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Reducing catheter associated urinary tract infections in hospitals: study protocol for a multi-site randomised controlled study

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Title: Reducing catheter associated urinary tract infections in hospitals: study protocol for a multi-site randomised controlled study

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Abstract

Introduction: Despite advances in infection prevention and control, catheter associated urinary tract infections (CAUTIs) are common and remain problematic. A number of measures can be taken to reduce the risk of CAUTI in hospitals. Appropriate urinary catheter insertion procedures are one such method. Reducing bacterial colonisation around the meatal or urethral area has the potential to reduce CAUTI risk. However, evidence about the best antiseptic solutions for meatal cleaning is mixed, resulting in conflicting recommendations in guidelines internationally. This paper presents the protocol for a study to evaluate the effectiveness (objective 1) and cost effectiveness (objective 2) of using chlorhexidine in meatal cleaning prior to catheter insertion, in reducing catheter associated asymptomatic bacteriuria and CAUTI.

Methods and analysis: A stepped wedge randomised controlled trial will be undertaken in three large Australian hospitals over a 32-week period. The intervention in this study is the use of chlorhexidine (0.1%) solution for meatal cleaning prior to catheter insertion. During the first eight weeks of the study, no hospital will receive the intervention. After eight weeks, one hospital will cross over to the intervention with the other two participating hospitals crossing over to the intervention at eight-week intervals respectively based on randomisation. All sites complete the trial at the same time in 2018.The primary outcomes for objective 1 (effectiveness) are the number of cases of CAUTI and catheter associated asymptomatic bacteriuria per 100 catheter days will be analysed separately using Poisson regression. The primary outcome for objective 2 (cost effectiveness) is the changes in costs relative to health benefits (incremental cost-effectiveness ratio) from adoption of the intervention.

Dissemination: Ethics approval has been obtained. Results will be disseminated via peer-reviewed journals and presentations at relevant conferences.

Trial registration: Australia New Zealand Clinical Trial Registry (No 12617000373370), approved 13/03/2017. Protocol version 1.1

Key words: Cost-effectiveness, Healthcare-associated infection, Urinary Tract Infections, Infection Control, Catheter-Related Infections.

Strengths and limitations of this study

- Results that will inform infection prevention and control practice and guidelines internationally
- Randomised control design
- Evaluation of efficacy and cost effectiveness
- Limited to evaluated saline versus chlorhexidine

Introduction

Indwelling urinary catheters are commonly used in healthcare facilities, with foundation work indicating that 26% of patients admitted to an Australian hospital receive an indwelling urinary catheter and 1% of these patients develop catheter-associated urinary tract infections (CAUTIs).[1] Catheter associated urinary tract infections have been associated with increased morbidity, mortality, increased length of stay in hospital and higher hospital costs for patients and health systems.[2] In Australia, an estimated 380,000 bed days are lost each year due to healthcare-associated urinary tract infections (UTIs), a large proportion of which are CAUTIs. Catheter associated urinary tract infections are also associated with higher risk of antimicrobial resistance (AMR), making the treatment of patients difficult.[3 4] Antimicrobial resistance in UTIs has also been shown to be increasing globally, further emphasising the need to develop interventions to reduce the incidence of CAUTIs.[5]

Despite advances in infection prevention and control, CAUTIs remain problematic, hence further research is needed to identify ways to reduce the burden they create.[6] Evidence shows that reducing bacterial colonisation around the meatal or urethral area has the potential to reduce CAUTI risk.[7] However, evidence about the best antiseptic solutions for meatal cleaning is mixed. Previous research also identified a lack of documentation and knowledge in relation to the meatal cleaning solution used prior to catheter insertion.[1] Unsurprisingly, there is variation in practice within Australian hospitals with respect to catheter insertion, and specifically the agent used to clean the meatal area prior to insertion. These issues provided a strong rationale for the study investigators to conduct a systematic review and meta-analysis of published literature, investigating the effectiveness of antiseptic cleaning during urinary catheter insertion for the prevention of CAUTI.[8] This review of current research knowledge identified the need for a well-designed intervention study as well as a limited number of studies evaluating the cost-effectiveness of using an antiseptic

during catheter insertion. As health budgets are finite, clinical practice needs to utilise cost-effective strategies. The cost of chlorhexidine 0.1% solution is considerably higher than 0.9% normal saline.

Given the importance of meatal colonisation in the pathogenesis of CAUTIs, emerging AMR, the frequency with which catheters are used and the burden of CAUTIs in Australia and in hospital settings worldwide, the generation of evidence using a high-quality randomised trial is needed to determine the efficacy and cost-effectiveness of meatal cleaning. This will inform infection prevention and control practice and policy in Australia and internationally.

Trial objectives

The trial objectives listed below pertain to both the cluster and individual level**.** The trial is registered with the Australia New Zealand Clinical Trial Registry (No 12617000373370).

Objective 1

The first objective is to evaluate the effectiveness of using chlorhexidine in meatal cleaning prior to catheter insertion, in reducing catheter associated asymptomatic bacteriuria (CA-ASB) and CAUTI.

Objective 2

The second objective is to estimate the cost effectiveness of the decision to adopt chlorhexidine in meatal cleaning prior to catheter insertion.

Methods

Study design

A stepped wedge randomised controlled trial will be undertaken in three large hospitals over a 32-week period (example trial timing are in Figure 1). The stepped wedge design includes an initial period where no hospitals are exposed to the intervention.[9] Afterwards, at 8 week intervals (the

"steps") each hospital sequentially crosses over from the control to the intervention until all hospitals are exposed to the intervention for the final eight weeks until conclusion in week 32. The study design enables each hospital to act as its own control, which removes the potential for some confounders such as variations in hospital size and case mix and differences between public and private hospitals. Staggered commencement and duration of the intervention, supports feasibility while maintaining the rigour of the study.[10] This design will also allow research staff to work with individual hospitals as they change over, maximising consistency of intervention and aiding implementation.[10] In addition, data collection continues throughout the study, so that each cluster contributes observations under both control and intervention observation periods.

Study population

Three Australian hospitals that fulfil the eligibility criteria will be enrolled in the study. These criteria are:

- Has an intensive care unit
- Be classified by the Australian Institute of Health and Welfare as a principal referral hospital OR a public acute group A hospital (with more than 400 beds), OR in the case of a private hospital has 400 inpatient beds OR has more than 30,000 patient admissions per year.

Other considerations

Hospitals could be excluded from the study if within the study time frame they are:

- undertaking a project that may influence the outcomes measured in this study
- opening, closing or relocating

Areas of hospital and patient-level inclusion and exclusion criteria

The study will be a hospital wide study, but will exclude patients with indwelling urinary catheters within a hospital that are not considered appropriate for the intervention, for example neonatal intensive care. Patients less than two years old, with an allergy, contraindication or other medical reason preventing the use of the intervention for cleaning the urethral meatal area will be excluded. Patients who require in-and-out or suprapubic catheterisation will also be excluded as well as those with symptoms and signs suggestive of UTI and patients already undergoing treatment for UTI. All data from any patient lost to follow-up (post-catheter insertion) will be excluded.

Recruitment

The study team will list all eligible sites then order the list to ensure (i) a representation of both private and public hospitals and (ii) representation from at least two Australian states and territories. The recruitment process will purposively select and approach eligible hospitals to optimise the feasibility and practicality of completing the trial.

Intervention

The intervention in this study is the use of chlorhexidine (0.1%) solution for meatal cleaning prior to catheter insertion. The control is the use of normal saline (0.9%) for meatal cleaning. During the first eight weeks of the study, no hospital will receive the intervention. After eight weeks, one hospital will cross over to the intervention with the other two participating hospitals crossing over to the intervention at eight-week intervals respectively based on randomisation.

Implementing the intervention

In the week prior to the intervention commencing, information sessions about the study will be provided to participating hospitals and staff. A variety of methods will be used to further alert staff and raise awareness about the intervention prior to it being rolled out. These methods include

placing wall posters in wards and key hospital locations, handing out hospital newsletters and information leaflets as well as branded promotional material, such as pens.

Chlorhexidine 0.1% solution will be used by clinical staff at participating hospitals for cleaning the meatal area of patients prior to urinary catheter insertion. To aid implementation of the intervention, investigators will work with participating hospitals and utilise hospital data collection and reporting systems currently in place. This will involve incorporation of the 0.1% chlorhexidine solution into existing catheter procedure packs at the hospitals where possible, visual reminders where urinary catheters are stored and temporary amendment to hospital procedural documentation.

As per hospital's usual practice, details of the catheter insertion will be documented by clinical staff. To achieve optimal documentation of the procedure, catheter insertion stickers may be made available to hospitals for use in patients' medical notes.

Potential confounders

Lubricants are used during the catheter insertion process and may contain an antiseptic. The lubricant used during the entire study (control and intervention periods) will remain constant in each hospital.

Randomisation and blinding

Hospitals will be randomly assigned to one of three dates to cross over to the intervention which will occur once every eight weeks over the trial duration of 32 weeks. All included hospitals will be provided with sufficient notice of the dates to cross over to the intervention. Computer-generated randomisation of the cross over dates for the hospitals will be performed independently by an investigator not involved in assessment or delivery of the intervention. Hospitals will not be blinded because it is not feasible to blind staff administering the intervention. The outcome of the

randomisation process will be revealed by the project manager to the participating hospitals prior to the commencement of the study.

Outcomes and definitions

The outcomes for each objective are outlined in Table 1. For objective 1, the primary outcomes are the cases of CA-ASB and CAUTI. For objective 2, the primary outcome is the cost effectiveness of the intervention.

Catheter associated asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming unit (cfu)/ml of ≥1 bacterial species in a single catheter urine specimen in a patient without symptoms compatible with UTI.[11]

Catheter associated urinary tract infection is defined according to the National Healthcare Safety Network criteria.[12 13] A patient must meet all three criteria below:

1. Patient had an indwelling urinary catheter that had been in place for > 2 days on the date of event (day of device placement = Day 1) AND was either present for any portion of the calendar day on the date of event or removed the day before the date of event.
2. Patient has at least one of the following signs or symptoms: fever (>38.0°C); suprapubic tenderness; costovertebral angle pain or tenderness; urinary urgency; urinary frequency; dysuria.
3. Patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium of $\geq 10^5$ cfu/ml.

Blood stream infection (BSI) associated with a urinary tract infection is defined according to National Healthcare Safety Network criteria.[12] A patient must meet the definition for CAUTI and have at least one organism from the blood specimen that matches an organism identified in the urine specimen that is used as an element to meet the CAUTI criterion. The blood specimen must be collected during the secondary BSI attribution period when the urinary catheter is in place.

Data collection

Data will be collected by a specific staff member or members at the hospital, with the support of the research team. The research team will provide the hospital staff member(s) with training about the project, data collection and submission process and data collection tools. For the purpose this paper, the dedicated hospital staff member(s) will be referred to as hospital personnel. Figure 2 summarises the data collection process.

Hospital personnel will prospectively collect data three days a week at each hospital during both control and intervention periods. Patients who receive an indwelling urinary catheter will be identified and followed-up during the trial period (for a period of 7 days post-catheter insertion, discharge or 48 hours post-catheter removal – whichever occurs first). Medical notes of patients will be reviewed to obtain demographic and clinical data such as hospital number, age, sex, date of admission, signs or symptoms of UTI. Co-morbidity data will be collected where possible. Details of catheter insertion specifically date and time of insertion, designation of person inserting catheter, catheter type and catheter size, will also be obtained from the patients' medical notes (where documented). If the insertion date is not documented, the patient will be excluded from the study. Denominator data on the number of catheter days over the trial period will be collected at each hospital during both control and intervention periods. The number of catheter days for each patient included in the study will be estimated from the date of catheter insertion and date of removal. Hospital personnel will record all captured data in a spreadsheet designed specifically for the purpose of the trial.

Information for the primary (CA-ASB and CAUTI) and secondary (BSI) outcome measures will be collected from the microbiology laboratory database of participating hospitals. Results of all positive urine cultures either attributable to bacteriuria or true UTI as well as positive blood cultures are registered in hospital microbiology laboratory databases. Hospital personnel will obtain weekly

reports from the microbiology laboratory of participating hospitals to identify the outcomes. The patient record number will be used to link demographic and clinical data of patients with a urinary catheter to microbiology laboratory data. To differentiate between CA-ASB and CAUTI, additional data on symptoms and signs of UTI will be collected from patients' medical notes by research assistants.

Information to inform changes to total costs and health benefits from a decision to adopt the intervention will be obtained. Changes to costs will include the resources required to implement the intervention and the changes to use of health services. Changes to health benefits will be captured by estimating quality adjusted life years (QALY) outcomes. Hospital personnel will prospectively obtain monthly data from each participating hospital on the cost of purchasing resources, such as catheter procedure packs, used for implementing the intervention. Hospital personnel will also obtain data on antimicrobial use for patients, specifically the name, dose and duration of antimicrobial, which will be used for estimating antimicrobial therapy costs in control and intervention periods. Hospital staff involved in the trial will be surveyed immediately following completion of the intervention to evaluate extra staff time spent in activities related to planning and implementing the intervention. To calculate QALYs, primary data on age obtained from medical notes of patients will be used along with estimates from the published literature.[14]

Power calculation

Sample size and power were calculated on the basis of CAUTI, as it is assumed that the power to detect an incremental cost effectiveness ratio was greater than that for relevant clinical endpoints. The at risk population are those that receive a catheter whilst in hospital. Based on pilot work, the estimated proportion of patients developing a CAUTI for this study is 3.4%.[1] We estimate a 20% reduction using a Cohen's d size effect measure at 0.2 (small effect). Based on individual randomization of two groups (control and intervention), power of 80%, alpha of 0.05%, effect size

of 0.2 and two-sided test for comparison of two means. As this is a stepped wedge design, we have used a sample size formula from Hussey and Hughes and operationalised the design effect from Hemming.[9 15] For the design effect, we have assumed 3 hospitals, 3 time periods, with N_1 being the sample size of 784. Three different scenarios were modelled, each with different intracluster correlation coefficients- 0.1, 0.05, 0.01. An intracluster correlation coefficient of 0.05 was subsequently determined and the sample size (m=220, M=880) for each cluster. The total calculated sample size is therefore 2,640 across all sites, that is total number of patients that receive a catheter in all three sites.

Pilot work identified that 26% of patients admitted to hospital in Australia receive a urinary catheter [1 16]. As we are excluding patients who had a catheter inserted in theatre, we estimated that 5% of admitted patients receive a catheter not inserted in theatre. To obtain the required sample size in each hospital, a hospital needs the potential insertion of 1500 catheters per year (1000 during the eight-month study period). This requires a hospital to have at least 30,000 patient admissions per year.

Analysis

Objective 1: Effectiveness of using chlorhexidine in meatal cleaning prior to catheter insertion

The number of CA-ASB, CAUTI and BSI will be analysed separately using Poisson regression, with the number of cases as the dependent variable and number of patient catheter days as the denominator. This denominator will help control for changes in catheter use during the study period. The key independent variable will be the intervention. The key outcomes will be estimated reduction in cases of CA-ASB, CAUTI and BSI due to the intervention. The characteristics of the hospital (e.g. size) will not be independent variables as these should remain roughly constant throughout the study observations. There is no expected delay in the effect of intervention on the outcome.

Objective 2: Cost effectiveness of the intervention

The effectiveness data from objective 1 will be a key parameter in the cost-effectiveness model. Final outcomes for the cost-effectiveness evaluation are the incremental cost-effectiveness ratio estimated as the cost per QALY gained, and the changes to costs in QALYs. Published guidelines for costing an intervention will be followed [17]. The changes to costs from adopting the intervention will be estimated by the extra staff time spent both planning and implementing the intervention, converted to a dollar figure using full employment costs. Other costs are product costs. These cost data will be collected prospectively on a monthly basis for product costs and a survey immediately after the intervention is implemented (staff costs). Quantities of resources will be standardised to all hospitals to ensure valid comparison of costs across all sites. This will reduce uncertainty in estimates which often results from using retrospective administrative data.

The major cost savings from reducing infections are characterised by the bed days saved from keeping patients infection free and hence discharging them earlier. The reasoning is that 90% of the costs of hospital services are fixed so bed days saved are an appropriate currency. Data from a previous study using multistate modelling to estimate the extra length of stay per case of urinary bacteriuria will be used in the model.[18] Other cost savings are averted laboratory diagnosis costs and antimicrobial therapy costs, estimated by counting the frequency of laboratory tests and antimicrobial therapy costs in the control and intervention periods. These will be collected prospectively as part of the data collection process. Laboratory costs using the relevant medical benefit scheme item costs will be used. For antimicrobial therapy costs, pharmaceutical benefits scheme costs will be used.

Changes to health benefits will be informed by the extra death risk due to infection. This parameter will come from a previously described analysis of mortality associated with urinary bacteriuria. These estimates used multi-state models that avoid time and length biases to estimate increases in mortality attributable to infection. The results are hazard ratios that can be used to predict reduction in deaths from avoided infections. The mean age of hospital patients will be used to predict years of life gained and preference based utility scores will be used to weight life expectancy, allowing us to calculate QALYs. We will not collect primary data on preference based utility scores. Instead, these estimates will be taken from the published literature.[19]

The change to total costs at the hospital level will be estimated by summing intervention costs and deducting cost savings from reduced lengths of stay and use of health care resources that arise from reduced incidences of infection. The changes to health benefits will be estimated in QALYs using: the number of life years saved from reduced infection outcomes; the expected duration of life (had infection not occurred) based on age and data from the published literature.[14] All costs and health benefits arising in future periods will be appropriately discounted. Uncertainties in parameter estimates will be captured using appropriate statistical distributions to describe the variability. For example, the beta distribution would be a good choice for infection risk as this distribution is restricted to interval 0–1. The parameters of the beta distribution will be chosen to reflect what we know about the mean and range in infection risk (e.g., a beta distribution with a mean rate of infection of 0.003 and 95% confidence interval of 0.001 to 0.005). The fitted distributions will be subject to random re-samples simulated 10,000 times. The distributions of all prior parameters are used to estimate the posterior distributions of 'change to costs' and 'change to QALY' outcomes.

The decision will be informed by plotting cost-effectiveness acceptability curves with threshold value between zero and 100,000 per QALY gained, and using the net monetary benefits framework.

These approaches are semi Bayesian and appropriately account for all parameter uncertainty for the adoption decisions.

Discussion

This study addresses an identified gap in infection control research and practice. Despite the frequency of urinary tract infections associated with indwelling urinary catheter use, there are few studies focusing on their surveillance and prevention. Aligning with the emphasis on quality and safety, this multi-centre randomised controlled trial, will evaluate the effectiveness and cost-effectiveness of an antiseptic versus non-antiseptic meatal cleaning agent to prevent CAUTIs, a world first. The ultimate objective is the prevention of healthcare-related CAUTIs, leading to benefits for patient safety.

Strengths

Few randomised controlled trials have investigated the effectiveness of antiseptics on CAUTI incidence during urinary catheter insertion and previous research has been limited mainly due to the lack of an appropriate sample size to demonstrate any possible beneficial effect from the use of antiseptics.[8] Our study utilises a rigorous approach and is sufficiently powered to detect the effect of antiseptics in reducing CAUTI. The inclusion of the cost-effectiveness analysis is an additional strength of this trial as to our knowledge previous trials have not evaluated the cost effectiveness of an antiseptic meatal cleaning agent in reducing CAUTI. Over the past decade, cost effectiveness analysis has evolved further emphasising the need to address this evidence gap.

This randomised controlled trial is also strengthened by the use of a stepped wedged design which has been found to be particularly useful in studies evaluating intervention effectiveness during routine implementation such as in the case of this study where the insertion of a urinary catheter is considered to be part of the usual care of the patient.[20] The study design also enables each hospital

to act as its own control, which removes the potential for some confounders such as variations in hospital size and case mix and differences between public and private hospitals. Further, this study identifies best practice among current practice.

Limitations

Exclusion of patients who have indwelling urinary catheters inserted in surgical theatre has the potential to prolong recruitment of participants given that surgical procedures are a common indication for urinary catheter insertion.[21 22] However, recruitment of these patients was not deemed feasible as it would require involvement of all surgeons including theatre staff in the study.

Significance

It is important that urinary catheter insertion strategies for CAUTI prevention are supported by evidence obtained from rigorously conducted research. This study's significance therefore lies in its ability to inform recommendations within national infection control guidelines globally. This study will also contribute to the development of strategies to reduce the incidence of CAUTI using cost-effective approaches. This is even more important in the context of finite health budgets.

Trial status

The study team is completing the recruitment of participating hospitals. The trial is due to commence in late 2017.

Abbreviations

AMR: Antimicrobial resistance; BSI: Blood stream infection; CA-ASB: Catheter associated asymptomatic bacteriuria; CAUTI: Catheter associated urinary tract infection; QALY: Quality adjusted life years; UTI: Urinary tract infection

Declarations

Ethics approval and consent to participate

This project has received ethics approval from Avondale College of Higher Education Human Research Ethics Committee (HREC) (approval number 2017:03), the Australian Capital Territory HREC (approval number ETH.4.17.083) and the Adventist HealthCare Limited Human Research Ethics Committee (approval number 2017-018). A waiver of individual patient consent was granted for this study. Any risks or harms associated with the study will be reported to the relevant HREC. Reporting of the trial and progress, including any audits, will be conducted consistent with the requests of the HRECs who approved the study. Any modification to the study that has ethical implications will be forwarded to the HRECs for approval.

Consent for publication

Not applicable

Data quality

Data will be stored in electronically in a secure location, by chief investigator BM at Avondale College of Higher Education. Data quality will be enhanced by the provision of a data collection form, quality checks by the project manager. A data collection guide has been developed to aide and document this process. Data monitoring will be overseen by chief investigator BM and the data monitoring committee consists of all chief investigators on the study. Any approved changes to the study protocol will be updated in Australia New Zealand Clinical Trial Registry.

Access to data

Chief investigator BM will hold data during and after study completion.

Competing interests

The authors declare that they have no competing interests.

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Dissemination

A dissemination plan it being developed. Results will be published in the peer review literature, presented at relevant conferences and communicated via professional networks.

Authors' contributions

All authors made contributions to the development of the trial protocol and have been involved in drafting this manuscript or revising it critically for important intellectual content. BM is the overall chief investigator. BM and AC lead on epidemiology and infection control. PC leads on infectious diseases. AC leads on statistics. NG leads on health economics. AG and JK lead on health policy and decision-making. OF leads on urinary tract infection. VG is the project manager. BM and OF led the initial protocol development. All authors have approved the final manuscript.

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Table 1 Key outcome measures

Objective 1 Effectiveness of using chlorhexidine in meatal cleaning prior to catheter insertion	Primary outcome	The number of cases of CA-ASB per 100 catheter days The number of cases of CAUTI per 100 catheter days
	Secondary outcome	The number of BSIs associated with a UTI
Objective 2 Cost effectiveness of the intervention	Primary outcome	Changes in costs relative to health benefits (incremental cost-effectiveness ratio) from adoption of the intervention Changes in costs associated with implementing the intervention relative to the change in QALYs

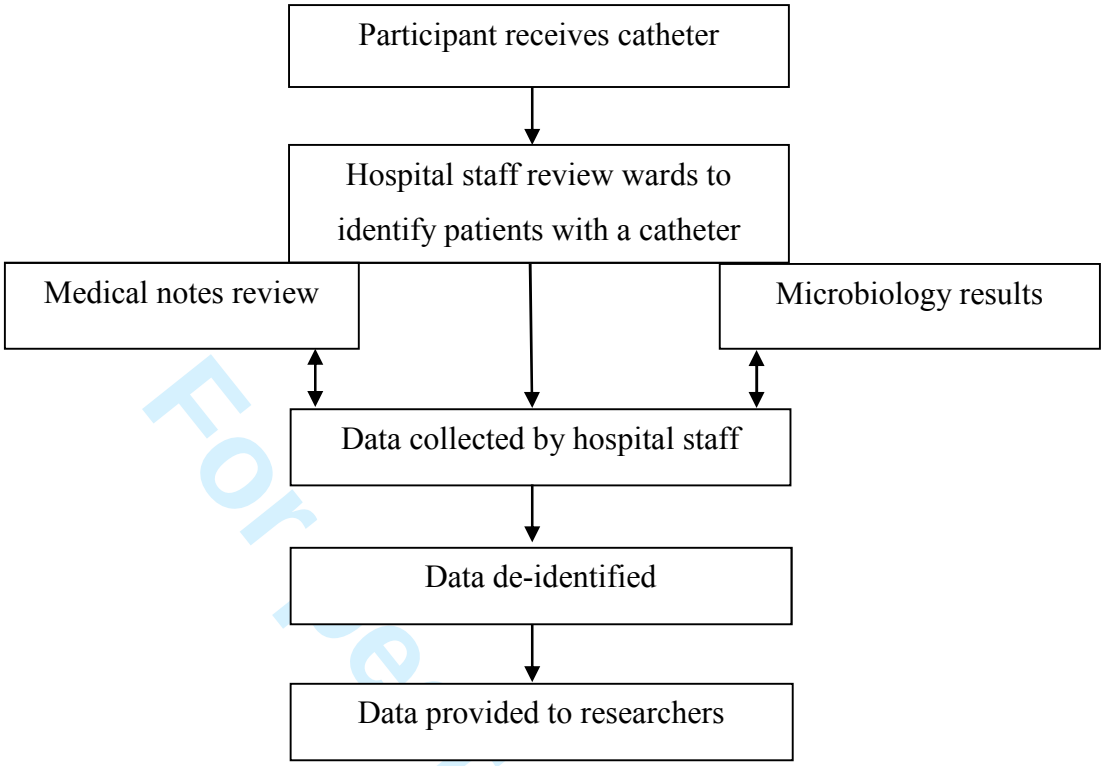
CA-ASB = catheter associated asymptomatic bacteriuria; CAUTI = catheter associated urinary tract infection; BSI = blood stream infection; QALY = quality adjusted life years

Figure 1 Study design overview

Blue = control; Green = intervention

Figure 2 Overview of data collection process

Hospital	2 months	4 months	6 months	8 months
A				
B				
C				



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Title: Reducing catheter associated urinary tract infections in hospitals: study protocol for a multi-site randomised controlled study

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Abstract

Introduction: Despite advances in infection prevention and control, catheter associated urinary tract infections (CAUTIs) are common and remain problematic. A number of measures can be taken to reduce the risk of CAUTI in hospitals. Appropriate urinary catheter insertion procedures are one such method. Reducing bacterial colonisation around the meatal or urethral area has the potential to reduce CAUTI risk. However, evidence about the best antiseptic solutions for meatal cleaning is mixed, resulting in conflicting recommendations in guidelines internationally. This paper presents the protocol for a study to evaluate the effectiveness (objective 1) and cost effectiveness (objective 2) of using chlorhexidine in meatal cleaning prior to catheter insertion, in reducing catheter associated asymptomatic bacteriuria and CAUTI.

Methods and analysis: A stepped wedge randomised controlled trial will be undertaken in three large Australian hospitals over a 32-week period. The intervention in this study is the use of chlorhexidine (0.1%) solution for meatal cleaning prior to catheter insertion. During the first eight weeks of the study, no hospital will receive the intervention. After eight weeks, one hospital will cross over to the intervention with the other two participating hospitals crossing over to the intervention at eight-week intervals respectively based on randomisation. All sites complete the trial at the same time in 2018.The primary outcomes for objective 1 (effectiveness) are the number of cases of CAUTI and catheter associated asymptomatic bacteriuria per 100 catheter days will be analysed separately using Poisson regression. The primary outcome for objective 2 (cost effectiveness) is the changes in costs relative to health benefits (incremental cost-effectiveness ratio) from adoption of the intervention.

Dissemination: Results will be disseminated via peer-reviewed journals and presentations at relevant conferences.

Ethics: Ethics approval has been obtained.

Trial registration: Australia New Zealand Clinical Trial Registry (No 12617000373370), approved 13/03/2017. Protocol version 1.1

Key words: Cost-effectiveness, Healthcare-associated infection, Urinary Tract Infections, Infection Control, Catheter-Related Infections.

Strengths and limitations of this study

- Randomised control design
- Evaluation of effectiveness and cost effectiveness
- Limited to hospitals in high income country

Introduction

Indwelling urinary catheters are commonly used in healthcare facilities, with foundation work indicating that 26% of patients admitted to an Australian hospital receive an indwelling urinary catheter and 1% of these patients develop catheter-associated urinary tract infections (CAUTIs).[1] Catheter associated urinary tract infections have been associated with increased morbidity, mortality, increased length of stay in hospital and higher hospital costs for patients and health systems.[2] Data from the International Nosocomial Infection Control Consortium (INICC) surveillance study, conducted in 703 intensive care units in low and middle income countries, suggests the incidence of CAUTI to be 4.8 per 1000 device days (years 2010-15).[3] In Australia, an estimated 380,000 bed days are lost each year due to healthcare-associated urinary tract infections (UTIs), a large proportion of which are CAUTIs. Catheter associated urinary tract infections are also associated with higher risk of antimicrobial resistance (AMR), making the treatment of patients difficult.[4 5] Antimicrobial resistance in UTIs has also been shown to be increasing globally, further emphasising the need to develop interventions to reduce the incidence of CAUTIs.[6]

Studies have shown, that the incidence of CAUTI can be reduced.[7 8] None the less, despite some advances in infection prevention and control, CAUTIs remain problematic.[9] Evidence shows that reducing bacterial colonisation around the meatal or urethral area has the potential to reduce CAUTI risk.[10] However, evidence about the best antiseptic solutions for meatal cleaning is mixed. Previous research also identified a lack of documentation and knowledge in relation to the meatal cleaning solution used prior to catheter insertion.[1] Unsurprisingly, there is variation in practice within Australian hospitals with respect to catheter insertion, and specifically the agent used to clean the meatal area prior to insertion. These issues provided a strong rationale for the study investigators to conduct a systematic review and meta-analysis of published literature, investigating the effectiveness of antiseptic cleaning during urinary catheter insertion for the prevention of CAUTI.[11] This review of current research knowledge identified the need for a well-designed intervention

study as well as a limited number of studies evaluating the cost-effectiveness of using an antiseptic during catheter insertion. As health budgets are finite, clinical practice needs to utilise cost-effective strategies. The cost of chlorhexidine 0.1% solution is considerably higher than 0.9% normal saline.

Given the importance of meatal colonisation in the pathogenesis of CAUTIs, emerging AMR, the frequency with which catheters are used and the burden of CAUTIs in Australia and in hospital settings worldwide, the generation of evidence using a high-quality randomised trial is needed to determine the efficacy and cost-effectiveness of meatal cleaning. This will inform infection prevention and control practice and policy in Australia and internationally.

Trial objectives

The trial objectives listed below pertain to both the cluster and individual level**.** The trial is registered with the Australia New Zealand Clinical Trial Registry (No 12617000373370).

Objective 1

The first objective is to evaluate the effectiveness of using chlorhexidine in meatal cleaning prior to catheter insertion, in reducing catheter associated asymptomatic bacteriuria (CA-ASB) and CAUTI.

Objective 2

The second objective is to estimate the cost effectiveness of the decision to adopt chlorhexidine in meatal cleaning prior to catheter insertion.

Methods

Study design

A stepped wedge randomised controlled trial will be undertaken in three large hospitals over a 32-week period (example trial timing are in Figure 1). The stepped wedge design includes an initial

period where no hospitals are exposed to the intervention.[12] Afterwards, at 8 week intervals (the "steps") each hospital sequentially crosses over from the control to the intervention until all hospitals are exposed to the intervention for the final eight weeks until conclusion in week 32. The study design enables each hospital to act as its own control, which removes the potential for some confounders such as variations in hospital size and case mix and differences between public and private hospitals. Staggered commencement and duration of the intervention, supports feasibility while maintaining the rigour of the study.[13] This design will also allow research staff to work with individual hospitals as they change over, maximising consistency of intervention and aiding implementation.[13] In addition, data collection continues throughout the study, so that each cluster contributes observations under both control and intervention observation periods.

Study population

Three Australian hospitals that fulfil the eligibility criteria will be enrolled in the study. These criteria are:

- Has an intensive care unit
- Be classified by the Australian Institute of Health and Welfare as a principal referral hospital OR a public acute group A hospital (with more than 400 beds), OR in the case of a private hospital has 400 inpatient beds OR has more than 30,000 patient admissions per year.

Other considerations

Hospitals could be excluded from the study if within the study time frame they are:

- undertaking a project that may influence the outcomes measured in this study
- opening, closing or relocating

Areas of hospital and patient-level inclusion and exclusion criteria

The study will be a hospital wide study, but will exclude patients with indwelling urinary catheters within a hospital that are not considered appropriate for the intervention, for example neonatal intensive care. Patients less than two years old, with an allergy, contraindication or other medical reason preventing the use of the intervention for cleaning the urethral meatal area will be excluded. Patients who require in-and-out or suprapubic catheterisation will also be excluded as well as those with symptoms and signs suggestive of UTI and patients already undergoing treatment for UTI. All data from any patient lost to follow-up (post-catheter insertion) will be excluded.

Recruitment

The study team will list all eligible sites then order the list to ensure (i) a representation of both private and public hospitals and (ii) representation from at least two Australian states and territories. The recruitment process will purposively select and approach eligible hospitals to optimise the feasibility and practicality of completing the trial.

Intervention

The intervention in this study is the use of chlorhexidine (0.1%) solution for meatal cleaning prior to catheter insertion. The control is the use of normal saline (0.9%) for meatal cleaning. During the first eight weeks of the study, no hospital will receive the intervention. After eight weeks, one hospital will cross over to the intervention with the other two participating hospitals crossing over to the intervention at eight-week intervals respectively based on randomisation.

Implementing the intervention

In the week prior to the intervention commencing, information sessions about the study will be provided to participating hospitals and staff. A variety of methods will be used to further alert staff and raise awareness about the intervention prior to it being rolled out. These methods include

placing wall posters in wards and key hospital locations, handing out hospital newsletters and information leaflets as well as branded promotional material, such as pens. To avoid potential confounding, information and awareness sessions are limited to just the change of product, not education around catheter insertion or management practices.

Chlorhexidine 0.1% solution will be used by clinical staff at participating hospitals for cleaning the meatal area of patients prior to urinary catheter insertion. To aid implementation of the intervention, investigators will work with participating hospitals and utilise hospital data collection and reporting systems currently in place. This will involve incorporation of the 0.1% chlorhexidine solution into existing catheter procedure packs at the hospitals where possible, visual reminders where urinary catheters are stored and temporary amendment to hospital procedural documentation.

As per hospital's usual practice, details of the catheter insertion will be documented by clinical staff. To achieve optimal documentation of the procedure, catheter insertion stickers may be made available to hospitals for use in patients' medical notes.

Potential confounders

Lubricants are used during the catheter insertion process and may contain an antiseptic. The lubricant used during the entire study (control and intervention periods) will remain constant in each hospital.

Randomisation and blinding

Hospitals will be randomly assigned to one of three dates to cross over to the intervention which will occur once every eight weeks over the trial duration of 32 weeks. All included hospitals will be provided with sufficient notice of the dates to cross over to the intervention. Computer-generated randomisation of the cross over dates for the hospitals will be performed independently by an

investigator not involved in assessment or delivery of the intervention. Hospitals will not be blinded because it is not feasible to blind staff administering the intervention. The outcome of the randomisation process will be revealed by the project manager to the participating hospitals prior to the commencement of the study.

Outcomes and definitions

The outcomes for each objective are outlined in Table 1. For objective 1, the primary outcomes are the cases of CA-ASB and CAUTI. For objective 2, the primary outcome is the cost effectiveness of the intervention.

Catheter associated asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming unit (cfu)/ml of ≥1 bacterial species in a single catheter urine specimen in a patient without symptoms compatible with UTI.[14]

Catheter associated urinary tract infection is defined according to the National Healthcare Safety Network criteria.[15 16] A patient must meet all three criteria below:

1. Patient had an indwelling urinary catheter that had been in place for > 2 days on the date of event (day of device placement = Day 1) AND was either present for any portion of the calendar day on the date of event or removed the day before the date of event.
2. Patient has at least one of the following signs or symptoms: fever (>38.0°C); suprapubic tenderness; costovertebral angle pain or tenderness; urinary urgency; urinary frequency; dysuria.
3. Patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium of $\geq 10^5$ cfu/ml.

Blood stream infection (BSI) associated with a urinary tract infection is defined according to National Healthcare Safety Network criteria.[15] A patient must meet the definition for CAUTI and have at least one organism from the blood specimen that matches an organism identified in the urine

specimen that is used as an element to meet the CAUTI criterion. The blood specimen must be collected during the secondary BSI attribution period when the urinary catheter is in place.

Data collection

Data will be collected by a specific staff member or members at the hospital, with the support of the research team. The research team will provide the hospital staff member(s) with training about the project, data collection and submission process and data collection tools. For the purpose this paper, the dedicated hospital staff member(s) will be referred to as hospital personnel. Figure 2 summarises the data collection process.

Hospital personnel will prospectively collect data three days a week at each hospital during both control and intervention periods. Patients who receive an indwelling urinary catheter will be identified and followed-up during the trial period (for a period of 7 days post-catheter insertion, discharge or 48 hours post-catheter removal – whichever occurs first). Medical notes of patients will be reviewed to obtain demographic and clinical data such as hospital number, age, sex, date of admission, signs or symptoms of UTI. Co-morbidity data will be collected where possible. Details of catheter insertion specifically date and time of insertion, designation of person inserting catheter, catheter type and catheter size, will also be obtained from the patients' medical notes (where documented). If the insertion date is not documented, the patient will be excluded from the study. Denominator data on the number of catheter days over the trial period will be collected at each hospital during both control and intervention periods. The number of catheter days for each patient included in the study will be estimated from the date of catheter insertion and date of removal. Hospital personnel will record all captured data in a spreadsheet designed specifically for the purpose of the trial.

Information for the primary (CA-ASB and CAUTI) and secondary (BSI) outcome measures will be collected from the microbiology laboratory database of participating hospitals. Results of all positive urine cultures either attributable to bacteriuria or true UTI as well as positive blood cultures are registered in hospital microbiology laboratory databases. Hospital personnel will obtain weekly reports from the microbiology laboratory of participating hospitals to identify the outcomes. The patient record number will be used to link demographic and clinical data of patients with a urinary catheter to microbiology laboratory data. To differentiate between CA-ASB and CAUTI, additional data on symptoms and signs of UTI will be collected from patients' medical notes by research assistants.

Information to inform changes to total costs and health benefits from a decision to adopt the intervention will be obtained. Changes to costs will include the resources required to implement the intervention and the changes to use of health services. Changes to health benefits will be captured by estimating quality adjusted life years (QALY) outcomes. Hospital personnel will prospectively obtain monthly data from each participating hospital on the cost of purchasing resources, such as catheter procedure packs, used for implementing the intervention. Hospital personnel will also obtain data on antimicrobial use for patients, specifically the name, dose and duration of antimicrobial, which will be used for estimating antimicrobial therapy costs in control and intervention periods. Hospital staff involved in the trial will be surveyed immediately following completion of the intervention to evaluate extra staff time spent in activities related to planning and implementing the intervention. To calculate QALYs, primary data on age obtained from medical notes of patients will be used along with estimates from the published literature.[17]

Power calculation

Sample size and power were calculated on the basis of CAUTI, as it is assumed that the power to detect an incremental cost effectiveness ratio was greater than that for relevant clinical endpoints.

The at risk population are those that receive a catheter whilst in hospital. Based on pilot work, the estimated proportion of patients developing a CAUTI for this study is 3.4%.[1] We estimate a 20% reduction using a Cohen's d size effect measure at 0.2 (small effect). Based on individual randomization of two groups (control and intervention), power of 80%, alpha of 0.05%, effect size of 0.2 and two-sided test for comparison of two means. As this is a stepped wedge design, we have used a sample size formula from Hussey and Hughes and operationalised the design effect from Hemming.[12 18] For the design effect, we have assumed 3 hospitals, 3 time periods, with N_1 being the sample size of 784. Three different scenarios were modelled, each with different intracluster correlation coefficients- 0.1, 0.05, 0.01. An intracluster correlation coefficient of 0.05 was subsequently determined and the sample size (m=220, M=880) for each cluster.

Pilot work identified that 26% of patients admitted to hospital in Australia receive a urinary catheter [1 19]. As we are excluding patients who had a catheter inserted in theatre, we estimated that 5% of admitted patients receive a catheter not inserted in theatre. To obtain the required sample size in each hospital, a hospital is to have at least 30,000 patient admissions per year.

Analysis

Objective 1: Effectiveness of using chlorhexidine in meatal cleaning prior to catheter insertion

The number of CA-ASB, CAUTI and BSI will be analysed separately using Poisson regression, with the number of cases as the dependent variable and number of patient catheter days as the denominator. This denominator will help control for changes in catheter use during the study period. The key independent variable will be the intervention. The key outcomes will be estimated reduction in cases of CA-ASB, CAUTI and BSI due to the intervention. The characteristics of the hospital (e.g. size) will not be independent variables as these should remain roughly constant throughout the study observations. There is no expected delay in the effect of intervention on the outcome.

Objective 2: Cost effectiveness of the intervention

The effectiveness data from objective 1 will be a key parameter in the cost-effectiveness model. Final outcomes for the cost-effectiveness evaluation are the incremental cost-effectiveness ratio estimated as the cost per QALY gained, and the changes to costs in QALYs. Published guidelines for costing an intervention will be followed [20]. The changes to costs from adopting the intervention will be estimated by the extra staff time spent both planning and implementing the intervention, converted to a dollar figure using full employment costs. Other costs are product costs. These cost data will be collected prospectively on a monthly basis for product costs and a survey immediately after the intervention is implemented (staff costs). Quantities of resources will be standardised to all hospitals to ensure valid comparison of costs across all sites. This will reduce uncertainty in estimates which often results from using retrospective administrative data.

The major cost savings from reducing infections are characterised by the bed days saved from keeping patients infection free and hence discharging them earlier. The reasoning is that 90% of the costs of hospital services are fixed so bed days saved are an appropriate currency. Data from a previous study using multistate modelling to estimate the extra length of stay per case of urinary bacteriuria will be used in the model.[21] Other cost savings are averted laboratory diagnosis costs and antimicrobial therapy costs, estimated by counting the frequency of laboratory tests and antimicrobial therapy costs in the control and intervention periods. These will be collected prospectively as part of the data collection process. Laboratory costs using the relevant medical benefit scheme item costs will be used. For antimicrobial therapy costs, pharmaceutical benefits scheme costs will be used.

Changes to health benefits will be informed by the extra death risk due to infection. This parameter will come from a previously described analysis of mortality associated with urinary bacteriuria. These estimates used multi-state models that avoid time and length biases to estimate increases in mortality attributable to infection. The results are hazard ratios that can be used to predict reduction in deaths from avoided infections. The mean age of hospital patients will be used to predict years of life gained and preference based utility scores will be used to weight life expectancy, allowing us to calculate QALYs. We will not collect primary data on preference based utility scores. Instead, these estimates will be taken from the published literature.[22]

The change to total costs at the hospital level will be estimated by summing intervention costs and deducting cost savings from reduced lengths of stay and use of health care resources that arise from reduced incidences of infection. The changes to health benefits will be estimated in QALYs using: the number of life years saved from reduced infection outcomes; the expected duration of life (had infection not occurred) based on age and data from the published literature.[17] All costs and health benefits arising in future periods will be appropriately discounted. Uncertainties in parameter estimates will be captured using appropriate statistical distributions to describe the variability. For example, the beta distribution would be a good choice for infection risk as this distribution is restricted to interval 0–1. The parameters of the beta distribution will be chosen to reflect what we know about the mean and range in infection risk (e.g., a beta distribution with a mean rate of infection of 0.003 and 95% confidence interval of 0.001 to 0.005). The fitted distributions will be subject to random re-samples simulated 10,000 times. The distributions of all prior parameters are used to estimate the posterior distributions of ‘change to costs’ and ‘change to QALY’ outcomes.

The decision will be informed by plotting cost-effectiveness acceptability curves with threshold value between zero and 100,000 per QALY gained, and using the net monetary benefits framework.

These approaches are semi Bayesian and appropriately account for all parameter uncertainty for the adoption decisions.

Discussion

This study addresses an identified gap in infection control research and practice. Despite the frequency of urinary tract infections associated with indwelling urinary catheter use, there are few studies focusing on their surveillance and prevention. Aligning with the emphasis on quality and safety, this multi-centre randomised controlled trial, will evaluate the effectiveness and cost-effectiveness of an antiseptic versus non-antiseptic meatal cleaning agent to prevent CAUTIs, a world first. The ultimate objective is the prevention of healthcare-related CAUTIs, leading to benefits for patient safety.

Strengths

Few randomised controlled trials have investigated the effectiveness of antiseptics on CAUTI incidence during urinary catheter insertion and previous research has been limited mainly due to the lack of an appropriate sample size to demonstrate any possible beneficial effect from the use of antiseptics.[11] Our study utilises a rigorous approach and is sufficiently powered to detect the effect of antiseptics in reducing CAUTI. The inclusion of the cost-effectiveness analysis is an additional strength of this trial as to our knowledge previous trials have not evaluated the cost effectiveness of an antiseptic meatal cleaning agent in reducing CAUTI. Over the past decade, cost effectiveness analysis has evolved further emphasising the need to address this evidence gap.

This randomised controlled trial is also strengthened by the use of a stepped wedged design which has been found to be particularly useful in studies evaluating intervention effectiveness during routine implementation such as in the case of this study where the insertion of a urinary catheter is considered to be part of the care of the patient.[23] The study design also enables each hospital to act

as its own control, which removes the potential for some confounders such as variations in hospital size and case mix and differences between public and private hospitals. Further, this study identifies best practice among current practice.

Limitations

Exclusion of patients who have indwelling urinary catheters inserted in surgical theatre has the potential to prolong recruitment of participants given that surgical procedures are a common indication for urinary catheter insertion.[24 25] However, recruitment of these patients was not deemed feasible as it would require involvement of all surgeons including theatre staff in the study. Unless the participating hospital can achieve implementation in theatre, patients who have catheters inserted in theatres will be excluded. The initiatives taken to introduce the intervention may inadvertently improve catheter management. To reduce this effect, no education on other aspects of catheter management (other than the product change) will be provided to staff.

Significance

It is important that urinary catheter insertion strategies for CAUTI prevention are supported by evidence obtained from rigorously conducted research. This study's significance therefore lies in its ability to inform recommendations within national infection control guidelines globally. This study will also contribute to the development of strategies to reduce the incidence of CAUTI using cost-effective approaches. This is even more important in the context of finite health budgets.

Trial status

The study team is completing the recruitment of participating hospitals. The trial is due to commence in late 2017.

Abbreviations

AMR: Antimicrobial resistance; BSI: Blood stream infection; CA-ASB: Catheter associated asymptomatic bacteriuria; CAUTI: Catheter associated urinary tract infection; QALY: Quality adjusted life years; UTI: Urinary tract infection

Declarations

Ethics approval and consent to participate

This project has received ethics approval from Avondale College of Higher Education Human Research Ethics Committee (HREC) (approval number 2017:03), the Australian Capital Territory HREC (approval number ETH.4.17.083) and the Adventist HealthCare Limited Human Research Ethics Committee (approval number 2017-018). A waiver of individual patient consent was granted for this study. Any risks or harms associated with the study will be reported to the relevant HREC. Reporting of the trial and progress, including any audits, will be conducted consistent with the requests of the HRECs who approved the study. Any modification to the study that has ethical implications will be forwarded to the HRECs for approval. No identifiable ore re-identifiable patient data will be collected by the researchers, thus protecting anonymity and confidentiality of participants.

Consent for publication

Not applicable

Data quality

Data will be stored in electronically in a secure (password protected) location, by chief investigator BM at Avondale College of Higher Education. Data quality will be enhanced by the provision of a data collection form, quality checks by the project manager. A data collection guide has been

developed to aide and document this process. Data monitoring will be overseen by chief investigator BM and the data monitoring committee consists of all chief investigators on the study. Any approved changes to the study protocol will be updated in Australia New Zealand Clinical Trial Registry.

Access to data

Chief investigator BM will hold data during and after study completion.

Competing interests

The authors declare that they have no competing interests.

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Dissemination

A dissemination plan it being developed. Results will be published in the peer review literature, presented at relevant conferences and communicated via professional networks.

Authors' contributions

All authors made contributions to the development of the trial protocol and have been involved in drafting this manuscript or revising it critically for important intellectual content. BM is the overall chief investigator. BM and AC lead on epidemiology and infection control. PC leads on infectious diseases. AC and PM lead on statistics. NG leads on health economics. AG and JK lead on health

policy and decision-making. OF leads on urinary tract infection. VG is the project manager. BM and OF led the initial protocol development. All authors have approved the final manuscript.

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Table 1 Key outcome measures

Objective 1 Effectiveness of using chlorhexidine in meatal cleaning prior to catheter insertion	Primary outcome	The number of cases of CA-ASB per 100 catheter days The number of cases of CAUTI per 100 catheter days
	Secondary outcome	The number of BSIs associated with a UTI
Objective 2 Cost effectiveness of the intervention	Primary outcome	Changes in costs relative to health benefits (incremental cost-effectiveness ratio) from adoption of the intervention Changes in costs associated with implementing the intervention relative to the change in QALYs

CA-ASB = catheter associated asymptomatic bacteriuria; CAUTI = catheter associated urinary tract infection; BSI = blood stream infection; QALY = quality adjusted life years

Figure 1 Study design overview

Blue = control; Green = intervention

Figure 2 Overview of data collection process

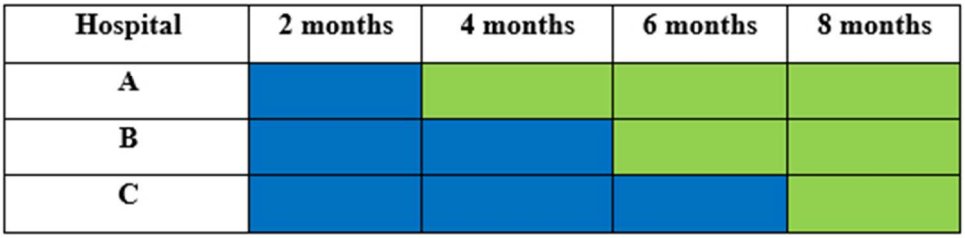

Figure 1 Study design overview

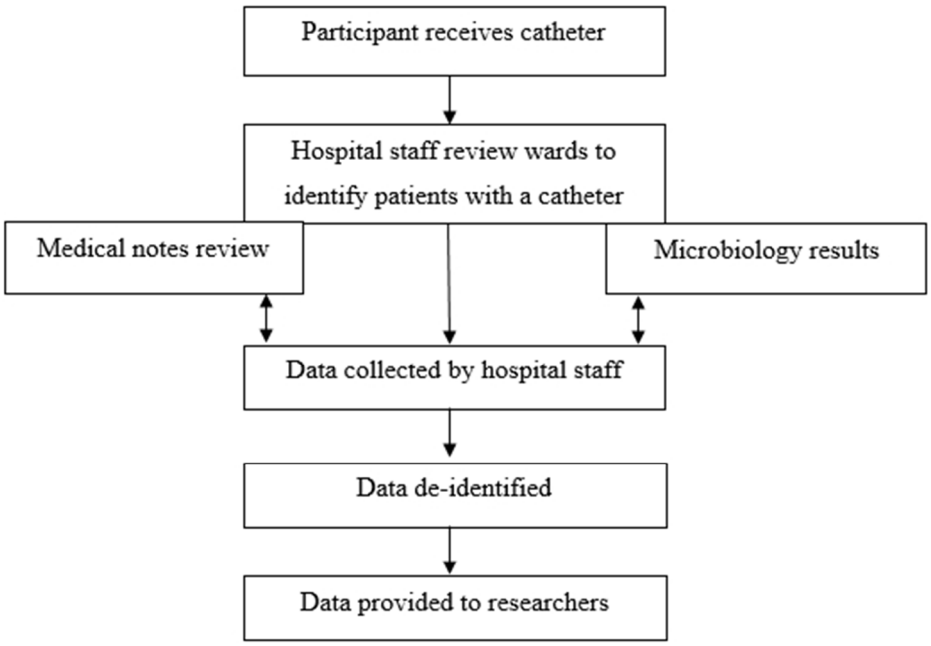

Figure 2 Overview of data collection process

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 18-19
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5

	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			9
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.