met, to improve it we may consider adapting or offering more training sessions.

9. STATISTICAL ANALYSIS

An appropriate summary of the baseline data is planned. A negative binomial regression using the log of the number of the days catheterized as an offset is to be used to analyse the primary outcome. Appropriate generalized linear models are chosen for the secondary outcomes and all regressions are adjusted for the minimization covariates. An intention to treat analysis is chosen and this is fully described in the statistical analysis plan. A per-protocol analysis will also be done as a sensitivity analysis.

Planned subgroup analyses: The following subgroup analyses are planned

- Women vs men
- Neuropathic bladder vs. non-neuropathic bladder
- Age groups: <45 vs. 45-64yrs vs. >65
- Participants with no history of LTC blockages versus those with recurrent blockages
- Participants with no history of S-CAUTI vs those with recurrent S-CAUTI
- Participants with baseline urinary pH: normal range vs alkaline vs acidic
- Participants who are recumbent vs. those who are non-recumbent

All subgroup analyses include an interaction between the subgroup and treatment and are at the 99% significance level.

Proposed frequency of analyses:
One definitive analysis is planned at end of the follow-up phase.

10. ECONOMIC EVALUATION

An economic evaluation is integrated into the trial and includes both a trial based analysis and a modelling exercise to extrapolate the results over the patient's lifetime. Outcomes and costs are assessed from the perspective of the NHS and patients. The alternatives compared are standard LTC care (current practice) and the catheter washout policies using either saline or acidic washout solutions. According to current NICE guidelines (NICE 2013) an annual discount rate of 3.5% is to be applied to all costs and health benefits incurred beyond year one.

10.1 Costs of intervention and any primary or secondary resource use

Resource use and associated costs incurred over the 24 month follow-up period of the trial are captured using the data collection instruments. The number of catheter blockages and adverse events are collected using the patient dairies and follow-up CRF phone calls by the research nurses. The level of resource use associated these events are recorded in detail during on the follow-up nurse CRFs; e.g. use of community health services, prescribed medications, use of secondary outpatient services, hospital admissions etc. Estimates of resource utilisation associated with LTC use and adverse events are to be combined with national unit cost data to estimate costs of health and social care. [22, 23] Costs associated with resource use are summed

across the follow-up period for each patient, to generate a total cost to the health service per patient. A secondary analysis also considers costs to patients and their relative, friend or informal carer. This utilises data on patient and relative, friend or informal carer time required to engage with the interventions and unplanned use of health services, in combination with costs associated with alternative uses of time. [24,25]

10.2 Health benefit measurement

Effectiveness in economic evaluation is measured in terms of quality adjusted life years (QALYs) gained for each washout policy compared to standard LTC care. QALYs are derived using response data from EQ-5D-5L administered at baseline, 6, 12, 18 and 24 months as part of the study questionnaires. EQ-5D response data are to be converted into health state utilities using UK population tariffs.[27] QALYs are calculated using an area under the curve approach, applying linear interpolation between the health state utility scores at baseline and the follow-up time points. Participants who die within the study follow-up period are to be assigned a zero utility weight from time of death.

10.3 Analysis of trial data

Multiple imputation methods are to be used to handle missing cost and utility data. The incremental cost-effectiveness ratio (ICER), calculated as the ratio of the difference in mean costs and QALYs between the alternative strategies, is to be estimated using generalized linear models with adjustment for minimisation variables and, where appropriate, baseline measures. Uncertainty surrounding the joint differences in mean costs and effects are to be characterised using non-parametric bootstrapping, and presented graphically on the cost-effectiveness plane and using cost effectiveness acceptability curves (CEAC). Sensitivity analysis is to be used to explore the impact of deterministic assumptions on the results of the economic analysis.

10.4 Long term extrapolation

A Markov decision model is to be developed to estimate cost-effectives over a longer time horizon (e.g. the participant's lifetime). The model is to be populated based on the analysis of individual patient data from the trial, supplemented where necessary with published and unpublished evidence in the field. The model will simulate the incidence of first and subsequent catheter related complications based on the statistical analysis of the trial primary and secondary outcomes. Separate analyses will estimate the mean additional cost and, if feasible, the marginal utility decrement associated with incident complications. These estimates are to be combined with the complication incidence rates in the model to extrapolate ongoing cost and effects. The model will also account for the costs of long-term catheter care as per treatment allocation. Where supplemental external data are required to inform the model, focussed literature reviews will be used to identify sources most relevant to the UK NHS context. Parameter and other forms of uncertainty are to be addressed in the model analysis using probabilistic and deterministic sensitivity analysis.

11. EMBEDDED QUALITATIVE WORK

Aims: A qualitative component is included to evaluate the participants' experiences of LTC-related AEs and their attitudes to and experiences of catheter washout (including training). Clinicians' views on washout policies and training will also be evaluated.

The five main aims of the qualitative work package are to explore:

1. Participants' experience of LTC-related AEs such as blockage, S-CAUTI, urinary incontinence, bladder pain
2. Participants' attitudes and preferences to washout versus no washout policies and expected outcomes (prior to randomisation or knowing their allocated study group)
3. Participants' experience with washout/ no washout policies and evaluation of outcomes
4. Clinicians attitudes towards influence of washout policies on outcomes
5. Participants' and clinicians' experience of training provided and enactment of the treatment skill.

Methods:

Catheter User Group interviews:

Consent to be contacted by the qualitative research team will be sought from participants in the CATHETER II study at time of the main study consent process. Once consent to be contacted has been given, a study information pack comprising a participant information sheet and a consent form will be given/sent to those individuals by the research nurse/study team.

Following receipt of the consent, participants will be contacted by the qualitative research team to confirm participation, answer any participant queries and arrange an appropriate time for interview. Agreement to participate in the interview will be confirmed verbally at the start of each interview.

Face-to-face and telephone interviews will be conducted with participants recruited to the catheter user group. These will be conducted by an experienced qualitative researcher. The interviews will be semi-structured and the topic guide will be informed by discussions between the study team, the scientific literature and the existing patient interviews on www.healthtalk.org with regards to the aims above (pre randomisation / commencing treatment and 6-12 months in to the study). Interviews will be recorded and transcribed verbatim. Consent to record the interviews, to have the recordings of interviews transcribed by an external provider to the University and to use anonymised quotations from interview transcription for publication will be sought as part of the consent process.

Purposive (non-probability) sampling will be used to ensure the diverse characteristics of the population sampled (e.g. age, sex, recurrent blockage, arm of study). It is anticipated a minimum of 30 to 40 interviews will be undertaken to effectively capture the opinions of those in all arms of the study. We aim to capture the same group at each time point.

Clinician Focus Groups:

Approximately twenty health care workers (including GPs, nurses, and care home staff]) will take part in focus groups to explore attitudes towards washout policies and views on likely outcomes (6 - 12 months in to the study). Focus groups will be recorded and transcribed verbatim (including descriptions of non-verbal factors). The group of health care workers will be recruited from those involved in the main CATHETER II study (recruitment to the study or delivery of the study). Consent to be contacted by the qualitative research team will be sought from clinicians in the CATHETER II study once the study has been underway for 4-6 months. Once consent to be contacted has been given, a study information pack comprising a participant information sheet and short demographic questionnaire will be given to those who express an initial interest to participate in the qualitative study.

Individuals can confirm participation by completing the reply slip on the PIL. Alternatively, individuals may be contacted by the qualitative research team to confirm participation, answer any participant queries and arrange an appropriate time for the focus groups. Written, informed consent will be obtained from all participants at the start of each focus group. The topic guide for the focus groups will be informed by discussions between the study team, the scientific literature and the existing patient interviews on www.healthtalk.org with regards to the aims above (6-12 months in to the study). Focus groups will be recorded and transcribed verbatim. Consent to record the focus groups, to have the recordings of focus groups transcribed by an external provider to the University and to use anonymised quotations from focus groups transcription for publication will be sought as part of the consent process.

The interview and focus group transcripts will be analysed using an explicit, structured qualitative method of thematic analysis. This method, called ‘Framework’ analysis, employs a number of distinct but interconnected stages in a systematic process. The 5 key stages are: familiarisation of the data; identifying a thematic framework; indexing themes; charting; mapping and interpretation. NVivo (version 10) will be used to support the analysis of qualitative data**.**

12. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 Trial office in Aberdeen

The Trial Office is based in the Centre for Healthcare Randomised Trials (CHaRT) within the Health Services Research Unit, University of Aberdeen. The Trial Office provides day to day support for the study sites. The Trial Manager take responsibility for the day to day transaction of trial activities, for example approvals, site set-up and training, oversight of recruitment and follow-up. The data co-ordinator provides clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal).

The Trial Office team meets formally at least monthly during the course of the trial to ensure smooth running of the trial.

12.2 Local organisation in sites

The PI and local study team at each site are responsible for all aspects of local organisation including identifying potential recruits, consenting, completing and maintaining appropriate documentation. The site agreement documents the full list of responsibilities for sites. Appropriate members of the local team are knowledgeable about the protocol and have appropriate Good Clinical Practice (GCP) training if applicable. A trial-specific delegation log is prepared for each site, detailing the responsibilities of each member of staff working on the trial. The local team is also responsible for notifying SAEs to the Trial Office (see section 7).

12.3 Project Management Group (PMG)

The trial is supervised by its Project Management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers/ experts are invited to attend at the discretion of the PMG. The PMG meet face to face or via teleconference at least quarterly throughout the study.

The PMG has the expertise to cover all aspects of the research.

12.4 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), with independent members, oversees the conduct and progress of the trial. The TSC Charter documents the terms of reference of the TSC, the template for reporting and the names and contact details of members of the TSC. This Charter is filed in the Trial Master File (TMF).

12.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) oversees the safety of subjects in the trial. The DMC Charter documents the terms of reference of the DMC and the names and contact details and is filed in the TMF. The Committee meets regularly to monitor the trial data and make recommendations as to any modifications that are required to the protocol or the termination of all or part of the trial. CHaRT has adopted the DAMOCLES Charter for DMCs.

13. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

13.1 Research Governance

CHaRT is a fully registered Clinical Trials Unit with particular expertise in running multicentre RCTs. The trial is run under the auspices of CHaRT based at HSRU, University of Aberdeen. This aids compliance with Research Governance and the principles of GCP, CHaRT provides centralised trial administration, database support and statistical analyses. CHaRT SOPs are followed.

The CI and the Sponsor ensures that, adequate systems are in place for monitoring the quality of the trial and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial.

13.2 Data protection

Data collected during the course of the research is kept strictly confidential and accessed only by members of the trial team, and may be looked at by individuals from the Sponsor organisation or NHS sites where it is relevant to the participant taking part in this trial.

Participants are allocated an individual trial number. Participant's details are stored on a secure database under the current Data Protection Legislation (General Data Protection Regulation (GDPR) and the Data Protection Act 2018). To comply with the 5th Principle of the Data Protection Act 2018, personal data is not kept for longer than is necessary for the purpose for which it is processed. The CHaRT senior IT Development manager (in collaboration with the CI) is responsible for managing access rights to the data set. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses.

13.3 Sponsorship

The University of Aberdeen and NHS Grampian are the Co-Sponsors for the trial.

14. ETHICS AND REGULATORY APPROVALS

The Wales REC 6 Research Ethics Committee (REC) reviewed this protocol. The trial is conducted according to the principles of GCP provided by Research Governance Guidelines. Annual progress reports, end of Trial declaration, and a final report are submitted to the Sponsor and the Wales REC 6 within the timelines defined in the regulations.

14.1 Protocol compliance and amendment

The Investigators conduct the trial in compliance with the protocol given favourable opinion by the REC. Any amendment to the trial is approved by the Sponsors and funder before application to REC and R&D, unless in the case of immediate safety measures when the Sponsor is notified as soon as possible. Any deviations from the protocol are fully documented using a breach report form.

15. QUALITY ASSURANCE

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the Sponsor's risk assessment of the trial. Investigators and their host institutions are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives, providing direct access to source data and documents as requested.

15.1 Risk assessment

An independent risk assessment has been carried out by the Sponsor.

16. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme. The necessary trial insurance is provided by the University of Aberdeen.

17. END OF TRIAL

The end of follow-up for each participant is defined as the final data capture on that individual.

The end of the trial is reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. If terminated prematurely, the Investigators inform participants and ensure that the appropriate follow up is arranged for all involved, if appropriate.

A summary report of the trial is provided to the Sponsor and REC within one year of the end of the trial. An end of trial report is also issued to the funder at the end of funding.

18. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Trial data are entered into the database by the designated local research team members working at each site. Questionnaires returned by post to the trial office are entered there. Staff in the Trial Office work closely with local team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks further enhance the quality of the data.

Responsibilities for archiving are documented in the co-sponsorship/site agreement. All essential data and documents (electronic and hard copy) are retained for a period of at least 10 years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs. Electronic data are archived by CHaRT using UoA facilities.

19. AUTHORSHIP AND PUBLICATION

To safeguard the integrity of the main trial, reports of explanatory or any satellite studies are not to be submitted for publication without prior agreement from the PMG.

Once the main trial findings have been published, we plan to send a lay summary of the findings to all involved in the trial.

Please refer to the Appendix I (authorship policy) for full details on authorship.

APPENDICES

Appendix I: Authorship Policy

CHaRT Authorship Policy
Version 3, Jan 2017

AUTHORSHIP POLICY FOR CATHETER II STUDY

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria[1]:

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

ii. Drafting the work or revising it critically for important intellectual content; AND

iii. Final approval of the version to be published; AND

iv. 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.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT studies should publish using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using bylines similar to “The CATHETER II trial group” or “Jane Doe, John Doe, John Smith, Ann Other and the CATHETER II trial group”. The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group') [2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. Determining authorship

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS

All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a study's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

4. DISCLAIMERS

All papers arising from CHaRT must include the full title of the Health Services Research Unit (HSRU) and the appropriate disclaimer specified by the Chief Scientist Office (CSO). For the current disclaimer please see Q-Pulse.

Authors should also ensure they include the study funder's disclaimer: refer to the funders website for details. Be aware that other disclaimers may also be required.

5. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the CATHETER II trial, including conference abstracts, should be peer reviewed by the Project Management Group. The Project Management Group will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member off the study team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

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