REDUCING CATHETER ASSOCIATED URINARY TRACT INFECTIONS IN HOSPITALS:
A MULTI-SITE RANDOMIZED CONTROLLED STUDY

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Confidential

Study Protocol

The full study protocol can be accessed at http://bmjopen.bmj.com/content/7/11/e018871

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Canberra Public Hospital – Wendy Beckingham and Andrea Menzies

Lismore Base Public Hospital – Vicki Denyer, Robyn Masters

Sydney Adventist Hospital – Jayne O'Connor, Holly Dodd and Laisa Kulavere

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EXECUTIVE SUMMARY

Introduction

Twenty-six percent 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] Evidence shows that reducing bacterial colonisation around the urethral area has the potential to reduce CAUTI risk[2]; however, evidence about the best antiseptic solutions for cleaning is mixed. A high-quality randomised trial was designed to determine the efficacy and cost-effectiveness of using chlorhexidine 0.1% solution for meatal cleaning prior to catheter insertion.

Objectives

To evaluate the efficacy (Objective 1), and cost-effectiveness (Objective 2) of using 0.1% chlorhexidine (the Intervention) in meatal cleaning prior to catheter insertion for the prevention of catheter-associated urinary tract infections (CAUTI), catheter associated asymptomatic bacteriuria (CA-ASB) and bloodstream infections (BSI) associated with a UTI.

Methods

A 32 week, stepped wedge randomised controlled trial was conducted at 3 large Australian hospitals between 1st August 2017 and 12th March 2018.

Results

Effectiveness of the intervention

Over the study period 1642 catheters were inserted. The mean age of participants who received a catheter was 64 years (range 16-102). In the control phase there were 13 CAUTI events and 29 bacteriuria events. In the intervention phase there were 4 CAUTI events and 16 bacteriuria events. The use of chlorhexidine was associated with a 74% reduction in the incidence rate of bacteriuria, and a 94% decrease in the incidence rate of CAUTI. There was no BSI recorded during both control and intervention periods.

Cost-effectiveness of the intervention

The main cost-effectiveness outcomes were the changes to health service cost in Australian dollars and the change to quality adjusted life years from a decision to adopt the intervention. Cost-effectiveness modelling was applied to analyse the intervention and indicated a 72% probability that adopting chlorhexidine 0.1% is cost-effective and a 35% probability it will be cost saving.

Conclusion

The results demonstrate the value of chlorhexidine 0.1% for meatal cleaning before urinary catheter insertion. The use of chlorhexidine has the potential to make significant improvements to patient safety, and is cost effective. The findings will inform clinical policy and practice in Australia and internationally.

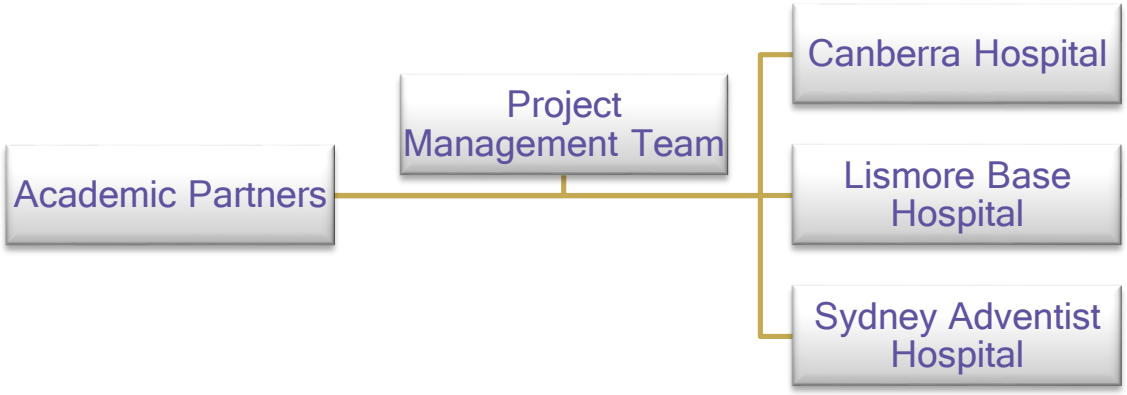
ABOUT THE STUDY

Funding and governance

Avondale College of Higher Education was the lead organisation in this study and was responsible for managing the study design, conducting the intervention, initial data analysis and interpretation, publication and dissemination of results. Academic project partners at Australian Catholic University (ACU), Queensland University of Technology (QUT), Monash University (MON) and Australian National University (ANU) provided in-kind contributions to the study design, conduct, data analysis and interpretation and the publication and dissemination of results.

The project is funded by the HCF Research Foundation (Category 1 Grant) and cash support from the Lifestyle Research Centre at Avondale College of Higher Education.

Figure 1: Project partners and governance structure



Ethics

The study is registered with the Australian and New Zealand Clinical Trials Registry; Trial registration number 12617000373370, approved 13/03/2017 Protocol version 1.1. The study protocol informed all aspects of the implementation of the study and reflected the Australian Code for the Responsible Conduct of research (http://www.nhmrc.gov.au/guidelines-publications/r39. This study received ethics approval from Avondale College of Higher Education Human Research Ethics Committee (HREC) (approval number 2017:03), ACT Health HREC (approval number ETH.4.17.083) and the Adventist HealthCare Limited Human Research Ethics Committee (approval number 2017-018).

Site specific authorization were granted by each participating hospital.

Aims and outcome measures

To evaluate the efficacy (Objective 1), and cost-effectiveness (Objective 2) of using 0.1% chlorhexidine (the Intervention) in urethral meatal cleaning prior to catheter insertion for the prevention of catheter-associated urinary tract infections (CAUTI), catheter associated asymptomatic bacteriuria (CA-ASB) and bloodstream infections (BSI) associated with a UTI.

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

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

BACKGROUND

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] CAUTIs have been associated with increased morbidity, mortality and higher hospital costs for patients and health systems.[3] In Australia, an estimated 380,000 bed days are lost each year due to healthcare-associated UTIs, a large proportion are CAUTIs. Research undertaken by CI Mitchell identified the frequency of these infections in Australia, and a world first: they are associated with an increased length of stay in hospital of up to four days.[4] CAUTIs are associated with higher risk of antimicrobial resistance (AMR), making the treatment of patients difficult and compounding the effects of AMR when treatment is provided.[5, 6]. AMR is an issue in UTIs.[7] A recent high-level meeting of the United Nations General Assembly addressed the topic of increasing AMR.[8]. This further emphasises the need to develop interventions to reduce the incidence of CAUTIs.

Despite advances in infection prevention and control, CAUTIs remain problematic[9] - further research is needed to identify ways to reduce the burden they create. Evidence shows that reducing bacterial colonisation around the urethral area has the potential to reduce CAUTI risk[2]; however, evidence about the best antiseptic solutions for cleaning is mixed. The lack of clarity has resulted in conflicting recommendations for national practice guidelines in the United States and in Australia. Unsurprisingly, there is variation in practice within Australian hospitals with respect to catheter insertion, and specifically the agent used to clean the urethral area prior to insertion. In addition, previous research undertaken by three of the investigators identified a lack of documentation and knowledge in relation to the meatal cleaning solution used prior to catheter insertion. [1]. 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 prevention of CAUTI. [10]. This work identified the need for a well-designed intervention study and also identified a limited number of studies evaluating the cost-effectiveness of using 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 normal saline.

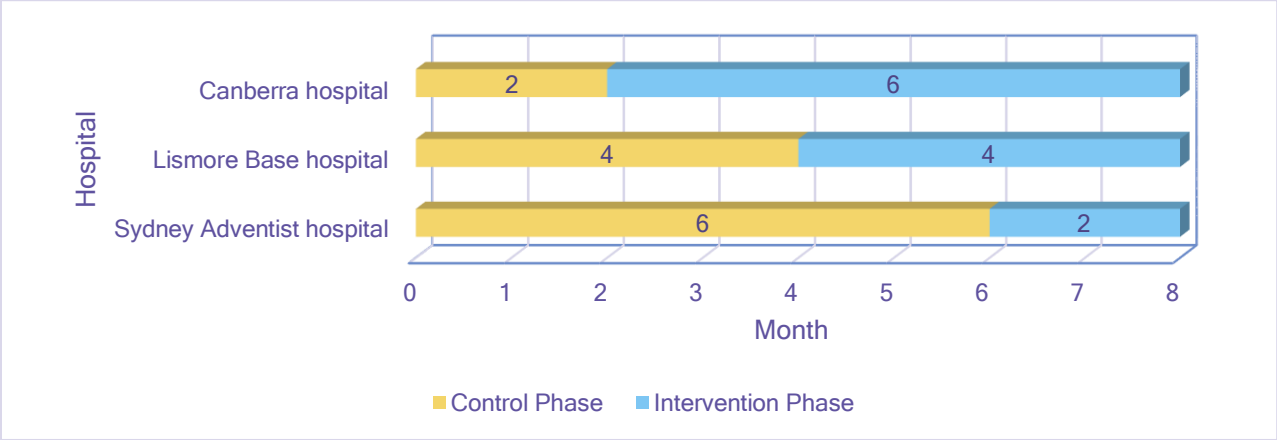
Given the importance of meatal colonisation in the pathogenesis of CAUTIs, emerging AMR, the frequency with which catheters are used and the burden of CAUTIs in Australia and in hospital settings worldwide, generation of evidence using a high-quality randomised trial was required to determine the efficacy and cost-effectiveness of meatal cleaning, in turn informing clinical practice and policy in Australia and internationally.

DESIGN AND METHODS

Study design

A stepped wedge randomised controlled trial was undertaken in three large Australian hospitals (large private, large tertiary and large regional hospital) over a 32-week period (Figure 2). The stepped wedge design included an initial period where no hospitals were exposed to the intervention. [11] Afterwards, at regular intervals (the "steps") one or more hospitals were randomised to cross over from the control to the intervention with the process continuing until all hospitals had crossed over.[11]. There was a random sequential allocation of the intervention to three hospitals, that is, each hospital was introduced to the intervention approximately every eight weeks until week 32, when all three hospitals had been exposed to the intervention. The study design enabled each hospital to act as its own control, which removed the potential for some confounders such as variations in hospital size, location (rural or urban), demographics and differences between public and private hospitals. Staggered commencement and duration of the intervention, supported feasibility while maintaining the rigour of the study.[12] The design allowed research staff to work with individual hospitals as they changed over, maximising consistency of intervention and aiding implementation.[12] In addition, data collection continued throughout the study, so that each cluster contributed observations under both control and intervention observation periods.

Figure 2. Stepped wedge study design.



Yellow = control; Blue = intervention

Intervention

The intervention for this study was chlorhexidine 0.1% solution 30ml ampule. The study evaluated the efficacy and cost-effectiveness of cleaning the urethral meatal area with chlorhexidine solution prior to urinary catheter insertion for the prevention of catheter-associated urinary tract infections.

Randomisation and masking

Hospitals were randomly assigned to one of three dates to cross over to the intervention using a computer-generated randomisation system. Randomisation was performed independently by an investigator not involved in assessment or delivery of the intervention. During the first eight weeks of the study, no hospitals were exposed to the intervention (control phase), after which each hospital

sequentially crossed over from the control to the intervention every eight weeks beginning from September 26, 2017 for hospital A. Hospitals B and C crossed over to the intervention on November 21, 2017 and January 16, 2018 respectively. Masking of hospitals was not possible because it was not feasible to blind staff administering the intervention. Prior to study commencement, randomisation allocation was unmasked and revealed to hospitals by the project manager.

Clinical staff at participating hospitals were responsible for cleaning the meatal area of participants prior to urinary catheter insertion. The procedure did not defer from usual clinical practice. Before commencement of the intervention, hospital staff were made aware of the change of cleaning solution and reminded about the clinical trial. Ward posters, information leaflets and branded promotional material were distributed to hospitals to either use at the beginning of the trial or pre intervention to raise awareness. To prevent the effect of confounding on the trial results, no additional education was given on catheter insertion and management practices and staff were expected to follow the hospital's usual practice.

To prevent the potential confounding effect of antiseptic-containing lubricants used during the catheterisation process, the lubricating agent remained constant in each hospital during both control and intervention periods. No lubricant in any hospital contained chlorhexidine. The type of lubricant used was checked prior to the commencement of the study and during the study.

Chlorhexidine was not readily available for staff to use during the control phase. During the intervention phase, chlorhexidine was either incorporated into existing catheter procedure packs and trial information stickers were attached to the packs or saline was replaced by chlorhexidine in the store room area with the catheter packs. A temporary amendment to hospital procedural documentation was implemented and an insert for internal communications was provided.

Participants who received a urinary catheter were identified prospectively and followed-up during thetrial period for seven days following catheter insertion, 48 hours following catheter removal or discharge, depending on which occurred first. The decision to collect a catheter urine specimen for culture was made by the treating physician. There was no change in the urine culture collection process during this study, at any hospital. Study investigators worked alongside hospitals to assist staff with implementation of the intervention by utilising hospital data collection and reporting systems currently in place.

Data were prospectively collected by hospital personnel from participants' medical records and recorded in a purpose-designed spreadsheet. Demographic and clinical data abstracted included: hospital number; age; sex; admission date; UTI symptoms or signs; comorbidities; catheter insertion date and time; designation of person inserting catheter; and catheter type and size. Data on UTI symptoms and signs were used to differentiate between CA-ASB and CAUTI. Denominator data on the number of catheter days over the trial period was collected at each hospital during both control and intervention periods. The number of catheter days for each participant included in the study was estimated from the catheter insertion and removal dates. Data on the primary and secondary outcomes were obtained from the hospitals' microbiology laboratory database.

The intervention was assessed against the Template for intervention description and replication (TIDier) Checklist.

Participating hospitals

Canberra public hospital (ACT), Lismore Base hospital (NSW) and Sydney Adventist hospital (NSW) participated in the study.

Lismore Base Hospital site visit. Vicki Denyer IPC Nurse Consultant and Project Manager raising awareness

Jayne O'Connor IPC Coordinator Sydney Adventist Hospital, education roadshow.

STUDY PHASES

Control phase

During the first eight weeks of the study, no hospital received the intervention. The control period for this trial involved hospitals using 0.9% normal saline for meatal cleaning prior to urinary catheter insertion.

Intervention phase

After eight weeks, Canberra hospital crossed over to the intervention with Lismore and Sydney Adventist hospitals crossing over to the intervention at eight-week intervals respectively based on randomisation. The intervention is the use of 0.1% chlorhexidine solution for meatal cleaning, prior to urinary catheter insertion.

From left to right, Vicky Gregory, project manager and Jayne O'Connor, Holly Dodd and Lisa Kulavere SAH, at ACIPC Conference Canberra 2017. Vicky Denyer, Clinical Nurse consultant Lismore Base Hospital, BMJ Open published protocol paper.

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Open Access Protocol

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

Brett G Mitchell,[1,2] Oyebola Fasugba,[1,3] Anne Gardner,[4] Jane Koerner,[4] Peter Collignon,[5,6] Allen C Cheng,[7,8] Nicholas Graves,[9] Peter Morey,[10] Victoria Gregory[1]

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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 8 weeks of the study, no hospital will receive the intervention. After 8 weeks, one hospital will cross over to the intervention with the other two participating hospitals crossing over to the intervention at 8-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.A dissemination plan it being developed. Results will be published in the peer review literature, presented at relevant conferences and communicated via professional networks.

Ethics Ethics approval has been obtained.

Trial registration number 12617000373370, approved 13/03/2017. Protocol version 1.1.

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] CAUTIs 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, suggest the incidence of CAUTI to be 4.8 per 1000 device days (years 2010–2015).[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. CAUTIs are also associated with higher risk of antimicrobial resistance (AMR), making the treatment of patients difficult.[4 5] AMR 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] Nonetheless, 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

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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 use 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

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 8 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.

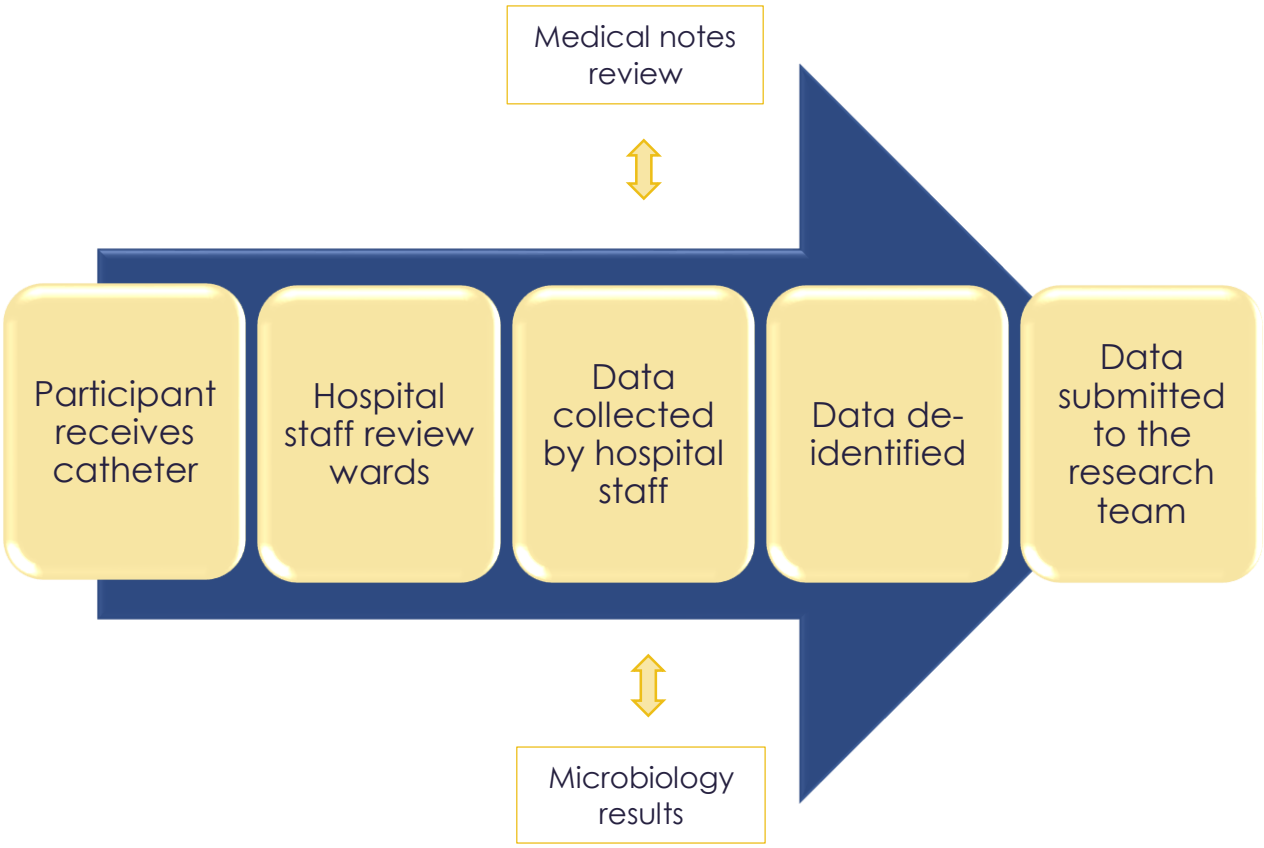
Study population

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

DATA COLLECTION

Data was collected by a specific staff member or members at the hospital, with the support of the research team. Where data collection resulted in an increase in workload for hospitals (i.e. not part of usual practice), the research team worked with the hospital in assisting with providing additional resources. The research team provided the hospital staff member(s) with training about the project, data collection process and the provision of data collection tools.

Figure 3. Overview of data collection process



Objective 1

Information for the primary outcome measure (CA-ASB and CAUTI) and the secondary outcome measure (BSI) were 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 obtained weekly reports from the microbiology laboratory of participating hospitals to identify the outcomes. The hospital number was 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 were collected from patients' medical notes by research assistants.

Objective 2

Information to inform changes to total costs and health benefits from a decision to adopt the intervention were organised. Changes to costs included the resources required to implement the intervention and the changes to use of health services. Changes to health benefits were captured by estimating QALY outcomes. The cost of purchasing resources, such as catheter procedure packs, used for implementing the intervention were collated by the research team. Data was also collected from the medical notes on the number of laboratory tests ordered for each patient included in the trial to estimate laboratory diagnosis costs. Hospital personnel obtained data on antimicrobial use for patients, specifically the name, dose and duration of antimicrobial, which was used for estimating antimicrobial therapy costs in control and intervention periods. Hospital staff involved in the trial were surveyed to evaluate extra staff time spent in activities related to planning and implementing the intervention. To calculate QALYs, primary data on age were obtained from medical notes of patients will be used along with estimates from the published literature. [13]

For a tabulated list of data collection variables see Appendix 1

DATA ANALYSIS

The effectiveness of the intervention

The number of CA-ASB was analysed using Poisson regression, with the number of cases as the dependent variable and number of patient catheter days as the denominator. This denominator helped control for changes in catheter use during the study period. The key independent variable is the intervention. The key outcome was the estimated reduction in cases of CA-ASB due to the intervention. The characteristics of the hospital (e.g. size) was not an independent variable as remained roughly constant throughout the study observations. There was no expected delay in the effect of intervention on the outcome.

The cost-effectiveness of the intervention

The effectiveness data from Objective 1 was a key parameter in a 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 and in QALYs. The changes to costs from adopting the intervention were estimated by the extra staff time spent both planning (policy) and implementing the intervention (staff and product), converted to a dollar figure. These cost data were collected prospectively and surveyed after the intervention was implemented (staff costs). Quantities of resources were standardised to all hospitals to ensure valid comparison of costs across all sites. This reduced uncertainty in estimates which often results from using retrospective administrative data.

The major cost savings from reducing infections were characterised by identifying the number of AUD hospital CEOs were willing to pay for an available hospital bed, such numbers are considerably conservative compared to costs identified with 'bed days saved' [14]. Other cost savings are 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 were collected prospectively as part of the data collection process. Laboratory costs using the relevant Medical Benefit Scheme item costs were used. For antimicrobial therapy costs, Pharmaceutical Benefits Scheme costs were used.

The change to total costs at the hospital level were estimated by summing intervention costs and deducting cost savings that arose from reduced incidences of infection. The changes to health benefits were 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.[15]

RESULTS

Effectiveness of the intervention

Over the study period 1642 catheters were inserted. The mean age of participants who received a catheter was 64 years (range 16-102). In the pre-intervention period, there were 13 CAUTI events and 29 bacteriuria events in 2889 catheter days. In the post-intervention period, there were 4 CAUTI events and 16 bacteriuria events in 2338 catheter days. The use of chlorhexidine was associated with a 74% reduction in the incidence rate of bacteriuria, and a 94% decrease in the incidence rate of CAUTI. There was no BSI recorded during both control and intervention periods.

The table below sets out participant characteristics by phase. There was a total of 1,642 participants, 697 participated in the control phase of the study and 945 in the intervention phase of the study. Hospital A had the longest intervention phase and was a larger hospital with greater numbers of patients. Comorbidities were recorded for cancer, liver disease and diabetes. The mean number of catheterized days was 4.16 in the control phase and 2.47 in the intervention phase.

Table 2. Participant characteristics by phase

Variable	Control (n=697)	Intervention (n=945)	P value
Age, mean (95%CI)	76 (74-77)	54 (52-55)	P<0.001
Sex			
Female	329 (47.7%)	620 (65.6%)	P<0.001
Male	368 (52.3%)	325 (34.4%)	
Comorbidities – Cancer			
No	496	819	P<0.001
Yes	201	126	
Comorbidities – Liver disease			
No	657	922	P<0.001
Yes	40	23	
Comorbidities – Diabetes			
No	572	841	P<0.001
Yes	125	104	
Days catheterised , mean (95%CI)	4.16 (3.98-4.34)	2.47 (2.34-2.60)	P<0.001

Table 3. Month of year, catheter inserted

Month	Frequency	Percent	Cumulative Percent
August 2017	122	7.4	43.1
September 2017	203	12.4	55.4
October 2017	262	16.0	71.4
November 2017	297	18.1	89.5
December 2017	173	10.5	100.0
January 2018	262	16.0	16.0
February 2018	249	15.2	31.1
March 2018	74	4.5	35.6
Total	1642	100.0	

The reduction in catheterisation in March occurred in all three hospitals and reflected the study end date.

The table below sets out the reason for censoring by hospitals.

Table 4. Reason for censoring

Hospital	Reason for censoring	Frequency	Percentage	Valid Percentage
Hospital A	End of follow up period (7 days)	99	14.3	14.8
	Discharged	18	2.6	17.4
	Catheter removed	570	82.6	100.0
	Total	690	100.0	
Hospital B	End of follow up period (7 days)	50	19.5	19.8
	Discharged	60	23.3	43.2
	Catheter removed	146	56.8	100.0
	Total	257	100.0	
Hospital C	End of follow up period (7 days)	185	26.6	26.8
	Discharged	111	16.0	42.7
	Catheter removed	398	57.3	100.0
	Total	695	100.0	

The table below sets out the number and rate of CA-ASB and CAUTI at each hospital site in the control and intervention phase. A total of 2889 catheter days contributed to the control phase and 2338 catheter days contributed to the intervention phase.

Table 5: Number and rate of CA-ASB and CAUTI at study sites

	Control		Intervention	
	Catheter days	**Number (rate*)**	**Catheter days**	**Number (rate*)**
CA-ASB				
• Hospital A	254	8 (3.15)	1327	11 (0.82)
• Hospital B	552	5 (0.91)	418	2 (0.48)
• Hospital C	2093	16 (0.76)	593	3 (0.49)
• Total	2889	29 (1.00)	2338	16 (0.68)
CAUTI				
• Hospital A	254	3 (1.18)	1327	4 (0.30)
• Hospital B	552	2 (0.36)	418	0 (0.00)
• Hospital C	2093	8 (0.38)	593	0 (0.00)
• Total	2889	13 (0.45)	2338	4 (0.17)

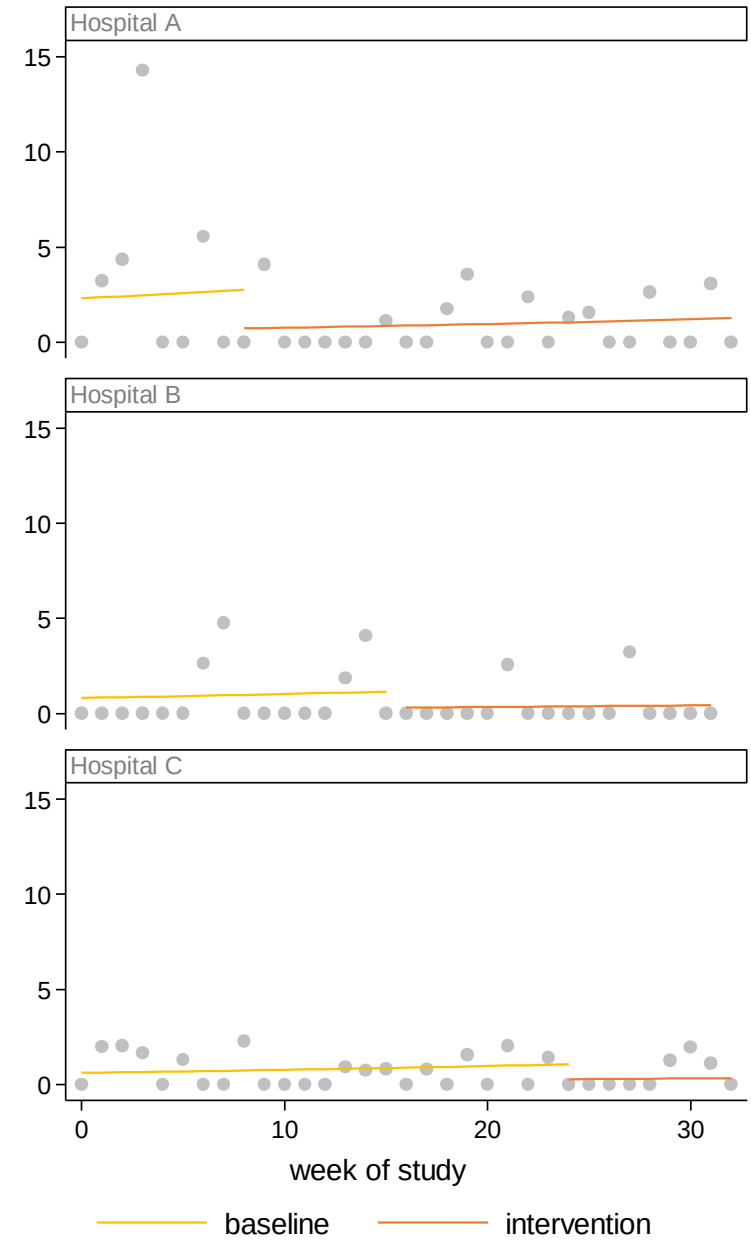
*per 100 catheter days

Table 6: Poisson regression results

	CA-ASB		**CAUTI**	
	Incidence rate ratio	p-value	Incidence rate ratio	p-value
Intervention	0.28 (0.08, 0.93)	0.037	0.06 (0.01, 0.32)	<0.001
Week	1.02 (0.97, 1.07)	0.408	1.07 (0.98, 1.16)	0.132
Hospital				
Hospital A	1 (referent)		1 (referent)	
Hospital B	0.39 (0.12, 1.23)	0.107	0.17 (0.04, 0.73)	0.018
Hospital C	0.26 (0.09, 0.75)	0.013	0.14 (0.04, 0.51)	0.003

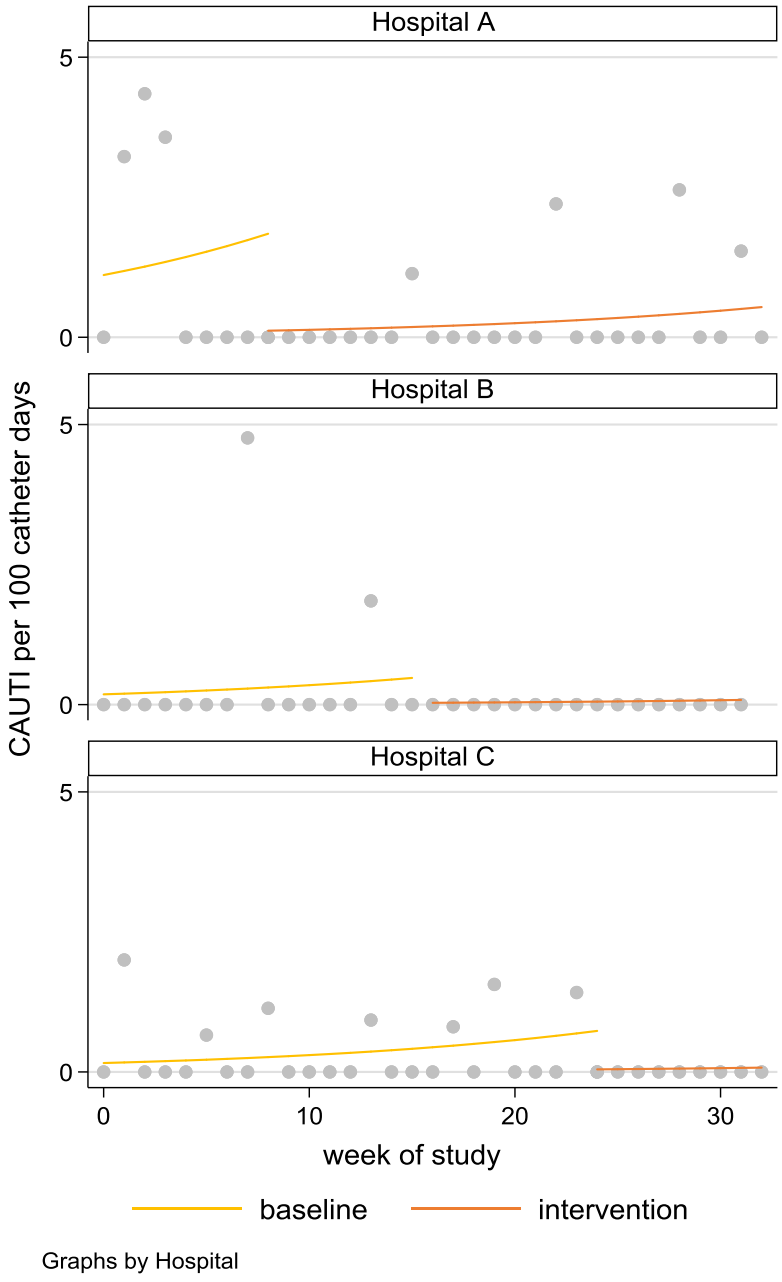
The graphs below indicate an observed and modelled weekly incidence of CA-ASB at each study site. The grey dots are the observed weekly incidence at hospital A, B and C. The yellow line represents the control phase and the orange line the intervention phase. The graph demonstrates that there was a greater incidence of bacteriuria per 100 catheter days in the control phase compared to the intervention phase at each hospital.

Figure 4 : Observed and modelled weekly incidence of CA-ASB at each study site



The graphs below indicate an observed and modelled weekly incidence of CAUTI at each study site. The grey dots are the observed weekly incidence at hospital A, B and C. The yellow line represents the control phase and the orange line the intervention phase. The graph demonstrates that there was a greater incidence of CAUTI per 100 catheter days in the control phase compared to the intervention phase at each hospital, with no CAUTIs observed at all during the intervention phase at hospitals B and C i.e. no grey dots above the orange line.

Figure 5: Observed and modelled weekly incidence of CAUTI at each study site



Need for sensitivity analysis

In exploratory analyses, it was noted that there was an unexpected difference in the age distribution of patients at hospital A, that was not reported at hospitals B and C. To determine whether the observed results could be confounded by this difference, two analyses were performed. The mean patient age at Hospital A was 79 years in the control phase and 35 years in the intervention. The mean patient age at Hospital B was 72 years in the control phase and 73 years in the intervention. The mean patient age at Hospital C was 80 years in the control phase and 82 years in the intervention.

Cost-effectiveness of the intervention

Healthcare resources are scarce so an investment in economic innovations makes sense. The main cost-effectiveness outcomes were the changes to health service cost in Australian dollars and the change to quality adjusted life years from a decision to adopt the intervention. Cost-effectiveness modelling was applied to analyse the intervention.

Monetary values for bed days were derived using two competing methods. The first was an accounting method and the second a valuation study of Australian Hospital Chief Executive Officers. They revealed their willingness to pay for bed days released by an infection prevention programme.

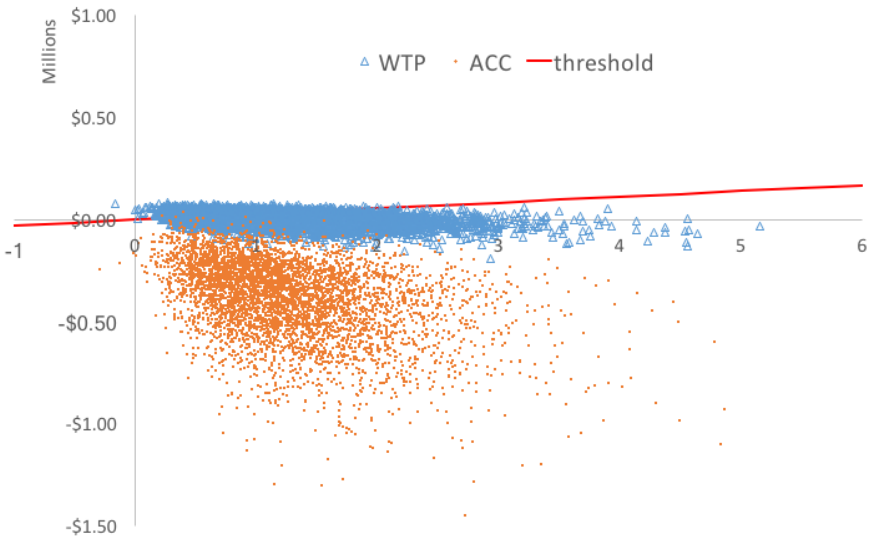
Values of $284 and $573 for a ward and an ICU bed day were used.

Figure 6 : Results of sampling from model parameters

Per 100,000 patients catheterised	Mean	Min	Max
Change to total costs (Accounting costs)	-$387,909	-$1,443,740	$70,697
Change to total costs (WTP costs)	$6,299	-$237,102	$91,537
Change to QALYS	1.25	-0.09	4.93
Cost of intervention	$89,012	$81,000	$97,000
Number asymptomatic Bacteriuria prevented	2450.60	-539.58	6369.21

The modelling capture below shows all blue dots, which represent a multiplicity of modelling outcomes associated with the cost-effectiveness of the intervention. Joint distribution of change to total costs and change to QALYS for two scenarios: bed days valued be accounting methods (dots) and by WTP methods (triangles).

Figure 7: Cost-effectiveness modelling



The red line shows a maximum willingness to pay for a marginal QALY threshold of $28,000 (ref Karnon). For the WTP analysis 72% of the simulations are below this threshold and 35% are below the x-axis indicating a 72% probability that an adoption decision is going to be cost-effective and a 35% probability it will be cost saving. For the ACC analysis 100% are below the x-axis indicating a 100% probability that an adoption decision is going to be cost saving; therefore, a decision to switch to chlorhexidine dominates a decision to remain with saline.

Harms

There were no reported harms or unintended events reported during the course of this study.

Discussion

This is the first multi-centre RCT comparing the effectiveness of 0.1% chlorhexidine solution and 0.9% normal saline solution for meatal cleaning prior to urinary catheterisation in preventing CA-ASB and CAUTI. The results showed a 74% reduction in the incidence of CA-ASB and a 94% reduction in the incidence of CAUTI in the intervention phase, suggesting that. 0·1% chlorhexidine solution is an effective meatal cleaning solution to use before urinary catheterisation in preventing CA-ASB and CAUTI.

Given the high costs associated with healthcare associated infections a cost-effectiveness analysis was also carried out, as chlorhexidine is more expensive than saline solution. The main cost-effectiveness outcomes were the changes to health service cost in Australian dollars and the change to quality adjusted life years from a decision to adopt the intervention. Cost-effectiveness modelling was applied to analyse the intervention and indicated a 72% probability that adopting chlorhexidine 0.1% is cost-effective and a 35% probability it will be cost saving.

CA-ASB and CAUTI are often in appropriately treated with antimicrobials, so by reducing the incidence of CA-ASB and CAUTI also decreases antimicrobial use.

The limitations of this study include the difference in the mean age of participants in hospital A in comparison to hospitals B and C. This was due to a larger proportion of young female obstetric patients who comprised the greater part of the sample in the intervention period in hospital A. Hospital A also had the longest intervention period and was the largest hospital in our study. While there was potential for this to skew the study findings, the sensitivity analysis, accounting for age and sex, found similar results to the original analysis. Although this was a hospital-wide study, patients catheterised in theatre were excluded. The obstetrics and gynecology department at Hospital B and the Maternity department at Hospital C declined to participate in the study. The reasons provided were that the obstetrics and gynecology department at Hospital B were not appropriately consulted during the site specific authorisation process and the Maternity department at Hospital C felt that chlorhexidine would compromise the vaginal flora of the birth canal and therefore requested to be excluded from the study.

The target sample size was achieved but the potential for selection bias cannot be excluded. The Hawthorn effect also cannot be excluded as awareness of the study at the participating hospital may have led to an increased awareness of urinary cathetrisation technique and maintenance. The potential for this was considered in the research planning phase and initial information booklet about the study did not provide information on urinary catheterisation technique or maintenance, but focused on study implementation only.

Despite the limitations, this study is the largest trial to date (3 hospitals; 1642 participants) to assess the effectiveness of using 0·1% chlorhexidine solution, compared to 0·9% normal saline for meatal cleaning prior to urinary catheter insertion, in reducing the incidence of CA-ASB and CAUTI. Reductions in CA-ASB and CAUTI were identified in all three participating hospitals, despite differences in their governance, funding, size and geographical location. The trial integrity is maintained by using a stepped-wedge design which removed the potential for confounders. A clear distinction was made between CA-ASB and CAUTI by reviewing patient data. Previous studies have not made this distinction.[16]

The research team carried out an assessment against the PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) which identified the study's replicability and ease of implementation to other hospitals.

The results demonstrate the value of chlorhexidine 0.1% for meatal cleaning before urinary catheter insertion. The use of chlorhexidine has the potential to make significant improvements to patient safety, and is cost effective. The findings will inform clinical policy and practice in Australia and internationally.

PUBLICATIONS AND DISSEMINATION

November 2017	**BMJ open** **Reducing catheter-associated urinary tract infections in hospitals: study protocol for a multi-site randomised controlled study**	Study protocol
November 2017	**Australasian College of Infection, Prevention and Control 2017, Canberra**	Abstract and Oral presentation, protocol paper
March 2018	**IPC Forum, IPC hospital Coordinators, Sydney**	Abstract and Oral presentation
September 2018	**Hospital Infection Society, Liverpool UK**	Abstract and Oral presentation, effectiveness and cost effectiveness results
September 2018	**Infection Prevention Society, Glasgow, UK**	Oral presentation, preliminary (effectiveness) results
October 2018	**Sydney Adventist hospital, Sydney. Nurse Directors and IPC staff.**	Results presentation
October 2018	**Canberra Public Hospital, Canberra. Nurse Directors and IPC staff.**	Results presentation
November 2018	**Lismore Base Hospital, Lismore. Nurse Directors and IPC staff.**	Results presentation
November 2018	**Australasian College of Infection, Prevention and Control 2018, Brisbane**	Results presentation
December 2018	**University of West London**	Results presentation
December 2018	**Swansea University**	Results presentation
December 2018	**Glasgow University**	Results presentation
December 2018	**Cardiff University**	Results presentation
January 2019	**World Health Organisation, Geneva**	Results presentation
Ongoing	**Twitter, Avondale website, Blogs, Hospital Bulletin, ABC news and other media**	Results
November 2018	**Catheter Insertion technique video**	To be published
November 2018	**Animated video presentations**	To be published
November 2018	**The Lancet (Infectious Disease)**	To be published
November 2019	**IPS, UK Conference**	TBC

APPENDIX 1

Data collected	Source	Collected by	Timing	Used for
Details of patient who received a catheter				
Hospital number	Medical notes	Hospital personnel	Control and intervention periods	Link to laboratory data
Date of birth	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness and cost effectiveness)
Sex	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness and cost effectiveness)
Date of admission	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness)
Reason for censoring follow-up (discharged, catheter removal, end of follow up period)	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness)
Censored date	Medical notes	Hospital personnel	Control and intervention periods	Calculating catheter days Data analysis (effectiveness)

Data collected	Source	Collected by	Timing	Used for
Any signs or symptoms of UTI prior to insertion (Y/N)	Medical notes	Hospital personnel	Control and intervention periods	Exclusion/inclusion
Control (saline) or intervention (chlorhexidine)	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness and cost effectiveness)
Co-morbidity data (where possible) on admission to any of the following (Y/N): myocardial infarction, heart failure, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissues disorder, peptic ulcer, liver disease, diabetes, diabetes complication, paraplegia, cancer, metastatic cancer, severe liver disease, HIV.	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness)
Details of catheter insertion	Medical notes	Hospital personnel		
Date and time of insertion	Medical notes	Hospital personnel	Control and intervention periods	Calculating catheter days Data analysis (effectiveness)
Designation of person inserting catheter	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness)

Data collected	Source	Collected by	Timing	Used for
Catheter type (long term/short term)	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness)
Catheter size	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (effectiveness)
Laboratory result^ of any patient who received a catheter		Hospital personnel		
Hospital number	Microbiology laboratory	Hospital personnel	Control and intervention periods	Link to laboratory data
Date of specimen collection	Microbiology laboratory	Hospital personnel	Control and intervention periods	Data analysis (effectiveness) Defining the outcome
Species isolated	Microbiology laboratory	Hospital personnel	Control and intervention periods	Defining the outcome
Colony count and white cell count where appropriate / provided	Microbiology laboratory	Hospital personnel	Control and intervention periods	Defining the outcome
Additional information in patients with a positive urine culture^		Hospital personnel		
Signs or symptoms of a CAUTI fever (>38.0°C) suprapubic tenderness	Medical notes	Hospital personnel	Control and intervention periods	Defining the outcome

Data collected	Source	Collected by	Timing	Used for
costovertebral angle pain or tenderness urinary urgency* urinary frequency* dysuria*				
Date of signs/symptoms	Medical notes	Hospital personnel	Control and intervention periods	Defining the outcome
Antimicrobial therapy (name, dose, duration of antimicrobial)	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (cost effectiveness)
Costs of implementing the intervention				
Survey immediately post intervention to capture time associated with implementing the intervention	Survey	Project manager	Control and intervention periods	Data analysis (cost effectiveness)
Number of microbiology laboratory tests ordered for each patient	Medical notes	Hospital personnel	Control and intervention periods	Data analysis (cost effectiveness)
Monthly cost of purchasing resources associated with implementing the intervention	Hospital administrative department	Hospital personnel & project manager	Control and intervention periods	Data analysis (cost effectiveness)

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