A tolerability and patient acceptability pilot study of a novel antimicrobial urinary catheter for long-term use

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Abstract:

Aims:

We have developed a novel antimicrobial urinary catheter (AUC) impregnated with rifampicin, triclosan, and sparfloxacin and demonstrated that it has long-term (~84days) protection against bacterial colonisation in vitro. This study aimed to assess the safety and patient acceptability of this device in long-term catheter users.

Methods:

Adults who use longterm (>28days) indwelling urinary catheters with capacity to consent were invited to receive the AUC at their next catheter change. The primary outcome measure was adverse events (AE) attributable to antimicrobial impregnation of the catheter. Secondary outcome measures included severity of related AEs, patient acceptability, early removal of the trial catheter, and degree of microbial colonisation of trial catheters. Except for the last, outcomes were assessed by telephone interviews. Original and trial catheters were collected, and the lumens and balloons were separated and analysed for microbiological colonisation.

Results:

Thirty participants were recruited. 84 AEs were reported, and only one was rated as 'probably' related to antimicrobial impregnation. The AE was mild and resolved within 48 hours. 82.14% of participants rated the catheter as no different or better than their usual catheter. Two participants chose to remove the AUC early due to it feeling shorter. There were significantly fewer bacterial isolates attached to the balloons of trial catheters compared to the matched original catheters.

Conclusions:

The AUC has an advantageous safety profile and was acceptable to the majority of participants. Information gained from this trial will support a larger randomised controlled study of efficacy.

Keywords: urinary catheters, catheter-related urinary tract infections, anti-infective agents, safety, clinical trial

Introduction:

Catheter-associated urinary tract infections (CAUTI) are costly for health care systems as well as distressing for those who suffer from repeated infections and blockages. Long-term indwelling catheter users, who require catheterisation for over 28 days, are particularly at risk of CAUTI [1]. Two antimicrobial catheters, a silver-alloy coated catheter and a nitrofurantoin-coated catheter have been commercially available, but a robust randomised controlled trial has demonstrated that neither significantly reduces CAUTI even in short-term catheter users. Also the patients who received the nitrofurantoin-coated catheter experienced greater discomfort than with the control catheter [2]. Therefore, there is no commercially available anti-CAUTI technology for those who require catheterisation for over 28 days.

We have previously developed a silicone urinary catheters impregnated, not coated, with rifampicin, sparfloxacin, and triclosan and demonstrated seven to 12 weeks of protective activity against colonisation by major uropathogens, including multi-drug resistant strains[3]. The long-term duration of activity is conferred by the migration of the antimicrobials through the silicone to the intraluminal, extraluminal and balloon surfaces. Particularly, in light of the discomfort experienced with the nitrofurantoin-coated catheter, this study aims to understand primarily the tolerability of this novel antimicrobial urinary catheter (AUC) in the target patient population. Specifically, this was determined by the rate of adverse events (AEs) attributable to the antimicrobials or the antimicrobial impregnation process. Other secondary outcomes included patient acceptability, trial withdrawal, severity of AEs, time to

occurrence of AEs, microbial colonisation of the AUC. The trial was not intended to determine efficacy in reducing CAUTI, but instead to determine in human participants for the first time, the tolerability and acceptability of a novel antimicrobial-impregnated catheter for long-term use.

Materials and Methods:

Patient and public involvement

Lay members who were either longterm catheter users or carers were recruited to a research management committee to meet several times yearly to review the trial protocol, trial progress, and trial results. All travel expenses were covered and lay members received payment for attendance.

Manufacture of trial devices

Two-hundred and five all-silicone, two-way urinary catheters in sizes 12-20Ch standard and female lengths were impregnated according to a previously published method[3-5]. Briefly, with any plastic ports and connectors removed, and catheters were immersed in a chloroform solution containing 0.2% w/v rifampicin (Sigma-Aldrich), 1.0% w/v triclosan (Irgacare MP, BASF) and 1.0% sparfloxacin (Sigma-Aldrich) for one hour. The catheters were removed and the chloroform was left to evaporate off under constant air flow for at least 12 hours. Surface residues were removed by rinsing in ethanol and the catheters left to dry. The catheters were packaged in individual plastic sleeves within Tyvek packaging with a clear front and opaque back. The catheters were sterilised by ethylene oxide and removal of ethylene oxide residuals was verified by gas chromatography by a Varian gas chromatograph using a 10 volt detector and 1 µL injection volume.

Chloroform removal was verified by gas-chromatography-mass spectrometry in which catheter segments were immersed in acetone to extract the chloroform. Analysis was carried out using a JEOL AccuTOF GCX (Jeol Ltd.) mass spectrometer and an Agilent

7890B (Agilent Technologies Inc.) gas chromatograph. An extended ion current trace at 82.9 mass to charge ratio (m/z) was used to detect chlorine isotopes.

High-performance liquid chromatography (HPLC) was employed to verify antimicrobial contents of the manufactured trial catheters. Please see Supporting Information Method 1 for the full method of drug content analysis. Briefly, the antimicrobials were extracted in chloroform, resolubilised in methanol, and analysed by an Agilent 1100 HPLC machine with a variable wavelength UV detection (Agilent Technologies Inc).

Participants and setting

Adults (age 16 years or greater) who were catheterised with a long-term indwelling urinary catheter and who required another long-term indwelling urinary catheter were initially considered for inclusion. Please see Table 1 for the full inclusion and exclusion criteria. Participants were recruited from the community and hospital settings through letters of invitation and screening as participants came through Urology clinics

Study design

This single-centre, non-randomised trial with the aim of evaluating the safety of a CE-marked medical device with modifications was carried out between November, 2016 and February, 2018. Eligible participants who provided informed consent were catheterised with the AUC (trial catheter) at their next scheduled catheter change date. They were catheterised with the AUC for their normal catheterisation length, which ranged from 28-84 days. Participants were interviewed by telephone at 24, 48, and 72 hours post-catheterisation and then once weekly for the rest of the trial duration. The original catheter and trial catheter were collected upon removal for laboratory analysis.

The primary outcome measure was the rate of adverse events (AE) attributable to the antimicrobials or the impregnation process. All AEs were recorded in the case report and a score of severity and a score of relatedness to the AUC was given to each adverse event by the research nurse and adjudicated by the principal investigator. AEs were detected by

patient self-reporting during the telephone interview and followed up by a review of the patient's notes. Relationship causality was classified as unrelated, unlikely, possible, probable or definite according to the algorithm given by the World Health Organisation[6]. Further classification grouped AEs as non-serious or serious. An AE was classified as serious (SAE) if it was fatal, life threatening, resulted in hospitalisation or prolonged hospitalisation or resulted in persistent or significant disability or incapacity.

Secondary outcome measures included time to occurrence of adverse events, patient acceptability which was captured by the telephone interviews, whether the trial device was removed before the planned end date of the trial (trial withdrawal), and microorganism colonisation of trial and original catheters.

Laboratory analysis of removed catheters

Catheters were analysed within 24 hours of removal. The balloon was separated from the lumen using a sterile scalpel and placed into a sterile Universal container and covered with phosphate buffered saline (PBS). The remaining ports on the catheter were also removed with a sterile scalpel and discarded. The remaining luminal tubing was filled with 1-2 mL of PBS, clamped using sterile, straight-jawed surgical clamps, and placed in a sterile container. The balloon and lumen components were sonicated for five minutes at 30 kHz to detach the bacteria into the surrounding PBS. The luminal tubing ends were cleaned with an alcoholic pre-injection swab and the lumen sonicate was drained into a sterile Bijou bottle (Sterilin). The balloon and lumen sonicates were plated onto cysteine-lactose electrolyte-deficient medium (Oxoid), and incubated overnight at 37°C. If culture - positive, the colonies were quantified and general microbiological identification performed. If culture - negative the plates were incubated for a further 24 hours.

Statistical analysis

Data were analysed and graphs were prepared using GraphPad Prism 7.01 (GraphPad Software Inc., LaJolla California, USA).

Results:

Manufacture of trial devices

Trial catheters were validated as being free of chloroform, and ethylene oxide sterilisation residuals were within the acceptable range. HPLC verified that the trial catheters were impregnated with 0.080% w/w (±0.013% w/w (IQR)) rifampicin, 1.084% w/w (± 0.138% w/w) triclosan, and 0.704% w/w (0.155% w/w) sparfloxacin.

Participant Demographics

Thirty participants were recruited and were catheterised with the AUC. Please see Figure 1 for a STROBE flow diagram of recruitment and participation. The majority of participants were male and except for one patient were catheterised urethrally (Table 2). The mean duration of catheterisation with the trial catheter was 56.03 days with a range of 1-84 days. There were a total of 1681 days of participants catheterised with the AUC.

Primary outcome: safety

Eighty-four adverse events were reported by participants (0-11 AEs per participant). The majority (72.62%) of AEs were 'unrelated' or 'unlikely' to be related to the antimicrobial impregnation process. The AEs considered to be 'possibly' related to the AUC (26.19%) included blockage of the catheter, CAUTI episodes, and stinging after catheterisation as these are AEs associated with all urinary catheterisation (Table 3). The exception to this was one participant who experienced increased stinging following catheterisation that the participant had not experienced with previous catheters. This AE was classified as 'probably' related to antimicrobial impregnation of the catheters due to the noticeable difference between the AUC and the normal catheters. The stinging subsided within 48 hours and the participant then went on to consider the AUC no different from their normal catheter.

Patient medical history was recorded at baseline and eight participants had a history of frequent CAUTIs. Four participants each experienced one CAUTI while using the AUC.

This provided a preliminary indication as to the potential efficacy of the AUC, but will need further systematic investigation.

Secondary outcome: severity of AEs

None of the AEs with any relationship to antimicrobial impregnation of the catheters was considered serious or severe as seen in Table 3. All SAEs were determined to be 'unrelated' to antimicrobial impregnation of the urinary catheters. The participants were not withdrawn from the trial as a result of the SAEs and there were no restrictions on treatments received.

Secondary outcome: time to occurrence of AEs

There was no difference between time to AE in the AE causality relationship groups (p=0.5252. Log rank test).

Secondary outcome: patient acceptability

82.14% of participants rated the AUC as no different or better than their previous catheters and 89.3% of participants reported the same amount of pain or less pain from the AUC at the last recorded interview (Table 4).

A full thematic analysis of the free responses can be found as Supporting Information Table 1. At the last interview, three patients reported reduced infections, six commented on increased comfort, three wanted to keep the AUC for longer, and two wanted to have a second AUC. Impacts on mental health included getting better quality of sleep due to less need to empty the bladder via a valve and increased confidence in their catheter not becoming infected.

Secondary outcome: trial withdrawal

Nine of the 30 participants ended the trial earlier than expected. Seven were withdrawn because of catheter expulsion, a burst balloon, or balloon deflation. Bladder

stones were confirmed for the patient who had a burst balloon. One catheter was changed by a district nurse due to concerns that it may have been pulled out of position. The remaining two participants voluntarily ended the trial early, both due to what they felt was a shorter catheter length. However, both had received standard length catheters, which were 400mm in length. No catheters were removed over safety concerns.

Secondary outcome: colonisation of original and trial catheters

Twenty-nine of the 30 original and 28 of the 30 AUCs were collected. The three lost catheters fell out in the community and could not be retrieved. The original catheters and AUCs were matched (n=27 pairs) and there were significantly fewer (p=0.0088, two-tailed t-test) species of microorganisms attached to the AUC balloons compared to the matched control catheter. The pairs were well matched for the duration of catheterisation (p=0.8428, two-tailed t-test).

The lumens of two trial catheters were culture - negative and no lumens of original catheters were culture - negative. One possible concern at the start of the study was that eradication of organisms sensitive to the activity of the AUC would allow replacement by other organisms. However, this was not seen in the catheter analyses. For example, *E. faecalis* is not sensitive to the activity of the AUC yet there was no overgrowth of *E. faecalis* in the AUCs. In fact, five fewer AUC balloons and two fewer lumens contained *E. faecalis* compared to the control catheters. In general, the presence of all groups of organisms was reduced in the AUCs, with the exception of *Pseudmonas spp.* in which there were two more AUC lumens colonised with *Pseudomonas spp.* compared to the control catheters. The main limitation of this analysis is that the numbers are small and future studies will be needed to monitor the colonising microorganism populations. It is important to emphasise that, though reduction in CAUTI was mentioned by three participants in the free comments (Supporting Information Table 1), this trial was not designed to quantify efficacy.

Discussion:

Antimicrobial urinary catheters were produced and validated for use in this study, which is the first human trial of this device. 84 AEs in 30 participants across 1681 catheterisation days were recorded, and of those only one was identified as being 'probably' related to antimicrobial impregnation. This event was worse stinging than usual at catheterisation and it resolved within 48 hours. The safety profile of the AUC appears favourable. Patient acceptability was positive with 82% of participants rating the AUC as 'no different' or better than their previous urinary catheters. Of the remaining 18% (5 participants) responding "a bit worse", two felt that their trial catheter was too short, despite it being of identical length to their standard catheter; one changed the type of drainage device and experienced disconnections; one experienced increased urinary urgency, and one experienced pain on passing urine using a catheter valve.

Microbiological analysis of the participant's original and trial catheters demonstrated a significant reduction of the number of species attached to the balloon of the AUCs. Importantly, the use of the AUC did not increase the prevalence of MDR organisms or increase the prevalence of microorganisms that are non-susceptible to the activity of the AUC.

The CATHETER trial was a multi-centre randomised controlled trial of anti-septic (silver-alloy and nitrofurazone coated) catheters for short-term use. Patients receiving experimental catheters reported increased discomfort following catheterisation (silver catheter 28.7%, nitrofural catheter 38.9%) and this was a motivation for our obtaining data on safety and patient acceptability before undertaking larger studies. Our findings regarding comfort and acceptability compared very favourably with these**.** Haematuria and septicaemia were two recorded significant clinical events included in the CATHETER trial[7]. Haematuria and blockage of the catheter due to a blood clot were recorded during this trial, but there were alternative reasons for the presence of blood such as taking aspirin and the presence of an enlarged prostate which is a recognised cause of haematuria[8]. During adjudication of AE causality, as haematuria was not present without other predisposing factors and was no

worse than previous episodes, the episodes were determined as 'possibly' related as it is related to catheterisation but not necessarily catheterisation with the AUC.

The ESCALE trial, a trial of silver-alloy catheters in spinal cord injury patients, reported more AEs possibly related to catheterisation with the experimental catheters compared to standard catheters, including itching which was not reported in the control group[9]. Other AEs captured by the ESCALE trial included haematuria, rash, blockage, and suprapubic pain[9]. Rash related to catheterisation and suprapubic pain were not reported by patients in our AUC safety trial. Blockage was reported during this trial.

Other unique AEs reported here included the sensation of needing to void, burning at the beginning and end of passing urine using a catheter valve, difficulty connecting the catheter bag to the catheter, and the catheter drainage system 'pushing off' the catheter connection. While these were mild events and mostly associated with the catheter drainage systems, they were still reported by participants as part of their catheter management. The base silicone urinary catheters that were impregnated with antimicrobials may have been from a different manufacturer than their normal catheter, which could have affected what the catheter user perceives as 'normal' for their catheter.

Although the follow-up was short, any AEs relating to the composition of the catheter material are likely to have manifested in the time period studied. Further studies will confirm long-term tolerability as well as clinical efficacy and will benefit from a control arm for comparison. Other limitations include that this was an unblinded study and this may have introduced an element of bias of the participant's in reporting. Although multi-centre trials provide a better generalisability of the results and therefore increased external validity, the participants represented many health conditions and were managed throughout several districts once catheterised with the trial catheter. Therefore, they were managed as standard according to their local policies and guidelines, which were not influenced by the clinical trial.

In this trial participants were excluded if they not did have sensation in the urethra and/or bladder as they would be unable to self-report some symptoms and also for their safety. If the AUC were to cause irritation, allergy or discomfort both the participant and

research team would be unaware. This by extension excluded patients with spinal cord injury or cauda equina syndrome. Likewise, many patients with impaired cognitive capacity may require a urinary catheter but were not eligible to participate due to the possible inability to self-report new symptoms or adhere to the telephone interview schedule. These exclusion criteria were put in place to protect patients and to preserve the accuracy of the data collected. They will be included in a further randomised controlled trial of efficacy.

Conclusions:

The AUC has an advantageous safety profile and was an acceptable alternative catheter to the majority of trial participants. Information gained from this trial will support future regulatory applications for commercialisation and larger randomised controlled studies of efficacy of the AUC.

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Table Legends:

Table 1: Inclusion and exclusion criteria

Table 2: Participant demographics of consented participants

Table 3: Description of adverse events (AEs), their relationship to antimicrobial impregnation of trial catheters and their severity

Table 4: Replies from last recorded telephone interview of participants

Figure Legends:

Figure 1: STROBE flow diagram of participants involved throughout the trial pathway

Abstract:

Aims:

We have developed a novel antimicrobial urinary catheter (AUC) impregnated with rifampicin, triclosan, and sparfloxacin and demonstrated that it has long-term (~84days) protection against bacterial colonisation in vitro. This study aimed to assess the safety and patient acceptability of this device in long-term catheter users.

Methods:

Adults who use longterm (>28days) indwelling urinary catheters with capacity to consent were invited to receive the AUC at their next catheter change. The primary outcome measure was adverse events (AE) attributable to antimicrobial impregnation of the catheter. Secondary outcome measures included severity of related AEs, patient acceptability, early removal of the trial catheter, and degree of microbial colonisation of trial catheters. Except for the last, outcomes were assessed by telephone interviews. Original and trial catheters were collected, and the lumens and balloons were separated and analysed for microbiological colonisation.

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using the AUC. This provided a preliminary indication as to the potential efficacy of the AUC, but will need further systematic investigation.

Secondary outcome: severity of AEs

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Secondary outcome: time to occurrence of AEs

There was no difference between time to AE in the AE causality relationship groups (p=0.5252. Log rank test).

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Secondary outcome: colonisation of original and trial catheters

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The lumens of two trial catheters were culture - negative and no lumens of original catheters were culture - negative. One possible concern at the start of the study was that eradication of organisms sensitive to the activity of the AUC would allow replacement by other organisms. However, this was not seen in the catheter analyses. For example, *E. faecalis* is not sensitive to the activity of the AUC yet there was no overgrowth of *E. faecalis* in the AUCs. In fact, five fewer AUC balloons and two fewer lumens contained *E. faecalis* compared to the control catheters. In general, the presence of all groups of organisms was reduced in the AUCs, with the exception of *Pseudmonas spp.* in which there were two more AUC lumens colonised with *Pseudomonas spp.* compared to the control catheters. The main limitation of this analysis is that the numbers are small and future studies will be needed to monitor the colonising microorganism populations. It is important to emphasise that, though reduction in CAUTI was mentioned by three participants in the free comments (Supporting Information Table 1), this trial was not designed to quantify efficacy.

Discussion:

Antimicrobial urinary catheters were produced and validated for use in this study, which is the first human trial of this device. 84 AEs in 30 participants across 1681 catheterisation days were recorded, and of those only one was identified as being 'probably' related to antimicrobial impregnation. This event was worse stinging than usual at catheterisation and it resolved within 48 hours. The safety profile of the AUC appears favourable. Patient acceptability was positive with 82% of participants rating the AUC as 'no different' or better than their previous urinary catheters. Of the remaining 18% (5 participants) responding "a bit worse", two felt that their trial catheter was too short, despite it being of identical length to their standard catheter; one changed the type of drainage device and experienced disconnections; one experienced increased urinary urgency, and one experienced pain on passing urine using a catheter valve.

Microbiological analysis of the participant's original and trial catheters demonstrated a significant reduction of the number of species attached to the balloon of the AUCs. Importantly, the use of the AUC did not increase the prevalence of MDR organisms or increase the prevalence of microorganisms that are non-susceptible to the activity of the AUC.

The CATHETER trial was a multi-centre randomised controlled trial of anti-septic (silver-alloy and nitrofurazone coated) catheters for short-term use. Patients receiving experimental catheters reported increased discomfort following catheterisation (silver catheter 28.7%, nitrofural catheter 38.9%) and this was a motivation for our obtaining data on safety and patient acceptability before undertaking larger studies. Our findings regarding comfort and acceptability compared very favourably with these**.** Haematuria and septicaemia were two recorded significant clinical events included in the CATHETER trial[7]. Haematuria and blockage of the catheter due to a blood clot were recorded during this trial, but there were alternative reasons for the presence of blood such as taking aspirin and the presence of an enlarged prostate which is a recognised cause of haematuria[8]. During adjudication of AE causality, as haematuria was not present without other predisposing factors and was no

worse than previous episodes, the episodes were determined as 'possibly' related as it is related to catheterisation but not necessarily catheterisation with the AUC.

The ESCALE trial, a trial of silver-alloy catheters in spinal cord injury patients, reported more AEs possibly related to catheterisation with the experimental catheters compared to standard catheters, including itching which was not reported in the control group[9]. Other AEs captured by the ESCALE trial included haematuria, rash, blockage, and suprapubic pain[9]. Rash related to catheterisation and suprapubic pain were not reported by patients in our AUC safety trial. Blockage was reported during this trial.

Other unique AEs reported here included the sensation of needing to void, burning at the beginning and end of passing urine using a catheter valve, difficulty connecting the catheter bag to the catheter, and the catheter drainage system 'pushing off' the catheter connection. While these were mild events and mostly associated with the catheter drainage systems, they were still reported by participants as part of their catheter management. The base silicone urinary catheters that were impregnated with antimicrobials may have been from a different manufacturer than their normal catheter, which could have affected what the catheter user perceives as 'normal' for their catheter.

Although the follow-up was short, any AEs relating to the composition of the catheter material are likely to have manifested in the time period studied. Further studies will confirm long-term tolerability as well as clinical efficacy and will benefit from a control arm for comparison. Other limitations include that this was an unblinded study and this may have introduced an element of bias of the participant's in reporting. Although multi-centre trials provide a better generalisability of the results and therefore increased external validity, the participants represented many health conditions and were managed throughout several districts once catheterised with the trial catheter. Therefore, they were managed as standard according to their local policies and guidelines, which were not influenced by the clinical trial.

In this trial participants were excluded if they not did have sensation in the urethra and/or bladder as they would be unable to self-report some symptoms and also for their safety. If the AUC were to cause irritation, allergy or discomfort both the participant and

research team would be unaware. This by extension excluded patients with spinal cord injury or cauda equina syndrome. Likewise, many patients with impaired cognitive capacity may require a urinary catheter but were not eligible to participate due to the possible inability to self-report new symptoms or adhere to the telephone interview schedule. These exclusion criteria were put in place to protect patients and to preserve the accuracy of the data collected. They will be included in a further randomised controlled trial of efficacy.

Conclusions:

The AUC has an advantageous safety profile and was an acceptable alternative catheter to the majority of trial participants. Information gained from this trial will support future regulatory applications for commercialisation and larger randomised controlled studies of efficacy of the AUC.

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Table Legends:

Table 1: Inclusion and exclusion criteria

Table 2: Participant demographics of consented participants

Table 3: Description of adverse events (AEs), their relationship to antimicrobial impregnation of trial catheters and their severity

Table 4: Replies from last recorded telephone interview of participants

Figure Legends:

Figure 1: STROBE flow diagram of participants involved throughout the trial pathway

Response to Reviewers
Manuscript ID: NAU-18-0409

Reviewer 2:

3. Why is the data from the normal catheters included in table 3? It would be nice to compare the two for all these outcomes.

Answer: Table 3 presents the adverse events recorded during catheterisation with the antimicrobial-impregnated urinary catheter and not the normal catheters.

Reply: This is a rather unsatisfying answer. You have evaluated normal catheters for bacterial evaluation and compared in large sections the antimicrobial catheters with normal catheters (culturing etc.) and mirror tolerability between the two (being either patient reported or else). The primary aim of your study is safety and part of this is tolerability of this new catheter, but why is this then not systematically evaluated / reported by comparing them with the normal catheter, while you did do it for many other aspects of your study? Evaluation of the applicability of the new antimicrobial catheter will be based on an established balance between efficacy (reduced CAUTI and tolerability compared to normal catheters. Because there is no evaluation of efficacy of the catheter (amount of CAUTI'S) in this study, there should therefore have been be a systematic focus on tolerability by comparing table 3 parameters with a normal catheter in my opinion.

Reply to reviewer: Please find additional information in the manuscript (Lines 164-167) regarding efficacy data from baseline and with catheterisation with the antimicrobial catheter.

A comparison of tolerability between normal and antimicrobial catheters by patient self-reporting was carried out at each telephone interview. This information was summarised in Table 4.

According to the trial protocol, eligible participants were consented and after consent their normal catheter was removed and collected for analysis. The participant was catheterised with the antimicrobial catheter and followed up according to the telephone interview schedule. Therefore, normal catheters were not followed up in the same systematic manner as the aim of this study was to understand the safety profile of the AUC 'Specifically, this was determined by the rate of adverse events (AEs) attributable to the antimicrobials or the antimicrobial impregnation process' (lines 53-54). **As we know which AEs are attributable to a normal urinary catheter, we determined that there was only one AE that was possibly related to antimicrobial impregnation, which was heightened stinging immediately following catheterisation. Comparison of patient responses when using the AUC with their experience of the previous, plain catheter (Table 4) showed that 42.31% found it an improvement and 39.29% found it no different. In this way, we consider that we have done as the Reviewer requested, in that we have a comparison of the AUC with the previous plain catheter. To express this in terms of individual responses for each patient would consume a large amount of space but would not, in our view, add useful data.**

A safety and patient acceptability pilot study of a novel antimicrobial urinary catheter for long-term use

Supporting Information

Method 1:

Three 1.0 cm segments from five catheters were individually immersed in 2.0 mL chloroform to extract the drugs. This was repeated twice more and the extracts in chloroform were pooled together and the chloroform was removed under constant air flow. The extracts were re-solubilised in 100% methanol (HPLC grade, Fisher Scientific). Analysis was carried out by an Agilent 1100 HPLC machine with a variable wavelength UV detector (Agilent Technologies Inc.) connected to a Chemstation operating system. Chromatographic separations were performed using an Eclipse XDB-C8 (5µm, i.d. 4.6mm x 150 mm) column (Agilent Technologies). The mobile phase was a mixture of 10% acetonitrile (HPLC grade, Fisher Scientific) and aqueous sodium dihydrogen phosphate (Sigma-Aldrich) adjusted to 15mM and pH 2.5. The organic phase was 100% methanol. A gradient method was employed and maintained a flow rate of 1.0 mL/min and an injection volume of 5.0 µL with each run lasting eight minutes. The starting solvent concentration was 90% aqueous phase, 10% methanol increasing to 90% methanol after one minute and decreasing to 10% methanol at four minutes. Eluted drugs were first read at a wavelength of 254 nm to detect rifampicin and sparfloxacin, and then 279 nm to detect triclosan. The retention times were approximately 3.0, 3.6, and 4.5 minutes for sparfloxacin, rifampicin, and triclosan, respectively.

Table 1: Thematic analysis of free text responses to the question 'How would you rate this catheter compared to your usual?' for the first and last telephone interviews along with the number of free responses fitting into each sub-theme

First Interview		Number	Last Interview		Number
Main Themes	**Sub-Themes**		**Main Themes**	**Sub-Themes**	
No noticeable difference to previous catheters	Too soon to make a judgement	6	No noticeable difference to previous catheters	Cannot tell a difference	9
	Cannot tell a difference	8	Catheter maintenance	Infection reduction	3
Catheter maintenance	Urine flow	4		Leakage and bypassing	2
	Leakage and bypassing	3		Catheter valve issues	2
Catheter comfort	Stinging and soreness	6	Catheter comfort	Improved comfort	6
	Improved sensation	3		Discomfort	3
Mental Health	Beneficial impact on mental health	2		Catheter material	1
			Mental Health	Beneficial impact on mental health	2
			Participant satisfaction	Desire to keep the AUC	3
				Desire to have a second AUC	2

Table 1:

Inclusion Criteria
Age: 16 years old or greater
Currently fitted with a urinary catheter for at least 28 days and will require another urinary catheter for 28 days or greater
Able to understand written English and speak English fluently
Able to verbally respond and to speak on the telephone
Exclusion Criteria
Pregnant or likely to become pregnant
Adults lacking the ability to consent for themselves
Allergy to: - Rifampicin - Sparfloxacin or any other fluoroquinolone antibiotics - Triclosan - Silicone
History of uncontrolled/unmanageable autonomic dysreflexia
Significantly impaired sensation of the bladder and/or urethra

Table 2:

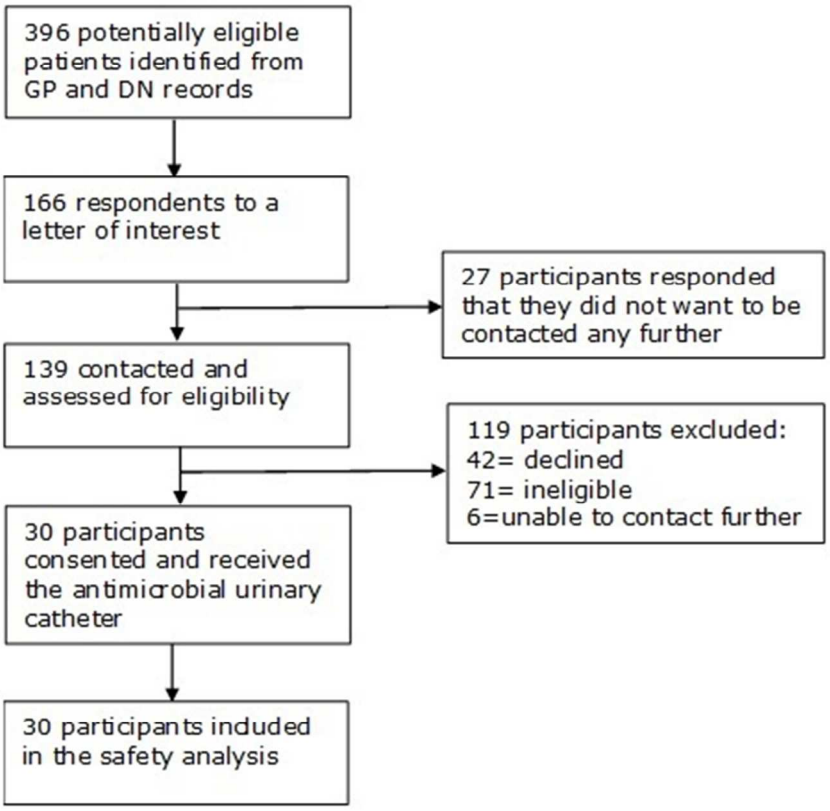
Trial Participants (n=30)		
Age (years)		
	Mean	71.4
	Range	43 - 92
Gender		
	Female	4/30 (13.3%)
	Male	26/30 (86.7%)
Catheterisation Route		
	Urethral	29/30 (96.7%)
	Suprapubic	1/30 (3.3%)
Reason for catheterisation		
	Acute retention	12/30 (40.0%)
	Chronic retention	11/30 (36.7%)
	Chronic retention with incontinence	2/30 (6.6%)
	Incontinence	2/30 (6.6%)
	Neurogenic bladder	1/30 (3.3%)
	Urethral stricture	1/30 (3.3%)
	Immobility	1/30 (3.3%)
Catheter lumen size		
	12 Ch	7/30 (23.3%)
	14 Ch	18/30 (60.0%)
	16 Ch	5/30 (16.7%)

Table 3:

AE relationship to antimicrobial impregnation of the trial catheters	Number of AEs			
	Mild	Moderate	Severe	Total
AE 'Unrelated'	**37**	**14**	**5**	**56 (66.67%)**
AE 'Unlikely'	**4**	**1**	**0**	**5 (5.95%)**
Pelvic infection	1			1
Dizzy after catheterisation	1			1
Catheter fell out spontaneously	1			1
Dizziness/generally unwell		1		1
Catheter displaced due to bag being full and falling off catheter strap	1			1
AE 'Possibly'	**19**	**3**	**0**	**22 (26.19%)**
CAUTI	2	2		4
Blockage	4	1		5
Burning at the beginning and end of passing urine via the flip flow valve	2			2
Early catheter change due to perceived shorter length	2			2
Catheter expulsion	1			1
Bypassing catheter	1			1
Sensation of needing to void	1			1
Catheter bag/valve pushing off connection	1			1
Haematuria	1			1
Stinging	1			1
Testicular ache	1			1
Difficulty connecting the catheter bag to catheter	1			1
Small sore on foreskin	1			1
AE 'Probably'	**1**	**0**	**0**	**1 (1.19%)**
Heightened stinging following catheterisation	1			1

Table 4:

Telephone interview question	Participant Responses	
	Response	Percentage of responses
'How would you rate this catheter compared to your usual catheter?'	Much better	35.17%
	A bit better	7.14%
	No different	39.29%
	A bit worse	17.86%
	Much worse	0.0%
'Have you had any pain from the catheter'	Less than usual	32.14%
	About the same	57.14%
	More than usual	10.71%



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