Peripherally InSerted CEntral catheter dressing and securement in patients with cancer: the PISCES trial. Protocol for a 2x2 factorial, superiority randomised controlled trial

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ABSTRACT

Introduction

Around 30% of peripherally inserted central catheters (PICCs) fail from vascular, infectious or mechanical complications. Patients with cancer are at highest risk, and this increases morbidity, mortality and costs. Effective PICC dressing and securement may prevent PICC failure; however, no large randomised controlled trial (RCT) has compared alternative approaches. We designed this RCT to assess the clinical and cost-effectiveness of dressing and securements to prevent PICC failure.

Methods and analysis

Pragmatic, multicentre, 2x2 factorial, superiority RCT of (1) dressings (chlorhexidine gluconate disc (CHG) vs no disc) and (2) securements (integrated securement dressing (ISD) vs securement device (SED)). A qualitative evaluation using a knowledge translation framework is included. Recruitment of 1240 patients will occur over 3 years with allocation concealment until randomisation by a centralised service. For the dressing hypothesis, we hypothesise CHG discs will reduce catheter-associated bloodstream infection (CABSI) compared with no CHG disc. For the securement hypothesis, we hypothesise ISD will reduce composite PICC failure (infection (CABSI/local infection), occlusion, dislodgement or thrombosis), compared with SED. Secondary outcomes: types of PICC failure; safety; costs; dressing/securement failure; dwell time; microbial colonisation; reversible PICC complications and consumer acceptability. Relative incidence rates of CABSI and PICC failure/100 devices and/1000 PICC days (with 95% CIs) will summarise treatment impact. Kaplan-Meier survival curves (and log rank Mantel-Haenszel test) will compare outcomes over time. Secondary end points will be considered between groups using parametric/non-parametric techniques; p values <0.05 will be considered statistically significant.

Ethics and dissemination

Ethical approval from Queensland Health (HREC/15/QRCH/241) and Griffith University (Ref. No. 2016/063). Results will be published.

Trial registration

Trial registration number is: ACTRN12616000315415.
and for frequent blood sampling. Although initially viewed as safer, cheaper and more durable than centrally inserted venous catheters, approximately 30% of PICCs fail before completion of treatment from complications, with prevalence highest in patients with cancer. As most cancer treatment is in ambulatory (outpatient) settings, PICC failure interrupting treatment poses substantial increases in lost outpatient booking times. It also depletes patients’ useable veins for future treatment and can obstruct vessels long-term. Moreover, delays to chemotherapy cycles reduce treatment efficacy and can affect subsequent survival.

PICC failure can be from infective, vascular or mechanical complications. Infections can be local insertion site infections which occur in 1% of PICCs in patients with cancer, or catheter-associated bloodstream infection (CABSIs) experienced by 7% hospitalised patients with cancer with PICCs, which increases mortality almost threefold. Vascular complications occur via PICC damage to the vessel endothelium, which may present as deep venous thrombosis (DVT) with severe pain and swelling, risk of thrombus detachment and potentially devastating pulmonary embolism. Patients with cancer frequently have increased DVT risk from coagulopathy or other haematological imbalances, and a recent meta-analysis reported DVT in 7% of those with PICCs.

Mechanical complications include partial or total dislodgement from the vein, occurring in 5%–13% of PICCs via ‘drag’ from multiple infusion tubes, or ‘catching’ on environmental structures (eg, clothing, chairs). Partial dislodgement malpositions the catheter tip which can cause infiltration of irritant infusion fluids and medication into tissue causing injury and potentially necrosis. Occlusion can result from build-up of blood or infusion products inside the PICC, or PICC compression by an irritated, swollen vein wall. Clinicians may fracture the PICC through excessive force when attempting to clear occlusion. Occlusion, with or without fracture, occurs in 4%–23% of PICCs.

It is projected that 7.2 million PICCs will be sold in the USA alone in 2017, with revenue of US$1.26 billion. Significant numbers are used worldwide, and the high incidence of PICC failure imposes substantial burden on patients and the health system. CABSIs alone (6% vs 11%, p=0.02) of PICCs reported lower CABSIs with CHG discs than SP alone (6% vs 11%, p=0.02). The skin of patients with cancer is often impaired from steroid, radiation and/or chemotherapy treatment, and CHG may further irritate or damage skin. There are also concerns about potential antimicrobial resistance, allergic reactions and systemic absorption in neonates, which may be limiting uptake.

Integrated securement devices (ISDs) are ‘next-generation’ SP dressings designed to replace both SP and SEDs. They have a tough fabric adhesive border, a second adhesive component that holds the PICC from beneath, and can be used with or without a CHG disc. A recent cohort study in PICCs (n=421) compared ISDs with historical SP+suture controls, finding ISDs associated with less CABSIs (6% vs 11%, p=0.13), dislodgement (4% vs 6%, p=0.27) and overall PICC failure (21% vs 25%, p=0.54). Occlusion in ISD-secured PICCs occurred significantly later, at 25 vs 8 days (p<0.01). Despite these promising findings, ISDs have not yet been tested in an RCT.

Cost-effectiveness analysis is lacking from the literature for PICC dressing and securement products, and data are needed to resolve this uncertainty. With millions of PICCs used globally, even small differences in cost-effectiveness could significantly reduce hospital budgets. For example, introduction of CHG discs for intensive care unit CVCs, saw net annual savings in the USA of US$275 million to US$2 billion for CABSIs.

We designed a pragmatic clinical trial that has three main objectives:
Table 1  Four groups within factorial randomised controlled trial

<table>
<thead>
<tr>
<th>2×2 factorial</th>
<th>Securement: SED (control)</th>
<th>Securement: ISD</th>
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<tbody>
<tr>
<td>Dressing: no CHG disc (control)</td>
<td>SD+SP, no CHG disc</td>
<td>ISD, no CHG disc</td>
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<tr>
<td>Dressing: CHG disc</td>
<td>SD+SP with CHG disc</td>
<td>ISD with CHG disc</td>
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CHG, chlorhexidine gluconate; ISD, integrated securement dressing; SD, securement dressing; SED, securement device; SP, standard polyurethane.

1. To compare the effectiveness of PICC dressing with (i) a CHG disc and (ii) no CHG disc to prevent CABSI and adverse events;
2. To compare the effectiveness of securement with (i) an SED and (ii) an ISD to prevent PICC failure and adverse events;
3. To evaluate the acceptability of ISD and CHG discs to patients and healthcare professionals, and to identify barriers, enablers and strategies for translation of results into policy and practice.

METHODS AND ANALYSIS
This pragmatic, multicentre, 2×2 factorial, superiority RCT will test the clinical efficacy and cost-effectiveness of (1) dressings (CHG disc vs no disc) and (2) securements (SD vs ISD) (table 1). Embedded in the RCT is a formative, qualitative evaluation of trial products and processes using a knowledge translation framework.

Hypotheses
Dressing hypothesis
1. The use of a CHG disc will reduce the incidence of PICC CABSI compared with the use of no disc.

Securement hypothesis
1. The use of an ISD will reduce the incidence of composite PICC failure, compared with the use of SED.

Sample size and study power
Dressing hypothesis
Our baseline CABSI is 8% with no CHG disc and we predict this incidence in the combined no CHG disc group. We expect 4% CABSI in the combined CHG disc groups, based on a risk ratio (RR) of 0.52 previously associated with CHG discs (n=7436).21 A one-sided inequality test of two proportions calculated that 602 PICCs per group (602 CHG disc vs SP+sutures in PICCs,34 and the pooled RR=0.63 seen as the midpoint between RR=0.84 associated with ISD and RR=0.73 associated with SED) is sufficient to show a 19% failure in the combined ISD groups (RR=0.73 vs SED; 608 SED) could compare 26% and 19% PICC failure with 90% power (p=0.05, PASS).

Because of the factorial design, we used the comparison that required the larger sample (608 per group), plus 2% for potential attrition, thus 620 per group (total trial 1240). This was split so that each of the four study groups had 310 PICCs. We assumed no interaction effect between the interventions, but tested this in a Cox proportional hazards model, and analysed CHG disc effect (vs no disc) and the ISD effect (vs SED) separately (at the margins) using similar techniques.27 43 A Data Safety Monitoring Committee reviewed blinded data and serious adverse events at n=400 and n=800 to advise on (i) sample size adjustments or (ii) study stopping for efficacy in one or more arms (multiplicity adjustment, p<0.017) or if one or more arms should be stopped due to futility.14 45 This advice was reviewed by CMR, NM, JW, MM and VC, who made the final decision to terminate the trial.

Setting and sample
After ethical, legal and governance approvals, adult and paediatric patients were recruited at three hospitals in Queensland, Australia (Lady Cilento Children’s Hospital; Princess Alexandra Hospital and Royal Brisbane and Women’s Hospital). Inclusion criteria were: haematological malignancy or solid tumour diagnosis; PICC required >24 hours and patient/parent gave informed consent. Exclusion criteria were: non-central PICC tip placement at baseline (eg, tip in subclavian/brachiocephalic/jugular vein); current BSI (<48 hours); PICCs inserted through diseased or hirsute skin; allergy to any study product; PICCs did not already had a CHG disc/dressing in place. Once a patient entered the trial, consecutive PICCs were studied (as long as the inclusion/exclusion criteria were met), with all PICCs per patient following the same randomisation allocation. To ensure generalisability, PICCs inserted after-hours were also studied if these additional criteria were met: (i) <24 hours since PICC insertion; (ii) no compromise in PICC function; (iii) predicted further use ≥24 hours; (iv) the treating clinician agreed it was safe to replace the initial dressing/securement.

Outcome measures and definitions
Dressing hypothesis
Primary outcome
The primary outcome was CABSI: a laboratory confirmed BSI (LCBSI 1; LCBSI 2 or LCBSI 3) that is not secondary to an infection at another body site (eg, mucosal barrier

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injury LCBSI), with PICC in place for >2 calendar days on
the day of the BSI (day of PICC placement being day 1), and
the PICC was in place on the date of the event or the
day before, when all elements of LCBSI were first present
together (see CDC National Healthcare Safety Network
for full criteria), confirmed by a blinded infectious
disease specialist using de-identified data.

Securement hypothesis
The primary outcome was PICC failure (composite of
infection, occlusion, dislodgement, thrombosis) for the
securement hypothesis.

► Infection
► CABS1: as above, or,
► Local infection (exit-site infection): microbiological
diagnosis—purulent discharge (microorganism
identified from exudate); or, clinical diagnosis—
erythema, induration and/or tenderness within
2 cm of PICC exit site and may be associated with
other signs and symptoms of infection such as
fever or purulent drainage; BOTH with or without
concomitant bloodstream infection, confirmed
by a blinded infectious disease specialist.

► Occlusion
► Occlusion: ≥1 lumens cannot be flushed,
aspirated or resolved post-thrombolytic dwell, or
► Fracture: visible split in PICC material with
leakage or radiographic evidence of extravasation
or infiltration into tissue, causing removal.

► Dislodgement
► Partial: change in PICC length from baseline
measurement closest to skin site or PICC
removal due to development of tip malposition
(diagnosed radiographically and/or by site
leakage on injection and/or infusion), or
development of non-central tip (eg, isolateral
jugular or contralateral brachiocephalic,
diagnosed radiographically and/or by site
measurement closest to skin site
or)
► Complete: PICC body completely leaves the vein.

► Venous thrombosis
► Suspected: removed as too painful for patient to
tolerate, or
► Confirmed: ultrasound-confirmed or venogram-
confirmed thrombosed vessel (brachial, basilica,
axillary or subclavian) at the PICC site in a
symptomatic (arm pain, swelling, redness and/
or tenderness over the PICC) patient, or
diagnosis by CT, MRI or other imaging, or a
symptomatic patient with a thrombus or fibrin
sheath occluding ≥1 lumen at PICC removal.

Secondary outcomes (for both the dressing and securement
hypotheses)
► Types of PICC failure: each failure type (local infection/
CABS1, occlusion, dislodgement or thrombosis),
in addition to PICC-related bloodstream infection
(laboratory confirmed matched organism from blood
and catheter tip, or differential time to positivity).

► Safety endpoints: skin rash, skin tears, blisters, pruritus,
local or systemic allergic reactions.
► Costs: direct costs to the hospital (in AUD) for the
total episode of care, including costs of device and
dressing replacement plus cost of treating PICC
complications.
► Dressing/securement failure: replacement before 7
days for loose, missing, bloodstained, diaphoresis
or secretion-soaked dressings/SEDs (dichotomous).
► PICC and dressing/securement dwell time: hours from
insertion/application until removal.
► Device/skin site colonisation: >15 cfu growth from skin
swab taken from PICC entry site, or PICC tip culture
after removal.
► Patient/parent and staff acceptability: 0–10 numerical
rating scales.
► Relative PICC failure in experimental groups:
the 2×2 experimental groups were compared.
► Reversible PICC complications: complications (eg,
occlusion, infection, fracture, internal malposition)
that did not cause PICC failure, but required an
intervention (eg, urokinase, alteplase, ethanol,
PICC mended, warmed saline, reposition or ‘pop’
technique).

Recruitment, randomisation, allocation concealment and
blinding
Research nurses (ReNs) screened patients, obtained
consent after a full explanation of the trial and responded
to any questions, randomised patients, educated clinical
staff, patients and families, monitored protocol compli-
ance and collected data. Central web-based randomisation
with allocation concealment was patient level with 1:1:1:1
ratio between groups (randomly varied block sizes) and
stratification by: (i) hospital, (ii) cancer type (haema-
tological malignancy or solid tumour), (iii) inpatient/
outpatient status and (iii) previous PICC treatment ever
(yes/no). Study products were in numbered prepacks
and ReNs liaised with inserters. It is not possible to blind
dressing and securements, since clinical staff must apply
and monitor these, and ReNs must assess protocol compli-
ance. The primary outcomes of CABS1/PICC failure are
objective, easily and routinely collected by clinical staff
(not investigators) in usual practice. Blinded microbiolo-
gists and infectious disease physicians assigned infection
outcomes. A blinded statistician analysed data.

Insertion and care of the PICC, dressing and securements
ReNs were not involved in PICC insertion, application
of study products or PICC care, but provided prestudy
and intrastudy education to hospital staff, including user
guides, to promote consistency. PICC inserters used
a large sterile drape and gown, prepared skin with 2% CHG
in alcohol and select ed insertion site, PICC type and
approach based on clinical judgement, then applied allo-
cated products. Numbered prepacks of allocated products
with a usage form was kept at the bedside and monitored
by the ReNs, who confirmed the timing and reason for
replacements and/or reinforcements with nursing staff. A protocol violation is ‘the randomised product was never used to secure the PICC’. A protocol deviation is if incorrect dressing and securements are used for a proportion of the PICC dwell. Unless contraindicated (eg, irritation), deviations were corrected and the proportion of PICC dwelled with deviations, and reasons for these were noted. Study products were changed weekly and as needed, with sterile gauze used temporarily if sites bled excessively or for excessive diaphoresis. Use of gauze and tape or additional products (eg, extra strips of tape, bandage) was recorded for proportion of dwell time in use, and reasons for use. If CABSI was suspected by treating medical staff, percutaneously drawn and CVAD-drawn blood cultures were taken, in addition to PICC tip (if removed) culture and purulent discharge (if any) culture. PICC removal was decided by treating clinical staff as per usual practice, with no involvement by investigators.

Data collection
The ReNs collected data from electronic and other charts, using hand-held devices and a REDCap database (Research Electronic Data CAPture, Vanderbilt). The ReNs reinforced the protocol with patients and staff. A study manager checked allocation integrity, inter-rater reliability for skin and dressing assessments and monitored 100% source data verification for first patient per site, consent forms, primary outcomes and a random 5% of other data for all patients. Site-specific hospital data at 3–6 monthly intervals noted any changes in local PICC policy or products.

At enrolment, ReNs collected patient demographics (eg, age, gender, weight); clinical factors (eg, diagnostic group, comorbidities, any infection, neutropenia, coagulopathy, skin integrity); PICC factors (eg, insertion site, inserter discipline, technology-assisted insertion, number of insertion attempts, PICC type, size, gauge, emergency insertion, side (right/left), insertion department) and treatment factors (immunosuppressants, anticancer treatment, transfusion, antimicrobials, parenteral nutrition, continuous or intermittent therapy). Clinicians rated ease of study product application using an 11-point scale (0=very difficult, 10=very easy), and noted previous number of applications of that product type. Data were collected on: all infusions given through the PICC (including any lock solutions); patient mobility and cognitive status and patient/parent satisfaction with the study products (0=completely dissatisfied, 10=completely satisfied). The removing nurse rated the difficulty of product removal (0=very difficult, 10=very easy), and number of previous removals of that product type. The reason for removal was recorded, including any complications/failure, and PICC dwell time. ReNs prepared blinded microbiological and clinical data, and an infectious disease physician assessed infection end points. Hospital length of stay and mortality were recorded.

Microbiological substudy
A blinded microbiologist compared numbers and type of skin bacteria under the dressing/securement products at removal (purposive sample of 31 patients per group, n=124). Patients were not able to be selected at random, as there were limited opportunities when ReNs were available at the time of the dressing replacement; however, we collected consecutive samples from 124 available patients at the Royal Brisbane and Women’s Hospital. This ensures samples were collected by a small number of research nurses (two) with extensive training and audit to standardise sampling methods. Approximately 2 cm² of skin at the insertion site was swabbed using a sterile cotton swabstick moistened with sterile saline for 10 s using back and forward motion and rolling motion, then placed in sterile tubes. Swabs and any available PICC tips were cultured on non-selective agar and incubated aerobically at 37°C. Total number of colonies were counted and bacteria were identified at 24 hours, repeated at 72 hours for slow-growing species. Antibiotic resistance was tested genetically (qacA/B and smr) and CHG tolerance was tested by minimum inhibitory concentrations for each isolate using broth microdilution. Any positive clinical isolates from other body sites were noted from hospital records and compared with skin swab results. Specimens have been stored for future studies of infection prevention, if patients consent to this.

Quantitative data analysis
The lead investigator, statistician and study manager had access to the final dataset. Analyses and reporting followed the Consolidated Standards of reporting Trials (CONSORT) Statement. Intention-to-treat analysis occurred with patients, the unit of randomisation and PICCs, the unit of measurement. Outlying figures, missing and implausible data were cleaned. Patients who withdrew from the intervention requested to allow collection of the primary end point. Lost to follow-up patients had outcome data modelled for best-case and worst-case scenarios, with multiple imputations considered if data were missing at random. A per-protocol analysis assessed the effect of withdrawn or lost to follow-up patients, postrandomisation exclusions and protocol violations. Sensitivity analyses considered the effect of temporary protocol deviations.

Pairwise, sequential comparisons were made for CHG versus SP, and ISD versus SED. Baseline group comparisons were done by clinical parameters. Relative incidence rates of PICC failure per 100 devices and per 1000 PICC days (95% CIs) summarised treatment impact, with group differences tested. Kaplan-Meier survival curves (and log rank M-H test) compared failure rates over time. Secondary end points were compared between groups using parametric and non-parametric techniques. The proportional hazards assumption was checked, and Cox regression tested the effect of group, patient, device and clinical variables on outcomes, and assessed for an interaction effect. Regression models allowed for stratification factors and clustering by site (gamma-shared frailty). Subgroup analysis tested for differences within and between hospital site including paediatric/adult; cancer diagnosis type and inpatient/outpatient status. p Values <0.05 were considered to be statistically significant.

**Estimating cost parameters**

We hypothesised significantly reduced costs in both treatments over controls from a direct hospital perspective for the episode of care (standardised AUD$, 2019/year). We quantified additional costs, benefits, net monetary benefit in the context of CABSI/PICC failure, re-insertions and the treatment costs of complications per group. Detailed resource use for PICC insertion/removal, plus dressing and securement application/removal was recorded for 100 procedures selected at random (25 per group). Staff wage costs for application, troubleshooting, replacement, consultation and equipment used were recorded. Direct observation of practice in response to CABSI or PICC failure informed total resource use and costs per group. Cost offsets due to reductions in adverse events were calculated on direct hospital costs, and for length of stay. Analysis with analysis of covariance compared mean costs per group.

**Qualitative data collection and analysis**

The following qualitative data complemented the trial results and informed translation:

1. Brief semi-structured interviews (approximately 10 per group, spread across sites) with patients/parents about their experience of study products, the trial and suggested improvements. The final sample was determined by data saturation. Interviews were audiotaped, transcribed and thematically analysed based on Norwood’s framework and an inductive process.

2. ReNs documented field notes related to positive or negative trial or study product feedback offered by any patient/parents or practitioners. Analysis was thematic as above.

3. We videorecorded approximately five episodes per group of study product use (including application, replacement and removal), with brief semi-structured interviews with the clinicians about the procedure. Final sample size was determined by data saturation, with data transcription and thematic analysis as above. Video data assessed procedural time and resource use (to inform health economic analysis), product usability and integrity of protocol delivery.

4. An Evidence Users’ Reference Group was established in the final year including investigators, patients/parents, nursing and medical clinicians from cancer, infection control, infectious diseases, radiology, vascular access and policy makers. The Group reflected on trial results and qualitative data from 1 to 3 above, identified likely barriers and enablers of implementation and developed an evidence use plan with tools and strategies.

**ETHICS AND DISSEMINATION OF RESULTS**

The trial had approval from the Children’s Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC) HREC/15/QRCH/241, and Griffith University HREC Ref. No. 2016/063. Minor adverse events (eg, skin reaction to dressing) were treated as per usual practice with no cost to patients. Clinical trial insurance was held by the Griffith University. Written informed consent to participate was obtained from participants or representatives, including an additional option to store specimens and data for future research. Consent could be later withdrawn. Identifying details were kept confidential via assigned numeric study IDs. Serious adverse events were monitored and reported to the HREC as were any important protocol modifications. If important protocol amendments were made (eg, changes to eligibility criteria), CMR updated all investigators, HRECs, updated patient information and consent forms and updated the trial registry. A Data Safety Monitoring Committee reviewed blinded interim data and adverse events at n=400 and 800 to advise on safety. Before qualitative interviews and video recordings, participants provided written informed consent. If patients/parents became distressed, they received initial support from the experienced qualitative reviewers and were referred to the relevant institutional contact. The trial and substudies were written by the investigators and published in peer-reviewed journals, consistent with the International Committee of Medical Journal Editors (ICMJE) Guidelines and authorship criteria.

**DISCUSSION**

PICC failure is unacceptably high in patients with cancer. CABSI has significant related morbidity and increases the risk of death almost threefold. PICC failure in all its forms (eg, dislodgement) wastes millions of health dollars annually through increased procedures, treatment of complications and extended hospital days. All PICC failure results in negative patient-related outcomes, including increased pain and anxiety; delays in treatment and unnecessary exposure to the risks associated with repeated reinsertions. Older dressing and securement
methods likely contribute to PICC failure, but there is inadequate data to resolve uncertainty about their efficacy or safety compared with newer alternatives. At present, practitioners and policy makers make decisions with uncertainty, due to lack of adequate evidence. This pragmatic, multicentre, factorial, superiority RCT will help to resolve uncertainty and inform international policy and practice.

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CMR, NM, JW, NG, RC, ALM, PM, AU, TK, VC, LZ, MM, EL, MAC, SK, EA, DM, MCM, DP, MC, GRB, IC, AH, EG designed the protocol. CMR, JW, RC, PM, EG, LZ, SK, AH, EA, AU, DM, MM, MCM, NG, TC, VC, NM secured funding. CMR, NM, JW, NG, RC, ALM, PM, AU, TK, VC, LZ, MM, EL, MAC, SK, EA, DM, MCM, DP, MC, GRB, MIC, AH, AC and EG prepared and approved the final version of the manuscript.

Competing interests
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Ethics approval
Queensland Health (HREC/15/QRCH241) and Griffith University (Ref. No. 2016/063).

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
No additional data are available.

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