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# BMJ Open

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

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1  
2 1 **Title:** Reducing catheter associated urinary tract infections in hospitals: study protocol for a multi-  
3 site randomised controlled study  
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1  
2 34 **Abstract**  
3 35

4 36 Introduction: Despite advances in infection prevention and control, catheter associated urinary tract  
5  
6 37 infections (CAUTIs) are common and remain problematic. A number of measures can be taken to  
7  
8 38 reduce the risk of CAUTI in hospitals. Appropriate urinary catheter insertion procedures are one  
9  
10 39 such method. Reducing bacterial colonisation around the meatal or urethral area has the potential to  
11  
12 40 reduce CAUTI risk. However, evidence about the best antiseptic solutions for meatal cleaning is  
13  
14 41 mixed, resulting in conflicting recommendations in guidelines internationally. This paper presents  
15  
16 42 the protocol for a study to evaluate the effectiveness (objective 1) and cost effectiveness (objective  
17  
18 43 2) of using chlorhexidine in meatal cleaning prior to catheter insertion, in reducing catheter  
19  
20 44 associated asymptomatic bacteriuria and CAUTI.  
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29 47 Methods and analysis: A stepped wedge randomised controlled trial will be undertaken in three  
30  
31 48 large Australian hospitals over a 32-week period. The intervention in this study is the use of  
32  
33 49 chlorhexidine (0.1%) solution for meatal cleaning prior to catheter insertion. During the first eight  
34  
35 50 weeks of the study, no hospital will receive the intervention. After eight weeks, one hospital will  
36  
37 51 cross over to the intervention with the other two participating hospitals crossing over to the  
38  
39 52 intervention at eight-week intervals respectively based on randomisation. All sites complete the trial  
40  
41 53 at the same time in 2018. The primary outcomes for objective 1 (effectiveness) are the number of  
42  
43 54 cases of CAUTI and catheter associated asymptomatic bacteriuria per 100 catheter days will be  
44  
45 55 analysed separately using Poisson regression. The primary outcome for objective 2 (cost  
46  
47 56 effectiveness) is the changes in costs relative to health benefits (incremental cost-effectiveness  
48  
49 57 ratio) from adoption of the intervention.  
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54  
55 59 Dissemination: Ethics approval has been obtained. Results will be disseminated via peer-reviewed  
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57 60 journals and presentations at relevant conferences.  
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**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.

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69 **Strengths and limitations of this study**

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

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## 79 Introduction

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

91

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

1  
2 104 during catheter insertion. As health budgets are finite, clinical practice needs to utilise cost-effective  
3  
4 105 strategies. The cost of chlorhexidine 0.1% solution is considerably higher than 0.9% normal saline.  
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7  
8 107 Given the importance of meatal colonisation in the pathogenesis of CAUTIs, emerging AMR, the  
9  
10 108 frequency with which catheters are used and the burden of CAUTIs in Australia and in hospital  
11  
12 109 settings worldwide, the generation of evidence using a high-quality randomised trial is needed to  
13  
14 110 determine the efficacy and cost-effectiveness of meatal cleaning. This will inform infection  
15  
16 111 prevention and control practice and policy in Australia and internationally.  
17  
18 112

### 19 20 21 113 **Trial objectives**

22 114 The trial objectives listed below pertain to both the cluster and individual level. The trial is  
23  
24 115 registered with the Australia New Zealand Clinical Trial Registry (No 12617000373370).  
25  
26 116

#### 27 28 29 117 *Objective 1*

30  
31 118 The first objective is to evaluate the effectiveness of using chlorhexidine in meatal cleaning prior to  
32  
33 119 catheter insertion, in reducing catheter associated asymptomatic bacteriuria (CA-ASB) and CAUTI.  
34  
35 120

#### 36 37 38 121 *Objective 2*

39  
40 122 The second objective is to estimate the cost effectiveness of the decision to adopt chlorhexidine in  
41  
42 123 meatal cleaning prior to catheter insertion.  
43  
44 124

### 45 46 47 125 **Methods**

#### 48 49 126 *Study design*

50  
51 127 A stepped wedge randomised controlled trial will be undertaken in three large hospitals over a 32-  
52  
53 128 week period (example trial timing are in Figure 1). The stepped wedge design includes an initial  
54  
55 129 period where no hospitals are exposed to the intervention.<sup>9</sup> Afterwards, at 8 week intervals (the  
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1 130 “steps”) each hospital sequentially crosses over from the control to the intervention until all  
2  
3 131 hospitals are exposed to the intervention for the final eight weeks until conclusion in week 32. The  
4  
5 132 study design enables each hospital to act as its own control, which removes the potential for some  
6  
7 133 confounders such as variations in hospital size and case mix and differences between public and  
8  
9 134 private hospitals. Staggered commencement and duration of the intervention, supports feasibility  
10  
11 135 while maintaining the rigour of the study.<sup>10</sup> This design will also allow research staff to work with  
12  
13 136 individual hospitals as they change over, maximising consistency of intervention and aiding  
14  
15 137 implementation.<sup>10</sup> In addition, data collection continues throughout the study, so that each cluster  
16  
17 138 contributes observations under both control and intervention observation periods.  
18  
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#### 24 140 *Study population*

25  
26 141 Three Australian hospitals that fulfil the eligibility criteria will be enrolled in the study. These  
27  
28 142 criteria are:

- 29  
30 143
- 31 • Has an intensive care unit
  - 32 • Be classified by the Australian Institute of Health and Welfare as a principal referral
  - 33 hospital OR a public acute group A hospital (with more than 400 beds), OR in the case
  - 34 of a private hospital has 400 inpatient beds OR has more than 30,000 patient admissions
  - 35 per year.
  - 36
  - 37
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#### 44 149 *Other considerations*

45  
46 150 Hospitals could be excluded from the study if within the study time frame they are:

- 47  
48 151
- 49 • undertaking a project that may influence the outcomes measured in this study
  - 50 • opening, closing or relocating
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2 154 *Areas of hospital and patient-level inclusion and exclusion criteria*

3  
4 155 The study will be a hospital wide study, but will exclude patients with indwelling urinary catheters  
5  
6 156 within a hospital that are not considered appropriate for the intervention, for example neonatal  
7  
8 157 intensive care. Patients less than two years old, with an allergy, contraindication or other medical  
9  
10 158 reason preventing the use of the intervention for cleaning the urethral meatal area will be excluded.  
11  
12 159 Patients who require in-and-out or suprapubic catheterisation will also be excluded as well as those  
13  
14 160 with symptoms and signs suggestive of UTI and patients already undergoing treatment for UTI. All  
15  
16 161 data from any patient lost to follow-up (post-catheter insertion) will be excluded.  
17  
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21 162

22 163 ***Recruitment***

23  
24 164 The study team will list all eligible sites then order the list to ensure (i) a representation of both  
25  
26 165 private and public hospitals and (ii) representation from at least two Australian states and territories.  
27  
28 166 The recruitment process will purposively select and approach eligible hospitals to optimise the  
29  
30 167 feasibility and practicality of completing the trial.  
31  
32

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35 169 ***Intervention***

36  
37 170 The intervention in this study is the use of chlorhexidine (0.1%) solution for meatal cleaning prior  
38  
39 171 to catheter insertion. The control is the use of normal saline (0.9%) for meatal cleaning. During the  
40  
41 172 first eight weeks of the study, no hospital will receive the intervention. After eight weeks, one  
42  
43 173 hospital will cross over to the intervention with the other two participating hospitals crossing over  
44  
45 174 to the intervention at eight-week intervals respectively based on randomisation.  
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49  
50 176 ***Implementing the intervention***

51  
52 177 In the week prior to the intervention commencing, information sessions about the study will be  
53  
54 178 provided to participating hospitals and staff. A variety of methods will be used to further alert staff  
55  
56 179 and raise awareness about the intervention prior to it being rolled out. These methods include  
57  
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1 180 placing wall posters in wards and key hospital locations, handing out hospital newsletters and  
2  
3  
4 181 information leaflets as well as branded promotional material, such as pens.

5  
6 182

7  
8 183 Chlorhexidine 0.1% solution will be used by clinical staff at participating hospitals for cleaning the  
9  
10 184 meatal area of patients prior to urinary catheter insertion. To aid implementation of the intervention,  
11  
12 185 investigators will work with participating hospitals and utilise hospital data collection and reporting  
13  
14 186 systems currently in place. This will involve incorporation of the 0.1% chlorhexidine solution into  
15  
16 187 existing catheter procedure packs at the hospitals where possible, visual reminders where urinary  
17  
18 188 catheters are stored and temporary amendment to hospital procedural documentation.

19  
20  
21  
22 189

23  
24 190 As per hospital's usual practice, details of the catheter insertion will be documented by clinical  
25  
26 191 staff. To achieve optimal documentation of the procedure, catheter insertion stickers may be made  
27  
28 192 available to hospitals for use in patients' medical notes.

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33 194 ***Potential confounders***

34  
35 195 Lubricants are used during the catheter insertion process and may contain an antiseptic. The  
36  
37 196 lubricant used during the entire study (control and intervention periods) will remain constant in each  
38  
39 197 hospital.

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44 199 ***Randomisation and blinding***

45  
46 200 Hospitals will be randomly assigned to one of three dates to cross over to the intervention which  
47  
48 201 will occur once every eight weeks over the trial duration of 32 weeks. All included hospitals will be  
49  
50 202 provided with sufficient notice of the dates to cross over to the intervention. Computer-generated  
51  
52 203 randomisation of the cross over dates for the hospitals will be performed independently by an  
53  
54 204 investigator not involved in assessment or delivery of the intervention. Hospitals will not be blinded  
55  
56 205 because it is not feasible to blind staff administering the intervention. The outcome of the  
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2 206 randomisation process will be revealed by the project manager to the participating hospitals prior to  
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4 207 the commencement of the study.  
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8 209 ***Outcomes and definitions***  
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10 210 The outcomes for each objective are outlined in Table 1. For objective 1, the primary outcomes are  
11  
12 211 the cases of CA-ASB and CAUTI. For objective 2, the primary outcome is the cost effectiveness of  
13  
14 212 the intervention.  
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17 213 Catheter associated asymptomatic bacteriuria is defined as the presence of  $\geq 10^5$  colony forming unit  
18  
19 214 (cfu)/ml of  $\geq 1$  bacterial species in a single catheter urine specimen in a patient without symptoms  
20  
21 215 compatible with UTI.<sup>11</sup>  
22

23  
24 216 Catheter associated urinary tract infection is defined according to the National Healthcare Safety  
25  
26 217 Network criteria.<sup>12 13</sup> A patient must meet all three criteria below:  
27

- 28 218 1. Patient had an indwelling urinary catheter that had been in place for > 2 days on the date of  
29  
30 219 event (day of device placement = Day 1) AND was either present for any portion of the calendar  
31  
32 220 day on the date of event or removed the day before the date of event.  
33  
34 221 2. Patient has at least one of the following signs or symptoms: fever ( $> 38.0^\circ\text{C}$ ); suprapubic  
35  
36 222 tenderness; costovertebral angle pain or tenderness; urinary urgency; urinary frequency; dysuria.  
37  
38 223 3. Patient has a urine culture with no more than two species of organisms identified, at least one of  
39  
40 224 which is a bacterium of  $\geq 10^5$  cfu/ml.  
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46 226 Blood stream infection (BSI) associated with a urinary tract infection is defined according to  
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48 227 National Healthcare Safety Network criteria.<sup>12</sup> A patient must meet the definition for CAUTI and  
49  
50 228 have at least one organism from the blood specimen that matches an organism identified in the urine  
51  
52 229 specimen that is used as an element to meet the CAUTI criterion. The blood specimen must be  
53  
54 230 collected during the secondary BSI attribution period when the urinary catheter is in place.  
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2 232 ***Data collection***  
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4 233 Data will be collected by a specific staff member or members at the hospital, with the support of the  
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6 234 research team. The research team will provide the hospital staff member(s) with training about the  
7  
8 235 project, data collection and submission process and data collection tools. For the purpose this paper,  
9  
10 236 the dedicated hospital staff member(s) will be referred to as hospital personnel. Figure 2  
11  
12 237 summarises the data collection process.  
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15 238

17 239 Hospital personnel will prospectively collect data three days a week at each hospital during both  
18  
19 240 control and intervention periods. Patients who receive an indwelling urinary catheter will be  
20  
21 241 identified and followed-up during the trial period (for a period of 7 days post-catheter insertion,  
22  
23 242 discharge or 48 hours post-catheter removal – whichever occurs first). Medical notes of patients  
24  
25 243 will be reviewed to obtain demographic and clinical data such as hospital number, age, sex, date of  
26  
27 244 admission, signs or symptoms of UTI. Co-morbidity data will be collected where possible.  
28  
29

30 245 Details of catheter insertion specifically date and time of insertion, designation of person inserting  
31  
32 246 catheter, catheter type and catheter size, will also be obtained from the patients' medical notes  
33  
34 247 (where documented). If the insertion date is not documented, the patient will be excluded from the  
35  
36 248 study. Denominator data on the number of catheter days over the trial period will be collected at  
37  
38 249 each hospital during both control and intervention periods. The number of catheter days for each  
39  
40 250 patient included in the study will be estimated from the date of catheter insertion and date of  
41  
42 251 removal. Hospital personnel will record all captured data in a spreadsheet designed specifically for  
43  
44 252 the purpose of the trial.  
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48 253

50 254 Information for the primary (CA-ASB and CAUTI) and secondary (BSI) outcome measures will be  
51  
52 255 collected from the microbiology laboratory database of participating hospitals. Results of all  
53  
54 256 positive urine cultures either attributable to bacteriuria or true UTI as well as positive blood cultures  
55  
56 257 are registered in hospital microbiology laboratory databases. Hospital personnel will obtain weekly  
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1  
2 258 reports from the microbiology laboratory of participating hospitals to identify the outcomes. The  
3  
4 259 patient record number will be used to link demographic and clinical data of patients with a urinary  
5  
6 260 catheter to microbiology laboratory data. To differentiate between CA-ASB and CAUTI, additional  
7  
8 261 data on symptoms and signs of UTI will be collected from patients' medical notes by research  
9  
10 262 assistants.

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15 264 Information to inform changes to total costs and health benefits from a decision to adopt the  
16  
17 265 intervention will be obtained. Changes to costs will include the resources required to implement the  
18  
19 266 intervention and the changes to use of health services. Changes to health benefits will be captured  
20  
21 267 by estimating quality adjusted life years (QALY) outcomes. Hospital personnel will prospectively  
22  
23 268 obtain monthly data from each participating hospital on the cost of purchasing resources, such as  
24  
25 269 catheter procedure packs, used for implementing the intervention. Hospital personnel will also  
26  
27 270 obtain data on antimicrobial use for patients, specifically the name, dose and duration of  
28  
29 271 antimicrobial, which will be used for estimating antimicrobial therapy costs in control and  
30  
31 272 intervention periods. Hospital staff involved in the trial will be surveyed immediately following  
32  
33 273 completion of the intervention to evaluate extra staff time spent in activities related to planning and  
34  
35 274 implementing the intervention. To calculate QALYs, primary data on age obtained from medical  
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37 275 notes of patients will be used along with estimates from the published literature.<sup>14</sup>

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#### 42 43 44 277 ***Power calculation***

45  
46 278 Sample size and power were calculated on the basis of CAUTI, as it is assumed that the power to  
47  
48 279 detect an incremental cost effectiveness ratio was greater than that for relevant clinical endpoints.

49  
50 280 The at risk population are those that receive a catheter whilst in hospital. Based on pilot work, the  
51  
52 281 estimated proportion of patients developing a CAUTI for this study is 3.4%.<sup>1</sup> We estimate a 20%

53  
54 282 reduction using a Cohen's d size effect measure at 0.2 (small effect). Based on individual

55  
56 283 randomization of two groups (control and intervention), power of 80%, alpha of 0.05%, effect size

1  
2 284 of 0.2 and two-sided test for comparison of two means. As this is a stepped wedge design, we have  
3  
4 285 used a sample size formula from Hussey and Hughes and operationalised the design effect from  
5  
6 286 Hemming.<sup>9 15</sup> For the design effect, we have assumed 3 hospitals, 3 time periods, with  $N_1$  being the  
7  
8 287 sample size of 784. Three different scenarios were modelled, each with different intracluster  
9  
10 288 correlation coefficients- 0.1, 0.05, 0.01. An intracluster correlation coefficient of 0.05 was  
11  
12 289 subsequently determined and the sample size ( $m=220$ ,  $M=880$ ) for each cluster. The total calculated  
13  
14 290 sample size is therefore 2,640 across all sites, that is total number of patients that receive a catheter  
15  
16 291 in all three sites.  
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21  
22 293 Pilot work identified that 26% of patients admitted to hospital in Australia receive a urinary catheter  
23  
24 294<sup>1 16</sup>. As we are excluding patients who had a catheter inserted in theatre, we estimated that 5% of  
25  
26 295 admitted patients receive a catheter not inserted in theatre. To obtain the required sample size in  
27  
28 296 each hospital, a hospital needs the potential insertion of 1500 catheters per year (1000 during the  
29  
30 297 eight-month study period). This requires a hospital to have at least 30,000 patient admissions per  
31  
32 298 year.  
33  
34

299

### 300 ***Analysis***

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

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

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4 313 *Objective 2: Cost effectiveness of the intervention*

5 314 The effectiveness data from objective 1 will be a key parameter in the cost-effectiveness model.

6 315 Final outcomes for the cost-effectiveness evaluation are the incremental cost-effectiveness ratio

7 316 estimated as the cost per QALY gained, and the changes to costs in QALYs. Published guidelines

8 317 for costing an intervention will be followed<sup>17</sup>. The changes to costs from adopting the intervention

9 318 will be estimated by the extra staff time spent both planning and implementing the intervention,

10 319 converted to a dollar figure using full employment costs. Other costs are product costs. These cost

11 320 data will be collected prospectively on a monthly basis for product costs and a survey immediately

12 321 after the intervention is implemented (staff costs). Quantities of resources will be standardised to all

13 322 hospitals to ensure valid comparison of costs across all sites. This will reduce uncertainty in

14 323 estimates which often results from using retrospective administrative data.

15 324

16 325 The major cost savings from reducing infections are characterised by the bed days saved from

17 326 keeping patients infection free and hence discharging them earlier. The reasoning is that 90% of the

18 327 costs of hospital services are fixed so bed days saved are an appropriate currency. Data from a

19 328 previous study using multistate modelling to estimate the extra length of stay per case of urinary

20 329 bacteriuria will be used in the model.<sup>18</sup> Other cost savings are averted laboratory diagnosis costs and

21 330 antimicrobial therapy costs, estimated by counting the frequency of laboratory tests and

22 331 antimicrobial therapy costs in the control and intervention periods. These will be collected

23 332 prospectively as part of the data collection process. Laboratory costs using the relevant medical

24 333 benefit scheme item costs will be used. For antimicrobial therapy costs, pharmaceutical benefits

25 334 scheme costs will be used.

26 335



1 336 Changes to health benefits will be informed by the extra death risk due to infection. This parameter  
2  
3 337 will come from a previously described analysis of mortality associated with urinary bacteriuria.  
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5 338 These estimates used multi-state models that avoid time and length biases to estimate increases in  
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7 339 mortality attributable to infection. The results are hazard ratios that can be used to predict reduction  
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9 340 in deaths from avoided infections. The mean age of hospital patients will be used to predict years of  
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11 341 life gained and preference based utility scores will be used to weight life expectancy, allowing us to  
12  
13 342 calculate QALYs. We will not collect primary data on preference based utility scores. Instead, these  
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15 343 estimates will be taken from the published literature.<sup>19</sup>  
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22 345 The change to total costs at the hospital level will be estimated by summing intervention costs and  
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24 346 deducting cost savings from reduced lengths of stay and use of health care resources that arise from  
25  
26 347 reduced incidences of infection. The changes to health benefits will be estimated in QALYs using:  
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28 348 the number of life years saved from reduced infection outcomes; the expected duration of life (had  
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30 349 infection not occurred) based on age and data from the published literature.<sup>14</sup> All costs and health  
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32 350 benefits arising in future periods will be appropriately discounted. Uncertainties in parameter  
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34 351 estimates will be captured using appropriate statistical distributions to describe the variability. For  
35  
36 352 example, the beta distribution would be a good choice for infection risk as this distribution is  
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38 353 restricted to interval 0–1. The parameters of the beta distribution will be chosen to reflect what we  
39  
40 354 know about the mean and range in infection risk (e.g., a beta distribution with a mean rate of  
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42 355 infection of 0.003 and 95% confidence interval of 0.001 to 0.005). The fitted distributions will be  
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44 356 subject to random re-samples simulated 10,000 times. The distributions of all prior parameters are  
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46 357 used to estimate the posterior distributions of ‘change to costs’ and ‘change to QALY’ outcomes.  
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53 359 The decision will be informed by plotting cost-effectiveness acceptability curves with threshold  
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55 360 value between zero and 100,000 per QALY gained, and using the net monetary benefits framework.  
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2 361 These approaches are semi Bayesian and appropriately account for all parameter uncertainty for the  
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4 362 adoption decisions.  
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8 364 **Discussion**  
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10 365 This study addresses an identified gap in infection control research and practice. Despite the  
11  
12 366 frequency of urinary tract infections associated with indwelling urinary catheter use, there are few  
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14 367 studies focusing on their surveillance and prevention. Aligning with the emphasis on quality and  
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16 368 safety, this multi-centre randomised controlled trial, will evaluate the effectiveness and cost-  
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18 369 effectiveness of an antiseptic versus non-antiseptic meatal cleaning agent to prevent CAUTIs, a  
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20 370 world first. The ultimate objective is the prevention of healthcare-related CAUTIs, leading to  
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22 371 benefits for patient safety.  
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26 373 *Strengths*  
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28 374 Few randomised controlled trials have investigated the effectiveness of antiseptics on CAUTI  
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30 375 incidence during urinary catheter insertion and previous research has been limited mainly due to the  
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32 376 lack of an appropriate sample size to demonstrate any possible beneficial effect from the use of  
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34 377 antiseptics.<sup>8</sup> Our study utilises a rigorous approach and is sufficiently powered to detect the effect  
35  
36 378 of antiseptics in reducing CAUTI. The inclusion of the cost-effectiveness analysis is an additional  
37  
38 379 strength of this trial as to our knowledge previous trials have not evaluated the cost effectiveness of  
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40 380 an antiseptic meatal cleaning agent in reducing CAUTI. Over the past decade, cost effectiveness  
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42 381 analysis has evolved further emphasising the need to address this evidence gap.  
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46 383 This randomised controlled trial is also strengthened by the use of a stepped wedged design which  
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48 384 has been found to be particularly useful in studies evaluating intervention effectiveness during  
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50 385 routine implementation such as in the case of this study where the insertion of a urinary catheter is  
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52 386 considered to be part of the usual care of the patient.<sup>20</sup> The study design also enables each hospital  
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2 387 to act as its own control, which removes the potential for some confounders such as variations in  
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4 388 hospital size and case mix and differences between public and private hospitals. Further, this study  
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6 389 identifies best practice among current practice.  
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#### 10 391 *Limitations*

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12 392 Exclusion of patients who have indwelling urinary catheters inserted in surgical theatre has the  
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14 393 potential to prolong recruitment of participants given that surgical procedures are a common  
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16 394 indication for urinary catheter insertion.<sup>21 22</sup> However, recruitment of these patients was not deemed  
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18 395 feasible as it would require involvement of all surgeons including theatre staff in the study.  
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#### 23 397 *Significance*

24  
25 398 It is important that urinary catheter insertion strategies for CAUTI prevention are supported by  
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27 399 evidence obtained from rigorously conducted research. This study's significance therefore lies in its  
28  
29 400 ability to inform recommendations within national infection control guidelines globally. This study  
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31 401 will also contribute to the development of strategies to reduce the incidence of CAUTI using cost-  
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33 402 effective approaches. This is even more important in the context of finite health budgets.  
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#### 39 404 **Trial status**

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41 405 The study team is completing the recruitment of participating hospitals. The trial is due to  
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43 406 commence in late 2017.  
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#### 54 411 **Abbreviations**

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2 412 AMR: Antimicrobial resistance; BSI: Blood stream infection; CA-ASB: Catheter associated  
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4 413 asymptomatic bacteriuria; CAUTI: Catheter associated urinary tract infection; QALY: Quality  
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6 414 adjusted life years; UTI: Urinary tract infection  
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10 416 **Declarations**

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12 417 *Ethics approval and consent to participate*

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14 418 This project has received ethics approval from Avondale College of Higher Education Human  
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16 419 Research Ethics Committee (HREC) (approval number 2017:03), the Australian Capital Territory  
17  
18 420 HREC (approval number ETH.4.17.083) and the Adventist HealthCare Limited Human Research  
19  
20 421 Ethics Committee (approval number 2017-018). A waiver of individual patient consent was granted  
21  
22 422 for this study. Any risks or harms associated with the study will be reported to the relevant HREC.  
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24 423 Reporting of the trial and progress, including any audits, will be conducted consistent with the  
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26 424 requests of the HRECs who approved the study. Any modification to the study that has ethical  
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28 425 implications will be forwarded to the HRECs for approval.  
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32 427 *Consent for publication*

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34 428 Not applicable  
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38 430 *Data quality*

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40 431 Data will be stored in electronically in a secure location, by chief investigator BM at Avondale  
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42 432 College of Higher Education. Data quality will be enhanced by the provision of a data collection  
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44 433 form, quality checks by the project manager. A data collection guide has been developed to aide and  
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46 434 document this process. Data monitoring will be overseen by chief investigator BM and the data  
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48 435 monitoring committee consists of all chief investigators on the study. Any approved changes to the  
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50 436 study protocol will be updated in Australia New Zealand Clinical Trial Registry.  
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54 438 *Access to data*  
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2 439 Chief investigator BM will hold data during and after study completion.

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6 441 *Competing interests*

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8 442 The authors declare that they have no competing interests.

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11  
12 444 *Funding*

13  
14 445 This work was supported by the HCF Foundation and cash support from Avondale College of

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16 446 Higher Education. The contents of the published material are solely the responsibility of the

17  
18 447 administering institution.

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22 449 *Dissemination*

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24 450 A dissemination plan is being developed. Results will be published in the peer review literature,

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26 451 presented at relevant conferences and communicated via professional networks.

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32 454 *Authors' contributions*

33  
34 455 All authors made contributions to the development of the trial protocol and have been involved in

35  
36 456 drafting this manuscript or revising it critically for important intellectual content. BM is the overall

37  
38 457 chief investigator. BM and AC lead on epidemiology and infection control. PC leads on infectious

39  
40 458 diseases. AC leads on statistics. NG leads on health economics. AG and JK lead on health policy

41  
42 459 and decision-making. OF leads on urinary tract infection. VG is the project manager. BM and OF

43  
44 460 led the initial protocol development. All authors have approved the final manuscript.

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48 462 *Acknowledgements*

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50 463 Not applicable.

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466 **References**

- 467 1. Gardner A, Mitchell B, Beckingham W, et al. A point prevalence cross-sectional study of  
468 healthcare-associated urinary tract infections in six Australian hospitals. *BMJ Open*  
469 2014;**4**(7).
- 470 2. Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. *Am J*  
471 *Infect Control* 2000;**28**(1):68-75.
- 472 3. Nicolle LE. Catheter associated urinary tract infections. *Antimicrobial resistance and infection*  
473 *control* 2014;**3**(1):23.
- 474 4. World Health Organisation. Antimicrobial resistance: global report on surveillance. Geneva  
475 World Health Organisation,, 2014.
- 476 5. Fasugba O, Mitchell BG, Mnatzaganian G, et al. Five-Year Antimicrobial Resistance Patterns of  
477 Urinary *Escherichia coli* at an Australian Tertiary Hospital: Time Series Analyses of  
478 Prevalence Data. *PLoS One* 2016;**11**(10):e0164306.
- 479 6. Saint S, Greene MT, Krein SL, et al. A program to prevent catheter-associated urinary tract  
480 infection in acute care. *N Engl J Med* 2016;**374**(22):2111-19.
- 481 7. Warren JW. Catheter-associated urinary tract infections. *Int J Antimicrob Agents*  
482 2001;**17**(4):299-303.
- 483 8. Fasugba O, Koerner J, Mitchell BG, et al. Systematic review and meta-analysis of the  
484 effectiveness of antiseptic agents for meatal cleaning in the prevention of catheter-associated  
485 urinary tract infections. *J Hosp Infect* 2017;**95**(3):233-42.
- 486 9. Hemming K, Haines T, Chilton P, et al. The stepped wedge cluster randomised trial: rationale,  
487 design, analysis, and reporting. *BMJ* 2015;**350**:h391.
- 488 10. Hall L, Farrington A, Mitchell BG, et al. Researching effective approaches to cleaning in  
489 hospitals: protocol of the REACH study, a multi-site stepped-wedge randomised trial.  
490 *Implementation Science* 2016;**11**(1):44.
- 491 11. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-  
492 associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines  
493 from the Infectious Diseases Society of America. *Clin Infect Dis* 2010;**50**(5):625-63.
- 494 12. Centers for Disease Control and Prevention. CDC/NHSN Surveillance Definitions for Specific  
495 Types of Infections, 2014.
- 496 13. Centers for Disease Control and Prevention. Urinary Tract Infection (Catheter-Associated  
497 Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection  
498 [UTI]) and Other Urinary System Infection [USI]) Events Centers for Disease Control and  
499 Prevention,, 2017.

- 1  
2 500 14. Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on health-  
3 501 related quality of life. *BJU Int* 2012;**110**(11 Pt C):E830-6.  
4  
5 502 15. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials.  
6 503 *Contemp Clin Trials* 2007;**28**(2):182-91.  
7  
8 504 16. Mitchell BG, Fasugba O, Beckingham W, et al. A point prevalence study of healthcare  
9 505 associated urinary tract infections in Australian acute and aged care facilities. *Infection,*  
10 506 *Disease & Health* 2016;**21**(1):26-31.  
11  
12 507 17. Page K, Graves N, Halton K, et al. Humans, 'things' and space: costing hospital infection  
13 508 control interventions. *J Hosp Infect* 2013;**84**(3):200-05.  
14  
15 509 18. Mitchell BG, Ferguson JK, Anderson M, et al. Length of stay and mortality associated with  
16 510 healthcare-associated urinary tract infections: a multi-state model. *J Hosp Infect*  
17 511 2016;**93**(1):92-99.  
18  
19 512 19. Cuthbertson BH, Scott J, Strachan M, et al. Quality of life before and after intensive care.  
20 513 *Anaesthesia* 2005;**60**(4):332-9.  
21  
22 514 20. Mdege ND, Man MS, Taylor Nee Brown CA, et al. Systematic review of stepped wedge cluster  
23 515 randomized trials shows that design is particularly used to evaluate interventions during  
24 516 routine implementation. *J Clin Epidemiol* 2011;**64**(9):936-48.  
25  
26 517 21. Tenke P, Kovacs B, Bjerklund Johansen TE, et al. European and Asian guidelines on  
27 518 management and prevention of catheter-associated urinary tract infections. *Int J Antimicrob*  
28 519 *Agents* 2008;**31 Suppl 1**:S68-78.  
29  
30 520 22. Wald HL, Ma A, Bratzler DW, et al. Indwelling urinary catheter use in the postoperative period:  
31 521 Analysis of the national surgical infection prevention project data. *Arch Surg*  
32 522 2008;**143**(6):551-57.  
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526 **Table 1** Key outcome measures

<b>Objective 1</b> 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
<b>Objective 2</b> 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

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

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**Figure 1** Study design overview

Blue = control; Green = intervention

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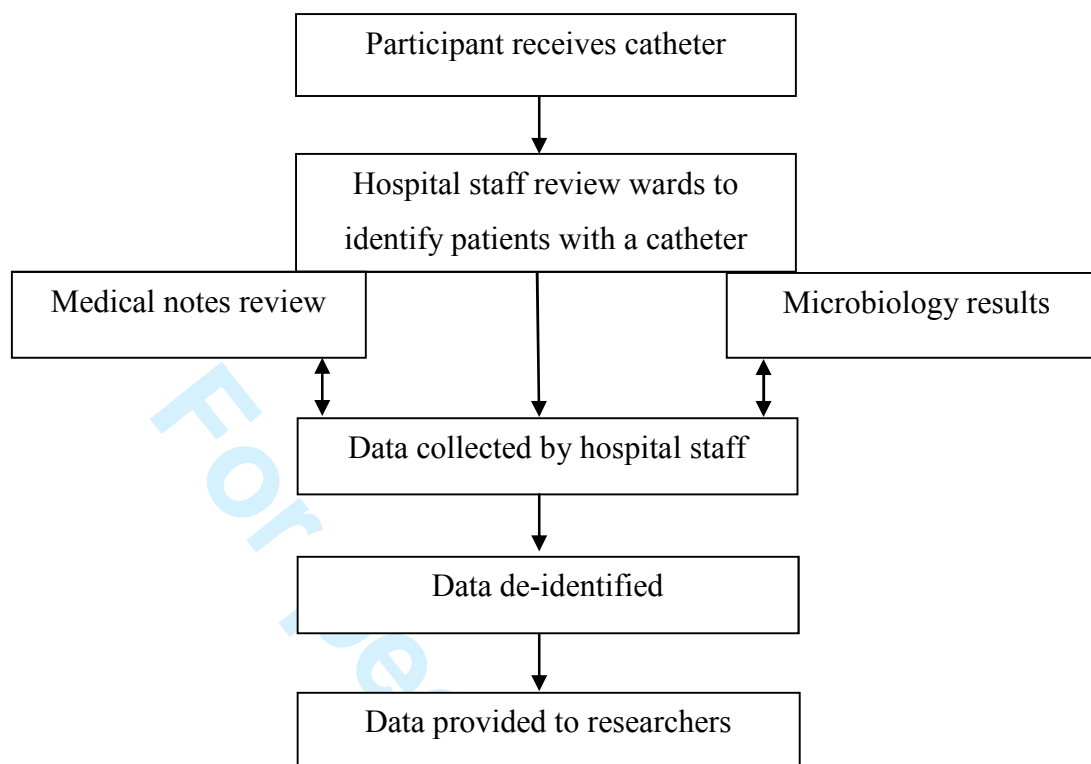
**Figure 2** Overview of data collection process

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Hospital	2 months	4 months	6 months	8 months
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B	Blue	Blue	Green	Green
C	Blue	Blue	Blue	Green

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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018871.R1
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<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	Urinary tract infections < UROLOGY, HEALTH ECONOMICS, Infection control < INFECTIOUS DISEASES

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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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## 34 Abstract

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

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

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

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61 Ethics: Ethics approval has been obtained.

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63 **Trial registration:** Australia New Zealand Clinical Trial Registry (No 12617000373370), approved  
64 13/03/2017. Protocol version 1.1

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

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2 70 **Strengths and limitations of this study**  
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- 4 71 • Randomised control design  
5 72 • Evaluation of effectiveness and cost effectiveness  
6 73 • Limited to hospitals in high income country  
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2 78 **Introduction**  
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4 79 Indwelling urinary catheters are commonly used in healthcare facilities, with foundation work  
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6 80 indicating that 26% of patients admitted to an Australian hospital receive an indwelling urinary  
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8 81 catheter and 1% of these patients develop catheter-associated urinary tract infections (CAUTIs).<sup>1</sup>  
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10 82 Catheter associated urinary tract infections have been associated with increased morbidity,  
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12 83 mortality, increased length of stay in hospital and higher hospital costs for patients and health  
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14 84 systems.<sup>2</sup> Data from the International Nosocomial Infection Control Consortium (INICC)  
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16 85 surveillance study, conducted in 703 intensive care units in low and middle income countries,  
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18 86 suggests the incidence of CAUTI to be 4.8 per 1000 device days (years 2010-15).<sup>3</sup> In Australia, an  
19  
20 87 estimated 380,000 bed days are lost each year due to healthcare-associated urinary tract infections  
21  
22 88 (UTIs), a large proportion of which are CAUTIs. Catheter associated urinary tract infections are  
23  
24 89 also associated with higher risk of antimicrobial resistance (AMR), making the treatment of patients  
25  
26 90 difficult.<sup>4,5</sup> Antimicrobial resistance in UTIs has also been shown to be increasing globally, further  
27  
28 91 emphasising the need to develop interventions to reduce the incidence of CAUTIs.<sup>6</sup>  
29  
30  
31  
32 92  
33  
34 93 Studies have shown, that the incidence of CAUTI can be reduced.<sup>7,8</sup> None the less, despite some  
35  
36 94 advances in infection prevention and control, CAUTIs remain problematic.<sup>9</sup> Evidence shows that  
37  
38 95 reducing bacterial colonisation around the meatal or urethral area has the potential to reduce CAUTI  
39  
40 96 risk.<sup>10</sup> However, evidence about the best antiseptic solutions for meatal cleaning is mixed. Previous  
41  
42 97 research also identified a lack of documentation and knowledge in relation to the meatal cleaning  
43  
44 98 solution used prior to catheter insertion.<sup>1</sup> Unsurprisingly, there is variation in practice within  
45  
46 99 Australian hospitals with respect to catheter insertion, and specifically the agent used to clean the  
47  
48 100 meatal area prior to insertion. These issues provided a strong rationale for the study investigators to  
49  
50 101 conduct a systematic review and meta-analysis of published literature, investigating the  
51  
52 102 effectiveness of antiseptic cleaning during urinary catheter insertion for the prevention of CAUTI.<sup>11</sup>  
53  
54 103 This review of current research knowledge identified the need for a well-designed intervention  
55  
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57  
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60

1  
2 104 study as well as a limited number of studies evaluating the cost-effectiveness of using an antiseptic  
3  
4 105 during catheter insertion. As health budgets are finite, clinical practice needs to utilise cost-effective  
5  
6 106 strategies. The cost of chlorhexidine 0.1% solution is considerably higher than 0.9% normal saline.  
7  
8 107

9  
10 108 Given the importance of meatal colonisation in the pathogenesis of CAUTIs, emerging AMR, the  
11  
12 109 frequency with which catheters are used and the burden of CAUTIs in Australia and in hospital  
13  
14 110 settings worldwide, the generation of evidence using a high-quality randomised trial is needed to  
15  
16 111 determine the efficacy and cost-effectiveness of meatal cleaning. This will inform infection  
17  
18 112 prevention and control practice and policy in Australia and internationally.  
19  
20  
21

22 113

#### 23 24 114 **Trial objectives**

25  
26 115 The trial objectives listed below pertain to both the cluster and individual level. The trial is  
27  
28 116 registered with the Australia New Zealand Clinical Trial Registry (No 12617000373370).  
29  
30

31 117

#### 32 33 118 *Objective 1*

34  
35 119 The first objective is to evaluate the effectiveness of using chlorhexidine in meatal cleaning prior to  
36  
37 120 catheter insertion, in reducing catheter associated asymptomatic bacteriuria (CA-ASB) and CAUTI.  
38  
39

40 121

#### 41 42 122 *Objective 2*

43  
44 123 The second objective is to estimate the cost effectiveness of the decision to adopt chlorhexidine in  
45  
46 124 meatal cleaning prior to catheter insertion.  
47  
48

49 125

#### 50 51 126 **Methods**

##### 52 53 127 *Study design*

54  
55 128 A stepped wedge randomised controlled trial will be undertaken in three large hospitals over a 32-  
56  
57 129 week period (example trial timing are in Figure 1). The stepped wedge design includes an initial  
58  
59  
60

1  
2 130 period where no hospitals are exposed to the intervention.<sup>12</sup> Afterwards, at 8 week intervals (the  
3  
4 131 “steps”) each hospital sequentially crosses over from the control to the intervention until all  
5  
6 132 hospitals are exposed to the intervention for the final eight weeks until conclusion in week 32. The  
7  
8 133 study design enables each hospital to act as its own control, which removes the potential for some  
9  
10 134 confounders such as variations in hospital size and case mix and differences between public and  
11  
12 135 private hospitals. Staggered commencement and duration of the intervention, supports feasibility  
13  
14 136 while maintaining the rigour of the study.<sup>13</sup> This design will also allow research staff to work with  
15  
16 137 individual hospitals as they change over, maximising consistency of intervention and aiding  
17  
18 138 implementation.<sup>13</sup> In addition, data collection continues throughout the study, so that each cluster  
19  
20 139 contributes observations under both control and intervention observation periods.  
21  
22  
23  
24  
25

#### 26 141 *Study population*

27  
28 142 Three Australian hospitals that fulfil the eligibility criteria will be enrolled in the study. These  
29  
30 143 criteria are:

- 31  
32  
33 144 • Has an intensive care unit
- 34  
35 145 • Be classified by the Australian Institute of Health and Welfare as a principal referral  
36  
37 146 hospital OR a public acute group A hospital (with more than 400 beds), OR in the case  
38  
39 147 of a private hospital has 400 inpatient beds OR has more than 30,000 patient admissions  
40  
41 148 per year.  
42  
43

#### 44 149 45 46 150 *Other considerations*

47  
48 151 Hospitals could be excluded from the study if within the study time frame they are:

- 49  
50 152 • undertaking a project that may influence the outcomes measured in this study
- 51  
52 153 • opening, closing or relocating

53  
54  
55 154  
56  
57  
58  
59  
60

1  
2 155 *Areas of hospital and patient-level inclusion and exclusion criteria*

3  
4 156 The study will be a hospital wide study, but will exclude patients with indwelling urinary catheters  
5  
6 157 within a hospital that are not considered appropriate for the intervention, for example neonatal  
7  
8 158 intensive care. Patients less than two years old, with an allergy, contraindication or other medical  
9  
10 159 reason preventing the use of the intervention for cleaning the urethral meatal area will be excluded.  
11  
12 160 Patients who require in-and-out or suprapubic catheterisation will also be excluded as well as those  
13  
14 161 with symptoms and signs suggestive of UTI and patients already undergoing treatment for UTI. All  
15  
16 162 data from any patient lost to follow-up (post-catheter insertion) will be excluded.  
17  
18  
19  
20

21 163

22 164 ***Recruitment***

23  
24 165 The study team will list all eligible sites then order the list to ensure (i) a representation of both  
25  
26 166 private and public hospitals and (ii) representation from at least two Australian states and territories.  
27  
28 167 The recruitment process will purposively select and approach eligible hospitals to optimise the  
29  
30 168 feasibility and practicality of completing the trial.  
31  
32

33 169

34  
35 170 ***Intervention***

36  
37 171 The intervention in this study is the use of chlorhexidine (0.1%) solution for meatal cleaning prior  
38  
39 172 to catheter insertion. The control is the use of normal saline (0.9%) for meatal cleaning. During the  
40  
41 173 first eight weeks of the study, no hospital will receive the intervention. After eight weeks, one  
42  
43 174 hospital will cross over to the intervention with the other two participating hospitals crossing over  
44  
45 175 to the intervention at eight-week intervals respectively based on randomisation.  
46  
47  
48

49 176

50  
51 177 ***Implementing the intervention***

52  
53 178 In the week prior to the intervention commencing, information sessions about the study will be  
54  
55 179 provided to participating hospitals and staff. A variety of methods will be used to further alert staff  
56  
57 180 and raise awareness about the intervention prior to it being rolled out. These methods include  
58  
59  
60

1 181 placing wall posters in wards and key hospital locations, handing out hospital newsletters and  
2  
3 182 information leaflets as well as branded promotional material, such as pens. To avoid potential  
4  
5 183 confounding, information and awareness sessions are limited to just the change of product, not  
6  
7 184 education around catheter insertion or management practices.  
8  
9

10 185

11  
12 186 Chlorhexidine 0.1% solution will be used by clinical staff at participating hospitals for cleaning the  
13  
14 187 meatal area of patients prior to urinary catheter insertion. To aid implementation of the intervention,  
15  
16 188 investigators will work with participating hospitals and utilise hospital data collection and reporting  
17  
18 189 systems currently in place. This will involve incorporation of the 0.1% chlorhexidine solution into  
19  
20 190 existing catheter procedure packs at the hospitals where possible, visual reminders where urinary  
21  
22 191 catheters are stored and temporary amendment to hospital procedural documentation.  
23  
24

25 192

26  
27  
28 193 As per hospital's usual practice, details of the catheter insertion will be documented by clinical  
29  
30 194 staff. To achieve optimal documentation of the procedure, catheter insertion stickers may be made  
31  
32 195 available to hospitals for use in patients' medical notes.  
33  
34

35 196

36  
37 197 ***Potential confounders***

38  
39 198 Lubricants are used during the catheter insertion process and may contain an antiseptic. The  
40  
41 199 lubricant used during the entire study (control and intervention periods) will remain constant in each  
42  
43 200 hospital.  
44

45 201

46  
47  
48 202 ***Randomisation and blinding***

49  
50 203 Hospitals will be randomly assigned to one of three dates to cross over to the intervention which  
51  
52 204 will occur once every eight weeks over the trial duration of 32 weeks. All included hospitals will be  
53  
54 205 provided with sufficient notice of the dates to cross over to the intervention. Computer-generated  
55  
56 206 randomisation of the cross over dates for the hospitals will be performed independently by an  
57  
58  
59  
60

1  
2 207 investigator not involved in assessment or delivery of the intervention. Hospitals will not be blinded  
3  
4 208 because it is not feasible to blind staff administering the intervention. The outcome of the  
5  
6 209 randomisation process will be revealed by the project manager to the participating hospitals prior to  
7  
8 210 the commencement of the study.  
9

10 211

### 12 212 *Outcomes and definitions*

13 213 The outcomes for each objective are outlined in Table 1. For objective 1, the primary outcomes are  
14  
15 214 the cases of CA-ASB and CAUTI. For objective 2, the primary outcome is the cost effectiveness of  
16  
17 215 the intervention.  
18  
19

20  
21 216 Catheter associated asymptomatic bacteriuria is defined as the presence of  $\geq 10^5$  colony forming unit  
22  
23 217 (cfu)/ml of  $\geq 1$  bacterial species in a single catheter urine specimen in a patient without symptoms  
24  
25 218 compatible with UTI.<sup>14</sup>  
26  
27

28 219 Catheter associated urinary tract infection is defined according to the National Healthcare Safety  
29  
30 220 Network criteria.<sup>15 16</sup> A patient must meet all three criteria below:  
31

- 32  
33 221 1. Patient had an indwelling urinary catheter that had been in place for > 2 days on the date of  
34  
35 222 event (day of device placement = Day 1) AND was either present for any portion of the calendar  
36  
37 223 day on the date of event or removed the day before the date of event.  
38  
39 224 2. Patient has at least one of the following signs or symptoms: fever ( $>38.0^\circ\text{C}$ ); suprapubic  
40  
41 225 tenderness; costovertebral angle pain or tenderness; urinary urgency; urinary frequency; dysuria.  
42  
43 226 3. Patient has a urine culture with no more than two species of organisms identified, at least one of  
44  
45 227 which is a bacterium of  $\geq 10^5$  cfu/ml.  
46  
47

48 228

49  
50 229 Blood stream infection (BSI) associated with a urinary tract infection is defined according to

51  
52 230 National Healthcare Safety Network criteria.<sup>15</sup> A patient must meet the definition for CAUTI and

53  
54 231 have at least one organism from the blood specimen that matches an organism identified in the urine  
55  
56  
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1  
2 232 specimen that is used as an element to meet the CAUTI criterion. The blood specimen must be  
3  
4 233 collected during the secondary BSI attribution period when the urinary catheter is in place.

5  
6 234

7  
8 235 ***Data collection***

9  
10 236 Data will be collected by a specific staff member or members at the hospital, with the support of the  
11  
12 237 research team. The research team will provide the hospital staff member(s) with training about the  
13  
14 238 project, data collection and submission process and data collection tools. For the purpose this paper,  
15  
16 239 the dedicated hospital staff member(s) will be referred to as hospital personnel. Figure 2  
17  
18 240 summarises the data collection process.

19  
20  
21  
22 241

23  
24 242 Hospital personnel will prospectively collect data three days a week at each hospital during both  
25  
26 243 control and intervention periods. Patients who receive an indwelling urinary catheter will be  
27  
28 244 identified and followed-up during the trial period (for a period of 7 days post-catheter insertion,  
29  
30 245 discharge or 48 hours post-catheter removal – whichever occurs first). Medical notes of patients  
31  
32 246 will be reviewed to obtain demographic and clinical data such as hospital number, age, sex, date of  
33  
34 247 admission, signs or symptoms of UTI. Co-morbidity data will be collected where possible.

35  
36 248 Details of catheter insertion specifically date and time of insertion, designation of person inserting  
37  
38 249 catheter, catheter type and catheter size, will also be obtained from the patients' medical notes  
39  
40 250 (where documented). If the insertion date is not documented, the patient will be excluded from the  
41  
42 251 study. Denominator data on the number of catheter days over the trial period will be collected at  
43  
44 252 each hospital during both control and intervention periods. The number of catheter days for each  
45  
46 253 patient included in the study will be estimated from the date of catheter insertion and date of  
47  
48 254 removal. Hospital personnel will record all captured data in a spreadsheet designed specifically for  
49  
50 255 the purpose of the trial.

51  
52  
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55 256



1  
2 257 Information for the primary (CA-ASB and CAUTI) and secondary (BSI) outcome measures will be  
3  
4 258 collected from the microbiology laboratory database of participating hospitals. Results of all  
5  
6 259 positive urine cultures either attributable to bacteriuria or true UTI as well as positive blood cultures  
7  
8 260 are registered in hospital microbiology laboratory databases. Hospital personnel will obtain weekly  
9  
10 261 reports from the microbiology laboratory of participating hospitals to identify the outcomes. The  
11  
12 262 patient record number will be used to link demographic and clinical data of patients with a urinary  
13  
14 263 catheter to microbiology laboratory data. To differentiate between CA-ASB and CAUTI, additional  
15  
16 264 data on symptoms and signs of UTI will be collected from patients' medical notes by research  
17  
18 265 assistants.  
19  
20  
21  
22 266

23  
24 267 Information to inform changes to total costs and health benefits from a decision to adopt the  
25  
26 268 intervention will be obtained. Changes to costs will include the resources required to implement the  
27  
28 269 intervention and the changes to use of health services. Changes to health benefits will be captured  
29  
30 270 by estimating quality adjusted life years (QALY) outcomes. Hospital personnel will prospectively  
31  
32 271 obtain monthly data from each participating hospital on the cost of purchasing resources, such as  
33  
34 272 catheter procedure packs, used for implementing the intervention. Hospital personnel will also  
35  
36 273 obtain data on antimicrobial use for patients, specifically the name, dose and duration of  
37  
38 274 antimicrobial, which will be used for estimating antimicrobial therapy costs in control and  
39  
40 275 intervention periods. Hospital staff involved in the trial will be surveyed immediately following  
41  
42 276 completion of the intervention to evaluate extra staff time spent in activities related to planning and  
43  
44 277 implementing the intervention. To calculate QALYs, primary data on age obtained from medical  
45  
46 278 notes of patients will be used along with estimates from the published literature.<sup>17</sup>  
47  
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51 279

### 52 280 ***Power calculation***

53  
54  
55 281 Sample size and power were calculated on the basis of CAUTI, as it is assumed that the power to  
56  
57 282 detect an incremental cost effectiveness ratio was greater than that for relevant clinical endpoints.  
58  
59  
60

1  
2 283 The at risk population are those that receive a catheter whilst in hospital. Based on pilot work, the  
3  
4 284 estimated proportion of patients developing a CAUTI for this study is 3.4%.<sup>1</sup> We estimate a 20%  
5  
6 285 reduction using a Cohen's d size effect measure at 0.2 (small effect). Based on individual  
7  
8 286 randomization of two groups (control and intervention), power of 80%, alpha of 0.05%, effect size  
9  
10 287 of 0.2 and two-sided test for comparison of two means. As this is a stepped wedge design, we have  
11  
12 288 used a sample size formula from Hussey and Hughes and operationalised the design effect from  
13  
14 289 Hemming.<sup>12 18</sup> For the design effect, we have assumed 3 hospitals, 3 time periods, with  $N_1$  being the  
15  
16 290 sample size of 784. Three different scenarios were modelled, each with different intraclass  
17  
18 291 correlation coefficients- 0.1, 0.05, 0.01. An intraclass correlation coefficient of 0.05 was  
19  
20 292 subsequently determined and the sample size ( $m=220$ ,  $M=880$ ) for each cluster.  
21  
22  
23  
24  
25

26 294 Pilot work identified that 26% of patients admitted to hospital in Australia receive a urinary catheter  
27  
28 295 <sup>1 19</sup>. As we are excluding patients who had a catheter inserted in theatre, we estimated that 5% of  
29  
30 296 admitted patients receive a catheter not inserted in theatre. To obtain the required sample size in  
31  
32 297 each hospital, a hospital is to have at least 30,000 patient admissions per year.  
33  
34  
35  
36

### 37 299 *Analysis*

38  
39 300 *Objective 1: Effectiveness of using chlorhexidine in meatal cleaning prior to catheter insertion*

40  
41 301 The number of CA-ASB, CAUTI and BSI will be analysed separately using Poisson regression,  
42  
43 302 with the number of cases as the dependent variable and number of patient catheter days as the  
44  
45 303 denominator. This denominator will help control for changes in catheter use during the study  
46  
47 304 period. The key independent variable will be the intervention. The key outcomes will be estimated  
48  
49 305 reduction in cases of CA-ASB, CAUTI and BSI due to the intervention. The characteristics of the  
50  
51 306 hospital (e.g. size) will not be independent variables as these should remain roughly constant  
52  
53 307 throughout the study observations. There is no expected delay in the effect of intervention on the  
54  
55 308 outcome.  
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2 3093  
4 3105  
6 3117  
8 312 *Objective 2: Cost effectiveness of the intervention*9  
10 313 The effectiveness data from objective 1 will be a key parameter in the cost-effectiveness model.11  
12 314 Final outcomes for the cost-effectiveness evaluation are the incremental cost-effectiveness ratio13  
14 315 estimated as the cost per QALY gained, and the changes to costs in QALYs. Published guidelines15  
16 316 for costing an intervention will be followed<sup>20</sup>. The changes to costs from adopting the intervention17  
18 317 will be estimated by the extra staff time spent both planning and implementing the intervention,19  
20 318 converted to a dollar figure using full employment costs. Other costs are product costs. These cost21  
22 319 data will be collected prospectively on a monthly basis for product costs and a survey immediately23  
24 320 after the intervention is implemented (staff costs). Quantities of resources will be standardised to all25  
26 321 hospitals to ensure valid comparison of costs across all sites. This will reduce uncertainty in27  
28 322 estimates which often results from using retrospective administrative data.29  
30 32331  
32 324 The major cost savings from reducing infections are characterised by the bed days saved from33  
34 325 keeping patients infection free and hence discharging them earlier. The reasoning is that 90% of the35  
36 326 costs of hospital services are fixed so bed days saved are an appropriate currency. Data from a37  
38 327 previous study using multistate modelling to estimate the extra length of stay per case of urinary39  
40 328 bacteriuria will be used in the model.<sup>21</sup> Other cost savings are averted laboratory diagnosis costs and41  
42 329 antimicrobial therapy costs, estimated by counting the frequency of laboratory tests and43  
44 330 antimicrobial therapy costs in the control and intervention periods. These will be collected45  
46 331 prospectively as part of the data collection process. Laboratory costs using the relevant medical47  
48 332 benefit scheme item costs will be used. For antimicrobial therapy costs, pharmaceutical benefits49  
50 333 scheme costs will be used.51  
52 33453  
54  
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1 335 Changes to health benefits will be informed by the extra death risk due to infection. This parameter  
2  
3 336 will come from a previously described analysis of mortality associated with urinary bacteriuria.  
4  
5  
6 337 These estimates used multi-state models that avoid time and length biases to estimate increases in  
7  
8 338 mortality attributable to infection. The results are hazard ratios that can be used to predict reduction  
9  
10 339 in deaths from avoided infections. The mean age of hospital patients will be used to predict years of  
11  
12 340 life gained and preference based utility scores will be used to weight life expectancy, allowing us to  
13  
14 341 calculate QALYs. We will not collect primary data on preference based utility scores. Instead, these  
15  
16 342 estimates will be taken from the published literature.<sup>22</sup>  
17  
18  
19 343

20  
21 344 The change to total costs at the hospital level will be estimated by summing intervention costs and  
22  
23 345 deducting cost savings from reduced lengths of stay and use of health care resources that arise from  
24  
25 346 reduced incidences of infection. The changes to health benefits will be estimated in QALYs using:  
26  
27 347 the number of life years saved from reduced infection outcomes; the expected duration of life (had  
28  
29 348 infection not occurred) based on age and data from the published literature.<sup>17</sup> All costs and health  
30  
31 349 benefits arising in future periods will be appropriately discounted. Uncertainties in parameter  
32  
33 350 estimates will be captured using appropriate statistical distributions to describe the variability. For  
34  
35 351 example, the beta distribution would be a good choice for infection risk as this distribution is  
36  
37 352 restricted to interval 0–1. The parameters of the beta distribution will be chosen to reflect what we  
38  
39 353 know about the mean and range in infection risk (e.g., a beta distribution with a mean rate of  
40  
41 354 infection of 0.003 and 95% confidence interval of 0.001 to 0.005). The fitted distributions will be  
42  
43 355 subject to random re-samples simulated 10,000 times. The distributions of all prior parameters are  
44  
45 356 used to estimate the posterior distributions of ‘change to costs’ and ‘change to QALY’ outcomes.  
46  
47  
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51 357  
52  
53 358 The decision will be informed by plotting cost-effectiveness acceptability curves with threshold  
54  
55 359 value between zero and 100,000 per QALY gained, and using the net monetary benefits framework.  
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1  
2 360 These approaches are semi Bayesian and appropriately account for all parameter uncertainty for the  
3  
4 361 adoption decisions.  
5

6 362

7  
8 363 **Discussion**  
9

10 364 This study addresses an identified gap in infection control research and practice. Despite the  
11  
12 365 frequency of urinary tract infections associated with indwelling urinary catheter use, there are few  
13  
14 366 studies focusing on their surveillance and prevention. Aligning with the emphasis on quality and  
15  
16 367 safety, this multi-centre randomised controlled trial, will evaluate the effectiveness and cost-  
17  
18 368 effectiveness of an antiseptic versus non-antiseptic meatal cleaning agent to prevent CAUTIs, a  
19  
20 369 world first. The ultimate objective is the prevention of healthcare-related CAUTIs, leading to  
21  
22 370 benefits for patient safety.  
23  
24 371

25 371

26 372 *Strengths*  
27

28  
29 373 Few randomised controlled trials have investigated the effectiveness of antiseptics on CAUTI  
30  
31 374 incidence during urinary catheter insertion and previous research has been limited mainly due to the  
32  
33 375 lack of an appropriate sample size to demonstrate any possible beneficial effect from the use of  
34  
35 376 antiseptics.<sup>11</sup> Our study utilises a rigorous approach and is sufficiently powered to detect the effect  
36  
37 377 of antiseptics in reducing CAUTI. The inclusion of the cost-effectiveness analysis is an additional  
38  
39 378 strength of this trial as to our knowledge previous trials have not evaluated the cost effectiveness of  
40  
41 379 an antiseptic meatal cleaning agent in reducing CAUTI. Over the past decade, cost effectiveness  
42  
43 380 analysis has evolved further emphasising the need to address this evidence gap.  
44  
45 381

46 381

47  
48 382 This randomised controlled trial is also strengthened by the use of a stepped wedged design which  
49  
50 383 has been found to be particularly useful in studies evaluating intervention effectiveness during  
51  
52 384 routine implementation such as in the case of this study where the insertion of a urinary catheter is  
53  
54 385 considered to be part of the care of the patient.<sup>23</sup> The study design also enables each hospital to act  
55  
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1  
2 386 as its own control, which removes the potential for some confounders such as variations in hospital  
3  
4 387 size and case mix and differences between public and private hospitals. Further, this study identifies  
5  
6 388 best practice among current practice.  
7

8 389

9  
10 390 *Limitations*

11  
12 391 Exclusion of patients who have indwelling urinary catheters inserted in surgical theatre has the  
13  
14 392 potential to prolong recruitment of participants given that surgical procedures are a common  
15  
16 393 indication for urinary catheter insertion.<sup>24 25</sup> However, recruitment of these patients was not deemed  
17  
18 394 feasible as it would require involvement of all surgeons including theatre staff in the study. Unless  
19  
20 395 the participating hospital can achieve implementation in theatre, patients who have catheters  
21  
22 396 inserted in theatres will be excluded. The initiatives taken to introduce the intervention may  
23  
24 397 inadvertently improve catheter management. To reduce this effect, no education on other aspects of  
25  
26 398 catheter management (other than the product change) will be provided to staff.  
27  
28

29 399

30  
31 400 *Significance*

32  
33 401 It is important that urinary catheter insertion strategies for CAUTI prevention are supported by  
34  
35 402 evidence obtained from rigorously conducted research. This study's significance therefore lies in its  
36  
37 403 ability to inform recommendations within national infection control guidelines globally. This study  
38  
39 404 will also contribute to the development of strategies to reduce the incidence of CAUTI using cost-  
40  
41 405 effective approaches. This is even more important in the context of finite health budgets.  
42  
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48 407 **Trial status**

49  
50 408 The study team is completing the recruitment of participating hospitals. The trial is due to  
51  
52 409 commence in late 2017.  
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5  
6 414 **Abbreviations**

7  
8 415 AMR: Antimicrobial resistance; BSI: Blood stream infection; CA-ASB: Catheter associated

9  
10 416 asymptomatic bacteriuria; CAUTI: Catheter associated urinary tract infection; QALY: Quality

11  
12 417 adjusted life years; UTI: Urinary tract infection

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14 418

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16  
17 419 **Declarations**

18  
19 420 *Ethics approval and consent to participate*

20  
21 421 This project has received ethics approval from Avondale College of Higher Education Human

22  
23 422 Research Ethics Committee (HREC) (approval number 2017:03), the Australian Capital Territory

24  
25 423 HREC (approval number ETH.4.17.083) and the Adventist HealthCare Limited Human Research

26  
27 424 Ethics Committee (approval number 2017-018). A waiver of individual patient consent was granted

28  
29 425 for this study. Any risks or harms associated with the study will be reported to the relevant HREC.

30  
31 426 Reporting of the trial and progress, including any audits, will be conducted consistent with the

32  
33 427 requests of the HRECs who approved the study. Any modification to the study that has ethical

34  
35 428 implications will be forwarded to the HRECs for approval. No identifiable or re-identifiable

36  
37 429 patient data will be collected by the researchers, thus protecting anonymity and confidentiality of

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39 430 participants.

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43 432 *Consent for publication*

44  
45 433 Not applicable

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49 435 *Data quality*

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51 436 Data will be stored in electronically in a secure (password protected) location, by chief investigator

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53 437 BM at Avondale College of Higher Education. Data quality will be enhanced by the provision of a

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55 438 data collection form, quality checks by the project manager. A data collection guide has been

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2 439 developed to aide and document this process. Data monitoring will be overseen by chief  
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4 440 investigator BM and the data monitoring committee consists of all chief investigators on the study.  
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6 441 Any approved changes to the study protocol will be updated in Australia New Zealand Clinical  
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8 442 Trial Registry.  
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12 444 *Access to data*

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15 445 Chief investigator BM will hold data during and after study completion.  
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19 447 *Competing interests*

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21 448 The authors declare that they have no competing interests.  
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26 450 *Funding*

27  
28 451 This work was supported by the HCF Foundation and cash support from Avondale College of  
29  
30 452 Higher Education. The contents of the published material are solely the responsibility of the  
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32 453 administering institution.  
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37 455 *Dissemination*

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39 456 A dissemination plan it being developed. Results will be published in the peer review literature,  
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41 457 presented at relevant conferences and communicated via professional networks.  
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48 460 *Authors' contributions*

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50 461 All authors made contributions to the development of the trial protocol and have been involved in  
51  
52 462 drafting this manuscript or revising it critically for important intellectual content. BM is the overall  
53  
54 463 chief investigator. BM and AC lead on epidemiology and infection control. PC leads on infectious  
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56 464 diseases. AC and PM lead on statistics. NG leads on health economics. AG and JK lead on health  
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2 465 policy and decision-making. OF leads on urinary tract infection. VG is the project manager. BM  
3  
4 466 and OF led the initial protocol development. All authors have approved the final manuscript.  
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8 468 *Acknowledgements*  
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10 469 Not applicable.  
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16 472 **References**

- 17 473 1. Gardner A, Mitchell B, Beckingham W, et al. A point prevalence cross-sectional study of  
18 474 healthcare-associated urinary tract infections in six Australian hospitals. *BMJ Open*  
19 475 2014;**4**(7).  
20  
21 476 2. Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. *Am J*  
22 477 *Infect Control* 2000;**28**(1):68-75.  
23  
24 478 3. Rosenthal VD, Al-Abdely HM, El-Kholy AA, et al. International Nosocomial Infection Control  
25 479 Consortium report, data summary of 50 countries for 2010-2015: Device-associated module.  
26 480 *Am J Infect Control*;**44**(12):1495-504.  
27  
28 481 4. Nicolle LE. Catheter associated urinary tract infections. *Antimicrobial resistance and infection*  
29 482 *control* 2014;**3**(1):23.  
30  
31 483 5. World Health Organisation. Antimicrobial resistance: global report on surveillance. Geneva  
32 484 World Health Organisation,, 2014.  
33  
34 485 6. Fasugba O, Mitchell BG, Mnatzaganian G, et al. Five-Year Antimicrobial Resistance Patterns of  
35 486 Urinary *Escherichia coli* at an Australian Tertiary Hospital: Time Series Analyses of  
36 487 Prevalence Data. *PLoS One* 2016;**11**(10):e0164306.  
37  
38 488 7. Rosenthal VD, Ramachandran B, Duenas L, et al. Findings of the International Nosocomial  
39 489 Infection Control Consortium (INICC), Part I: Effectiveness of a multidimensional infection  
40 490 control approach on catheter-associated urinary tract infection rates in pediatric intensive  
41 491 care units of 6 developing countries. *Infect Control Hosp Epidemiol* 2012;**33**(7):696-703.  
42  
43 492 8. Rosenthal VD, Todi SK, Alvarez-Moreno C, et al. Impact of a multidimensional infection control  
44 493 strategy on catheter-associated urinary tract infection rates in the adult intensive care units  
45 494 of 15 developing countries: findings of the International Nosocomial Infection Control  
46 495 Consortium (INICC). *Infection* 2012;**40**(5):517-26.  
47  
48 496 9. Saint S, Greene MT, Krein SL, et al. A program to prevent catheter-associated urinary tract  
49 497 infection in acute care. *N Engl J Med* 2016;**374**(22):2111-19.  
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- 1 498 10. Warren JW. Catheter-associated urinary tract infections. *Int J Antimicrob Agents*  
2 499 2001;**17**(4):299-303.
- 3 500 11. Fasugba O, Koerner J, Mitchell BG, et al. Systematic review and meta-analysis of the  
4 501 effectiveness of antiseptic agents for meatal cleaning in the prevention of catheter-associated  
5 502 urinary tract infections. *J Hosp Infect* 2017;**95**(3):233-42.
- 6 503 12. Hemming K, Haines T, Chilton P, et al. The stepped wedge cluster randomised trial: rationale,  
7 504 design, analysis, and reporting. *BMJ* 2015;**350**:h391.
- 8 505 13. Hall L, Farrington A, Mitchell BG, et al. Researching effective approaches to cleaning in  
9 506 hospitals: protocol of the REACH study, a multi-site stepped-wedge randomised trial.  
10 507 *Implementation Science* 2016;**11**(1):44.
- 11 508 14. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-  
12 509 associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines  
13 510 from the Infectious Diseases Society of America. *Clin Infect Dis* 2010;**50**(5):625-63.
- 14 511 15. Centers for Disease Control and Prevention. CDC/NHSN Surveillance Definitions for Specific  
15 512 Types of Infections, 2014.
- 16 513 16. Centers for Disease Control and Prevention. Urinary Tract Infection (Catheter-Associated  
17 514 Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection  
18 515 [UTI]) and Other Urinary System Infection [USI]) Events Centers for Disease Control and  
19 516 Prevention,, 2017.
- 20 517 17. Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on health-  
21 518 related quality of life. *BJU Int* 2012;**110**(11 Pt C):E830-6.
- 22 519 18. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials.  
23 520 *Contemp Clin Trials* 2007;**28**(2):182-91.
- 24 521 19. Mitchell BG, Fasugba O, Beckingham W, et al. A point prevalence study of healthcare  
25 522 associated urinary tract infections in Australian acute and aged care facilities. *Infection,*  
26 523 *Disease & Health* 2016;**21**(1):26-31.
- 27 524 20. Page K, Graves N, Halton K, et al. Humans, 'things' and space: costing hospital infection  
28 525 control interventions. *J Hosp Infect* 2013;**84**(3):200-05.
- 29 526 21. Mitchell BG, Ferguson JK, Anderson M, et al. Length of stay and mortality associated with  
30 527 healthcare-associated urinary tract infections: a multi-state model. *J Hosp Infect*  
31 528 2016;**93**(1):92-99.
- 32 529 22. Cuthbertson BH, Scott J, Strachan M, et al. Quality of life before and after intensive care.  
33 530 *Anaesthesia* 2005;**60**(4):332-9.

- 1  
2 531 23. Mdege ND, Man MS, Taylor Nee Brown CA, et al. Systematic review of stepped wedge cluster  
3 532 randomized trials shows that design is particularly used to evaluate interventions during  
4 533 routine implementation. *J Clin Epidemiol* 2011;**64**(9):936-48.  
5  
6 534 24. Tenke P, Kovacs B, Bjerklund Johansen TE, et al. European and Asian guidelines on  
7 535 management and prevention of catheter-associated urinary tract infections. *Int J Antimicrob*  
8 536 *Agents* 2008;**31 Suppl 1**:S68-78.  
9  
10 537 25. Wald HL, Ma A, Bratzler DW, et al. Indwelling urinary catheter use in the postoperative period:  
11 538 Analysis of the national surgical infection prevention project data. *Arch Surg*  
12 539 2008;**143**(6):551-57.  
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543 **Table 1** Key outcome measures

<b>Objective 1</b> 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
<b>Objective 2</b> 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

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

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**Figure 1** Study design overview

Blue = control; Green = intervention

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7 570 **Figure 2** Overview of data collection process  
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Hospital	2 months	4 months	6 months	8 months
A	Blue	Green	Green	Green
B	Blue	Blue	Green	Green
C	Blue	Blue	Blue	Green

Figure 1 Study design overview

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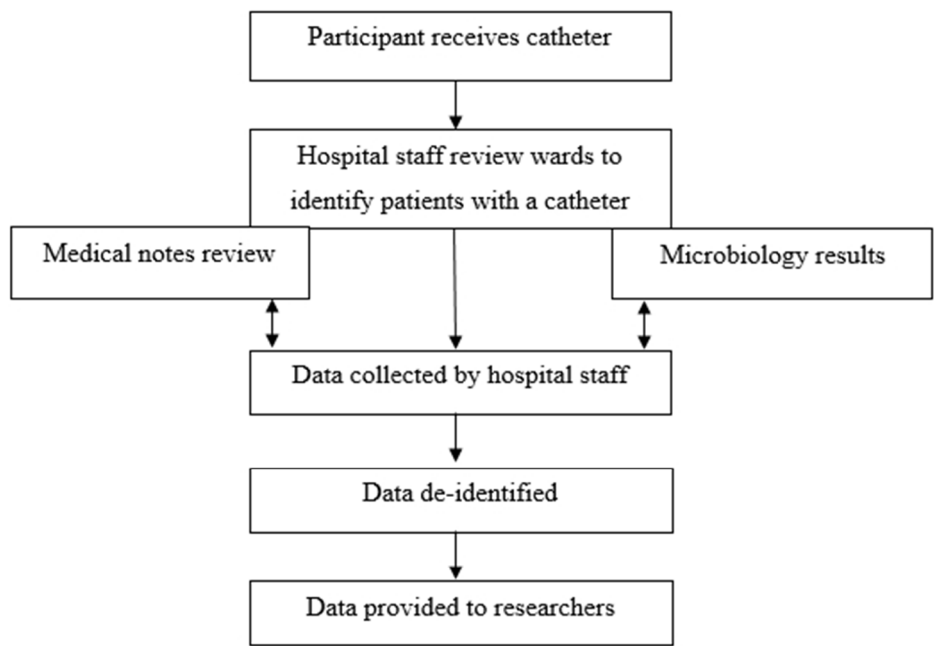


Figure 2 Overview of data collection process

Review only





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

Section/item	ItemNo	Description	Page
<b>Administrative information</b>			
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
<b>Introduction</b>			
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

1		6b	Explanation for choice of comparators	4-5
2				
3	Objectives	7	Specific objectives or hypotheses	6
4				
5	Trial design	8	Description of trial design including type of trial (eg,	6
6			parallel group, crossover, factorial, single group),	
7			allocation ratio, and framework (eg, superiority,	
8			equivalence, noninferiority, exploratory)	
9				
10				
11	<b>Methods: Participants, interventions, and outcomes</b>			
12				
13	Study setting	9	Description of study settings (eg, community clinic,	6-7
14			academic hospital) and list of countries where data	
15			will be collected. Reference to where list of study sites	
16			can be obtained	
17				
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If	7-8
20			applicable, eligibility criteria for study centres and	
21			individuals who will perform the interventions (eg,	
22			surgeons, psychotherapists)	
23				
24	Interventions	11a	Interventions for each group with sufficient detail to	8-9
25			allow replication, including how and when they will be	
26			administered	
27				
28				
29		11b	Criteria for discontinuing or modifying allocated	
30			interventions for a given trial participant (eg, drug	
31			dose change in response to harms, participant	
32			request, or improving/worsening disease)	
33				
34		11c	Strategies to improve adherence to intervention	
35			protocols, and any procedures for monitoring	
36			adherence (eg, drug tablet return, laboratory tests)	
37				
38				
39		11d	Relevant concomitant care and interventions that are	
40			permitted or prohibited during the trial	
41				
42	Outcomes	12	Primary, secondary, and other outcomes, including	10
43			the specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline,	
45			final value, time to event), method of aggregation (eg,	
46			median, proportion), and time point for each outcome.	
47			Explanation of the clinical relevance of chosen	
48			efficacy and harm outcomes is strongly recommended	
49				
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51	Participant	13	Time schedule of enrolment, interventions (including	17
52	timeline		any run-ins and washouts), assessments, and visits	
53			for participants. A schematic diagram is highly	
54			recommended (see Figure)	
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1	Sample size	14	Estimated number of participants needed to achieve	12-13
2			study objectives and how it was determined, including	
3			clinical and statistical assumptions supporting any	
4			sample size calculations	
5				
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7	Recruitment	15	Strategies for achieving adequate participant	8-9
8			enrolment to reach target sample size	
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

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

1				
2	Data	19	Plans for data entry, coding, security, and storage,	18
3	management		including any related processes to promote data	
4			quality (eg, double data entry; range checks for data	
5			values). Reference to where details of data	
6			management procedures can be found, if not in the	
7			protocol	
8				
9	Statistical	20a	Statistical methods for analysing primary and	13-16
10	methods		secondary outcomes. Reference to where other	
11			details of the statistical analysis plan can be found, if	
12			not in the protocol	
13				
14				
15		20b	Methods for any additional analyses (eg, subgroup	
16			and adjusted analyses)	
17				
18		20c	Definition of analysis population relating to protocol	
19			non-adherence (eg, as randomised analysis), and any	
20			statistical methods to handle missing data (eg,	
21			multiple imputation)	
22				
23				
24	<b>Methods: Monitoring</b>			
25				
26	Data monitoring	21a	Composition of data monitoring committee (DMC);	18
27			summary of its role and reporting structure; statement	
28			of whether it is independent from the sponsor and	
29			competing interests; and reference to where further	
30			details about its charter can be found, if not in the	
31			protocol. Alternatively, an explanation of why a DMC	
32			is not needed	
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35		21b	Description of any interim analyses and stopping	
36			guidelines, including who will have access to these	
37			interim results and make the final decision to	
38			terminate the trial	
39				
40	Harms	22	Plans for collecting, assessing, reporting, and	18
41			managing solicited and spontaneously reported	
42			adverse events and other unintended effects of trial	
43			interventions or trial conduct	
44				
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46	Auditing	23	Frequency and procedures for auditing trial conduct, if	18
47			any, and whether the process will be independent	
48			from investigators and the sponsor	
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51	<b>Ethics and dissemination</b>			
52				
53	Research ethics	24	Plans for seeking research ethics	18
54	approval		committee/institutional review board (REC/IRB)	
55			approval	
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2	Protocol	25	Plans for communicating important protocol	18
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC/IRBs, trial participants, trial	
6			registries, journals, regulators)	
7				
8	Consent or	26a	Who will obtain informed consent or assent from	18
9	assent		potential trial participants or authorised surrogates,	
10			and how (see Item 32)	
11				
12		26b	Additional consent provisions for collection and use of	N/A
13			participant data and biological specimens in ancillary	
14			studies, if applicable	
15				
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17	Confidentiality	27	How personal information about potential and enrolled	18
18			participants will be collected, shared, and maintained	
19			in order to protect confidentiality before, during, and	
20			after the trial	
21				
22	Declaration of	28	Financial and other competing interests for principal	19
23	interests		investigators for the overall trial and each study site	
24				
25	Access to data	29	Statement of who will have access to the final trial	19
26			dataset, and disclosure of contractual agreements	
27			that limit such access for investigators	
28				
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30	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and	NA
31	post-trial care		for compensation to those who suffer harm from trial	
32			participation	
33				
34	Dissemination	31a	Plans for investigators and sponsor to communicate	19
35	policy		trial results to participants, healthcare professionals,	
36			the public, and other relevant groups (eg, via	
37			publication, reporting in results databases, or other	
38			data sharing arrangements), including any publication	
39			restrictions	
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42		31b	Authorship eligibility guidelines and any intended use	20
43			of professional writers	
44				
45		31c	Plans, if any, for granting public access to the full	19
46			protocol, participant-level dataset, and statistical code	
47				
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49	<b>Appendices</b>			
50	Informed consent	32	Model consent form and other related documentation	N/A
51	materials		given to participants and authorised surrogates	
52				
53	Biological	33	Plans for collection, laboratory evaluation, and	N/A
54	specimens		storage of biological specimens for genetic or	
55			molecular analysis in the current trial and for future	
56			use in ancillary studies, if applicable	
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\*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.

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