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Title

Antimicrobial catheters for reduction of symptomatic urinary tract infection in adults requiring short-term catheterisation in hospital: a multicentre randomised controlled trial.

Authors

Robert Pickard[#], Thomas Lam[#], Graeme MacLennan, Kath Starr, Mary Kilonzo, Gladys McPherson, Katie Gillies, Alison McDonald, Katherine Walton, Brian Buckley, Cathryn Glazener, Charles Boachie, Jennifer Burr, John Norrie, Luke Vale, Adrian Grant and James N'Dow.

[#]Both authors contributed equally to this publication

Affiliations

Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
R Pickard MD*

Academic Urology Unit, University of Aberdeen, Aberdeen, UK
T Lam PhD, K Starr BSc, J N'Dow MD

Centre for Healthcare Randomised Trials, Health Services Research Unit, University of Aberdeen, Aberdeen, UK
J Burr MSc, A McDonald MSc, G McPherson PhD, J Norrie MSc, K Starr BSc

Health Services Research Unit, University of Aberdeen, Aberdeen, UK
K Gillies PhD, C Glazener PhD, C Boachie MSc, G MacLennan MSc

Health Economics Research Unit, University of Aberdeen, Aberdeen, UK
M Kilonzo MSc

Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
K Walton FRCPath

Department of General Practice, National University of Ireland, Galway, Ireland and College of Medicine, University of the Philippines, Manila
B Buckley PhD

Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK
L Vale PhD

Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
A Grant DM

*Corresponding Author – Email: robert.pickard@newcastle.ac.uk, Tel: +44 (0) 191 222 3896. Fax: +44 (0) 191 222 0723

Summary

Background

Catheter-associated urinary tract infection (CAUTI) is a major preventable cause of harm for patients in hospital. We aimed to establish whether short term routine use of antimicrobial catheters reduced risk of CAUTI.

Methods

This was a three parallel group superiority trial whereby silver alloy-coated catheters and nitrofurazone-impregnated catheters were compared with the control of standard polytetrafluoroethylene-coated catheters. Adults requiring short-term catheterisation were recruited in 24 UK hospitals and randomised using remote computer allocation. Patients undergoing unplanned catheterisation were also randomised and consent for participation sought retrospectively. Participants and trial staff were not blinded. Data were collected by trial staff and by patient questionnaire for six weeks after randomisation. The primary outcome was incidence of symptomatic CAUTI for which an antibiotic was prescribed. We hypothesised that a 3.3% absolute reduction in CAUTI was sufficient benefit for routine use of antimicrobial catheters to be considered.

Findings

Of 7102 randomised participants, 708 (10%) were either not catheterised, did not confirm consent or withdrew. Of 6394 included in the analysis, 2097 were allocated to silver alloy, 2153 to nitrofurazone, and 2144 to control. Compared to control, the difference in incidence of CAUTI up to six weeks post-randomisation (95% confidence interval) was -0.1% (-2.4 to 2.2) for silver alloy, and -2.1% (-4.2 to 0.1) for nitrofurazone catheters. The nitrofurazone group had higher catheter-related discomfort.

Interpretation

Silver alloy-coated catheters were not effective at reducing symptomatic CAUTI. The reduction in CAUTI associated with nitrofurazone-impregnated catheters was less than that considered clinically important and we therefore conclude that the trial has shown no evidence to support their routine use.

Trial registration:

ISRCTN75198618

Funding:

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Introduction

Urinary tract infection (UTI) associated with indwelling catheters that drain urine during and after surgery or critical illness is the second most common cause of hospital-acquired infection worldwide with a conservative estimate of 145,000 adults affected in the United States in 2010[1,2,3] and 47% of newly catheterised patients in the Philippines[4]. Catheter-associated UTI (CAUTI) causes avoidable patient morbidity and increased healthcare costs in high-income and developing countries[5,6]. Implementation of evidence-based prevention strategies including avoidance of catheter use, aseptic catheter insertion, and minimisation of duration of catheterisation[7,8] have been associated with a 50% reduction in CAUTI in hospitals[3,9]. Another option is to use catheters with antimicrobial coatings to delay bacterial colonisation; two widely available examples are a silver alloy-coated latex catheter and a nitrofurazone-impregnated silicone catheter, which both inhibit urinary pathogens[10]. A Cochrane review[11] found that although these devices may reduce bacterial contamination of urine, their usefulness in combating symptomatic CAUTI and avoiding need for antibiotic treatment was uncertain. Recent guidance called for more evidence of effectiveness prior to routine implementation and emphasised the need to focus on clinical outcomes such as symptomatic UTI[8]. We report a pragmatic randomised controlled trial commissioned by the United Kingdom (UK) National Institute for Health Research (NIHR) which aimed to establish whether antimicrobial catheters reduced risk of clinical CAUTI in short term (≤ 14 days) use compared to a standard catheter. The primary objective was to determine the comparative effectiveness of a silver alloy-coated catheter and a nitrofurazone-impregnated catheter against a standard polytetrafluoroethylene (PTFE) catheter in reducing incidence of symptomatic CAUTI treated with antibiotics. Secondary objectives were to assess comparative effectiveness in reducing microbiologically-proven CAUTI and rates of bacteriuria. We intended to provide these data to clinicians, patients and healthcare policy makers to inform them of the merit of these devices in the setting of routine hospital care.

Methods

Participants

Between July 2007 and October 2010 adults undergoing urethral catheterisation for an anticipated duration of up to 14 days were identified from 24 UK National Health Service (NHS) hospitals providing surgical care across various specialties (Web Extra Table i). Participants requiring planned catheterisation as part of standard care were identified by local researchers. Instances of unplanned catheterisation with an anticipated short duration were identified by ward staff. We used wide eligibility criteria including people with diabetes and those treated with immune suppressive agents. Exclusion criteria included symptomatic UTI at baseline, having a urological procedure in the last seven days, and allergy to catheter materials. Participants gave written, informed consent before randomisation except those having unplanned catheterisation who were randomised and then invited to consent when sufficiently recovered; if they declined they were excluded. The trial was approved by a UK NHS Research Ethics Committee and overseen by Trial Steering and Data Monitoring Committees.

Interventions

Participants were allocated using simple randomisation in a 1:1:1 ratio to one of the two experimental interventions; a silver alloy-coated latex catheter, and a nitrofurazone-impregnated silicone catheter, or to the control of standard PTFE-coated latex catheter. Randomisation was implemented using a computer generated system that was concealed and remote from the users via a constantly available automated telephone service or secure website. Compliance with the allocated intervention was recorded. Participants, clinicians and the trial team were not blinded to the allocated intervention due to the distinctive appearances of each catheter. Where the period of catheterisation was unexpectedly longer than 14 days trial data were collected as if the catheter had been removed on day 14.

Outcomes
The primary outcome was the incidence of symptomatic CAUTI, defined as the presence of participant-reported UTI symptoms and clinician prescription of antibiotic for a UTI at any time up to six weeks after randomisation. Secondary outcomes included incidence of microbiologically-confirmed symptomatic CAUTI, defined as those with the primary outcome and a positive urine culture; incidence of bacteriuria at up to three days after catheter removal; changes in health-related quality of life during the six week period of trial participation; and urethral discomfort related to catheterisation.

Study Procedures
Baseline data came from clinical records and self-completed participant questionnaire. Outcome data were collected from clinical records by local trial staff during hospitalisation and by self-completed participant questionnaire or diary at three days following catheter removal, one and two weeks after catheter removal and at six weeks after randomisation. Participant questionnaires included symptoms of UTI, catheter discomfort (categorised as mild, moderate, or severe), antibiotic use, and the generic health-related quality of life measure; EQ-5D©[12]. Participant report of an episode of CAUTI after leaving hospital was verified by contacting the primary care physician to confirm prescription of an antibiotic for UTI. Mid-stream voided urine samples, or alternatively samples of urine taken directly from the catheter were collected at baseline, at up to three days after catheter removal and, if feasible, at the time of CAUTI and were analysed according to microbiology laboratory protocols in UK NHS hospitals with a positive result defined as bacterial counts ≥ 10^4 cfu/mL of no more than two microorganisms.

Statistical analysis
Considering the degree of benefit required to change practice we specified a 3.3% absolute reduction based on estimated incidence in the control group of 11% (30% relative reduction; odds ratio 0.67). For 90% power and at the 2.5% significance level to account for the two comparisons, and allowing for an attrition rate of 15%, required 2,345 participants for each arm; 7,035 participants in total. Two comparisons of equal importance were tested in the trial; silver alloy *versus* PTFE catheters, and nitrofurazone *versus* PTFE catheters. Estimates of UTI outcomes were analysed using logistic regression and summarised as absolute percentage risk differences and odds ratios, both with 95% confidence intervals (CI) calculated as 97.5% confidence intervals to adjust for the two comparisons. All included participants were analysed in their allocated group regardless of the catheter received according to intention to treat principles and were assumed to have not suffered a symptomatic CAUTI unless fulfilling primary outcome criteria. Outcomes were reported unadjusted and using adjusted models corrected for age, gender, co-morbidity, indication for catheterisation and antibiotic use prior to catheterisation. Sensitivity analysis was carried out using recruiting hospital as a random effect. The influence of factors known to modify CAUTI risk on the observed effectiveness of the experimental catheters relative to control was examined by tests for interaction at the 1% significance level given their exploratory nature. A post-hoc effect modification sensitivity analysis was carried out to explore any potential effects of duration of catheterisation on observed effectiveness. All subgroup and treatment effect modification analyses were carried out using the same generalised linear modelling framework as the main analyses. Responses to the EQ-5D© were plotted as mean and standard deviation at 3 days and 1 and 2 weeks post catheter removal, and at 6 weeks post randomisation and changes assessed by calculating the area under the curve. Sensitivity to missing data was explored using the missing at random assumption but no imputation was performed. All outcomes related to symptoms and catheter associated discomfort were analysed using ordered logit models suitable for ordinal outcome data. Analyses were carried out using SAS 9.2 (SAS Institute Inc. 2010. SAS/GRAPH® 9.2. Cary, NC USA: SAS Institute Inc.) and Stata 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX USA: StataCorp LP.).

Trial registration
Registration number ISRCTN75198618. The trial protocol[13] was peer-reviewed by *The Lancet*.

Role of the funding source
The funder had no role in design, collection, analysis, or interpretation of data, or writing of the report. RP, TL, JN'D, CB, MK, GMcP, GM and LV had full access to data collected for the trial. All authors agreed to submit for publication.

Results
We randomised 7,102 patients of whom 430 either did not provide retrospective consent or withdrew their consent prior to catheterisation and were excluded. A further 278 randomised and consenting individuals became ineligible predominantly because they did not undergo urethral catheterisation due to changed clinical care decisions. Data from 6,394 (90%) randomised participants, including 520 (8%) who gave retrospective consent following unplanned catheterisation, were included in the intention to treat analysis. A total of 272 (4%) participants included in the analysis did not receive the allocated catheter because clinical staff substituted an alternative catheter instead (Figure 1). Reason for catheterisation was recorded for 6296 participants of whom 5966 (95%) required peri-operative monitoring of urine output and 277 (5%) had urinary retention. The proportion of participants under the care of different specialities recruiting to the trial was balanced across the three groups (Web Extra Table ii). Baseline characteristics (Table 1) and response rates to postal questionnaire (Figure 1) were similar across groups. Primary outcome data for the intention-to-treat analysis was obtained for all but one non-responder in whom it was assumed that no CAUTI occurred.

Incidence of symptomatic CAUTI up to six weeks post-randomisation was 12.5% amongst participants randomised to silver alloy catheter, and 10.6% in those randomised to nitrofurazone catheter, compared to 12.6% for the PTFE control giving absolute risk differences (95% CI) of -0.1% (-2.4 to 2.2) and -2.1% (-4.2 to 0.1) respectively. The odds ratio (95% CI) for symptomatic CAUTI compared to control was 0.99 (0.81 to 1.22; p= 0.92) for use of the silver alloy catheter, and 0.82 (0.66 to 1.01; p= 0.037) for use of the nitrofurazone catheter (Table 2). A sensitivity analysis incorporating recruiting hospital gave practically identical results (Table 3). There were no reported admissions to intensive care unit or deaths attributed to CAUTI. There was no difference between groups in duration of catheterisation and hospitalisation (Table 1). There was no interaction between observed effectiveness of the antimicrobial catheters and presence of risk factors for CAUTI (Figure 2a-c). In particular the modelled interaction between catheter duration and both the silver alloy *versus* control and the nitrofurazone *versus* control comparisons was not significant (p = 0.83 and p = 0.19 respectively). The time of occurrence of CAUTI relative to catheter removal is shown in Table 4. The nitrofurazone catheter used in the trial was associated with a lower incidence of microbiologically-proven symptomatic CAUTI (p = 0.02) and a lower rate of bacteriuria (p = 0.001), but also greater participant-reported discomfort during use and at removal (Table 2). There were no statistically significant differences in health status between trial groups over the period of observation (Table 5).

Discussion
We sought to determine whether short-term use of either of two available antimicrobial catheters was clinically effective in reducing CAUTI compared to the PTFE control. Interpretation of the findings depends on the level of benefit thought sufficient to justify changes in practice. From the clinician perspective and taking into account previously reported effect sizes[15,16,17], we considered that use of an antimicrobial catheter would be worthwhile if about one in 30 people avoided suffering a CAUTI (3.3% absolute reduction)

and powered our trial accordingly. It is possible that others, such as patients needing short-term catheterisation or the healthcare funders with a finite budget, would have required lesser or greater degrees of benefit. Consideration from different perspectives of trial estimates of clinical effectiveness with their associated uncertainties will determine how our results are interpreted.

Silver alloy-coated catheters

Our best estimate of the effectiveness of the silver alloy catheter compared with control was close to no difference. The results suggest that 1,000 people would need to receive a silver alloy catheter to prevent one CAUTI, with the true effect lying between one infection prevented in 42 people and one infection caused in 45 people. As the CI did not include the pre-stated effect size but did include zero we conclude that the silver alloy catheter is not effective. Our conclusion is important since hospitals in the USA and UK have implemented silver alloy-coated catheters for routine short-term use as part of CAUTI prevention[17,18,19]. This followed a meta-analysis of previous trials showing a relative risk (95% CI) of 0.54 (0.43-0.67) for bacteriuria[11], a finding that did not change substantially on re-analysis taking into account possible bias[20]. We felt that bacteriuria did not map closely to clinical diagnosis of UTI and therefore used a primary patient-reported UTI outcome backed by clinician action of antibiotic prescription without requirement for microbiological proof, assessed for at least four weeks after catheter removal. This was to better reflect clinical care and patient experience with an adequate observation period to capture relevant events, and to fulfil research priorities set out in international public health policy guidelines[7,21,22]. Our secondary outcomes of microbiologically-proven symptomatic CAUTI and bacteriuria at up to three days after catheter removal align better with previous trials but again showed the silver alloy catheter to be ineffective. The early change in practice made by some hospitals was based on limited evidence of effectiveness primarily from underpowered studies; the contrast between the finding of no difference from a robustly designed, large, multi-centre pragmatic trial, and initial promising findings from smaller explanatory trials has been observed previously[23].

Nitrofurazone-impregnated catheter

The best estimate of effectiveness for the nitrofurazone catheter is that they would prevent one symptomatic CAUTI in every 48 people catheterised, but that the true effect could lie between one in 24 people and no protective effect at all. This estimate was less than the effect size sought and the confidence interval included zero so we conclude that routine use of nitrofurazone catheters for short term catheterisation did not give the degree of benefit that we consider to be clinically relevant. The potential increased discomfort experienced by about one in 9 people, adding to the distress of an already intimate invasive intervention should also be noted. The estimate of effectiveness seen in our trial was smaller than that from meta-analyses of previous trials[8,11] and in particular contrasts with an earlier report of a relative risk (95% CI) for antibiotic-treated CAUTI recorded as a secondary outcome of 0.27 (0.10 to 0.69) in favour of nitrofurazone catheters[24]. Use of bacteriuria as a primary outcome and missing data for the secondary outcomes in this report limits useful comparison with our results. The contrasting lack of effectiveness seen in our trial may reflect wider eligibility criteria, shorter catheter duration and pragmatic design. Our results for microbiological CAUTI and bacteriuria were suggestive of a relevant antimicrobial effect, but this might be offset by public health concerns regarding widespread antimicrobial use. Current evidence suggests that nitrofuran-based antimicrobials are less prone to development of bacterial resistance[25] although this was not monitored in our trial. The silicone material of manufacture may have contributed to greater antimicrobial effect compared to latex control, but we did not explore this since we aimed to test the effectiveness of the device as an available technology and accordingly rejected the option of including a standard silicone catheter as a second control arm.

Strengths and limitations of the trial

This trial was pragmatically designed to evaluate clinical effectiveness of two widely available antimicrobial catheters. We sought to resolve uncertainty concerning benefit of antimicrobial catheters for short term use, focusing on the clinically relevant outcome of symptomatic UTI treated with antibiotics rather than microbiologically defined bacteriuria[8]. We considered that our chosen primary outcome would be measurable and represent a clinically important event reflecting patient experience. This definition and our successful attribution of the outcome across the trial population allowed strong and practically useful conclusions to be drawn concerning the clinical effectiveness of antimicrobial catheters. We also adopted a pragmatic approach to recruitment ensuring participants reflected the broad spectrum of patients needing short term catheterisation in hospital, with particular focus on those admitted for elective surgery, the population most often requiring this intervention, meaning that the results can be readily generalised. The wide spectrum of hospital type, specialities, and surgical procedures was protective against selection bias but we did not recruit patients admitted directly to intensive care units and the number of eligible patients identified and recruited from acute medical wards was small.

The trial was powered at 90% to detect what we considered to be a clinically meaningful benefit from routine use of the antimicrobial catheters tested. For both comparisons the central estimate was less than the effect size sought and the confidence interval included zero. The results therefore allow a firm conclusion to be made that there is no statistically significant difference between either the silver alloy or the nitrofurazone catheters and control. Assuming that our hypothesised effect size of 3.3% and CAUTI incidence with a standard catheter of 11% were correct there remains an approximate 10% chance of a type II error causing us to wrongly conclude that they are ineffective. It is possible that others may have considered a lesser absolute difference in CAUTI risk to be worth exploring and powered the study accordingly. We are however confident that the 3.3% difference we set out to identify is a plausible estimate of the minimum benefit required to change routine practice.

To minimise misclassification of participants' self-report of UTI we successfully resolved any missing data and confirmed CAUTI through verification of clinician prescription of antibiotic. Given the size of the trial and available resources we could not independently verify that participants reporting no CAUTI after discharge from hospital had not received a prescription of antibiotic for UTI. We consider it unlikely that any misclassification of absence of CAUTI could be differential across trial groups since decisions by participants not to report symptoms and treatment decisions by primary care clinicians would not be influenced by the type of catheter used. It is possible that some episodes of community-acquired UTI were captured, particular for participants with short catheter duration. However recent catheterisation would remain a risk factor and there was no interaction between duration and effectiveness. Telephone and internet-based trial entry with computer-generated simple randomisation minimised risk of allocation bias. Post-randomisation withdrawals were primarily due to patients not being catheterised and refusal to participate after unplanned catheterisation with no relation to the catheter allocated. We could not mask the allocated catheter, but clinical staff who inserted the catheter were unlikely to be involved in decisions regarding timing of removal or antibiotic prescription for CAUTI.

We used $\geq 10^4$ cfu/mL as the threshold for a positive urine culture since this was consistently reported by participating hospital laboratories. This may have resulted in higher absolute rates for microbiologically-driven outcomes compared to the more usual $\geq 10^5$ cfu/mL criterion but we have no evidence that it resulted in any bias to our comparisons. We did not monitor use of other CAUTI prevention actions in participating hospitals, but found no evidence for interaction between hospital and comparative effectiveness. This provides some reassurance that any possible differences between institutions or individual clinicians in terms of diagnosis of clinical CAUTI or criteria used to initiate antibiotic treatment did not

impact on our primary outcome. It is possible that catheter duration experienced by most participants was too short to allow the anti-microbial effect of the tested catheters to become apparent. The study was designed to align with routine hospital practice and it is unlikely in this setting that patients anticipated as requiring differing short periods of catheterisation could be separated and receive different catheters. Furthermore we found no significant interaction between catheter duration and differences in incidence of CAUTI. The median duration seen in our trial is representative of current practice [26].

Implications of trial findings for clinical practice and research

Our results give no support for the routine use of silver alloy-coated catheters. The nitrofurazone catheter was not effective according to our pre-stated criterion and we would therefore regard our trial as showing no evidence to justify its use. However some, particularly patients requiring short term catheterisation, or providers seeking to reduce healthcare-acquired infection rates, may judge that a lesser degree of benefit might be sufficient and be encouraged by our finding of statistical significance for secondary microbiological outcomes. We caution against such alternative conclusions since they are not supported by the primary trial result. Hospitals will need to carefully consider the lack of effectiveness of the tested catheters taking into account differences between the UK NHS and their own healthcare system. Those who have already implemented use of silver alloy catheters may have an opportunity to reallocate resources without loss of benefit, while organisations planning their implementation may wish to reconsider. Overall it would seem appropriate for patients, clinicians and healthcare providers to persist with simple strategies to prevent CAUTI and await any adjustment of guidance on CAUTI prevention in the light of our results before making a decision[1,7,22,27].

Word count:

Abstract 263, Text 3,385

Panel: Research in Context

Systematic review

This trial was commissioned because a Cochrane Review published in 2004 and updated in 2008 found that although the summarised evidence from published randomised trials suggested that antimicrobial catheters reduced the rate of microbiological bacteriuria, there was no evidence for an associated reduction in patient morbidity related to symptomatic catheter-associated urinary tract infection (CAUTI). This was confirmed by a further systematic review and re-appraisal of the Cochrane meta-analysis published by the United States Centres for Disease Control and Prevention (CDC) in 2009 which emphasised the need for large pragmatic trials using symptomatic CAUTI as the primary outcome.

Interpretation

The pragmatic design and large sample size of this trial, and use of primary outcomes combining patient, clinician, and healthcare provider perspectives, gives clear information regarding the relative benefit of two widely available antimicrobial catheters. Our finding that neither the silver alloy-coated catheter nor the nitrofurazone-impregnated catheter reached our pre-stated minimum level of clinical effectiveness will allow better decisions to be made concerning use of these devices in healthcare.

Contributors

JN'D was the chief investigator of the study; he had complete involvement and oversight of the study design, execution and data collection, and was responsible for the final manuscript. RP contributed his clinical expertise to the design of the study, supported conduct of the trial, interpreted the trial findings and contributed to the manuscript as first author. TL contributed his clinical expertise to the design of the study, helped with clinical

support of the trial and contributed to the manuscript as co-first author. GM led the statistical analysis of the study and writing up and display of the results. KS was responsible for the day-to-day management of the trial and also contributed to the manuscript. MK performed the health-related quality of life analysis. GMcP designed the programming of the study database, data analysis and contributed to writing the manuscript. KG was responsible for the establishment of the trial, and its initial day-to-day management. AM contributed to the design of the study, and provided design support to the trial staff. KW led the microbiological aspects of trial design and planning, advised on conduct of the trial, and provided the microbiologist perspective for data interpretation and manuscript preparation. BB contributed to the consumer aspect of the study and writing of the manuscript. CG contributed to the design of the study and the writing of the manuscript. CB performed much of the statistical analysis required for the trial results. JB contributed to the delivery of the trial and to the writing of the manuscript. JN was instrumental for the design of the study. LV contributed extensively to manuscript writing. AG contributed to the overall study design and gave expert guidance on the final manuscript.

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Conflicts of interest

RP has no conflict of interest. AG receives salary support from the NIHR for his role as Director of their Programme Grants for Applied Research Programme. TL and KG authored the Cochrane Review on antimicrobial catheters, GM, KS, MK, GMcP, AM, KW, BB, CG, CB, JB, JN, LV, and JN'D declared no conflict of interest.

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Table 1: Baseline and other participant characteristics

	Silver alloy N = 2097	Nitrofurazone N = 2153	PTFE control N = 2144
Age in years: mean [SD]	59 [16]	59 [16]	59 [16]
Female	1319 (63)	1333 (62)	1325 (62)
Unplanned catheterisation	94 (5)	94 (5)	89 (4)
Co-morbidity associated with increased CAUTI risk – valid N	2084	2138	2136
Urological condition	196 (9)	214 (10)	214 (10)
Diabetes	207 (10)	197 (9)	216 (10)
Immune suppression*	144 (7)	135 (6)	151 (7)
Antibiotics given within seven days prior to randomisation	370 (18)	396 (18)	385 (18)
Prophylactic antibiotics given prior to surgical procedure	1529 (73)	1537 (71)	1547 (72)
Antibiotics given during period of catheterisation for reasons other than CAUTI	533(25)	511 (24)	474 (22)
Antibiotics given after catheter removal for reasons other than CAUTI	193 (9)	178 (8)	204 (10)
Baseline urine sample - valid N	2002	2074	2057
MSU	1709 (85)	1735 (84)	1721 (84)
CSU	293 (15)	339 (16)	336 (16)
Baseline number of cfu/mL - valid N	1998	2071	2054
No reported growth	1830 (92)	1923 (93)	1901 (93)
≥ 10^4	168 (8)	148 (7)	153 (7)
Median duration of catheterisation in days (interquartile range)	2 (1-3)	2 (1-3)	2 (1-3)
Prolonged catheterisation > 14 days	73 (4)	79 (4)	67 (3)
Median duration of hospitalisation in days (interquartile range)	6 (3-8)	6 (3-9)	6 (3-9)

*Cell values are n (%) unless otherwise stated. PTFE = polytetrafluoroethylene, SD = standard deviation, MSU = mid-stream specimen of urine, CSU = catheter specimen of urine, cfu = colony-forming unit. *Immune suppression was defined as a participant being currently treated with an immunosuppressive therapy including corticosteroids, methotrexate, and chemotherapeutic agents.*

Table 2: Primary and other trial outcomes

		Silver alloy	Nitrofurazone	PTFE control
Primary outcome: Symptomatic antibiotic-treated UTI within six weeks of randomisation		**N = 2097**	**N = 2153**	**N = 2144**
Incidence n (%)		263 (12.5)	228 (10.6)	271 (12.6)
Absolute percentage risk difference (95% CI) compared to PTFE control		-0.1 (-2.4 to 2.2)	-2.1 (-4.2 to 0.1)	
Odds Ratio (95%CI); [p-value]·	unadjusted	0.99 (0.81 to 1.22); [0.92]	0.82 (0.66 to1.01); [0.037]	
Odds Ratio (95%CI); [p-value]·	adjusted	0.96 (0.78 to 1.19); [0.69]	0.81 (0.65 to 1.01); [0.031]	
Secondary outcome: Symptomatic UTI treated with antibiotics any time up to six weeks post-randomisation and associated with positive urine culture (≥10^4 cfu/mL)		**N = 2097**	**N = 2153**	**N = 2144**
Incidence n (%)		105 (5.0)	69 (3.2)	99 (4.6)
Absolute percentage risk difference (95% CI) compared to PTFE control		0.4 (-1.2 to 1.9)	-1.4 (-2.7 to -0.1)	
Odds Ratio (95%CI); [p-value]·	unadjusted	1.08 (0.78 to 1.52); [0.55]	0.68 (0.48 to 0.99); [0.017]	
Odds Ratio (95%CI); [p-value]·	adjusted	1.09 (0.78 to 1.51); [0.58]	0.68 (0.47 to 0.98); [0.019]	
Secondary outcome: Bacteriuria (symptomatic and asymptomatic) detected by urine culture at anytime up to three days after catheter removal (≥10^4 cfu/mL)		**N = 1785**	**N = 1846**	**N = 1839**
Incidence n (%)		310 (17.4)	249 (13.5)	321 (17.5)
Absolute percentage risk difference (95% CI) compared to PTFE control		-0.1 (-3.2 to2.8)	-4.0 (-6.7 to –1.2)	
Odds Ratio (95%CI); [p-value]·	unadjusted	0.99 (0.82 to 1.21); [0.94]	0.74 (0.60 to 0.91); [0.001]	
Odds Ratio (95%CI); [p-value]·	adjusted	0.99 (0.81 to 1.21); [0.89]	0.73 (0.59 to 0.90); [0.001]	
Secondary outcome: Self-reported participant discomfort ratings with catheter in place		**N = 1829**	**N = 1879**	**N = 1889**
Incidence of any discomfort n (%)		322 (17.6)	496 (26.4)	396 (21)
Absolute percentage risk differences (95% CI) for experiencing grades of discomfort compared to PTFE control		-3.4 (-6.4 to -0.4)	5.4 (2.2 to 8.7)	
Odds ratio of experiencing discomfort (95% CI):		0.81 (0.67 to 0.98)	1.35 (1.13 to 1.62)	
Secondary outcome: Self-reported participant discomfort ratings for catheter removal		**N = 1817**	**N = 1867**	**N = 1881**
Incidence of any discomfort n (%)		521 (28.7)	707 (38.9)	499 (26.5)
Absolute percentage risk difference (95% CI) for experiencing grades of discomfort compared to PTFE control		2.2 (-1.3 to 5.6)	11.3 (7.8 to 14.9)	
Odds ratio of experiencing discomfort (95% CI)		1.11 (0.94 to 1.31)	1.69 (1.44 to 1.97)	

Adjusted models corrected for age, gender, co-morbidity, indication for catheterisation and antibiotic use prior to catheterisation. Analysis by intention-to-treat. PTFE = polytetrafluoroethylene, UTI = urinary tract infection, CI = confidence interval. Absolute risk difference derived from logistic regression models using delta method.

Table 3: Sensitivity analysis of interaction between recruiting hospital and primary effectiveness outcome [odds ratio (95% confidence interval) for comparative incidence of symptomatic CAUTI between experimental and control]

Comparison		
Silver Alloy vs. PTFE control		
	Fixed Effects	***Random Effects***
unadjusted	0.99 (0.81 to 1.22); [0.92]	1.00; (0.84, 1.22); [0.88]
adjusted	0.96 (0.78 to 1.19); [0.69]	0.99; (0.81, 1.20); [0.88]
Nitrofurazone vs. PTFE control		
	Fixed Effects	***Random Effects***
unadjusted	0.82 (0.66 to 1.01); [0.037]	0.83 (0.69, 1.02); [0.039]
adjusted	0.81 (0.65 to 1.01); [0.031]	0.83 (0.68, 1.02) ;[0.045]

Cell values are odds ratio (95% confidence interval) [p value]. CAUTI = catheter-associated urinary tract infection; PTFE = polytetrafluoroethylene.

Table 4: Timing of report of CAUTI relative to catheterisation status

		Silver alloy N=2097	Nitrofurazone N=2153	PTFE control N=2144
No CAUTI	n	1834	1925	1873
	%	87	89	87
CAUTI during catheterisation	n	34	28	33
	%	2	1	2
CAUTI reported prior to completion of week one diary	n	99	77	92
	%	5	4	4
CAUTI reported in week one or week two diary or on six week questionnaire	n	127	122	144
	%	6	6	7
Missing*	n	3	1	2

*CAUTI = Catheter-associated urinary tract infection. *Participants whose catheterisation status could not be ascertained*.

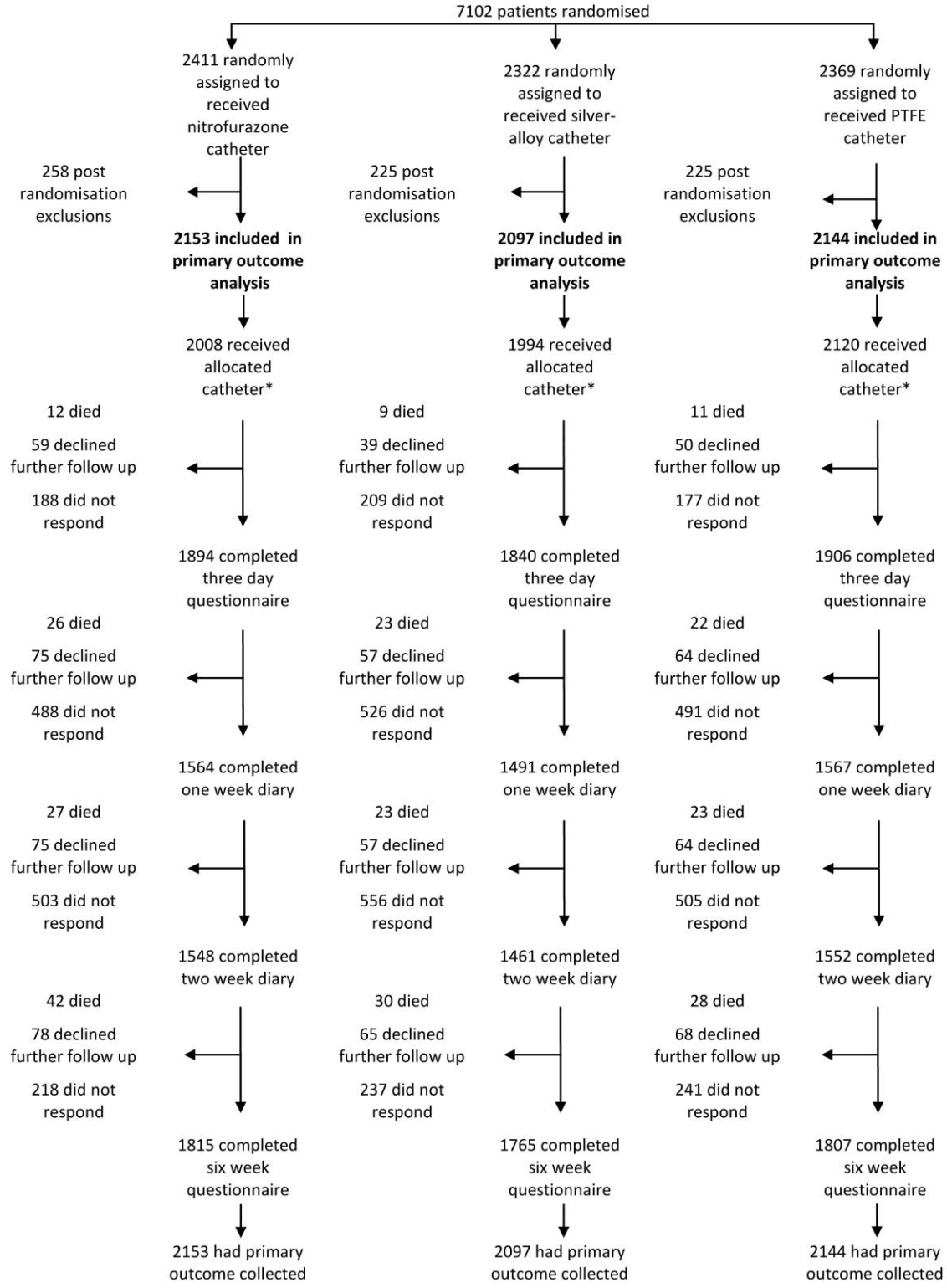
Table 5: Participant health state measured by responses to the EQ-5D© questionnaire at study time-points for each trial arm*

Follow-up time point	Silver alloy N = 2097		Nitrofurazone N = 2153		PTFE control N = 2144	
Baseline prior to randomisation	2076,	0.72 (0.29)	2127,	0.72 (0.29)	2123,	0.72 (0.3)
3 days after catheter removal	1801,	0.58 (0.28)	1860,	0.59 (0.27)	1871,	0.59 (0.27)
1 week after catheter removal	1308,	0.60 (0.29)	1363,	0.62 (0.27)	1366,	0.61 (0.27)
2 weeks after catheter removal	1328,	0.69 (0.27)	1405,	0.70 (0.26)	1398,	0.70 (0.25)
6 weeks after randomisation	1665,	0.78 (0.24)	1705,	0.78 (0.24)	1721,	0.80 (0.23)

Cell contents are valid n, mean (SD), higher score represents better health status. SD = standard deviation.

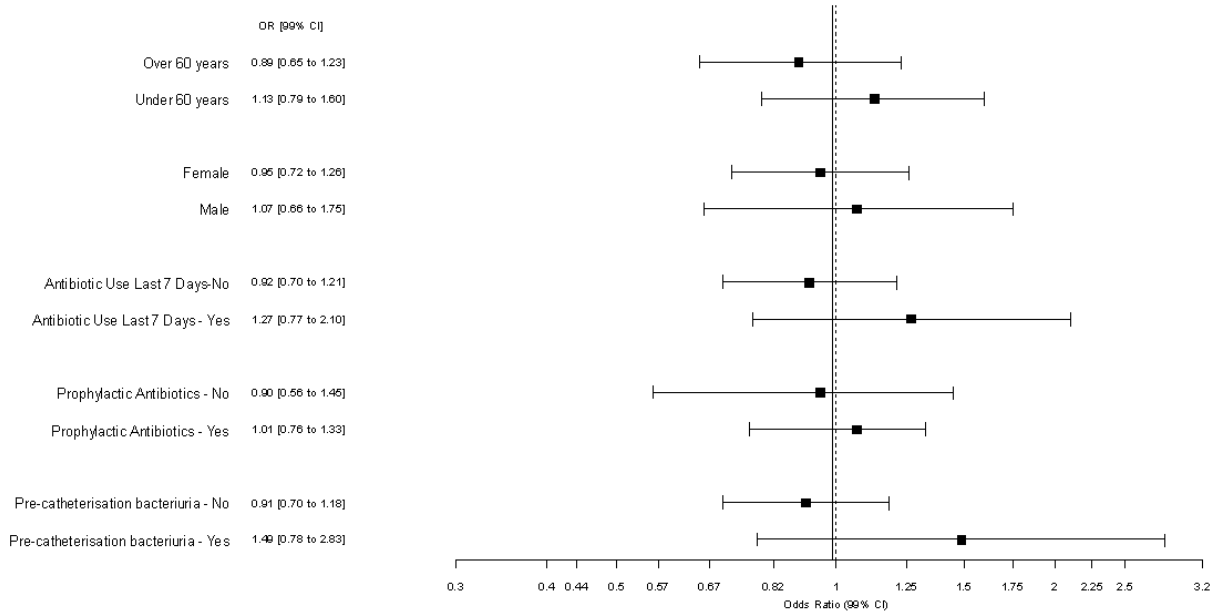
** The EQ-5D, a generic health status measurement tool, divides health status into 5 dimensions (mobility, self care, usual activities, pain/comfort and anxiety /depression)[12,] Each of these dimensions has three levels, therefore, there are 243 possible health states. The utility scores were used to calculate QALYs by multiplying the time spent in each health state by the utility score for that state [14].*

Figure 1: Progress of participants through the trial



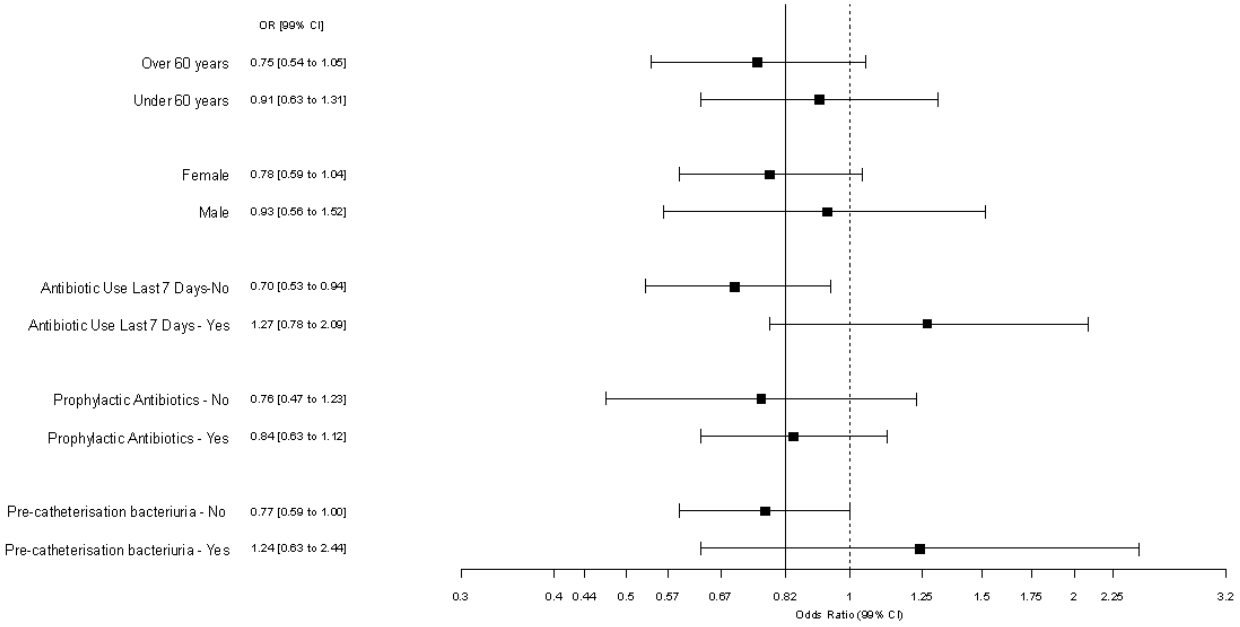
** Generally participants underwent catheterisation in the operating suite. In 272 (4.3%) of cases an alternative catheter to that allocated by randomisation was inserted mainly due to error by clinical staff. The numbers of participants dying, declining further follow up or not responding are cumulative in direction of participant flow. The questionnaires and diaries were completed at three days and at one and two weeks after catheter removal and finally at six weeks after the day of randomisation.*

Figure 2a: Forest plots of subgroup analyses; catheter-associated urinary tract infection at any point up to six weeks post randomisation for silver alloy *versus* polytetrafluoroethylene control comparison



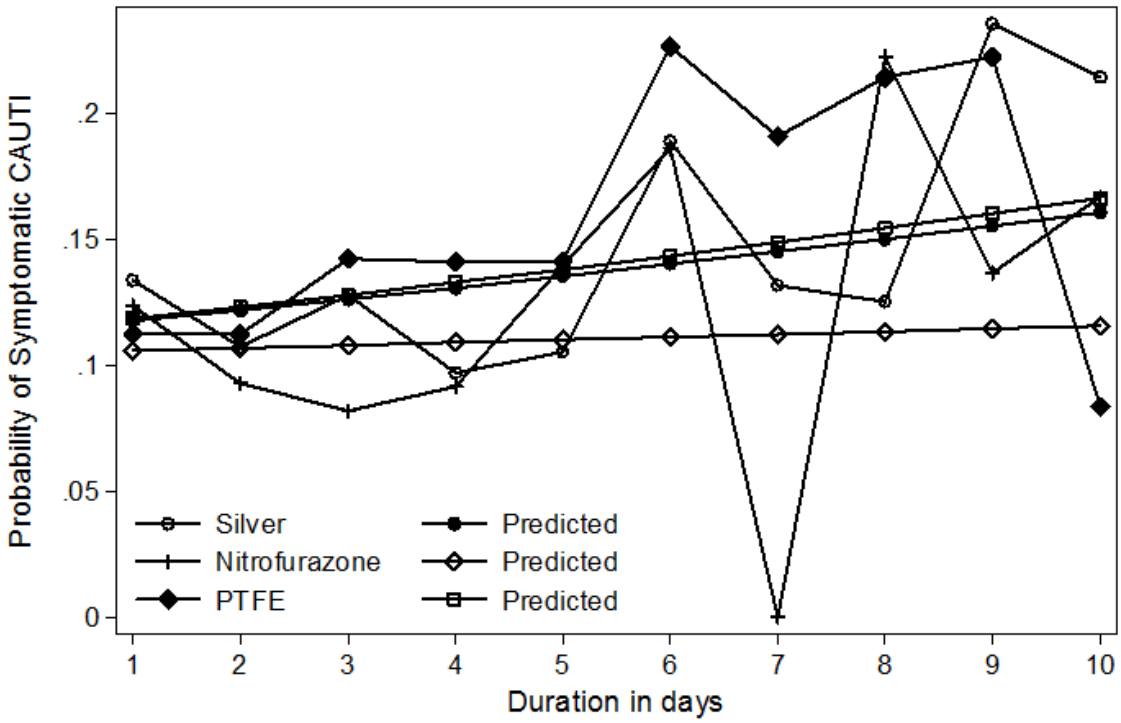
OR = odds ratio, CI = confidence interval

Figure 3b: Forest plots of subgroup analyses. Catheter-associated urinary tract infection at any time up to six weeks post randomisation for nitrofurazone *versus* polytetrafluoroethylene control comparison



OR = odds ratio, CI = confidence interval.

Figure 3c: Graphical plot of incidence of catheter associated urinary tract infection at up to six weeks following randomisation against duration of catheterisation for trial groups showing both the observed incidence and that predicted by the statistical model



Accompanying data table for Figure 3c

Day	1	2	3	4	5	6	7	8	9	10
Silver alloy	89/666 (13.3)	74/691 (10.7)	31/243 (12.8)	15/155 (9.7)	8/76 (10.5)	10/53 (18.9)	5/38 (13.2)	2/16 (12.5)	4/17 (23.5)	3/14 (21.4)
Nitrofurazone	90/728 (12.4)	65/701 (9.3)	21/257 (8.2)	14/153 (9.2)	12/86 (14.0)	8/43 (18.6)	0/28 (0)	4/18 (22.2)	3/22 (13.6)	1/6 (16.7)
PTFE control	81/721 (11.2)	79/704 (11.2)	33/232 (14.2)	21/149 (14.1)	11/78 (14.1)	12/53 (22.6)	8/42 (19.0)	6/28 (21.4)	4/18 (22.2)	1/12 (8.3)

Cell counts are n/N (%) where N = number of participants with catheter duration of specified number of days and n = number with episode of CAUTI within six weeks of randomization

PTFE = polytetrafluoroethylene control, CAUTI = catheter-associated urinary tract infection

Web Extra Material

Table i: Hospitals and specialties recruiting to the trial

Hospital	Specialties recruiting	Silver Alloy N = 2097	Nitrofurazone N = 2153	PTFE control N = 2144
Aberdeen Royal Infirmary	Cardiothoracic, general surgery, vascular, obstetrics & gynaecology	459(21.9)	430(20.0)	434(20.2)
Royal Blackburn & Burnley General Hospitals	Obstetrics & gynaecology	33(1.6)	40(1.9)	36(1.7)
Blackpool Victoria Hospital	Cardiothoracic, obstetrics & gynaecology	69(3.3)	64(3.0)	69(3.2)
Bristol Royal Infirmary	Cardiothoracic, general surgery	1(0.0)	3(0.1)	2(0.1)
Edinburgh Royal Infirmary	Obstetrics & gynaecology	36(1.7)	42(2.0)	28(1.3)
Guy's Hospital, London	Renal transplant	72(3.4)	75(3.5)	81(3.8)
Harrogate District Hospital	Obstetrics & gynaecology	3(0.1)	0(0.0)	1(0.0)
Hillingdon Hospital	General surgery, obstetrics & gynaecology	60(2.9)	72(3.3)	66(3.1)
Hinchingbrooke Hospital	Orthopaedics	20(1.0)	22(1.0)	14(0.7)
Raigmore Hospital, Inverness	Orthopaedics, general surgery	269(12.8)	270(12.5)	243(11.3)
Liverpool Women's Hospital	Obstetrics & gynaecology	46(2.2)	57(2.6)	45(2.1)
Newcastle General Hospital	Neurosurgery, general surgery	240(11.4)	250(11.6)	264(12.3)
Freeman Hospital, Newcastle	Cardiothoracic	147(7.0)	155(7.2)	165(7.7)
Royal Victoria Infirmary, Newcastle	Obstetrics & gynaecology	95(4.5)	95(4.4)	113(5.3)
Norfolk and Norwich University Hospital	Orthopaedics, obstetrics & gynaecology	5(0.2)	14(0.7)	9(0.4)
North Tyneside General Hospital	General surgery, urology, obstetrics & gynaecology, medical ward, orthopaedics	144(6.9)	156(7.2)	155(7.2)
Nottingham City Hospital	Orthopaedics, obstetrics & gynaecology	47(2.2)	46(2.1)	51(2.4)
Queen Alexandra Hospital, Portsmouth	Obstetrics & gynaecology	43(2.1)	50(2.3)	51(2.4)
Royal Preston Hospital	Obstetrics & gynaecology	37(1.8)	34(1.6)	36(1.7)
Southampton General Hospital	Cardiothoracic	187(8.9)	189(8.8)	178(8.3)
Sunderland Royal Hospital	Obstetrics & gynaecology	16(0.8)	18(0.8)	29(1.4)
Musgrove Park Hospital, Taunton	General Surgery, orthopaedics	10(0.5)	8(0.4)	6(0.3)
Torbay Hospital	General Surgery, medical ward	22(1.0)	27(1.3)	26(1.2)
Yeovil District Hospital	General Surgery, obstetrics & gynaecology	36(1.7)	36(1.7)	42(2.0)

Cell values are n (%) of participants recruited and included in analysis. PTFE = polytetrafluoroethylene

Table ii: Participant recruitment according to specialty

Specialty	Silver alloy N = 2087	Nitrofurazone N = 2146	PTFE control N = 2141
Medical	5 (<1)	3(<1)	4 (<1)
Urology	45 (2)	44 (2)	56 (3)
Cardiothoracic and vascular	567 (27)	580 (27)	567 (27)
General surgery	194 (9)	202 (9)	220 (10)
Obstetrics and gynaecology	705 (34)	732 (34)	737 (34)
Orthopaedics	328 (16)	335 (16)	295 (14)
Neurosurgery/Ear, nose and throat/Maxillofacial	243 (12)	250 (12)	262 (12)

Cell values are n (%). PTFE = polytetrafluoroethylene