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BMJ Open Protect peripheral intravenous catheters: a study protocol for a randomised controlled trial of a novel antimicrobial dressing for peripheral intravenous catheters (ProP trial)

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ABSTRACT

Introduction Peripheral intravenous catheters (PIVCs) are the most commonly used vascular access device in hospitalised patients. Yet PIVCs may be complicated by local or systemic infections leading to increased healthcare costs. Chlorhexidine gluconate (CHG)-impregnated dressings may help reduce PIVC-related infectious complications but have not yet been evaluated. We hypothesise an impregnated CHG transparent dressing, in comparison to standard polyurethane dressing, will be safe, effective and cost-effective in protecting against PIVC-related infectious complications and phlebitis.

Methods and analysis The ProP trial is a multicentre, superiority, randomised clinical and cost-effectiveness trial with internal pilot, conducted across three centres in Australia and France. Patients (adults and children aged ≥6 years) requiring one PIVC for ≥48 hours are eligible. We will exclude patients with emergent PIVCs, known CHG allergy, skin injury at site of insertion or previous trial enrolment. Patients will be randomised to 3M Tegaderm Antimicrobial IV Advanced Securement dressing or standard care group. For the internal pilot, 300 patients will be enrolled to test protocol feasibility (eligibility, recruitment, retention, protocol fidelity, missing data and satisfaction of participants and staff), primary endpoint for internal pilot, assessed by independent data safety monitoring committee. Clinical outcomes will not be reviewed. Following feasibility assessment, the remaining 2624 (1312 per trial arm) patients will be enrolled following the same methods. The primary endpoint is a composite of catheter-related infectious complications and phlebitis. Recruitment began on 3 May 2023.

Ethics and dissemination The protocol was approved by Ouest I ethic committee in France and by The Queensland Children's Hospital Human Research Ethics Committee in Australia. The findings will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration number NCT05741866.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This large international multi-centre clinical trial is the first to rigorously evaluate the effectiveness of chlorhexidine-impregnated dressings in securing peripheral intravenous catheters, the most widely used invasive medical device in hospitals.
- ⇒ Adults and children from three Australian and French hospitals will be recruited, and routine catheter care will not be impacted by the research, apart from the type of dressing used to secure the catheter. The results of the research will thus be generalisable to all patients requiring a peripheral intravenous catheter.
- ⇒ Research physicians and nurses will visit enrolled patients daily to collect relevant data, check protocol compliance, assess adverse events related to the research and answer questions from clinical staff, patients and caregivers.
- ⇒ The impact of the lack of masking due to the nature of the intervention will be limited by assessing the primary outcome by research staff using pre-defined and robust criteria. The statistician and microbiologists will be blinded for analysis.

INTRODUCTION

Peripheral intravenous catheters (PIVCs) are the most used vascular access device in healthcare, with most hospitalised patients receiving at least one during hospital admission.¹ PIVC insertion breaches the skin protective barrier, placing patients at risk of local and systemic infections.^{2–3} Traditionally, a transparent dressing alone has been considered adequate to safely secure a PIVC, with no consideration given to potential risk of local and systemic complications.⁴ PIVCs have the lowest incidence rate of infection of all vascular access

devices (0.1%, 0.5 per 1000 catheter-days)² and, for this reason, are often overlooked when targeting interventions to reduce hospital-acquired infections. However, with nearly two billion purchased globally each year,⁵ there is significant patient morbidity and economic cost associated with PIVC-related infection. Further, a large number of patients develop phlebitis, including early signs of reddened, painful insertion sites and later signs of purulence and cellulitis, which may then lead to bloodstream infections (BSI).⁶⁻⁸

Antiseptics, such as chlorhexidine gluconate (CHG), impregnated into dressing products are used extensively to reduce microbial colonisation at the insertion site of central venous and arterial catheters.^{9 10} Clinical trials have shown that CHG-impregnated dressings lower the incidence of exit-site/tunnel infection in neutropenic patients,¹¹ and BSIs in the haematology/oncology and intensive care populations.^{9 10 12} However, CHG dressings are yet to be rigorously tested as an intervention to prevent PIVC-related infection, and traditional products are cost-prohibitive for use in the large cohort of patients with PIVCs. This infection is commonly caused by resident skin flora and results in inflammation of the skin (dermatitis), subcutaneous tissue (cellulitis) or vein (phlebitis).^{13 14}

A new dressing for PIVCs consists of a transparent semi-permeable film window, with 2% CHG formulated into the dressing adhesive providing a more cost-effective option to antimicrobial dressings designed for central venous catheters. In-house testing by the manufacturer reported that on skin decontamination with 70% isopropyl alcohol or 2% CHG in 70% isopropyl alcohol dressing suppressed skin flora regrowth for up to 7 days, compared with non-antimicrobial dressings (3M data). As skin flora is the most common source of PIVC-related infection,¹⁵ a dressing that suppresses microbial growth might be beneficial as an infection prevention strategy.

To provide evidence to inform clinical practice, we will test the effectiveness of a PIVC antimicrobial dressing compared with standard dressings in patients (adults and children) requiring a PIVC, using a two-phase randomised controlled trial (RCT). In the first phase, we will test the feasibility to conduct a definitive RCT based on reaching seven criteria. In the second phase of the trial, we will test the hypotheses that the new dressing, in comparison with the standard one, is more effective and safe in protecting against PIVC-related infectious complications and phlebitis; is more cost-effective in preventing PIVC-related infectious complications and phlebitis; and is preferred by patients and caregivers.

METHODS AND ANALYSIS

Trial design and setting

The ProP trial is an international multicentre, two-arm, parallel-group RCT conducted in two centres in Australia (Royal Brisbane and Women's Hospital (RBWH), medical and surgical wards and Queensland Children's Hospital

(QCH) in Brisbane) and in one centre in France (Poitiers University Hospital (PUH) in Poitiers).

The trial will be conducted in two phases (internal pilot), with defined criteria for the progression to the second phase. First, 300 participants will be enrolled to test protocol feasibility and clinical safety profile. No statistical analysis on efficacy is planned for Phase 1, instead an independent Data Safety Monitoring Committee (DSMB) will assess the safety of pursuing the trial. Inclusions began for Phase 1 on 3 May 2023. Phase 2 (continue to 2624 patients in total) will begin if feasibility and adverse events are acceptable to DSMB and investigators, hospital sites have the capacity to continue participating and funding is available. The core protocol will remain unchanged from Phase 1. If this scenario is not achieved, then assessed clinical outcomes will be analysed and reported at the end of Phase 1.

Participant eligibility and consent

Patients will be enrolled in general medical/surgical departments (RBWH), predominantly surgical departments (QCH), and both emergency and medical departments at PUH in France. Patients predicted to require a PIVC for 48 hours or longer will be screened for eligibility. Patients meeting all eligibility criteria will be invited to participate. Eligible patients will receive a participant information and consent form for their review and signature and will be enrolled only once written consent has been obtained. Substitute decision makers (typically parents or legal guardian in children) will be approached for adults unable to give their own consent and for children (<18 years).

Inclusion criteria

- ▶ Patients predicted to require a PIVC for 48 hours or longer (based on prescribed therapy or planned medical care)
- ▶ Written informed consent
- ▶ Age 6 years (due to dressing size) or older in Australia, and 18 years or older in France

Exclusion criteria

- ▶ Catheter placement under emergency conditions, not allowing for compliance with recommended hygiene rules for catheter insertion
- ▶ Burned, non-intact or scarred skin at the catheter insertion site
- ▶ Known allergy to CHG or transparent dressing adhesives
- ▶ Palliative care patients on end-of-life pathway
- ▶ Previous participation in the trial (only one catheter per patient)

Additional exclusion criteria for Australian participants

- ▶ Non-English-speaking patients without interpreter
- ▶ Under the care of Child and Family Services and unable to gain consent from case worker (paediatric patients) (Australian legislation).

Additional exclusion criteria for French participants

- ▶ Predictably difficult vascular access (IV drug addiction, obesity)
- ▶ Known pregnant or breastfeeding women (French legislation)
- ▶ Patients not benefiting from the French Social Security scheme or not benefiting from it through a third party (French legislation)
- ▶ Persons benefiting from enhanced protection, namely, minors, persons deprived of their liberty by a judicial or administrative decision and adults under legal protection (French legislation)

Sample size calculation

In Phase 1, an internal pilot, we will recruit 300 patients (200 in Australia and 100 in France) with 150 patients per arm. This sample size is not determined by statistical power but to test protocol feasibility.^{16 17}

In Phase 2, we will continue recruitment to a sample of 2624 participants in total (1312 per group, 875 per centre), which would have 90% power to detect a predicted absolute 5% reduction in the primary outcome from 22% to 17% (two-sided alpha 0.05). Sample size calculation was based on rates observed in previous trials of PIVC interventions at the study sites and undertaken using an on-line calculator (<http://powerandsamplesize.com/calculators>). We do not expect hospital site differences in the effect of the intervention.

Interventions, randomisation and allocation concealment

Patients will be randomised 1:1 to Tegaderm Antimicrobial IV Advanced Securement dressing (3M, Minneapolis) or standard care non-antimicrobial dressings using a central, web-based randomisation service, with allocation concealment until study entry. We will use stratified block randomisation with hospital as stratifying factor and randomly permuted block sizes of 4 and 6 to achieve reasonable balance across treatments and to ensure concealment of the allocation sequence. Besides the type of dressing used to secure the PIVCs, which will depend on the randomisation arm to which the patient belongs, placement, maintenance and removal of PIVCs will follow standard practices at the participating sites. Before study commencement, all caregivers will be trained on dressing (both intervention and control) application, follow-up and removal.

In the control group, PIVCs will be dressed and secured as follows:

- ▶ At RBWH and PUH, with bordered polyurethane dressing (Tegaderm IV Advanced 1683, 3M, St Paul) and non-sterile tape strip over extension tubing.
- ▶ At QCH, with bordered polyurethane dressing (Tegaderm IV Advanced 1682 and 1683 and 3M, St Paul) and secured with tubular bandage+/- arm board and non-sterile stretchy tape if PIVC over flexible joint, ±tissue adhesive (SecurePort IV) as per clinician preference.

In the intervention group, PIVCs will be dressed and secured as follow:

- ▶ At RBWH and PUH, with Tegaderm Antimicrobial IV Advanced Securement (9132) dressing and secured with non-sterile tape over extension tubing.
- ▶ At QCH, with Tegaderm Antimicrobial IV Advanced Securement (9132) dressing and secured with tubular bandage+/- arm board and non-sterile stretchy tape if PVAD over flexible joint, ±tissue adhesive (SecurePort IV) as per clinician preference.

All PIVCs will be inserted by experienced caregivers with or without ultrasound guidance, adhering to local policy, specifically the insertion procedure bundle (including hand hygiene, ANTT approach, site disinfection with 2% CHG in 70% alcohol). The type of PIVC will be:

- ▶ At QCH: BD Nexiva (long or short), with needleless connector (Nanoclave, ICU Medical, San Clemente)
- ▶ At RBWH: BD Insyte Autoguard BC non-winged (long or short) or Introcan Safety (B Braun) with needleless connector, MicroClave Clear (ICU Medical, San Clemente)
- ▶ At PUH: BD Insyte Autoguard BC Winged (long or short) without needleless connector. All catheters are connected to an infusion line with a three-way stopcock

Intravenous treatment will be administered through a three-way stopcock (BD) and/or needleless connector, after disinfecting the connector hub with a sterile gauze soaked with 70% alcohol-based antiseptic (Australia—70% isopropyl alcohol (RBWH) or 2% CHG in 70% alcohol (QCH) prepared wipes, both Reynard Health (Artarmon); France 70% ethanol on gauze prepared by nurse). PIVC and needleless connector choice will be dictated by each hospital's individual stock availability with product variances recorded.

All ongoing PIVC maintenance and care will be by clinical staff, not study investigators and in accordance with international and local policy.^{18 19} IVCs will be reviewed by clinical staff for complications at least once each nursing shift. This is a pragmatic trial, and subsequently, there will be patient and clinician-directed variation in care that is consistent with the spectrum of the usual clinical practice. Subsequent dressings (both intervention and control) will be replaced with the allocated product by treating clinical staff if soiled, loose or moist (or otherwise indicated/deemed appropriate by clinical staff), as per hospital policy, and will be recorded. We will record any additional products used by clinicians, for example, tissue adhesive, additional tapes or bandages. Removal of the PIVC will be at the discretion of the treating team using usual hospital criteria, namely, PIVC complication necessitating removal and/or completion of therapy.

The Research Nurse (ReN; Australia) or medical investigators (France) will visit patients daily (7 days a week, France; 5 days a week, Australia) to reinforce the clinical investigation protocol with patients and nurses. In Australia, recruitment is weighted to Monday–Wednesday so that most PIVCs have daily follow-up by ReNs until

PIVC removal (average dwell is <3 days). Patients will be visited or contacted by phone if discharged to check for complications that occurred up to 48 hours post removal. Blood cultures will be ordered by the treating clinical teams as per the usual routine care if PIVC infection is suspected. The research teams will not be involved in this decision.

In Australia, PIVC insertion site swabs are collected using a sterile dry swab, circled around the PIVC insertion site with a twisting motion for 5 s and transported in a Amies Agar Gel for testing.

In both countries, skin site samples are cultured for 48 hours in the hospital or university pathology laboratories. Colonisation will be reported semi-quantitatively as scant, 1+, 2+3+. Organism identification will be performed using the VitekMS instrument. A positive culture is any growth of a pathogen.

In all centres, PIVC tips will be sent for culture at removal. Specimens will be processed in hospital or university laboratories. A positive tip culture will be defined as ≥ 15 colony-forming units (CFU, roll plate method) or ≥ 1000 cfu per mL (quantitative broth dilution culture technique) of a pathogen.⁶ Identification will be via MALDI-ToF (bioMérieux, Marcy-l'Étoile, France). Positive PIVC tip specimens from the research laboratory will not be used to directly inform clinical care as they will not be undertaken in a NATA-accredited laboratory using standard methods. However, any positive specimens will be discussed as soon as possible with a local infectious disease physician and if the results are deemed to be potentially of interest to the clinical team they will be notified.

Each participant will remain in the study until 48 hours after catheter removal or he/she decides to stop participating in the study. The clinical investigation may be prematurely suspended in the event of unexpected adverse events necessitating review of safety profile. On the same token, in the event of unexpected developments or new information pertaining to the device and showing that the objectives of phase 1 of the clinical investigation are not to be reached, the sponsor will be to prematurely suspend the clinical investigation.

Study outcomes

Phase 1

For phase 1, the feasibility of conducting a definitive RCT will be assessed against the following criteria^{20 21}:

1. Eligibility ($\geq 80\%$ of screened participants will be eligible)
2. Recruitment ($\geq 80\%$ of eligible participants will provide informed consent)
3. Retention (<10% of participants will be lost to follow-up)
4. Protocol fidelity ($\geq 80\%$ of participants will receive the allocated intervention)
5. Missing data (<5% of outcome data will be unable to be collected)

6. Satisfaction (<10% of participants and staff report 'low' satisfaction with the intervention arm (rated low/medium/high with respective prompts of 'I'd rather use a different dressing next time'/'The dressing was ok, but I'm happy to try other types'/'It was a really good dressing and I'd like to use this one again')

The phase 2 progression will be dependent on available funding.

Phase 2

For phase 2, the primary endpoint will be a composite of catheter-related infectious complications²² and phlebitis, identified as priorities by both consumers and clinicians.^{23 24} We chose to include phlebitis in this endpoint, as phlebitis can be bacterial and indicate early infections that do not progress to clinically diagnosed infection due to the PIVC being removed in response to phlebitis.⁶⁻⁸ The primary endpoint includes at least one of the following items:

1. PIVC tip colonisation (≥ 15 CFU of a pathogen using the roll plate semi-quantitative method or ≥ 1000 CFU of a pathogen per mL using the quantitative broth dilution culture technique^{6 25})
2. PIVC local infection (NHSN 2021 criteria for Cardiovascular System VASC-Arterial or Venous Infection (CVS-VASC)²⁶; adult criteria that is, at least one of the following:
 - a. Patient has organism(s) from extracted arteries or veins identified by a culture or non-culture-based microbiology testing method, which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing (ASC/AST)
 - b. Patient has evidence of arterial or venous infection on gross anatomic or histopathologic exam
 - c. Patient has at least one of the following signs or symptoms: fever ($>38.0^\circ\text{C}$), pain*, erythema* or heat at involved vascular site* AND more than 15 colonies cultured from intravascular cannula tip using semi-quantitative culture method
 - d. Patient has purulent drainage at involved vascular site

*With no other recognised cause
3. PIVC-associated BSI (Laboratory Confirmed Bloodstream Infection that is not secondary to an infection at another body site (NHSN 2021 adult criteria²⁶), that is, meets one of the following criteria:
 - a. Patient of any age has a recognised bacterial or fungal pathogen, not included on the NHSN common commensal list:
 - i. Identified from one or more blood specimens obtained by a culture OR
 - ii. Identified to the genus or species level by non-culture-based microbiologic testing (NCT)* methods (eg, T2 magnetic resonance (T2MR) or Karius test)

AND

- iii. Organism(s) identified in blood is not related to an infection at another site
 - b. For patient of any age with at least one of the following signs or symptoms: fever ($>38.0^{\circ}\text{C}$), chills or hypotension
 - AND
 - i. Organism(s) identified in the blood is not related to an infection at another site
 - AND
 - ii. The same NHSN common commensal is identified by a culture from two or more blood specimens collected on separate occasions (see Blood Specimen Collection). Common commensal organisms include, but are not limited to, diphtheroids (*Corynebacterium* spp. not *C. diphtheria*), *Bacillus* spp. (not *B. anthracis*), *Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis*), viridans group streptococci, *Aerococcus* spp. *Micrococcus* spp. and *Rhodococcus* spp. For a full list of common commensals, see the NHSN Organisms List²⁷ or
 4. Phlebitis (one or more of pain/tenderness (>1 out on a 0 to 10 VAS scale)) in adults or children ≥ 10 years, or at least 2 of erythema, swelling, purulence or a palpable cord (in all patients).²⁰ More than 70 phlebitis definitions and scales exist, but most have poor or unknown validity and reliability.²⁸ We focus on predominantly pain and tenderness as these have the strongest inter-rater agreement.²⁹ The primary endpoint will be treated as a binomial (yes/no) variable based on the presence of any of the above-mentioned criteria or absence of all. We will assess the usefulness of this primary endpoint (infectious outcomes and phlebitis) by separating its components as secondary endpoints.
- Secondary endpoints**
1. Efficacy
 - a. PIVC colonisation (as defined above)
 - b. PIVC local infection without BSI (CVS-VASC) (as defined above)
 - c. PIVC-associated BSI (as defined above)
 - d. Phlebitis (as defined above)
 - e. PIVC device failure: a composite of infiltration/extravasation, blockage/occlusion (with/without leakage), phlebitis (as defined above), thrombosis, dislodgement (complete/partial) or infection (as defined above)
 - f. Dressing durability assessed as (i) the dressing remains adhered to the skin on all four sides until PIVC removal and (ii) accidental dislodgement (excluding patients who deliberately remove their PIVC)
 - g. Skin colonisation (reported semi-quantitatively as scant, 1+, 2+3+)
 2. Safety
 - a. Skin adverse events at the PIVC site (mechanical, eg, pressure injury, skin tears, blisters, bruising, or inflammatory complications, such as contact/allergic dermatitis, skin rash and pruritus)
 - b. Serious adverse events limited to anaphylactic reaction to chlorhexidine in dressing or death related to PIVC infection
 3. Cost-effectiveness

Direct and indirect healthcare costs to the health system, including cost per complication avoided. This will include:

 - The average costs of catheter insertion, catheter replacement and catheter removal
 - The average cost of dressing change
 - The average cost of each day of using the venous line (excluding the cost of treatments administered)
 - The average treatment cost of complications, estimated from the cost of necessary material and nursing time and including any additional hospital length of stay attributable to complications

Resources and unit costs will be estimated from the average cost of necessary material and nursing time for each study group by the UHP physicians.
 4. Stakeholder feedback

Patient reported overall satisfaction of the dressing rated low/medium/high with respective prompts of 'I'd rather use a different dressing next time'/'The dressing was ok, but I'm happy to try other types'/'It was a really good dressing and I'd like to use this one again' Clinicians reported overall satisfaction at the time of insertion and removal of the dressing rated low/medium/high with respective prompts of 'I'd rather use a different dressing next time'/'The dressing was ok, but I'm happy to try other types'/'It was a really good dressing and I'd like to use this one again'.
- Data collection**
- Data will be collected by Research Nurses (ReNs) or medical officers using handheld devices and a purpose-built database (REDCap Research Electronic Data CAPture). Data sources will be the patients' medical records, direct observation of the PIVC site, the patient or parent/carer and clinical staff caring for the patient. Deidentified data will be entered using a unique Study ID, only re-identifiable by a securely held screening log. To ensure data security, REDCap databases will only be accessible by ReNs and principal investigators. The following data will be recorded.
- Characteristics of patients at baseline**
- Patients' demographics (eg, age, gender, weight) and clinical factors (eg, admission diagnosis, co-morbidities, diaphoresis, immunocompromised status, current infection/s, antibiotic use during the last 15 days) were collected.
- Characteristics of catheters**
- The insertion site, insertion department, inserter discipline, technology assisted insertion, number of insertion attempts, size/gauge, length, side, current intravenous

therapy through device, hair clipping and current IV therapy through device.

Characteristics of dressing

The type of dressing used (allocated or not), tissue adhesive used, additional tapes or bandages and staff satisfaction.

Daily parameters

The presence and condition of allocated dressing, site and skin complication at the PIVC site, quality of the dressing, dressing change, IV drug or oral administration, blood culture and adverse and serious adverse events.

Catheter removal

Date, time and reason for removal, insertion site assessment, drug or oral administration and adverse and serious adverse events. Patients reported overall satisfaction of the dressing. Staff reported satisfaction of the removal dressing.

Parameters collected two days after catheter removal

Microbiology results of blood cultures, PIVC tips and catheter insertion site cultures and any other positive microbiology sampling, the treatment given for local or bloodstream infection, or phlebitis, skin complication at PIVC site (mechanical or inflammatory complications) will be collected by the ReN if the patient was already hospitalised or by phone if he/she discharged from hospital.

Safety

Adverse events will be recorded and any serious adverse events (defined as anaphylactic reaction to chlorhexidine or deaths related to PIVC infection) will be reported to the human research ethics committee in Australia and to the French National Agency for Medicines and Health Products Safety in France, within the mandatory reporting timeframe. Only a small number of patients will develop adverse events in both groups potentially related to the dressing, mostly minor, as currently occurs in standard practice (eg, skin tear generally requires no further treatment other than a dry dressing for a day or two). It is very unlikely that patients will experience serious adverse events related to the study products, as the concentration of chlorhexidine into the dressing is very low. We will also report non-serious adverse events (eg, mild skin irritation).

Statistical analysis

Statistical analyses will be performed in Australia after merging the two REDCap databases.

Phase 1

After the initial 300 patients, proportions of eligibility, recruitment, retention, protocol fidelity, missing data and satisfaction will be calculated and compared with the pre-study determined feasibility targets. Adverse events will also be tallied. Clinical outcomes will not be reviewed

unless the trial is stopped after this phase. An independent DSMB comprised of two clinician trialists from the specialty groups and a biostatistician will review feasibility and adverse event data and recommend whether continuing to the full trial of 2624 patients is feasible. If the trial ceases after phase 1, then relative effects between groups will be analysed for clinical outcomes and reported.

Phase 2

The CONSORT statement will be used to report trial results. All randomised patients will be primarily analysed by the intention to treat, regardless of dressing received, except those who withdrew their consent to participate. Patients wrongly included or lost to follow-up will be described. Protocol deviations will be described and excluded from a per-protocol analysis. Continuous data will be summarised as mean (SD) or median (IQR), depending on normality testing by Shapiro–Wilk's test. Categorical data will be reported as count and percentage.

The effect of intervention on the primary clinical outcome (PIVC-related infectious complications and phlebitis) will be analysed using mixed effects logistic regression with centre as a random effect and intervention as a fixed effect and will be reported using ORs with 95% CIs. We will undertake additional multiple regression with potential covariables shortlisted including the hospital site, risk factors from prior studies including gender,^{30–32} catheter gauge,^{30 32} cancer diagnosis,^{33 34} infection at baseline, insertion site and insertion in another department.³⁰ Correlations between covariables will be tested and considered during the multivariable model building. Assumptions of mixed effect logistic regression will be tested for our final model. For secondary outcomes, Mixed Effects Cox Proportional-Hazards regression will be conducted with centres as random effects and significant patient, device and clinical variables as fixed effects. The proportional-hazards assumption will be checked and the 'goodness of fit' checked using Cox–Snell residuals. Incidence rates of the primary outcome per 1000 PIVC-hours and their ratios between groups will be calculated. Kaplan–Meier survival curves and log-rank tests will be used to compare group failure over dwell time.

Continuous secondary clinical outcomes will be compared between study groups using T-test or Mann–Whitney U test depending on the normality of data. Categorical outcomes will be compared between study groups using X^2 test or Fisher's exact test if the assumptions of X^2 test not met.

Microorganisms identified will be reported by species and counts. Cost-effectiveness analysis will be conducted from the perspective of the healthcare system for each country. The cost calculations include direct and indirect costs at the patient level. The incremental cost-effectiveness ratio (ICER) will be depicted on a scatter plot and the differences in costs between study groups divided by the difference in outcome between study groups. P values of <0.05 will be considered significant.

Missing data will be described, but no imputation will be performed. Statistical analyses will be performed using Stata (StataCorp, LP College Station, Texas) and R Studio (R Studio Team, Boston).

The safety analysis will be done on participants who are exposed to at least one dressing. The proportion of adverse events according to their causality, severity and intensity will be presented by arm and compared with X^2 test or Fisher's exact test as appropriate. The proportion of adverse events leading to the change of dressing type will be compared between arms. Adverse events will be described according to the different hierarchical levels of the MedDRA classification (latest version at the time of freezing the database). The results of the safety analysis will be presented according to Consort Harms recommendations.

A detailed analysis plan will be defined by the study statistician in conjunction with the principal investigator and made available prior to the analysis.

Cost-effectiveness analysis

The primary outcome of the economic evaluation will be the incremental cost per incremental complication avoided from a health system perspective (ICER). A decision analytic model will be used to estimate the ICER with results presented on an incremental cost-effectiveness plane. Uncertainty will be explored using one way and probabilistic sensitivity analyses. Probabilistic sensitivity analysis will be conducted using Monte Carlo simulation methods of at least 1000 draws with each input into the model sampled from their respective distribution and provide a 95% credible interval surrounding the mean estimate. Analyses will be undertaken separately for each country reflecting different healthcare settings and using country-specific resource unit prices. As no a priori threshold value for a complication avoided is available, a cost-effectiveness acceptability curve will be presented over a range of threshold values. Exploratory cost-utility analyses will be undertaken to estimate the incremental cost per incremental quality adjusted life year gained where estimates of disutility associated with infection will be sourced from the literature.

Patient and public involvement

The research question and study protocol were informed by our previously reported consumer experience work.^{23 35} The results of the study will be disseminated to study participants who provide an email on the consent document in the form of a short summary of study findings.

DISCUSSION

We will conduct the first randomised, large-scale study evaluating the value of a chlorhexidine-impregnated dressing to secure IPCs. The study will be done in two Australian centres and one French centre. Both adults and children will be included. The number of exclusion

criteria is low and meets regulatory requirements. The usual care of participants will be respected apart from the choice of dressing. We believe these elements will facilitate the generalisation of our findings. The choice of a two-phase study design is to ensure feasibility and safety before conducting the full study, limiting the number of participants needlessly exposed in case of failure. A research team will prospectively monitor patients to ensure compliance with the protocol, collect data for the study and answer any questions from participants or caregivers, improving the quality of research.

ETHICS AND DISSEMINATION

Research ethics approval

In Australia, we sought approval of the Queensland Children Hospital Human Research Ethics Committee for each participating site in accordance with Australian regulations. In France, the Ouest I Ethics Committee, the French National Agency for Medicines and Health Products Safety and National Commission for Information Technology and Civil Liberties approved in accordance with French regulations. The trial is registered in ClinTrials.gov. The intervention product is currently registered with the Foods and Drug Administration, and a clinical trial notification was submitted to the Australian TGA.

Protocol amendments

Any substantial change, that is, any change that is likely to have a significant impact on the protection of persons, on the conditions of validity and on the results of the research, on the quality and safety of the products tested and on the interpretation of scientific documents that support the conduct of the research or the way in which the research is conducted, is subject to a written amendment submitted to the sponsor. The latter must obtain, prior to its implementation, a favourable opinion from the ethic committee of both countries.

Non-substantial changes, that is, those that do not have a significant impact on any aspect of the research, are communicated to the ethic committees for information.

All changes are validated by the sponsor and by all research stakeholders involved in the change, before submission to the ethic committees. This validation may require the meeting of all committees formed for the research.

All changes to the protocol must be made known to investigators, who are participating in the research. The investigators undertake to respect the content.

Any modification that changes participant care or the benefits, risks and constraints of the research is the subject of a new information note and a new consent form whose collection follows the same procedure above.

Consent

Written informed consent of participants will be sought prior to enrolment. The investigators will provide clear

oral and written information to the patient about the protocol and its risks. The patient will be given time to consider their participation in the research before written informed consent is obtained (information and consent form is provided in online supplemental appendices 1 and 2).

Confidentiality

People with direct access to the study data will take all appropriate precautions to preserve confidentiality. All data collected during the study will be anonymised. Only patients' initials and inclusion numbers will be recorded in the REDCap databases.

Dissemination policy

We will report the outcome of the ProP trial in accordance with the CONSORT reporting guidelines. Findings will be published in an open-access peer-reviewed infectious disease or infection control journal. We will also submit abstracts to disseminate the study results at relevant conferences such as the Association of Vascular Access, the Infection Prevention Society conference and French and Australian congresses. In addition, we will promote the study findings through social media accounts and professional networks.

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Contributors CMR, AU, AC, NMM, TK, JB, DB, COB and OM conceived the study and coordinated its design. CMR, AU, NMM, AC and DB wrote the Australian funding application. OM wrote the French funding application. BD wrote the first draft of the manuscript. CMR, BD, AC, AU, NMM, DB, COB, TK, JG, RC, KLMC, SS, GB, JB, JS, SFZ and OM undertook critical appraisal and revision of the manuscript. JB and SFZ provided health economics and statistical expertise, respectively. All authors approved the final manuscript prior to submission. CMR is the guarantor.

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Disclaimer The University of Queensland.

Competing interests CMR's employer (The University of Queensland or Griffith University) has received unrestricted research grants on her behalf from BD, Cardinal Health, Eloquest and consultancy payments from 3M, BD, BBraun, and ITL Biomedical. AU's employer (The University of Queensland or Griffith University) has received unrestricted research grants or consultancies on her behalf from BD, 3M, Sterile Care and Medline. NMM—Griffith University and The University of Queensland have received on her behalf investigator-initiated research grants or consultancies from Cardinal Health, 3M, Eloquest, Medline and Becton Dickinson. AC has received unrestricted investigator-initiated research grants, paid to her employer (Griffith University), from Cardinal Health, 3 M and Eloquest. TMK's employer (The University of Queensland or Griffith University) has received unrestricted research grants on her behalf from BD, and consultancy payments from 3M, BD, BBraun, Medical Specialties Australia, and Smiths Medical. OM, BD and JG received funding for congress attendance, and research funding from Becton Dickinson and 3M. JB's employer (Griffith University) has received unrestricted research grants on his behalf from BD and Navi Technologies, and consultancy payments from 3M, and BD. COB has no conflicts of interest.

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