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Trial to compare mixed-use (multi-use and single-use) intermittent catheter management with single-use management over 12 months (The MultICath Trial): protocol for a non-inferiority randomised controlled trial

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ABSTRACT

Introduction Evaluating the safety and acceptability of reusing catheters for intermittent catheterisation (IC) is one of the top 10 continence research priorities identified by the UK James Lind Alliance Priority Setting Partnership in 2008. There are an estimated 50 000 IC users in England and this number is rising. Globally, both single-use catheters (thrown away after use) and multi-use/reusable ones (cleaned between uses) are used. Using multi-use catheters as well as single-use ones (mixed-use) could bring benefits (eg, reducing plastic waste and patients never running out of catheters) and offer more choice to users. Evidence is needed that mixed-use is at least as safe and acceptable as using only single-use catheters.

Methods The MultICath Trial is a non-inferiority randomised controlled trial involving 578 participants. The aim is to compare mixed-use catheter management with single-use catheter management over 12 months. Participants are randomised on a 1:1 basis to either mixed-use catheter management, which includes an evidence-based cleaning method for the multi-use catheters (intervention) or single-use catheter management (control). Following randomisation, participants are followed up for 12 months. The primary outcome is at least one episode of microbiologically confirmed symptomatic urinary tract infection with help-seeking or self-help behaviour over the 12-month follow-up period. Laboratory analysis of patient-initiated urine samples is blind. Secondary outcomes include antibiotic use, microhaematuria, visible blood on catheter/in urine, quality of life and health economics. A qualitative sub-study to examine participant experiences using mixed-use is included.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The first large clinical trial comparing mixed-use (multi-use and single-use) catheter management with single-use catheter management.
⇒ Uses an evidence-based cleaning method derived from laboratory testing and developed with catheter users.
⇒ Includes blinded laboratory analysis of urine microbiology in the primary outcome together with a robust method of capturing urine samples in community settings to minimise missing data.
⇒ Remote trial delivery and recruitment through two hubs and multiple participant identification centres (general practices and nurse prescribing teams) enables national recruitment not limited to geographic sites.
⇒ A limitation is that the catheter used in the trial (Cliny) is the only CE-marked multi-use catheter available and has different characteristics (silicone-based, more flexible, requires lubrication) to most standard single-use catheters.

Ethics and dissemination Ethical review was undertaken by South Central-Hampshire A Research Ethics Committee and favourable opinion was granted on 12 July 2019 (reference: 19/SC/0334). Written, informed consent to participate was obtained from all participants. Results will be disseminated in peer-reviewed publications, in the National Institute for Health and Care Research journal library and to participants and the public via a lay summary published on the trial website.

Trial registration number ISRCTN42028483.

INTRODUCTION

Background

Clinical problem

Incomplete emptying of the bladder is a common urological problem which frequently causes incontinence, repeated urinary tract infections (UTI) and other urinary symptoms due to residual urine in the bladder.[1] If there is no treatable cause for the urinary retention, the standard method of management is to teach the individual or their carer clean intermittent catheterisation (IC). IC is the term used to describe the passing and removal of a urinary catheter into the bladder to drain urine. The process is repeated as needed according to urine output and bladder capacity, typically 4–5 times per day.

IC has transformed the lives of many people with bladder emptying problems and is accepted as the optimum strategy when corrective treatment is not possible.[2] Using prescription data from 2016, Fisher *et al* estimated there to be around 50 000 IC users in England[3] and this number is expected to rise with the increasing number of older people and use of treatments for bladder problems that can cause urinary retention for example, intravesical Botox injections for overactive bladder.

Intermittent catheters

In 1972, IC was first described using catheters cleaned and reused multiple times by an individual user.[4] In 1993, the EU Directive on medical devices (93/42/EEC)[5] required reprocessing (cleaning) instructions for products intended for multiple use. Intermittent catheters prescribed in the UK were subsequently supplied sterile with labelling indicating single-use and bearing a sign prohibiting multiple use (see figure 1). Worldwide, there is variation in practice and while IC using single-use catheters is the norm in many countries, in others, multi-use of catheters is common.

Evidence

Recent evidence reviews[6–8] report that there is a lack of high-quality randomised controlled trials (RCTs) comparing different catheter designs and recommend a broader range of outcomes including patient preference and quality of life (QoL). A revised Cochrane review[9] concludes that there is uncertainty regarding any difference between single-use and multiple-use catheters in the risk of symptomatic UTI because the level of evidence is low.

Environmental issues

The environmental cost of using single-use catheters has been estimated to be around 206 million litres of waste per annum in the USA.[10] Multi-use catheters have the potential to reduce waste but the lack of certainty regarding their safety has limited their development. There are very few intermittent catheters designed specifically for multiple use, and clinicians are uncertain about recommending them.[11] Users in some countries, therefore, do not have the choice to reuse catheters should they wish to do so.

Cost and cost-effectiveness

The total cost of single-use catheters has risen as the number of IC users has grown. In the Netherlands, the total costs of disposable catheters increased from 16.4 million euros in 1997 to 74.6 million euros in 2018.[12] Multi-use catheters may be cost-effective[6] because they can be used multiple times and are not discarded after use, but this is not certain. A Cochrane review reports that no trials of multi-use catheters that were included in the review had undertaken health economic analyses.[9] Healthcare costs from infections, hospitalisations, trauma and cleaning costs would need to be evaluated as well as the costs of catheters to determine cost-effectiveness.

Mixed-use (multi-use and single-use catheters)

Single-use and multi-use catheters have different strengths and limitations.[13] Using both types (mixed-use) could bring benefits such as ability to use single-use catheters when using public toilets, but never worrying about running out of catheters. Testing mixed-use of catheters may also be more feasible than requiring patients to change completely to multi-use catheters.

The MultICath programme

The MultICath Trial is the final part of the MultICath programme, which included a preliminary phase of four preparatory modules:

1. Development of the cleaning method intervention. We used laboratory techniques[14] and worked with a series of patient panels to test different cleaning methods and develop the intervention.
2. Identification of user symptoms and management strategies for UTI.[15]
3. Interviews with users to understand user perspectives of single and multi-use.[13]

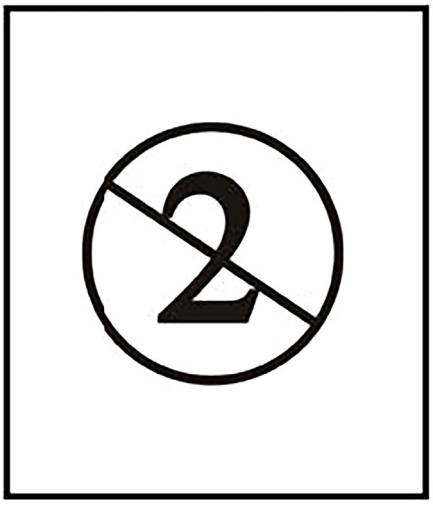

Figure 1 Sign that identifies a catheter is prohibited from multiple use.

4. Interviews with and survey of healthcare professionals involved in IC.[11]

METHODS AND ANALYSIS

Trial methods and analysis are reported as per Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[16]

Aim

The MultICath Trial aims to find out whether mixed-use (multi-use and single-use) catheter management is no worse for safety, acceptability and cost-effectiveness than single-use catheter management.

Trial design

MultICath is a non-inferiority RCT, incorporating an internal pilot. Participants were recruited nationally by two non-NHS (National Health Service) hubs (University of Southampton and Glasgow Caledonian University).

Trial outcomes

Primary outcome

The primary outcome is at least one episode of Microbiologically Confirmed Symptomatic UTI with Help-seeking or Self-help (MCS-UTI+HS) behaviour over the 12-month follow-up period. This is a binary outcome (yes/no) that demands that all of three dichotomous measures (a microbiological measure and two participant-reported measures) meet criteria for the primary outcome to be achieved. The composite outcome was used to minimise the risk of the outcome being vulnerable to bias and to maximise our chances of capturing events that are of patient and clinical importance. This approach was endorsed by our patient and public involvement and engagement group. As a secondary outcome (see below), the symptom set was limited to those listed in the Infectious Diseases Society of America (IDSA) guidelines.[17]

1. A positive urine culture is defined as $\geq 10^3$ colony-forming units (cfu)/ml of ≥1 bacterial species in a single catheter urine specimen taken during a symptomatic episode (microbiological measure).
   - Participants are supplied with urine sample pots containing boric acid and instructions to take a urine sample via their sterile, single-use catheter when they experience onset of signs or symptoms of urine infection and before starting antibiotics. Urine samples are sent in Royal Mail-approved biological specimen boxes to the trial laboratory for analysis as soon as possible following sampling. Samples are processed using laboratory standard operating procedures (see laboratory analysis below). The count of $\geq 10^3$ cfu/ml follows IDSA guidelines.[17]
2. The presence of at least one sign or symptom that is new or worsening and that the participant believes is indicative of a UTI (participant-reported measure).
   - This is recorded on a self-report UTI questionnaire starting at the time signs or symptoms occur. Using terminology developed in consultation with intermittent catheter users they include but are not limited to the following:
     - Urine changes: changed colour; became cloudy; became smelly; blood in urine.
     - Urinary symptoms: pain/stinging/burning on passing urine or catheterisation; pain in penis (men); passing urine more often than usual (with or without catheter); unable to pass urine; leaking urine.
     - Pain: bladder discomfort; tummy pain; kidney/back pain.
     - Systemic symptoms: Feel hot/feverish; feel run-down or unwell; feel anxious; feel dizzy/vertigo.
     - Neurogenic symptoms: Autonomic dysreflexia; increased spasticity.
     - Other symptoms include shivers/feeling cold; feeling confused; headache or any other symptom that the participant recognises as indicating a UTI. Participants have an option to complete free text description of symptoms.
3. A positive recording of at least one help-seeking and/or self-help behaviour (participant-reported measure).
   - This is recorded on a self-report UTI questionnaire at the time of the action. Behaviours include but are not limited to:
     - Contacting general practitioner (GP), hospital consultant or other healthcare professional for help; sending/taking a urine sample to GP; increasing fluid intake or taking other self-help action; taking self-purchased products/medication; taking prescribed or acquired antibiotics or other medication. Participants have an option to complete free text description of help seeking and/or self-help actions.

Secondary outcome measures

Secondary outcomes derived from the primary outcome measures:

- At least one episode over the first 6 months of follow-up of MCS-UTI+HS as defined for the primary outcome.
- The number of MCS-UTI+HS over 6 and 12 months follow-up measured as an incidence rate.
- At least one episode of, and the number of, symptomatic UTI with Help-seeking or Self-help (S-UTI+HS) (with or without microbiological confirmation or with no specimen available for analysis) over 6 and 12 months follow-up.
- At least one episode of, and the number of, MCS-UTI+HS restricted to symptoms mapped to the IDSA guidelines for catheter-associated UTI[17] over 6 and 12 months follow-up.
- Antibiotic use: Rate per month of antibiotics for presumed S-UTI (with or without meeting MCS-UTI+HS definition above) over 6 and 12 month follow-up periods as reported monthly.

Other secondary outcomes

- Microhaematuria (microbiological measure): Number of 6 monthly urine samples meeting criteria of microhaematuria defined as >10/mm^3 RBC as reported by routine urine samples during the 12-month follow-up collected as described above.
- Visible blood (participant-reported measure): Rate per month of any report of visible blood (from around or on catheter or in urine) as an indicator of trauma, over 6-month and 12-month follow-up periods as reported on monthly questionnaire.
- Problems with catheterisation including pain, sticking and difficulties with insertion and removal (participant-reported measure): Over 6-month and 12-month follow-up periods as reported on monthly questionnaire.
- User QoL (participant-reported measure): QoL recorded by Intermittent Self-Catheterisation Questionnaire[18] (ISC-Q)at 6 and 12 months. A weighted average of the two score completions will be used for the intervention (mixed-use) group; the weights will reflect the proportion of time catheters were used as single and multi-use.
- Adverse events (AEs) (participant-reported measure): Monthly reports of all health-related events that are not trial outcomes are recorded as AEs following processes described in the Safety Reporting section below.

Health economics outcomes

- Catheter management preferences (participant-reported measure): As reported at 6 and 12 months on the 6-month/end of study questionnaire for the intervention group.
- Costs of managing multi-use catheters versus single-use catheters only (product and medication costs; participant-reported measure): As reported on the monthly questionnaire and 7-day catheter diary.
- Cost-effectiveness of a mixed package (multi-use and single-use) compared with single-use only, derived from the monthly questionnaire, health service utilisation questionnaire (participant-reported measure 6 monthly) and the self-reported health status questionnaire (EQ-5D-5L)[19] (participant-reported measure 3 monthly) expressed as quality-adjusted life years (QALYs)—see the 'Health Economics sub-study' section.

Trial intervention: mixed-use (multi-use and single-use) catheter management

This is defined as use of both the participant's usual single-use catheters and multi-use trial catheters. The trial multi-use catheter is the uncoated, 100% silicone, reusable Cliny catheter (Create Medic Co., Ltd.), with a standard Nelaton tip in Charriere sizes 10–16, and lengths 40 cm, 30 cm and 16.5 cm. These catheters are CE marked for repeated use over 28 days when cleaned between uses with an appropriate disinfectant.[20] In the MultICath trial, the cleaning method is based on the Milton cold water method, that is, wash with soapy water followed by a 15 min soak in Milton solution (sodium hypochlorite 0.6%).[14] Participants are asked to use, clean and reuse their Cliny catheters, for as many of their catheterisations as they can, and for a maximum of 28 days before replacing with a new one. Participants may also use their single-use catheters at times when they feel unable to use the multi-use catheter, for example, when at work or during the night.

Control: single-use catheter management

Participants allocated to the control arm continue to use their own single-use catheter supplied by their GP or nurse prescribing team (NPT). Control participants who report that they reuse single-use catheters are asked to use them once only during the trial.

Internal pilot

An internal pilot to assess set up, screening and recruitment methods was conducted at the two trial hubs, with defined remedial actions for different levels of recruitment below the target of 30 or more participants over 4 months. Participants recruited during the internal pilot were identified, screened, consented, recruited, randomised and followed up in the same way as proposed for the main trial. Their data will be included in the final analysis. The target number of 30 participants was achieved and progression to the main trial was agreed with the funders (see figure 2: participant flow diagram).

Patient identification, recruitment and consent

Patients are screened and approached through GP practices and NPTs acting as patient identification centres who are themselves identified by the National Institute for Health and Care Research (NIHR) Clinical Research Networks (CRN) across England and Wales. In Scotland, potential participants were identified via the Scottish Primary Care Research Network and NHS clinics. Intermittent catheter users who come to know about the trial through other routes such as charities, consumer, or health organisations, or via the MultICath website, contact the MultICath research staff directly.

Potentially eligible patients are sent invitation letters, the participant information sheet (see online supplemental file 1) and an expression of interest form (EOI) either directly by the GP surgery or, on their behalf, by the hybrid mail service Docmail.[21] Interested patients return the EOI by post in a prepaid envelope to one of the two hubs or contact the teams by email or phone. Secondary care teams within the two research hubs may directly approach patients and seek verbal consent to pass their contact details directly to the research team.

Consent is obtained in accordance with the principles of the UK policy framework for health and social care research[22] by an appropriately qualified

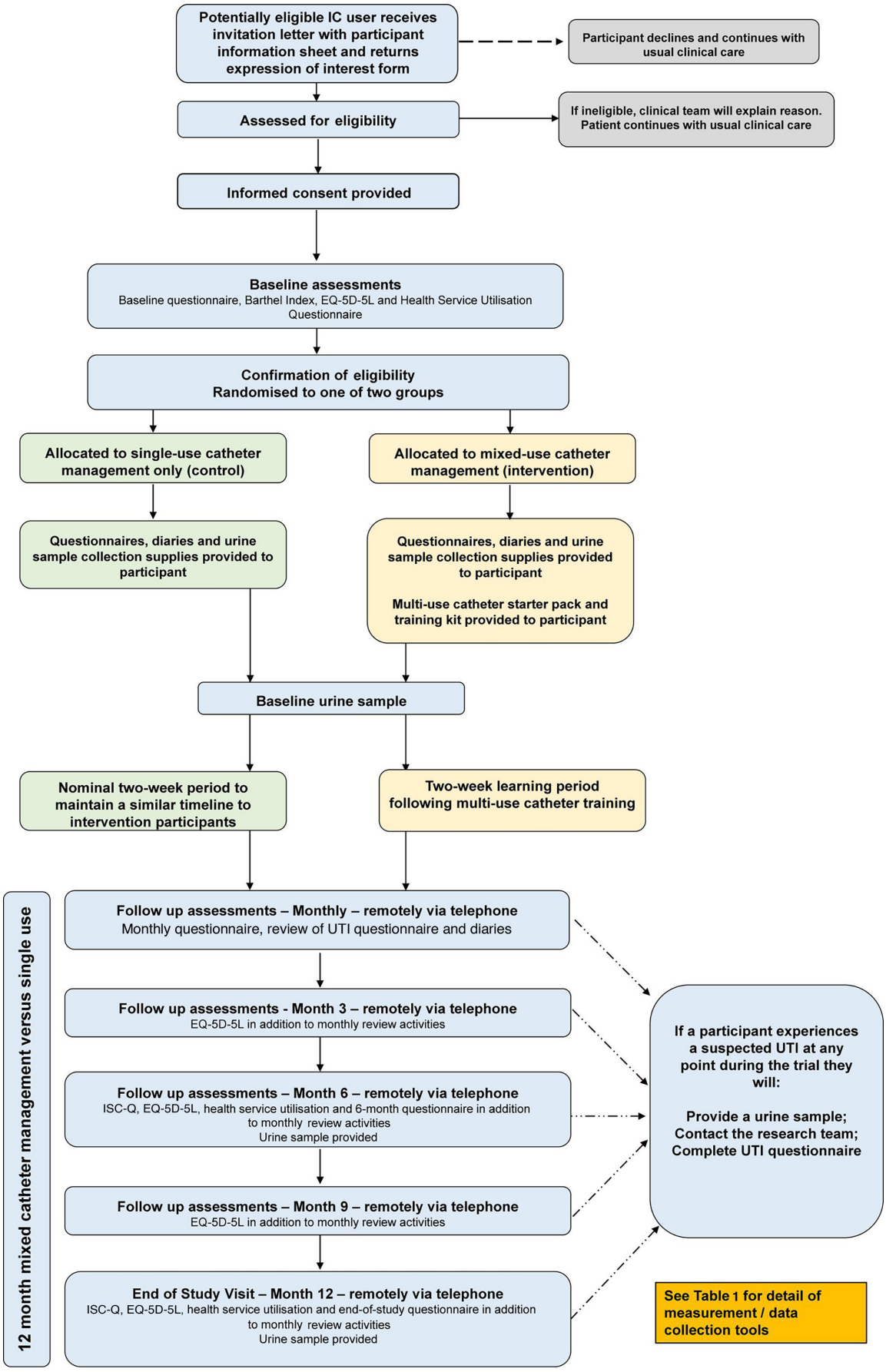

Figure 2 Participant journey through trial and data collection time points including outcome measures used. UTI, urinary tract infection.

Table 1 Data collection tools

Outcome	Measurement/data collection tool	Time point
Primary outcome		
At least one episode of Microbiologically Confirmed Symptomatic Urinary Tract Infection with Help-seeking or Self-help (MCS-UTI^{+}HS)	► Urine sample (microbiological measure) ► UTI questionnaire* ► Monthly questionnaire*†	► At time of UTI ► At time of UTI ► Monthly
Secondary outcomes derived from the primary outcome measure		
At least one episode of MCS-UTI^{+}HS over the first 6 months	► As above	► As above
Number of MCS-UTI^{+}HS over 6 and 12 months follow-up measured as an incidence rate.		
At least one episode of, and the number of, MCS-UTI^{+}HS restricted to IDSA symptoms over 6 and 12 months follow-up.		
At least one episode of, and the number of, symptomatic UTI (S-UTI^{+}HS) (not microbiologically confirmed) over 6 and 12 months follow-up.	► UTI questionnaire* ► Monthly questionnaire*	► At time of UTI ► Monthly
Antibiotic use: Rate per month of antibiotics for presumed S-UTI over 6 and 12 month follow-up periods.	► As above	► As above
Other secondary outcomes		
Microhaematuria	► Urine sample (microbiological measure)	► Baseline, 6 and 12 months
Visible blood (frequency of visible blood from around or on catheter or in urine)	► Monthly questionnaire (4 questions)*	► Monthly
Problems with catheterisation (frequency of pain, difficulties with insertion/removal, sticking)	► Monthly questionnaire (6 questions)*	► Monthly
Quality of life	► ISC-Q*	► 6 and 12 months
Adverse events	► Event diary*	► Anytime (checked monthly)
Health economics		
Catheter management preferences	► 6 month/end of study questionnaire (two questions)*	► 6 and 12 months (for the intervention group)
Costs of managing multi-use catheters vs single-use catheter only (product and medication costs)	► Monthly questionnaire (eight questions)* ► 7 day catheter diary*	► Monthly
Cost-effectiveness of a mixed package (multi-use and single-use) compared with single-use only (includes product and medication costs as above)	► Health service utilisation questionnaire (11 questions)* ► EQ-5D-5L*	► Baseline, 6 and 12 months ► Baseline, 3, 6, 9 and 12 months
Participant characteristics		
Demographics and health history	► Baseline questionnaire	► Baseline
Activities of daily living	► Barthel Index	► Baseline

*Participant-reported measure.
†Monthly questionnaire completed at monthly phone call includes questions on UTI questionnaire to ensure all data are captured.
IDSA, Infectious Diseases Society of America; ISC-Q, Intermittent Self-Catheterisation Questionnaire.

and delegated member of the research team. Patients expressing an interest are contacted by a researcher for additional screening. The trial is discussed with the patient, and all questions are answered. Eligible patients who wish to proceed are sent a trial consent form (see online supplemental file 2) and asked to provide written informed consent by signing and dating the consent form. Patients return their signed consent form to the research team for countersigning prior to any research-related tasks taking place and are then sent a fully signed copy.

Following consent and in preparation for randomisation, participants are sent a urine specimen kit and a copy of the data collection tools used at randomisation.

Eligibility criteria

Eligibility criteria for this pragmatic-design trial were developed to include participants from all major groups of IC users.

Inclusion criteria:

► Men and women aged ≥18 years.

- Currently using IC (via the urethra), performed by self or sole carer.
- Patients who have been IC users for ≥6 weeks.
- Patients where IC planned to continue for >12 months and 2 weeks.
- Able and willing to adhere to a 12-month follow-up period.
- Patient has provided written informed consent for participation in the trial prior to any trial-specific procedures.

Exclusion criteria:

- <18 years.
- Use of IC for self-dilatation of urethral stricture without bladder drainage.
- Non-urethral route for catheterisation, for example, Mitrofanoff.
- Use of less than one catheter per day or seven per week.
- External, non-sole carer required for IC (ie, where sterile technique and catheter are required, eg, visiting community nurse performs IC).
- Inability to give informed consent or have primary outcome information collected.
- Employee or relation of employee of a manufacturer or distributor of IC catheters.
- Women who report they are pregnant or who plan to become pregnant during the trial.
- Participation in another trial.
- Patients in the terminal stages of an illness.
- Anything that, in the opinion of the chief investigator or a delegated member of the research team, prohibits the patient's participation in the trial.

Randomisation

Randomisation is administered centrally by the Newcastle Clinical Trials Unit (NCTU) secure 24-hour web-based system. Participants are randomised to either mixed-use (intervention arm) or single-use only (control arm) on a 1:1 basis using a method of permuted random blocks of variable length, generated by the system itself, stratified by gender and hub. This is carried out by appropriately delegated members of the research team and access with individual logins.

Blinding

Blinding of the participants and research staff is not possible because of differences in the intervention, trial catheters and processes. Central laboratory staff analysing participant urine samples and the senior statistician are unaware of the allocated group.

Trial processes: intervention arm

Intervention catheter and cleaning kit

Participants in the intervention arm are sent a MultI-Cath kit box containing Cliny (multi-use) catheters and other items for the intervention, including lubricant and Milton tablets. They are asked to watch a short video which demonstrates the cleaning method and to read an instruction booklet. Participants then receive additional training from a researcher via videoconference or phone. This session is also used to familiarise participants with the data collection tools and the processes for sending urine specimens and responding to signs and/symptoms of UTI.

Learning period

During the intervention development phase, feedback from patient panel members highlighted the need for a period of adjustment when starting to use multi-use catheters, including concerns that they may be more at risk of developing a UTI. We, therefore, built in a 2-week 'learning period' following the training session to allow for gradual adaptation to the new multi-use catheter. During this learning period, participants begin 'mixed-use'; they start to use the Cliny catheter, first disposing of them after a single use for one of their daily catheterisations (days 1 and 2). Participants then gradually increase usage of the Cliny catheter with the aim of using them for as many of their catheterisations as they feel able to. On days 7 and 14, participants have a preplanned phone call with their researcher to answer questions and ensure they have the products required to enter the main trial on day 14.

Supply of products

Intervention participants are provided throughout the trial with 'top up' supplies of Cliny catheters and other consumables needed for their use. They continue to obtain their single-use catheters via prescription as needed.

Trial processes: control arm

Control participants continue to use only their usual single-use catheters obtained in their normal way and are required to stop reusing catheters if they are doing so. Following randomisation, their start date is delayed by 2 weeks to maintain a similar timeline to the intervention participants. On day 14 participants have a preplanned phone call with a researcher to familiarise them with data collection tools and the processes for sending urine specimens and responding to signs and/or symptoms of UTI.

Follow-up

For participants in both arms, follow-up lasts for 12 months (see online supplemental table 1 for full schedule of events). During this time, data are collected using a range of data collection tools (see table 1).

Process of recording UTI

Participants are asked to take the following actions if they suspect they have a UTI:

1. Send a urine specimen to the trial laboratory. The process for collecting and sending a urine specimen to the trial laboratory is described in the primary outcome section.
2. Record UTI signs and/or symptoms and help-seeking/self-help activities. Participants are asked to complete a self-report UTI questionnaire which is sent directly to

the NCTU for data entry. UTI data are also recorded by researchers at monthly follow-ups to ensure all data are captured.

Laboratory analysis

A central laboratory based at The Newcastle upon Tyne Hospitals NHS Foundation Trust is processing urine samples on behalf of the trial. Two types of urine samples are collected from trial participants:

- Routine urine samples—collected at baseline, 6 and 12 months.
- Ad hoc urine samples at the onset of a suspected UTI.

The following outcomes contribute to the trial's primary and secondary outcomes and are reported to NCTU:

- The number of colony-forming units (cfu/ml) of bacteria and the species that are present.
- The presence of microhaematuria (>10/mm^3 RBC).

Analysis and storage of trial urine samples is carried out according to the MultICath Laboratory Manual. Results of urine analysis are uploaded to the MACRO database from reports produced by the central laboratory.

Post-trial care

Participants are asked to revert to standard care which is continued use of their usual single-use catheters only.

Qualitative sub-study

Semi-structured qualitative interviews lasting approximately 30–60 min are conducted with up to 40 participants randomised to mixed-use catheter management. The purpose is to understand participants' experiences of the multi-use catheter and the burden of cleaning catheters in different circumstances and places.

Health economics sub-study

The economic analysis will initially be conducted as a cost–consequence analysis, identifying additional health service and patientborne costs associated with multiuse catheters, potential changes in use of single-use catheters and other health sector resources associated with IC use. The primary economic analysis will be from the NHS and personal social services perspective. Costs will be estimated based on responses to individual patient-reported data including use of resources by treatment group, hospital and community-care use and combined with routine sources such as the Unit Costs for Health and Social Care.[23] The economic analysis will report cost-effectiveness over the trial period for the mixed catheter management compared with single-use for intermittent urinary catheterisation using methods appropriate for economic analysis in non-inferiority designs.[24] QALYs will be estimated based on responses to the EQ-5D-5L from which the incremental cost per QALY gained will be estimated. Incremental cost-effectiveness ratios will be calculated if one treatment does not dominate (ie, less costly and more effective) by estimating the difference in costs and effects (QALYs) between the two randomised groups. It is not planned for data from this economic analysis to be combined with any other trials.

Withdrawals

Participants can withdraw from the trial at any time without giving a reason. They can partially withdraw (withdrawal from the intervention but continuing to provide follow-up data) or completely withdraw (withdrawal from both the intervention and provision of follow-up data). Consent is sought from participants choosing to completely withdraw from the trial to retain data collected up to the point of withdrawal.

Effort is made to minimise withdrawals by providing support during planned monthly follow-up. The participants' preferred methods (email, phone, videoconferencing, texting) are used and reminders sent to ensure that meetings are not missed. Between planned follow-ups participants are encouraged to contact the research team if they have any concerns and where possible the same researcher follows up the same participants to help build rapport.

Data management

Participant identification is via a unique trial identifier. Data are collected using case report forms (CRF) and participant-completed questionnaires (paper). CRF and questionnaire data are entered at site into the trial-specific electronic CRFs held within the MACRO database by a delegated hub team member. Participant UTI questionnaires are sent to NCTU for central data entry into the same database. Results of urine analysis are uploaded to the MACRO database from reports produced by the central laboratory.

Access to the trial database is password limited and restricted to delegated staff. The NCTU trial management team have 'monitor role' access to the trial database. Data collected within MACRO are regularly reviewed and built-in validation checks are applied regularly to ensure the completeness and accuracy of data reported.

Sample size and analysis

Given that not all IC users will experience UTIs, we aim to demonstrate that the mixed package does not increase the proportion affected. To calculate the sample size, we determined the non-inferiority margin, informed by the clinically important difference or ratio. Clinical importance in this context is not well defined in the literature: but a difference of around 20% in UTI rates has been taken to be important,[25] though a smaller difference of 15% would be a safer choice.

As there are no reliable data on the proportion of patients experiencing UTIs in this mixed patient group, the non-inferiority margin is expressed as an OR of 2.0, as otherwise, the sample size calculation is too sensitive to the UTI rate in the control group. Using this non-inferiority margin of OR=2.0 equates to a margin based on a difference in UTI rates being higher in the intervention group by 12% if 70% of controls developed UTIs, higher by 15% if 60% of controls developed UTIs, or higher by 17% if the control risk were 50%.

Data from 208 patients per trial arm would provide 90% power to rule out an increase in UTIs expressed as an OR of 2.0 using a one-sided test (α=0.025). Initially, we aimed to recruit at least 520 in total, assuming an attrition rate of 20%. However, our attrition rate has been higher than anticipated and we have revised our sample size to account for 28% withdrawal and we, therefore, aimed to recruit 578.

The primary outcome (MCS-UTI+HS) will be calculated by the statistician using programming to bring together the various data sources. This will then be compared between the two treatment groups and a two-sided 95% CI will be calculated for the OR of the UTI rates. Non-inferiority will be accepted if the upper bound of the interval is below 2.0. Logistic regression will be used to explore the influence of covariates including gender, age, medical condition, Barthel index,[26] carer/no carer and antibiotic prophylaxis on the incidence of UTI in the two groups. Analyses will be carried out on the per-protocol population, and as a secondary analysis, based on intention to treat.[27] For participants who are lost to follow-up by 12 months, their information will be included in the ITT analysis up to the point that they are lost to follow-up, but a minimum of 6 months is required for the per-protocol analysis. For a participant to be included in the per-protocol analysis in the intervention group, their percentage reuse must be at least 25% or an average of 0.75 times per day during their potential time on intervention. If more than 10% of participants have missing primary endpoint data then multiple imputation may be attempted, performing at least 10 separate sets of multiple imputations by treatment group using chained equations. In addition, if judged to be appropriate, a tipping point analysis may be performed to test the robustness of the conclusion of the primary outcome analysis. All analyses will be fully described in the Statistical Analysis Plan.

In relation to analysis of the secondary outcomes, the number of MCS-UTI+HSs as an incidence rate, visible blood (from around or on catheter or in urine), antibiotic prescriptions and episodes of microhaematuria per participant will be modelled by Poisson regression comparing rates in single and multi-use trial arms with the exploration of the influence of covariates as above. If the data are overdispersed, negative binomial regression will be used instead. Binary secondary outcomes will be analysed using methods analogous to the primary analysis. Missing secondary outcome data will be considered as described for the primary outcome analysis above. Missing items from a partially completed validated QoL questionnaires will be handled as described in the relevant scoring manual.

There could be substantial attrition during the 12-month follow-up which would have the potential to influence conclusions around the primary outcome. If there were no difference in outcomes between the intervention and control arms at 12 months, this could potentially be due to excessive attrition with few or even no participants continuing by then with reuse. To allow for this possibility the data collected at 6 months will be analysed for the relevant outcome measures. These 6-month measures will be considered to be further secondary outcomes and analyses will be analogous to those performed for the 12-month data.

Safety reporting

AEs are recorded at monthly phone calls or ad hoc phone calls and entered into MACRO. An assessment of seriousness, severity and causality is undertaken for each AE. This assessment must be determined by the PI, subinvestigator or suitably qualified researcher delegated these duties by the principal investigator.

Events or symptoms related to UTI, difficulty or inability to pass the catheter, pain or discomfort passing the catheter, difficulties with catheter removal, pain or discomfort experienced following catheter removal and visible blood associated with catheterisation, are not reportable AEs. They are collected and reported as part of the primary and secondary outcomes of the trial.

Serious adverse events (SAEs) are AEs that meet the definition of serious and are reported to the chief investigator (CI), CTU and sponsor within 24 hours of the research team being made aware of the event. Unexpected serious adverse device effects (USADEs) are reported to the Research Ethics Committee within the required reporting timelines. Pre-existing conditions and any preplanned hospitalisations (eg, elective surgery) not associated with clinical deterioration are not classed as SAEs.

AEs terms are built-in to MACRO with the ability to use the Medical Dictionary for Regulatory Activities (MedDRA) to code AE data. All coded AEs are reviewed by the CI (or a delegated person with sufficient clinical experience) to ensure appropriate MedDRA codes have been assigned to events.

Trial conduct and governance

The trial is conducted in accordance with the UK Policy Framework for Health and Social Care including guidelines for Good Clinical Practice.[28] Before any hub could enrol patients into the trial, that hub must have been in receipt of Health Research Authority approval and have issued capacity and capability confirmation (English site) or have local Research and Development approval in place (Scottish site). They must also have been issued the green light to commence recruitment by the sponsor.

The Trial Management Group is responsible for the day-to-day management of the trial, overseeing all aspects of the conduct of the trial to ensure that the protocol is adhered to and taking appropriate actions to ensure patient and data safety. The Trial Steering Committee (TSC) monitors progress and supervises the trial to ensure it is conducted to high standards in accordance with the protocol, relevant regulations and guidelines. The Independent Data Monitoring Committee (IDMC) independently monitors safety and data throughout the trial. The TSC and IDMC include independent experts

(clinicians and statisticians) and the TSC also includes an independent patient representative. A charter has been put in place for each committee and clearly outlines each committee's roles and responsibilities.

Patient and public involvement and engagement

Patient and public involvement and engagement has been integral in the development and design of the intervention and the trial. This active collaboration improved the intervention and research design and aided with the development of trial documentation as well as recruitment of participants. The trial also includes an independent lay member in the TSC.

ETHICS AND DISSEMINATION

Favourable ethical opinion has been obtained from South Central—Hampshire A Research Ethics Committee (reference 19/SC/0334). The trial has been included in the NIHR CRN portfolio (NIHR CRN study ID: 42679). The trial sponsor is Southampton University (rgoinfo@soton.ac.uk). The trial sponsor has delegated responsibility for trial management to NCTU.

Trial results will be disseminated through patient and professional organisations and through media outlets including web resources, lay press, conferences and peer-reviewed journal publication.

Trial status

This trial opened to recruitment on 19 February 2021 with the first participant recruited on 21 April 2021. The last participant was recruited on 15 June 2023. Follow-up is now expected to complete by August 2024. The overall grant end date is 30 June 2025. Although it was planned that this protocol paper would be submitted prior to recruitment closing, the need for additional recruitment time and subsequent workload/time pressures delayed this. This funding is based on the current approved MultICath protocol Version 17.0, 05 July 2024. The MultICath trial is the final phase of Programme grant RP-PG-0610-10078.

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Contributors MF is the chief investigator for the study, lead applicant on the grant and the guarantor. MMacaulay is the project manager and member of the Southampton site team for the study. NG, CS and GW perform trial management. AA is the lead database manager. NW and TJC provide statistical oversight and analysis. JJ provides health economic oversight and analysis. MRA, JB, BC and CM are members of the Southampton site team. SD, KG, SH and DM are members of the Glasgow site team. BSB is a PPI coapplicant on the grant. CPJ was a PPI representative for the trial. AC, PL, CRM, IR and AT are coapplicants on the grant. JP is the infection prevention advisor and a coapplicant. RK replaced JML as a coapplicant. SAW is the microbiology advisor. MMoore is the primary care recruitment advisor. All authors have read, provided input and approved the final manuscript.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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