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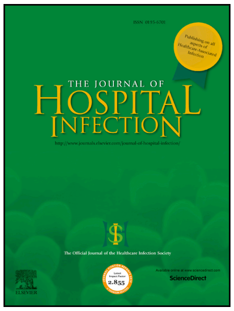

Chlorhexidine gluconate or polyhexamethylene biguanide disc dressing to reduce the incidence of Central-Line-Associated Blood Stream Infection: a feasibility randomised controlled trial (the CLABSI trial)

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(i) Title: Chlorhexidine gluconate or polyhexamethylene biguanide disc dressing to reduce the incidence of Central-Line-Associated Blood Stream Infection: a feasibility randomised controlled trial (the CLABSI trial)

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The CLABSI trial

SUMMARY

Background: A number of antimicrobial impregnated discs to prevent central-line associated blood stream infection (CLABSI) are marketed but it is unclear which disc is most effective.

Aim: To investigate the feasibility and safety of comparing two antimicrobial impregnated discs to prevent CLABSI.

Methods: We conducted a single-centre, parallel group, randomised controlled trial in a 929-bed, tertiary referral hospital. Hospital in-patients requiring a peripherally inserted central catheter were randomised to chlorhexidine gluconate (CHG) or polyhexamethylene biguanide (PHMB) disc dressing group. Dressings were replaced every 7-days, or earlier, if clinically required. Participants were followed until device removal or hospital discharge. Feasibility outcomes included: proportion of potentially eligible participants who were enrolled; proportion of protocol violations; and proportion of patients lost to follow-up**.** Clinical outcomes were**:** CLABSI incidence, diagnosed by a blinded infection control practitioner; all cause BSI; and product-related adverse events.

Findings: Of 143 patients screened, 101 (42%) were eligible. Five (3.5%) declined participation. There was one post-randomisation exclusion. Two (2%) protocol violations occurred in the CHG group. No patients were lost to follow-up. Three (3%) blood stream infections occurred; two (2%) were confirmed CLABSIs (one in each group) and one a mucosal barrier injury-related BSI. 1217 device days were studied; resulting in 1.64 CLABSI/1000 catheter days. One (1%) disc-related adverse events occurred in the CHG group.

Conclusion: Disc dressings containg PHMB are safe to use for infection prevention at catheter insertion sites. An adequately powered trial to compare PHMB and CHG discs is feasible.

Keywords:

Catheter-Related Infections; Randomised Controlled Trial; Feasibility Studies; Chlorhexidine; polyhexamethylene biguanide.

Central venous catheters (CVC) including peripherally inserted central catheters (PICCs) are frequently required for the long-term delivery of therapies, such as lipids, blood transfusions and anti-cancer drugs. CVCs are not without risk, an estimated 250,000 catheter- related blood stream infections occur each year in the USA, with the incidence varying between 0.1 – 22.5% depending on the population studied.[1] In Australian intensive care units (ICU), the average rate of CLABSI for the year July 2015 – June 2016 was 0.44/1,000 line days. Such infections increase a patient's risk of death, and add to the patient's discomfort, cost and length of hospital stay.[2] For example, a case of central line associated blood stream infection (CLABSI) in Australia adds at least AUD $14,000 (2010 dollars) to the cost of care.[3] In the USA, CLABSI accounts for an estimated 28,000 deaths and up to US 2.3 billion annually.[4]

There are a number of sources of CLABSI but the most common cause is thought to be the migration of organisms, originating from the patient's skin, along the outer surface of the catheter and into the insertion site.[5] To reduce catheter colonisation, interventions such as central line insertion and maintenance 'care bundles'[6], antimicrobial coatings/impregnation of catheters and equipment[7] and antimicrobial catheter lock solutions[8] have been introduced. Another approach has been the use of a chlorhexidine gluconate (CHG) impregnated sponge disc dressing (Biopatch®, Johnson & Johnson, New Jersey, USA) that is designed to release chlorhexidine and inhibit bacterial and fungal growth, for at least seven days around the catheter insertion site[9]. Based on a systematic review (nine randomised trials; 6067 participants) showing a 40.0% (RR 0.60, 95% CI, 0.41; 0.88) reduction in catheter-related blood stream infection,[10] a CHG disc dressing is now used in some hospitals as part of a CLABSI-prevention post-insertion bundle. However, most of the included trials were conducted in intensive care units, so limited data exists for the effectiveness of a CHG disc dressing in other settings or at risk populations such as cancer care and haemodialysis. Also, some adverse events, such as necrosis at the insertion site, have been associated with chlorhexidine patches but evidence for this problem is sparse.[11]

Despite these limitations, a decision was taken at our hospital to include a CHG disc dressing as part of the dressing for all central lines. We estimated that this decision increased our central catheter-related costs by approximately $AUD 77,000 annually. An alternate, less expensive product has been recently introduced. It is similar in shape to the CHG disc but instead contains polyhexamethylene biguanide (PHMB), a broad-spectrum antimicrobial that is effective up to 7-days (Kendall™ AMD Foam Disc®, Covidien, Basingstoke, UK). The disc has been shown to reduce biofilms in wounds[12] and reduce wound pain and wound size.[13] More importantly, PHMB has been shown to inhibit the growth of *Staphylococcus aureus*[14], a common and serious pathogen in CLABSI. To date, there are no randomised controlled trials (RCTs) comparing the effectiveness of the PHMB disc with other products to reduce CLABSI; nor has the CHG disc dressing been tested in head-to-head studies with any other antimicrobial dressing. Consequently, given the burden and cost of CLABSI, the growing cost and prevalence of these products and lack of evidence to show superiority of one product over another, the objective of this study was to conduct an independent, high quality trial to test the safety and efficacy of products to prevent CLABSI.

METHODS

Research design

Because no studies of in-vivo use of the PHMB disc have been published, our study aims were to assess i) the safety of the product and ii) the feasibility of conducting a larger, adequately powered trial. We used a single-centre, parallel, randomised controlled trial to meet these aims. The trial was prospectively registered on the Australian and New Zealand Clinical Trials Registry (ANZCTR: 12615000883516; registered 24/8 2015); we also had approval from the hospital's Human Research Ethics Committee (HREC/15/QRBW/300).

Population and setting

The study hospital is a tertiary referral teaching hospital with over 900 beds, located in South East Queensland, Australia. Non-ICU patients, who were scheduled to have a PICC catheter inserted, were potentially eligible. Inclusion criteria were: i) patients ≥ 18 years of age; ii) requiring a PICC for at least three days; iii) no previous central catheter this admission; and iv) informed consent to participate. Patients were excluded if they: i) had a current bloodstream infection (positive blood culture within 48 hours); ii) were non-English speakers without an interpreter; iii) had been previously enrolled in the study; or had known allergy to CHG or PHMB.

Data collection

Recruitment and randomisation

We designed and conducted the trial in accordance with The Consolidated Standards of Reporting Trials (CONSORT) Statement.[15] Each week day, a research nurse approached consecutive patients who were scheduled to have a PICC line inserted and provided them with written and oral information about the trial. A person independent of the recruiting nurse prepared a computer-generated allocation sequence (1:1 ratio) using randomly varied block sizes of 4 and 8 and no stratification. Eligible, consenting patients were randomly assigned to one of two groups (CHG disc dressing or PHMB disc) via a telephone service. Allocation was concealed from the recruiting nurse, clinical staff and patients until study entry. Following randomisation, blinding was not possible for patients, clinical staff or research staff because the appearance of the discs differed; one product was white and the other had a blue film-top. However, to eliminate detection bias, the laboratory scientist and the outcome assessor for the clinical outcomes of CLABSI and all cause BSI were blinded to the product used.

Feasibility outcomes:

(i) Eligibility: ≥ 80% of potentially eligible patients screened will be eligible;

(ii) Recruitment: ≥ 80% of eligible participants will agree to enrol;

(iii) Protocol fidelity: ≥ 95% of participants in the intervention group will receive prescribed intervention;

(iv) Retention: < 5% of patients will be lost to follow up.

Clinical outcomes:

(i) Incidence of CLABSI following the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) standardized case definitions. Blood stream infections were considered to be central-line-associated if the PICC line was in place at the time or within 48 hours before the onset of the infection.[16] The diagnosis was made by a blinded infection control practitioner.

(ii) All cause BSI defined as bacteremia or fungemia obtained from a peripheral vein and taken while the PICC was in-situ, or within 48 hours of removal.[16]

(iii) Product-related adverse event rates: skin reactions (assessed as yes/no and as disc area only/greater than disc area); pain (assessed by the patient on a scale from 0 to 10).

Procedure:

Before recruitment commenced, a series of information sessions occurred with staff, to orient them to trial processes and to address any concerns. In line with hospital policy, the PICC insertion site for all patients was clipped for hirsute patients, cleansed with 2% chlorhexidine gluconate in 70% isopropyl alcohol and allowed to dry. Catheters were polyurethane single lumen (4 French) or double lumen (5 French) Groshgong® Power PICC Solo®2 with Sherlock 3CG tip positioning system stylet (Bard Access Systems, Inc. Salt Lake City, USA); or radio-opaque polyurethane Arrow® Pressure injectable PICC™, single lumen (4 French) or double lumen (5 French) (Teleflex®, Morrisville, USA); or Cook radio-opaque polyurethane Turbo-Ject™ Power-Injectable PICC set (Cook® Medical Inc. Bloomingham, USA). PICCs were inserted by physicians or nurses under full sterile conditions using ultrasound guidance; correct placement was confirmed radiologically for catheters inserted in the department of medical imaging but not for PICCs that were inserted elsewhere. The PICC insertion site was covered with a standard polyurethane IV3000[◊] (Smith and Nephew, Kingston upon Hull, UK) and held in place with a securement device (Statlock®, PICC Plus stabilization device, Bard, Inc. Salt Lake City, USA). Following enrollment, the research nurse inspected dressings at 24 hours post-insertion and then on alternate days until hospital discharge or until the device was removed, whichever was sooner. During these visits, any protocol violations, dressing changes and dressing condition (clean, dry, intact) were documented. All data was recorded on a hand-held device, using REDcap software (Research Electronic Data CAPture, Vanderbilt). Depending on the group allocation, a new CHG or PHMB disc was applied every 7-days, unless there was an indication to change the dressing earlier. Decisions to remove catheters were made by clinical, not research staff. However, if research staff observed an indication for a dressing change, ward staff were notified. Blood cultures were obtained at the discretion of the attending physician. Patient risk factors were collected at enrolment. Clinical outcome data was collected from the patient's medical record and from the hospital's adverse event data base. Data collected for each patient, in addition to demographics and outcome data, included factors shown to have been associated with CLABSI in other studies, such as multiple CVCs, number of lumens, severity of illness, length of hospital stay, brand of PICC, other site infections, location of the catheter, number of insertion attempts, person placing the catheter. Skin integrity was assessed in three categories: i) Good' (healthy, well hydrated and elastic); ii) Fair (intact, mildly dehydrated, reduced elasticity); and iii) Poor (papery, dehydrated, small amount or no elasticity). Seven days after hospital discharge; an attempt was made to contact patients by phone or at follow-up clinic to check for any adverse reaction to the study products.

Sample size estimate:

For our feasibility outcomes, we based our sample size on the 95% confidence intervals for an estimated rate, using the formula suggested by Hooper. [17] Using this formula, we calculated with a sample of 50 per group we would be able to estimate our non-eligibility and inability to recruit rates of 20% to within 95% confidence intervals of +/- 4%. This sample size would also be sufficient to estimate our protocol fidelity and loss to follow-up rates of 5% to within 95% confidence intervals of +/- .02%.

Data analysis

Clinical data from REDcap was imported into SPSS and analysis was performed using the intention-to-treat principle, meaning all patients were analysed in the group to which they were assigned, with the exception of the one randomised patient who did not have a PICC inserted therefore had no outcomes. Feasibility outcomes were reported descriptively and compared against a priori determined feasibility cut offs of: eligibility 80%; recruitment 80%; protocol fidelity $\geq$ 95%; and retention < 5% lost to follow up. Dwell time was not normally distributed so results are shown as median and first and third quartiles. The sample size was not calculated to test statistical differences between groups so only descriptive data is reported. The CLABSI rate per 1000 inpatient device days was calculated by dividing the number of infections by the number of inpatient device days, multiplied by 1000.

Results

Between 1st February 2016 and 13th July 2016 a total of 143 patients were potentially eligible and 101 (70.6%) were recruited. Reasons for exclusion by group, are shown in Figure 1. The majority of patients were admitted for surgical procedures and 69 (69%) had a suspected or confirmed infection on admission. Seventy five (75%) patients were receiving antibiotics when recruited. A total of 66 (66%) PICCs were Bard (Groshong); and devices were most frequently inserted into the basilic vein (87; 87%). Nurses inserted 86 (86%) of the PICCs with a radiographer inserting 13 (13%) and a medical doctor one (1%). The mean study device dwell time was 12.2 days (SD 8.04; range 2 – 42 days). Fourty-seven patients (19 CHG; 28 PHMB) were discharged home with their PICC line still in place. Among the 100 included patients, a total of 249 discs were applied (100 initial discs and 149 changes); an average of 2.5 discs per patient during their in-patient stay. Details of demographic and clinical characteristics, by group, are shown in Table 1.

Feasibility outcomes

As shown in Figure 1,143 patients were potentially eligible. Of these, a total of 19 (13.2%) patients had their PICC insertion cancelled, and 18 (12.6%) were too unwell to be approached for consent, which made them ineligible. Consequently 106 (74.1%) of the patients we screened remained eligible; a rate less than our eligibility target of 80.0%. Of the remaining 106 eligible patients, five (4.7%) declined to consent, therefore our recruitment target was met. There were two (2%) complete protocol violations; one person received a PHMB disc instead ofa a CHG disc dressing and one person in the CHG group did not receive either disc. Thus, our 'protocol fidelity' target was met. There was one post-randomisation exclusion in a patient whose PICC insertion was cancelled. For four participants (3 CHG and 1 PHMB), no disc was applied initially, due to excessive ooze but then corrected with the next dressing change. In 11 (11%) patients, a partial violation occurred where the correct disc dressing was applied at randomisation but, subsequently, an incorrect product was used for some, but not all of the PICC dwell time. In these cases, the PHMB disc was incorrectly replaced with a CHG disc at the routine 7-day change. All patients were able to be followed until their hospital discharge, consequently, no patients (0%) were lost to follow-up.

Clinical outcomes

Three (3%) laboratory confirmed blood stream infections (BSI) were reported; two (2.0%) were confirmed CLABSIs (one in each group) and one was a mucosal barrier injury-related BSI. Dwell times for the two CLABSIs were: CHG dressing 6.1 days/147.3 hours; PHMB dressing 6.6 days/158.8 hours.The infective organism in the PHMB group was *Staphyloccocus epidermidis* and in the CHG group *Staphyloccocus hominis.* Twelve skin reactions were reported. Eleven of these (eight in the PHMB group and three in the CHG group) matched the rectangular area covered by the securement dressing, rather than the disc, so we believe these were polyurethane-related reactions. One rash, in the shape of the CHG disc dressing, was the only study disc-related event. The rash had resolved by the next two-day check and the PICC was removed shortly after, as treatment had been completed. The total number of device days was 1109 (PHMB 562; CHG 547); resulting in a CLABSI rate per 1000 catheter days of 1.8 (PHMB 1.8; CHG 1,8).

Discussion

The primary goal of this study was to examine a number of feasibility outcomes while also collecting safety and clinical data. The main exclusions were unavoidable, being patients who were too unwell to approach for consent, or who had their PICC insertion cancelled. While this 74% eligibility of screened patients was lower than our target of 80%, this had very little impact on the study feasibility. The time spent on screening was minimal, with the majority of patients being excluded simply by checking computer lists. This screening could be achieved between patient recruitment or while waiting for new patients to arrive at the medical imaging unit.

The important outcomes of recruitment and retention were easily met. Only 3.5% of patients declined to consent and retention was 100% so we demonstrated an ability to follow patients until their hospital discharge.

The target for protocol fidelity was met in that 98% of patients received the allocated intervention at study entry. However the incidence of partial violations was much higher with the majority of violations involving clinical nurses (not research staff) incorrectly replacing PHMB discs with a CHG disc at a dressing change. Despite several methods to identify group allocation (stickers on the patients medical record;

their day care plan; and on the dressing), errors occurred. CHG was standard care, so the process is entrenched and the product easily accessable. The fidelity problem was identified early in the trial and largely resolved after a further series of information sessions and storage of the allocated study product in the patient's bedside. Of course these violations would not occur if PHMB was the only product available at dressing changes.

Our positive CLABSI incidence rate was 2.0% (1.8 per 1000 device days); a rate that is in line with reported rates from other non-ICU cohorts[18] but higher than in centres where there has been a focus on reaching a zero CLABSI rate.[19,20] While the trial was not designed to test for differences, it provides some preliminary data on the efficacy of the two products. Both of the CLABSI-positive patients in the trial had a white cell count >1.0/L however, the first, in the CHG group, was a cancer patient who was neutropenic (neutrophil count 0.37 cells/µl) and febrile. The second was a critically ill, surgical orthopaedic patient with a low haemoglobin level (68 g/L) and otherwise asymptomatic. Niether of the PICC entry sites were inflamed.

Reactions to chlorhexidine and polyhexamethylene biguanide discs were minimal in our trial with only one disc-related event reported in the CHG group. Whist rare, CHG disc-related contact dermatitis has been reported in other studies. For example Timsit et al found a similar CHG-related contact dermatitis rate of 1.1% (5.3 per 1000 catheters) among critically ill patients.[21] We also found that reactions to the commonly used polyurethane dressing were 12 times more likely than reactions to the CHG disc dressing. This result differed from the findings of a systematic review of CHG discs used in the prevention of catheter related infections in newborns, where 19 (2.3%) infants in the chlorhexidine disc dressing group developed contact dermatitis compared to none in a polyurethane dressing group.[22] Consequently, chlorhexidine products have been not approved for use in children under two months of age for some years.[23] It is difficult to understand these disparate results, unless infant's skin responds differently to polyurethane than the skin of the older and quite unwell patients recruited to our trial. The skin integrity of just under half of those recruited to our trial was rated as only 'fair' or 'poor'.

Despite the use of an aseptic technique when inserting a PICC, we have not implemented a hospital wide, multi-modal CLABSI prevention program. Without such a program, it may be optimistic to assume that CLABSI rates will fall, simply by introducing a new dressing.

Study limitations.

The trial was not powered to find differences between groups for our secondary, *clinical* outcomes. However, we did have sufficient participants to investigate our primary *feasibility* outcomes. The study was also conducted in a single centre, so results may not be externally valid. The majority of patients were receiving antibiotics at the time of recruitment; this may have impacted on our CLABSI rate. Finally, we recruited only patients with PICC lines, and we did not follow patients into the community setting, so results also may not be applicable to other types of central lines.

Conclusion:

Disc dressings containg polyhexamethylene biguanide are safe to use for skin disinfection around catheter insertion sites. The study has established that it would be feasibile to compare PHMB and CHG disk dressings in an adequately powered trial.

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Conflicts of interest: Griffith University has received unrestricted investigator initiated research/educational grants or consultancy payments on Claire M Rickard's behalf from manufacturers of central line dressings not used in this study (3M, BD/Carefusion; Centurion Medical Products; Entrotech).

None of the other authors have a financial or other beneficial interest in any of the products mentioned in the study, or in any competing products.

Authorship and manuscript preparation: No-one, other than the named authors, has had a role in gathering or preparing the data or in writing the manuscript.

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Table 1: Demographic characteristics, clinical and intravenous access risk factors for the two groups.[1]

Risk factors	**PHMB[2]** n=51	**CHG[3]** n=49
General risks		
Age	56.5 [14.98]	60.65 [15.78]
Female	23 (45)	26 (53)
Weight	81.15 [24.42]	88.00 [23.21]
Clinical risks		
Skin integrity		
- Good	29 (57)	26 (53)
- Fair	14 (28)	16 (33)
- Poor	8 (16)	7 (14)
Admission category		
- Oncology/haematology	13 (25)	10 (20)
- Medical	13 (26)	17 (35)
- Surgical	25 (49)	22 (45)
Number of comorbidities >3	24 (47)	25 (51)
Any infection at recruitment	38 (75)	31 (63)
Wound infection	18 (35)	13 (27)
Skin infection/cellulitis	3 (6)	5 (10)
Antibiotic at recruitment	37 (73)	30 (78)

Risk factors	**PHMB**[2] n=51	**CHG**[3] n=49
Intravenous access risks		
Device brand		
- Arrow	20 (39)	12 (25)
- Bard (Groshong)	30 (59)	36 (74)
- Cook	1 (2)	1 (2)
Number of lumens (two)[4]	42 (82)	30 (61)
PICC[5] location (basillic)	43 (84)	44 (90)
PICC inserter (nurse)	43 (84)	43 (88)
Dwell time (median and first and third quartiles in days)	7.1 (4.1-15.3)	8.2 (4.4 – 14.5)
Radiologically inserted	22 (43)	16 (33)

[1] Data is presented as number and percent (%) or mean and standard deviation [SD]

[2] polyhexamethylene biguanide

[3] chlorhexidine gluconate

[4] single lumen PICC catheters were 4 French, double lumen PICC catheters were 5 French; no triple lumen catheters were used in the study

[5] Peripherally inserted central catheter

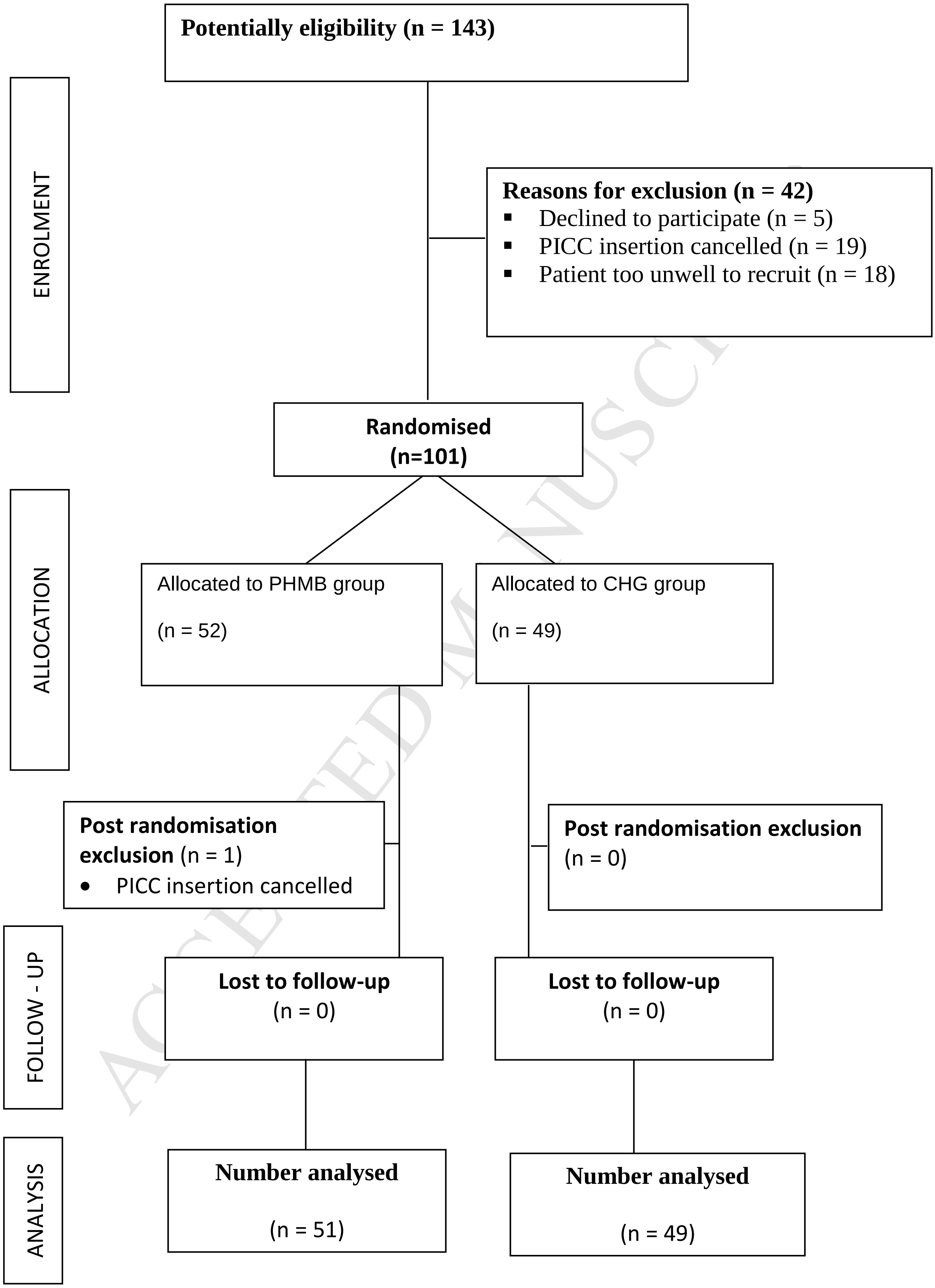

Figure 1: Flow of participants through the trial