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Central venous Access device SeCurement And Dressing Effectiveness (CASCADE) in paediatrics: protocols for pilot randomised controlled trials

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Title: Central venous Access device SeCurement And Dressing Effectiveness (CASCADE) in paediatrics: protocol for pilot randomised controlled trials

Short title: CASCADE Junior protocol

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Abstract:

Introduction: Paediatric central venous access devices (CVAD) are associated with a 25% incidence of failure. Securement and dressing are strategies used to reduce failure and complication, however innovative technologies have not been evaluated for their effectiveness across device types. The primary aim of this research is to evaluate the feasibility of launching a full-scale randomised controlled efficacy trial across three CVAD types regarding CVAD securement and dressing, using pre-defined feasibility criteria.

Methods and analysis: Three feasibility randomised, controlled trials are to be undertaken at the Royal Children's Hospital and the Lady Cilento Children's Hospital, Brisbane, Australia. CVAD securement and dressing interventions under examination compare current practice with sutureless securement devices, integrated securement-dressings and tissue adhesive. In total, 345 paediatric patients requiring a peripherally inserted central catheter (n=100); non-tunnelled CVAD (n=180) and tunnelled CVAD (n=65) to be inserted will be recruited and randomly allocated to CVAD securement and dressing products. Primary outcomes will be study feasibility measured by eligibility, recruitment, retention, attrition, missing data, parent / staff satisfaction and effect size. CVAD failure and complication (catheter-associated bloodstream infection, local infection, venous thrombosis, occlusion, dislodgement and breakage) will be compared between groups.

Ethics and dissemination: Ethical approval to conduct the research has been obtained. All dissemination will be undertaken using the CONSORT Statement recommendations. Additionally, the results will be sent to the relevant organisations which lead CVAD focussed clinical practice guidelines development.

Trial registration number: Australian and New Zealand Clinical Trial Registration: peripherally inserted central catheter ACTRN12614001327673; non-tunnelled CVAD ACTRN12615000977572; tunnelled CVAD ACTRN12614000280606.

STRENGTHS AND LIMITATIONS:

- Pilot randomized controlled design to enhance reliability of results using predetermined primary outcomes of feasibility.
- Securement and dressing products being trialled are not amenable to blinding of patients, family members, clinical staff or research staff. Radiological and laboratory staff assessing outcomes will be blinded.

INTRODUCTION

Central venous access devices (CVADs) are used for monitoring and medication in critically and chronically unwell patients in a variety of inpatient and outpatient settings. [1 2] More than five million CVADs are used in the USA per year alone.[3] Conventionally, non-tunnelled CVADs (nt-CVADs) have been advocated for use when central venous access is required for a short time, [4-6] peripherally inserted central catheters (PICCs) for short to medium time, [4 6] and tunnelled CVADs (t-CVAD) and totally implantable devices for longer time periods. [6 7]

Children requiring CVADs to facilitate treatment are extremely vulnerable to the risk of adverse events associated with insertion and management. [8 9] Twenty five percent of paediatric CVADs fail prior to treatment being complete. [10] This includes CVADs becoming partially or wholly dislodged, occlusions, venous thrombosis, fractured catheters, site erosion, severe pain, or a bloodstream infection. The consequences of failure include the morbidity and mortality associated with the cause of the complication (e.g., catheter associated bloodstream infection (CABSI); with an attributable mortality as high as 35%),[11 12] interruption of medical treatment and the insertion of replacement CVADs, involving the additional risk of procedural complications. Many CVAD complications are preventable with the consistent use of evidence-based CVAD insertion and maintenance practices.[6 13 14]

An essential component to prevent post-insertion CVAD complications is the securement and dressing product chosen. To prevent complications, CVADs require: (1) insertion site protection from

microbial contamination from the surrounding skin and environment; (2) the external portion to be secured to prevent venous dislodgement; and (3) securement to prevent micro-motion within the vein and at the insertion site.[15] Micro-motion is believed to irritate the vein wall, causing inflammation, thrombosis, occlusion, vessel erosion, and encourages skin bacteria to enter the insertion wound. [15-17] Since the 1980s, pervasive practice has been to suture CVADs for securement, with adhesive, polyurethane dressings placed over the sutured site (see Figure 1a).[18] Transparent polyurethane dressings are claimed to be impermeable to microorganisms but semi-permeable to oxygen, carbon dioxide and water vapour. [11 15 18]

<insert Figure 1>

Recent evidence supports the introduction of chlorhexidine gluconate-impregnated (CGI) CVAD dressing products within critical care, as a strategy to reduce the incidence of site colonisation and CABSI in non-tunnelled devices. The recent Cochrane systematic review by Ullman and colleagues[18] , found moderate quality evidence that CGI dressings reduced the frequency of catheter-related BSI per 1, 000 patient days compared with conventional polyurethane dressings (relative risk (RR) 0.51, 95% confidence interval (CI) 0.33 to 0.78; P=0.002). The prevalence of catheter tip colonisation was also significantly reduced (RR=0.58; 95% CI 0.47-0.73; P<0.001). The transferability of these results outside of the critical care population has yet to be established, considering the different CVAD dwell times, insertion technique and clinician groups caring for CVADs in the various healthcare settings.[15 18]

Alternative securement and dressing options have become available that may be superior to suturing and polyurethane dressings for preventing complications, but these have not yet been adequately tested for efficacy, acceptability or cost-effectiveness. [15] Sutureless securement devices (SSD) have large adhesive padded footplates with CVAD-locking clasps of plastic or Velcro (see Figure 1b). They aim to reduce movement, kinking and flow impedance [16] and are used with polyurethane dressings. A manufacturer-sponsored randomised controlled trial (RCT) in PICCs (*n*=170) found significantly reduced CABSI with SSD (9.4% suture vs 1.2% SSD; P=0.04), and non-significant

reduction in unplanned removal (36% suture vs 24% SSD). [19] An independent RCT in dialysis devices (*n*=72), found reduced haematoma, thromboses and dislodgement (13.9% suture vs 8.3% SSD; P=NS). [20] Neither of these studies included the paediatric population.

Integrated Securement-Dressing (ISD) are 'next generation' polyurethane dressings with a tough fabric adhesive border around the central polyurethane with continued adhesive over and underneath the CVAD body (Figure 1c).[15] ISDs claim to eliminate the need for a separate securement device (e.g. sutures), and a reduction in costs and procedural complexity. They also include an absorbent layer around the polyurethane, which is claimed to move moisture away from the wound. This may be useful for newly inserted CVADs, which commonly ooze and require more frequent replacement which increases CABSI risk. [21] A recent adult cohort study [22] (n=327 ISD; n=94 historical suture controls) reported ISD to be associated with significantly delayed onset of occlusion (from 8 to 25 days; P<0.01) in comparison to sutures.

Tissue Adhesive (TA) is medical grade 'superglue' (cyanoacrylate) used as an alternative to sutures in both internal and external wounds. [23] (Figure 1d) Case reports in adults suggest TA reduces CVAD dislodgement from 12% to 4%, with no skin reactions or mechanical complications. [24 25] TA is bactericidal and inhibits growth of all Gram-positive organisms (predominant in CABSI), including methicillin resistant *Staphylococcus aureus* (MRSA). [24] TA forms an occlusive healing environment and a physical barrier to micro-organisms, with haemostatic properties to reduce ooze and haematomas.[24] When used with a polyurethane dressing, TA remains for four to seven days, sloughs off slowly, and can be reapplied or removed easily with commercial wipes or petroleum jelly. [26] TA may hold the key to avoiding sutures and CVAD complications by reducing pistoning, accidental removal, infection and bleeding.

These new technologies potentially reduce complications associated with the use of CVADs in the paediatric population. There are currently no strong data supporting their relative effectiveness and safety across the diverse range of CVADs and patients in paediatric clinical practice. Randomised, experimental, efficacy trials, with measures to prevent bias, are necessary to provide true estimates of

relative effectiveness and inform practice.[27] The United Kingdom's Medical Research Council's *Developing and evaluating complex interventions* framework [27] highlights the importance of piloting prior to undertaking large efficacy trials, to prevent problems of acceptability, compliance, intervention implementation, recruitment and retention, and underpowered studies, [27] Pilot studies should examine the key uncertainties that have been identified during research development. This involves testing of intervention and data collection procedures, estimating recruitment and retention numbers, and determining effect estimates for future sample size calculations.

<insert Figure 2>

The primary aim of this research is to evaluate the feasibility of launching a full-scale randomised controlled efficacy trial of PICC, nt-CVAD and t-CVAD securement and dressing, using pre-defined feasibility criteria for recruitment, retention, protocol fidelity and product acceptability. The secondary aim is to compare the effectiveness of dressings and securement products on CVAD complications and failure due to infection, occlusion, dislodgement, thrombosis, or breakage, for children in acute care facilities.

METHODS AND ANALYSIS

Design

Three separate pilot RCTs involving PICC, nt-CVAD and t-CVAD are being undertaken to provide information for the planning and justification of a future efficacy RCT, allowing refinement of the study components including the protocol, processes and outcomes. [28 29] The trials are referred to as: Central venous Access device SeCurement And Dressing Effectiveness in paediatrics (the CASCADE Junior trials).

Study setting

The three pilot RCTs were initially conducted at the Royal Children's Hospital, Brisbane, Australia; and, after local hospital mergers, the larger Lady Cilento Children's Hospital, Brisbane, Australia. These are tertiary level, specialist paediatric teaching hospitals in Queensland, providing full-spectrum health services to children and young people from birth to 18 years of age. Referrals are from throughout Queensland, northern New South Wales and the Pacific Rim.

Participants

Peri-operative patients requiring an elective CVAD insertion for medical treatment; or those with a non-trial CVAD insitu and requiring device replacement, as well as those requiring urgent CVAD insertion within the intensive care unit will be recruited. One hundred participants will be recruited to PICC-CASCADE Junior allowing 30 participants per study arm and potential 10% attrition. One hundred and eighty participants will be recruited to nt-CASCADE Junior allowing 55 participants per study arm and potential 10% attrition. Sixty-five participants will be recruited to t-CASCADE Junior, allowing 15 participants per study arm and potential 10% attrition. As the aim of these pilot studies is to test the feasibility of the definitive RCTs, and not hypothesis testing, the power level was not a valid consideration for sample size. The CASCADE junior pilot sample sizes are in accordance with recommendations by Thabane, et al. [30] and Hertzog [31]; to facilitate accurate estimates of effect size while minimizing unnecessary costs, time and recruitment of future definitive study participants.

Patients who meet all the inclusion criteria and no exclusion criteria described in Table 1 are eligible for enrolment.

Table 1: Inclusion and exclusion criteria for the CASCADE Junior trials

Inclusion criteria	Exclusion criteria
• Patients < 18 years of age • Will remain admitted to the Royal Children's Hospital or Lady Cilento Children's Hospital for >24 hours • Informed consent to participate **PICC- CASCADE Junior** • PICC to be inserted and will remain *insitu* for > 24 hours **nt-CASCADE Junior** • nt-CVAD to be inserted and will remain *insitu* for >24 hours **t-CASCADE Junior** • t-CVAD to be inserted and will remain *insitu* for > 24 hours	• All other intravascular device types (e.g. totally implanted CVADs, peripheral intravascular devices) • Current bloodstream infection • Non-English speakers without an interpreter • CVADs inserted through diseased burned, scarred or extremely diaphroetic skin • Known allergy to any study product • Current skin tear / 'papery' skin at high risk of tear • Previous enrolment in the CASCADE Junior studies within this hospital admission

CVAD=Central venous access device; nt=Non-tunnelled; PICC= Peripherally inserted central catheter; t= Tunnelled

Interventions

The intervention arms for each CVAD study have been individualised to the three device requirements (PICC, nt-CVAD and t-CVAD). Details regarding the intervention arms can be seen in Table 2, with the dressing and securement technologies under evaluation illustrated in Figure 1. Researchers and local clinicians developed the intervention arms; taking into consideration current local practice, best available evidence, and the safety of all participants.

Table 2: Intervention arms for the CASCADE Junior trials

PICC-CASCADE Junior

1) Standard care:
   - Sutureless securement device (Statlock® VPPCSP ; Bard, Georgia); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
2) Tissue adhesive:
   - Tissue adhesive (Histoacryl®; B. Braun, Germany); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
3) Integrated dressing-securements:
   - Integrated dressing-securements (SorbaView SHIELD® SV353; Centurion Medical Products, Williamston)

nt-CASCADE Junior

1) Standard care:
   - Suture (Prolene®; Ethicon, New Jersey);
   - Chlorhexidine-impregnated disc (Biopatch® 44150; Johnson & Johnson, NJ); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
2) Tissue adhesive:
   - Suture (Prolene®; Ethicon, New Jersey);
   - Tissue adhesive (Histoacryl®; B. Braun, Germany); and
   - Chlorhexidine-impregnated disc (Biopatch® 44150; Johnson & Johnson, NJ); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
3) Integrated dressing-securements:
   - Suture (Prolene®; Ethicon, New Jersey);
   - Chlorhexidine-impregnated disc (Biopatch®; Johnson & Johnson, NJ); and
   - Integrated dressing-securements (SorbaView SHIELD® SV430 or SV254; Centurion Medical Products, Williamston)

t-CASCADE Junior

1) Standard care:
   - Suture (Prolene®; Ethicon, New Jersey); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
2) Sutureless securement device:
   - Suture (Prolene®; Ethicon, New Jersey);
   - Sutureless securement device (Statlock® VFDSSP; Bard, Georgia or GripLok® 3601CVC; TIDI, Neenah WI); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
3) Tissue adhesive:
   - Tissue adhesive (Histoacryl®; B. Braun, Germany); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
4) Integrated dressing-securements:
   - Suture (Prolene®; Ethicon, New Jersey); and
   - Integrated dressing-securements (SorbaView SHIELD® SV254; Centurion Medical Products, Williamston)

PICC=Peripherally inserted central catheter; nt=non-tunnelled; t=tunnelled

Outcomes

Primary outcome

The primary outcome is feasibility of full efficacy trials. This will be established by composite analysis of elements of feasibility as described by Lancaster and colleagues [28], Thabane and colleagues [30] and Hertzog [31]. Full definitions of the primary and secondary outcomes are provided in Table 3.

Table 3: Primary and secondary outcomes of the CASCADE Junior trials

Primary outcome
1. Feasibility of full efficacy trials: Composite analysis of elements of feasibility: *Eligibility:* ≥ 70% of patients screened will be eligible; *Recruitment:* ≥ 70% of patients eligible agree to enrol; *Retention and attrition:* < 15% of participants are lost to follow-up or withdraw from study; *Protocol adherence:* ≥ 80% of participants receive their allocated treatment throughout their study participation; *Missing data:* <10% of data are missed during study data collection; *Satisfaction and acceptability:* Parent and healthcare staff levels of satisfaction and acceptability using structured point-based questions; and *Sample size estimates:* A reduction in all-cause CVAD failure or complication (defined in the secondary outcomes) by at least an absolute proportion of 5% in the experimental arms, in comparison to standard care.
Secondary outcomes
A. CVAD failure: Cessation of function prior to completion of therapy; (10) B. CVAD complication: A composite of CABSI, local infection, occlusion, dislodgement, venous thrombosis or breakage (defined below); C. Catheter-associated bloodstream infection (CABSI): A laboratory-confirmed bloodstream infection (LCBI) in a patient who had a central line within the 48 hour period before the development of the BSI, and that is not related to an infection at another site. The CLABSI must meet one of the following criteria of LCBI: Criterion 1: Patient has a recognised pathogen cultured from one or more blood cultures and Organism cultured from blood is not related to an infection at another site. OR Criterion 2: Patient has at least one of the following signs or symptoms: fever (greater than 38 degrees C), chills, or hypotension, and signs and symptoms and positive laboratory results are not related to an infection at another site, and common skin contaminant* is cultured from two or more blood cultures drawn on separate occasions. Examples of common skin contaminants: diphtheroids [Corynebacterium spp.], Bacillus [not B. anthracis] spp., Propionibacterium spp., coagulasenegative staphylococci [including S. epidermidis], viridans group streptococci, Aerococcus spp., Micrococcus spp. (34) Determined by blinded infectious disease specialist; D. Local infection: Purulent discharge, or redness extending 1cm beyond the site that prompts clinician to order removal, or commence antimicrobial therapy; E. Venous thrombosis: Development of thrombosed vessel (partial or complete) at the CVAD site diagnosed radiologically as requested by the treating clinician in a symptomatic patient; (37) F. Dislodgement: *Partial* –change in CVAD length from hub to tip, as measured by marking closest to hub, *or* CVAD removal because tip is no longer in superior or inferior vena cava (diagnosed by xray/leakage from site on injection/infusion).(21) *Complete*: CVAD body completely leaves the vein; G. Occlusion: Partial, ≥1 lumens cannot be flushed and/or aspirated, or resolved after anticoagulant dwell. Complete, all lumens cannot be flushed and/or aspirated despite anticoagulant dwell; H. CVAD breakage: Visible split in CVAD material diagnosed by leakage or radiographic evidence of extravasation from a portion of the CVAD into tissue; I. CVAD-related BSI: Laboratory confirmed with matched organism from blood and catheter tip culture; (34) J. Securement-dressing failure: Replacement in under seven days for loose, missing, bloodstained, diaphoresis or secretion soaked dressings; K. CVAD and first securement-dressing dwell period: Days from insertion/application of CVAD/dressing until removal; L. Cost effectiveness: Estimates of direct product costs, healthcare resource utilisation (including additional equipment, staff time) and failure-associated resource usage using previously established cost estimates; (36) and M. Safety: Skin complications including skin rash, skin tears, blisters, pruritis, local or systemic allergic reaction.(35)

Study procedures

The research nurse (ReN) will screen patients daily, obtain written informed consent, and undertake randomisation. The ReN will have prepared study packs with securement and dressing products and will liaise closely with the CVAD insertion clinicians. Randomisation will be web-based via Griffith University https://www151.griffith.edu.au/random.This will ensure full compliance with best practice standards for randomisation generation and allocation concealment until study entry. Randomisation will be generated on a 1:1:1:1 (t-CASCADE Junior) or 1:1:1 (PICC- and nt-CASCADE Junior) ratio for the study groups. Block size will vary randomly. The Project Manager will undertake quality checks to ensure allocation integrity. CVAD securement and dressings are not amenable to blinding of patients, clinical staff or ReNs.

Data collection will be facilitated using REDCap (Research Electronic Data CAPture http://project-redcap.org/) by the ReN. The ReN will visit patients daily to inspect the CVAD and dressing securement products, view medical records and talk to staff, patients and caregivers. They will collect data until four weeks after insertion, study withdrawal, removal of the CVAD, or hospital discharge. CVADs still insitu at four weeks or discharge will be censored from the study at that time. ReN will collect data on primary and secondary outcomes. Demographic data will be collected to describe the participant group and enable comparisons to inform future generalisability. Data will also be collected regarding patient and device-related characteristics that are known to increase the risk of CVAD failure. [1 35-40] Variables to be collected include age, gender, diagnostic category, immunocompromise, existing infection, presence of stoma, parenteral nutrition, length of hospital stay, level of consciousness, diaphoresis, CVAD utilisation, insertion site and technique, experience of the CVAD inserter. ReN will inspect site and collect data on all adverse events. At CVAD removal (or within 24 hours), the ReN will ask the patient or caregivers, and healthcare staff about their assessment of the acceptability and satisfaction with the dressing and securement product (numeric rating scale 0-10).

CVAD procedures

The pilot studies are pragmatic in order to maximise applicability to future efficacy trials and future generalisability, therefore ReNs will not be involved in CVAD insertion and will minimise their involvement in CVAD care. Standardised CVAD insertions include; a large sterile drape, sterile gloves, gown and mask. The CVAD inserter will select site (e.g. jugular, subclavian), CVAD type (e.g. number of lumens) and approach (tunnelled or non-tunnelled) based on clinical judgement of patient needs, and then apply the allocated products. [41] The ReNs will ask inserters to rate ease of application using an 11-point scale (0=very difficult, 10 = very easy).

Extensive education activities and user guides will be provided to hospital staff to ensure consistency and protocol adherence. Nursing staff will change study products weekly and as clinically indicated. Product replacements/reinforcements, including tape, and the reasons for these will be recorded.

Clinical staff will take blood and CVAD tip cultures on suspicion of infection, as per standard hospital and pathology protocols. [42 43] Diagnoses of CABSI and CVAD-related BSI will be made by an independent, blinded infectious diseases specialist. Similarly ultrasound for the identification of symptomatic venous thrombosis will be requested by the clinical team coordinating the participants' care, with diagnosis made by an independent, blinded radiologist using standard department protocols.

Reliability and validity

The reliability of the CASCADE junior trials will be ensured through the adherence to the *a priori* study protocol. [44] Internal validity will be maintained by following the study protocol monitored by the Project Manager, with adherence to reporting safeguards to minimise bias. Use of computer generated randomisation and allocation concealment will avoid risk of selection and allocation bias. The CVAD securement and dressing products being trialled are not amenable to blinding of patients, family members, clinical staff or research staff. Radiological and laboratory staff assessing the CABSI and venous thrombosis outcomes will be blinded. With an intention to treat approach, all participants

will be accounted for in the final analysis, following randomisation. [45] The CONSORT Guidelines,[46] including the checklist and diagram, will be used to report the CASCADE Junior trials findings.

Statistical methods

Each pilot study will be analysed separately. Descriptive statistics will be used to ascertain the primary outcome of feasibility for the larger trial. All randomised patients will be analysed on an Intention to Treat (ITT) basis. Comparability of groups at baseline will be assessed using clinical parameters. Incidence rates of CVAD device failure (per 1,000 device days) and CVAD complication (per 100 devices) will summarise the impact of each dressing regimen; group differences will be evaluated by calculating 95% confidence intervals and p-values. CVADs insitu after four weeks or at hospital discharge will be censored from analysis at this point. Kaplan-Meier survival curves (with log rank test) will compare CVAD failure and complication over time. Secondary endpoints including dwell-time, dislodgment, infection and safety will be compared between groups using parametric or nonparametric techniques as appropriate. In addition to group, multivariate regression (Cox) models will test the effect of patient and device variables associated with CVAD failure e.g. insertion site, dwell time, length of stay, diagnostic group, age, sex, mobility, co-morbidities and IV medications. Prior to analysis, data cleaning of outlying figures, missing, and implausible data will be undertaken, and a random 5% sample of source data re-entered and checked. All attempts will be made to collect the primary endpoint. A per-protocol analysis will assess the effect of protocol violations. P values of <0.1 will be evaluated as indicating some evidence against a null hypothesis, and values <0.05 will be considered statistically significant.

Estimating cost parameters

Trial costs will be collected as direct product costs (material costs) and healthcare resource utilisation (labour costs), including failure-associated costs using previously established cost estimates.[34]. Health resource utilisation will be measured by assessing the staff time and equipment associated with

CVAD insertion (PICC, t and nt) and dressing changes.[43] Group differences will be tested using a non-parametric statistical test.

ETHICS AND DISSEMINATION

Ethics and safety considerations

Ethics approval for the CASCADE Junior trials has been gained from the Children's Health Services Queensland (HREC/13/QRCH/181) and Griffith University (NRS/10/14/HREC) Human Research Ethics Committees (HREC). The CASCADE Junior trials were also registered with the Australian and New Zealand Clinical Trial Registry (PICC-CASCADE ACTRN12614001327673; nt-CASCADE ACTRN12615000977572; t-CASCADE ACTRN12614000280606). Adverse events (e.g. skin irritation) will be recorded and Serious Adverse Events (e.g. death) will be reported to the HRECs.

Parents/legal guardians will be given an Information Sheet, time to read and fully understand it, and an opportunity to ask questions. Children will be provided a Youth Assent form if older than six years of age and developmentally appropriate. All children will be provided with information regarding the study and given the opportunity to provide assent for participation. Withdrawal from the study will, in no way, affect the care they receive from the hospitals. Participant confidentiality will be ensured and anonymity guaranteed. Only aggregate data will be published and data will be stored according to National Health & Medical Research Council guidelines [47].

Dissemination

In accordance with the primary outcome of feasibility, the results of this research will be used to inform the design of further efficacy RCTs of CVAD securement in paediatrics. The results of this research will also be disseminated locally at the involved children's hospital, and at relevant local,

national and international vascular access and paediatric scientific meetings. Each pilot study will be separately published in a relevant healthcare journal, presented in accordance with the CONSORT Statement recommendations[48]. Additionally, the results will be sent to the relevant organisations which lead CVAD focussed clinical practice guidelines development. The funding organisations will not be involved in the analysis or preparation of publications resulting from the research.

Trial status

Recruitment of patients to the PICC- and t-CASCADE Junior trials commenced in April 2014. Recruitment was paused from November 2014 to March 2015, due to the hospital merger, for the safety of all participants. Recruitment of patients to the nt-CASCADE Junior trial will commence in January 2016. It is expected that recruitment will be completed for all pilots by December 2016.

DISCUSSION

The risk of paediatric CVAD failure and complication varies between device types.[10] CVAD dressing and securement devices need to be evaluated for effectiveness and suitability across the CVAD range. A 'one size fits all' approach to CVAD securement is inappropriate and likely to be ineffective[49]. Depending upon insertion site and length, CVADs have different tensile strength requirements.[15] For example, tunnelled and cuffed devices, in comparison to other CVAD types, may have lower strength requirements after tissue engraftment. PICCs may have higher strength requirements due to limb movement and device length.

The contrasting external shapes of CVADs mean some securement products may not be suitable or vary in their effectiveness to prevent complication. For example, many of the SSD products anchor devices using the CVAD 'wings', which are absent in tunnelled cuffed CVADs such as Hickman® or Broviac® catheters. The limited skin space available to secure and dress jugular, non-tunnelled CVADs in infants and neonates can result in some securement devices also being impractical.

Individual testing of CVAD securement and dressing products in paediatrics between CVAD types is necessary.

CVAD securement and dressing products provide an important contribution to the prevention of CVAD failure and complication. The ideal CVAD securement and dressing should: 1) prevent accidental removal, micro-motion and pistoning; 2) block bacteria entering the wound; 3) have antimicrobial properties; 4) assist with haemostasis 5) be comfortable for patients; 6) be easy for staff to use; and 7) be cost-effective. Although many alternatives to suture and polyurethane dressings exist, how these meet the above criteria is largely unknown. Systematic and narrative reviews have highlighted the dearth of literature to support practice in this area.[15 50] The CASCADE Junior trials will contribute new knowledge to inform the individual efficacy of each dressing and securement type for each of the populations and devices utilising them.

Authors contributions

AJU conceived the study, wrote grant, developed protocol and funding applications, wrote the first draft of manuscript and approved the final draft. TK and DL assisted with proposal development, grant application, managed the study, reviewed manuscript and approved the final draft. CRM conceived the study, wrote grant, developed protocol, setting, reviewed manuscript and approved the final draft. GM contributed to statistical methods, proposal development, reviewed the manuscript and approved the final draft. VG and TW contributed in data collection, assistance with study management and primary end point assignment, reviewed the manuscript and approved the final draft. MC contributed in grant application, prepared and reviewed the manuscript, and approved the final draft. AH and CM contributed in grant application, oversight data collection, reviewed the manuscript and approved the final draft.

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Competing interests statement

In addition to funding disclosed in the funding statement, AJU, CRM, TK have received funding through Griffith University for their research from product manufacturers (Becton Dickinson; 3M; Carefusion; Centurion Medical Products). The remaining authors have no conflicts of interest relevant to this article to disclose.

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Legend for figures:

Figure 1: Illustration of products tested within the CASCADE junior trials:

a: Simple polyurethane and suture; b: Sutureless securement device with simple polyurethane; c: Integrated securement dressing product; d: Tissue adhesive

Figure 2: Medical Research Council framework for the evaluation of complex interventions [27]: reproduced with permission

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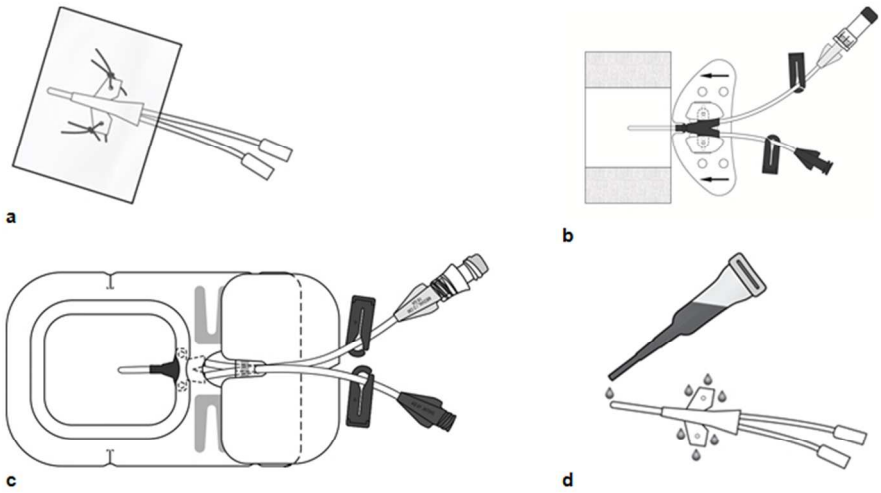

Figure 1: Illustration of products tested within the CASCADE junior trials:

a: Simple polyurethane and suture; b: Sutureless securement device with simple polyurethane; c: Integrated securement dressing product; d: Tissue adhesive

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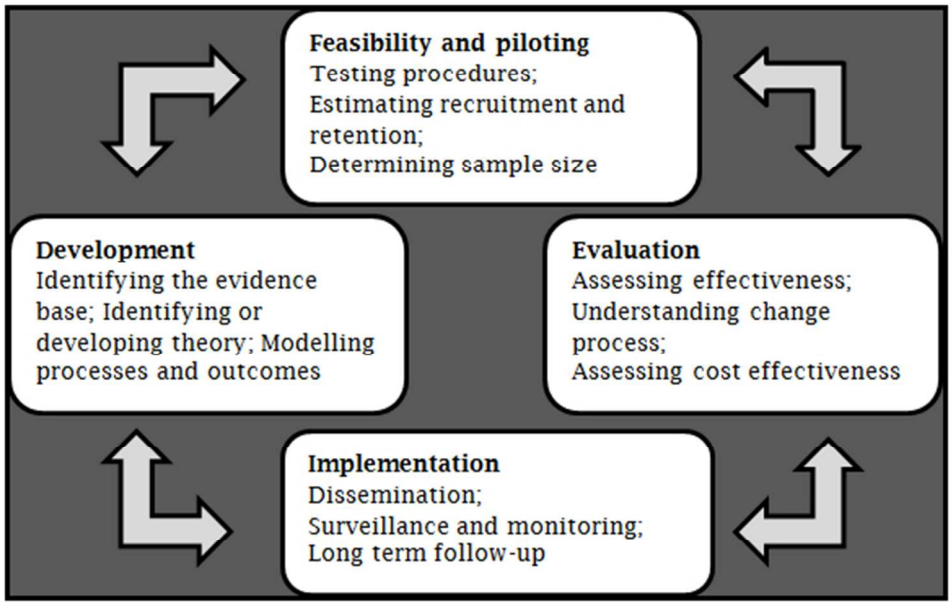

Figure 2: Medical Research Council framework for the evaluation of complex interventions [27]: reproduced with permission
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Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____Title page__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	____1_____
Funding	4	Sources and types of financial, material, and other support	_____17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____16_____
	5b	Name and contact information for the trial sponsor	___17_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___17_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___16_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	9-10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6,11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11,12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11,12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Central venous Access device SeCurement And Dressing Effectiveness (CASCADE) in paediatrics: protocols for pilot randomised controlled trials

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Title: Central venous Access device SeCurement And Dressing Effectiveness (CASCADE) in paediatrics: protocol for pilot randomised controlled trials

Short title: CASCADE Junior protocol

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Abstract:

Introduction: Paediatric central venous access devices (CVAD) are associated with a 25% incidence of failure. Securement and dressing are strategies used to reduce failure and complication, however innovative technologies have not been evaluated for their effectiveness across device types. The primary aim of this research is to evaluate the feasibility of launching a full-scale randomised controlled efficacy trial across three CVAD types regarding CVAD securement and dressing, using pre-defined feasibility criteria.

Methods and analysis: Three feasibility randomised, controlled trials are to be undertaken at the Royal Children's Hospital and the Lady Cilento Children's Hospital, Brisbane, Australia. CVAD securement and dressing interventions under examination compare current practice with sutureless securement devices, integrated securement-dressings and tissue adhesive. In total, 328 paediatric patients requiring a peripherally inserted central catheter (n=100); non-tunnelled CVAD (n=180) and tunnelled CVAD (n=48) to be inserted will be recruited and randomly allocated to CVAD securement and dressing products. Primary outcomes will be study feasibility measured by eligibility, recruitment, retention, attrition, missing data, parent / staff satisfaction and effect size. CVAD failure and complication (catheter-associated bloodstream infection, local infection, venous thrombosis, occlusion, dislodgement and breakage) will be compared between groups.

Ethics and dissemination: Ethical approval to conduct the research has been obtained. All dissemination will be undertaken using the CONSORT Statement recommendations. Additionally, the results will be sent to the relevant organisations which lead CVAD focussed clinical practice guidelines development.

Trial registration number: Australian and New Zealand Clinical Trial Registration: peripherally inserted central catheter ACTRN12614001327673; non-tunnelled CVAD ACTRN12615000977572; tunnelled CVAD ACTRN12614000280606.

STRENGTHS AND LIMITATIONS:

- Pilot randomized controlled design to enhance reliability of results using predetermined primary outcomes of feasibility.
- Securement and dressing products being trialled are not amenable to blinding of patients, family members, clinical staff or research staff. Radiological and laboratory staff assessing outcomes will be blinded.

INTRODUCTION

Central venous access devices (CVADs) are used for monitoring and medication in critically and chronically unwell patients in a variety of inpatient and outpatient settings. [1 2] More than five million CVADs are used in the USA per year alone.[3] Conventionally, non-tunnelled CVADs (nt-CVADs) have been advocated for use when central venous access is required for a short time, [4-6] peripherally inserted central catheters (PICCs) for short to medium time, [4 6] and tunnelled CVADs (t-CVAD) and totally implantable devices for longer time periods. [6 7]

Children requiring CVADs to facilitate treatment are extremely vulnerable to the risk of adverse events associated with insertion and management. [8 9] Twenty five percent of paediatric CVADs fail prior to treatment being complete. [10] This includes CVADs becoming partially or wholly dislodged, occlusions, venous thrombosis, fractured catheters, site erosion, severe pain, or a bloodstream infection. The consequences of failure include the morbidity and mortality associated with the cause of the complication (e.g., catheter associated bloodstream infection (CABSI); with an attributable mortality as high as 35%),[11 12] interruption of medical treatment and the insertion of replacement CVADs, involving the additional risk of procedural complications. Many CVAD complications are preventable with the consistent use of evidence-based CVAD insertion and maintenance practices.[6 13 14]

An essential component to prevent post-insertion CVAD complications is the securement and dressing product chosen. To prevent complications, CVADs require: (1) insertion site protection from

microbial contamination from the surrounding skin and environment; (2) the external portion to be secured to prevent venous dislodgement; and (3) securement to prevent micro-motion within the vein and at the insertion site.[15] Micro-motion is believed to irritate the vein wall, causing inflammation, thrombosis, occlusion, vessel erosion, and encourages skin bacteria to enter the insertion wound. [15-17] Since the 1980s, pervasive practice has been to suture CVADs for securement, with adhesive, polyurethane dressings placed over the sutured site (see Figure 1a).[18] Transparent polyurethane dressings are claimed to be impermeable to microorganisms but semi-permeable to oxygen, carbon dioxide and water vapour. [11 15 18]

<insert Figure 1>

Recent evidence supports the introduction of chlorhexidine gluconate-impregnated (CGI) CVAD dressing products within critical care, as a strategy to reduce the incidence of site colonisation and CABSI in non-tunnelled devices. The recent Cochrane systematic review by Ullman and colleagues[18] , found moderate quality evidence that CGI dressings reduced the frequency of catheter-related BSI per 1, 000 patient days compared with conventional polyurethane dressings (relative risk (RR) 0.51, 95% confidence interval (CI) 0.33 to 0.78; P=0.002). The prevalence of catheter tip colonisation was also significantly reduced (RR=0.58; 95% CI 0.47-0.73; P<0.001). The transferability of these results outside of the critical care population has yet to be established, considering the different CVAD dwell times, insertion technique and clinician groups caring for CVADs in the various healthcare settings.[15 18]

Alternative securement and dressing options have become available that may be superior to suturing and polyurethane dressings for preventing complications, but these have not yet been adequately tested for efficacy, acceptability or cost-effectiveness. [15] Sutureless securement devices (SSD) have large adhesive padded footplates with CVAD-locking clasps of plastic or Velcro (see Figure 1b). They aim to reduce movement, kinking and flow impedance [15 16] and are used with polyurethane dressings. A manufacturer-sponsored randomised controlled trial (RCT) in PICCs (*n*=170) found significantly reduced CABSI with SSD (9.4% suture vs 1.2% SSD; P=0.04), and non-significant

reduction in unplanned removal (36% suture vs 24% SSD). [19] An independent RCT in dialysis devices (*n*=72), found reduced haematoma, thromboses and dislodgement (13.9% suture vs 8.3% SSD; P=NS). [20] Neither of these studies included the paediatric population.

Integrated Securement-Dressing (ISD) are 'next generation' polyurethane dressings with a tough fabric adhesive border around the central polyurethane with continued adhesive over and underneath the CVAD body (Figure 1c).[15] ISDs claim to eliminate the need for a separate securement device (e.g. sutures), and a reduction in costs and procedural complexity. They also include an absorbent layer around the polyurethane, which is claimed to move moisture away from the wound. This may be useful for newly inserted CVADs, which commonly ooze and require more frequent replacement which increases CABSI risk. [21] A recent adult cohort study [22] (n=327 ISD; n=94 historical suture controls) reported ISD to be associated with significantly delayed onset of occlusion (from 8 to 25 days; P<0.01) in comparison to sutures.

Tissue Adhesive (TA) is medical grade 'superglue' (cyanoacrylate) used as an alternative to sutures in both internal and external wounds. [23] (Figure 1d) Case reports in adults suggest TA reduces CVAD dislodgement from 12% to 4%, with no skin reactions or mechanical complications. [24 25] TA is bactericidal and inhibits growth of all Gram-positive organisms (predominant in CABSI), including methicillin resistant *Staphylococcus aureus* (MRSA). [24] TA forms an occlusive healing environment and a physical barrier to micro-organisms, with haemostatic properties to reduce ooze and haematomas.[24] When used with a polyurethane dressing, TA remains for four to seven days, sloughs off slowly, and can be reapplied or removed easily with commercial wipes or petroleum jelly. [26] TA may hold the key to avoiding sutures and CVAD complications by reducing pistoning, accidental removal, infection and bleeding.

These new technologies potentially reduce complications associated with the use of CVADs in the paediatric population. There are currently no strong data supporting their relative effectiveness and safety across the diverse range of CVADs and patients in paediatric clinical practice. Randomised, experimental, efficacy trials, with measures to prevent bias, are necessary to provide true estimates of

relative effectiveness and inform practice.[27] The United Kingdom's Medical Research Council's *Developing and evaluating complex interventions* framework (see Figure 2) [27] highlights the importance of piloting prior to undertaking large efficacy trials, to prevent problems of acceptability, compliance, intervention implementation, recruitment and retention, and underpowered studies, [27] Pilot studies should examine the key uncertainties that have been identified during research development. This involves testing of intervention and data collection procedures, estimating recruitment and retention numbers, and determining effect estimates for future sample size calculations.

<insert Figure 2>

The primary aim of this research is to evaluate the feasibility of launching a full-scale randomised controlled efficacy trial of PICC, nt-CVAD and t-CVAD securement and dressing, using pre-defined feasibility criteria for recruitment, retention, protocol fidelity and product acceptability. The secondary aim is to compare the effectiveness of dressings and securement products on CVAD complications and failure due to infection, occlusion, dislodgement, thrombosis, or breakage, for children in acute care facilities.

METHODS AND ANALYSIS

Design

Three separate pilot RCTs involving PICC, nt-CVAD and t-CVAD are being undertaken to provide information for the planning and justification of a future efficacy RCT, allowing refinement of the study components including the protocol, processes and outcomes. [28 29] The trials are referred to as: Central venous Access device SeCurement And Dressing Effectiveness in paediatrics (the CASCADE Junior trials).

Study setting

The three pilot RCTs were initially conducted at the Royal Children's Hospital, Brisbane, Australia; and, after local hospital mergers, the larger Lady Cilento Children's Hospital, Brisbane, Australia. These are tertiary level, specialist paediatric teaching hospitals in Queensland, providing full-spectrum health services to children and young people from birth to 18 years of age. Referrals are from throughout Queensland, northern New South Wales and the Pacific Rim.

Participants

Peri-operative patients requiring an elective CVAD insertion for medical treatment; or those with a non-trial CVAD insitu and requiring device replacement, as well as those requiring urgent CVAD insertion within the intensive care unit will be recruited. One hundred participants will be recruited to PICC-CASCADE Junior allowing 30 participants per study arm and potential 10% attrition. One hundred and eighty participants will be recruited to nt-CASCADE Junior allowing 55 participants per study arm and potential 10% attrition. Forty-eight participants will be recruited to t-CASCADE Junior, allowing 12 participants per study arm. As the aim of these pilot studies is to test the feasibility of the definitive RCTs, and not hypothesis testing, the power level was not a valid consideration for sample size. The CASCADE junior pilot sample sizes are in accordance with recommendations by Thabane, et al. [30] and Hertzog [31]; to facilitate accurate estimates of effect size while minimizing unnecessary costs, time and recruitment of future definitive study participants.

Patients who meet all the inclusion criteria and no exclusion criteria described in Table 1 are eligible for enrolment.

Table 1: Inclusion and exclusion criteria for the CASCADE Junior trials

Inclusion criteria	Exclusion criteria
• Patients < 18 years of age • Will remain admitted to the Royal Children's Hospital or Lady Cilento Children's Hospital for >24 hours • Informed consent to participate **PICC- CASCADE Junior** • PICC to be inserted and will remain *insitu* for > 24 hours **nt-CASCADE Junior** • nt-CVAD to be inserted and will remain *insitu* for >24 hours **t-CASCADE Junior** • t-CVAD to be inserted and will remain *insitu* for > 24 hours	• All other intravascular device types (e.g. totally implanted CVADs, peripheral intravascular devices) • Current bloodstream infection • Non-English speakers without an interpreter • CVADs inserted through diseased burned, scarred or extremely diaphroetic skin • Known allergy to any study product • Current skin tear / 'papery' skin at high risk of tear • Previous enrolment in the CASCADE Junior studies within this hospital admission

CVAD=Central venous access device; nt=Non-tunnelled; PICC= Peripherally inserted central catheter; t= Tunnelled

Interventions

The intervention arms for each CVAD study have been individualised to the three device requirements (PICC, nt-CVAD and t-CVAD). Details regarding the intervention arms can be seen in Table 2, with the dressing and securement technologies under evaluation illustrated in Figure 1. Researchers and local clinicians developed the intervention arms; taking into consideration current local practice, best available evidence, and the safety of all participants.

Table 2: Intervention arms for the CASCADE Junior trials

PICC-CASCADE Junior

1) Standard care:
   - Sutureless securement device (Statlock® VPPCSP ; Bard, Georgia); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
2) Tissue adhesive:
   - Tissue adhesive (Histoacryl®; B. Braun, Germany); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
3) Integrated dressing-securements:
   - Integrated dressing-securements (SorbaView SHIELD® SV353; Centurion Medical Products, Williamston)

nt-CASCADE Junior

1) Standard care:
   - Suture (Prolene®; Ethicon, New Jersey);
   - Chlorhexidine-impregnated disc (Biopatch® 44150; Johnson & Johnson, NJ); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
2) Tissue adhesive:
   - Suture (Prolene®; Ethicon, New Jersey);
   - Tissue adhesive (Histoacryl®; B. Braun, Germany); and
   - Chlorhexidine-impregnated disc (Biopatch® 44150; Johnson & Johnson, NJ); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
3) Integrated dressing-securements:
   - Suture (Prolene®; Ethicon, New Jersey);
   - Chlorhexidine-impregnated disc (Biopatch®; Johnson & Johnson, NJ); and
   - Integrated dressing-securements (SorbaView SHIELD® SV430 or SV254; Centurion Medical Products, Williamston)

t-CASCADE Junior

1) Standard care:
   - Suture (Prolene®; Ethicon, New Jersey); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
2) Sutureless securement device:
   - Suture (Prolene®; Ethicon, New Jersey);
   - Sutureless securement device (Statlock® VFDSSP; Bard, Georgia or GripLok® 3601CVC; TIDI, Neenah WI); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
3) Tissue adhesive:
   - Tissue adhesive (Histoacryl®; B. Braun, Germany); and
   - Bordered polyurethane dressing (Tegaderm® 1655 or 1616; 3M, St Paul)
4) Integrated dressing-securements:
   - Suture (Prolene®; Ethicon, New Jersey); and
   - Integrated dressing-securements (SorbaView SHIELD® SV254; Centurion Medical Products, Williamston)

PICC=Peripherally inserted central catheter; nt=non-tunnelled; t=tunnelled

Outcomes

Primary outcome

The primary outcome is feasibility of full efficacy trials. This will be established by composite analysis of elements of feasibility as described by Lancaster and colleagues [28], Thabane and colleagues [30] and Hertzog [31]. Full definitions of the primary and secondary outcomes are provided in Table 3.

Table 3: Primary and secondary outcomes of the CASCADE Junior trials

Primary outcome
1. Feasibility of full efficacy trials: Composite analysis of elements of feasibility: *Eligibility:* ≥ 70% of patients screened will be eligible; *Recruitment:* ≥ 70% of patients eligible agree to enrol; *Retention and attrition:* < 15% of participants are lost to follow-up or withdraw from study; *Protocol adherence:* ≥ 80% of participants receive their allocated treatment throughout their study participation; *Missing data:* <10% of data are missed during study data collection; *Satisfaction and acceptability:* Parent and healthcare staff levels of satisfaction and acceptability using structured point-based questions; and *Sample size estimates:* A reduction in all-cause CVAD failure or complication (defined in the secondary outcomes) by at least an absolute proportion of 5% in the experimental arms, in comparison to standard care.
Secondary outcomes
A. CVAD failure: Cessation of function prior to completion of therapy; [10] B. CVAD complication: A composite of CABSI, local infection, occlusion, dislodgement, venous thrombosis or breakage (defined below); C. Catheter-associated bloodstream infection (CABSI): A laboratory-confirmed bloodstream infection (LCBI) in a patient who had a central line within the 48 hour period before the development of the BSI, and that is not related to an infection at another site. The CLABSI must meet one of the following criteria of LCBI: Criterion 1: Patient has a recognised pathogen cultured from one or more blood cultures and Organism cultured from blood is not related to an infection at another site. OR Criterion 2: Patient has at least one of the following signs or symptoms: fever (greater than 38 degrees C), chills, or hypotension, and signs and symptoms and positive laboratory results are not related to an infection at another site, and common skin contaminant* is cultured from two or more blood cultures drawn on separate occasions. Examples of common skin contaminants: diphtheroids [Corynebacterium spp.], Bacillus [not B. anthracis] spp., Propionibacterium spp., coagulasenegative staphylococci [including S. epidermidis], viridans group streptococci, Aerococcus spp., Micrococcus spp. [32] Determined by blinded infectious disease specialist; D. Local infection: Purulent discharge, or redness extending 1cm beyond the site that prompts clinician to order removal, or commence antimicrobial therapy; E. Venous thrombosis: Development of thrombosed vessel (partial or complete) at the CVAD site diagnosed radiologically as requested by the treating clinician in a symptomatic patient; F. Dislodgement: *Partial* –change in CVAD length from hub to tip, as measured by marking closest to hub, *or* CVAD removal because tip is no longer in superior or inferior vena cava (diagnosed by xray/leakage from site on injection/infusion).[19] *Complete*: CVAD body completely leaves the vein; G. Occlusion: *Partial – resolved*: ≥1 lumens cannot be flushed and/or aspirated, but resolves after line clearance strategy; *Partial – unresolved*: ≥1 lumens cannot be flushed and/or aspirated, and does not resolve after line clearance strategy; *Complete*: all lumens cannot be flushed and/or aspirated and does not resolve after line clearance strategy; H. CVAD breakage: Visible split in CVAD material diagnosed by leakage or radiographic evidence of extravasation from a portion of the CVAD into tissue; I. CVAD-related BSI: Laboratory confirmed with matched organism from blood and catheter tip culture;[32] J. Securement-dressing failure: Replacement in under seven days for loose, missing, bloodstained, diaphoresis or secretion soaked dressings; K. CVAD and first securement-dressing dwell period: Days from insertion/application of CVAD/dressing until removal; L. Cost effectiveness: Estimates of direct product costs, healthcare resource utilisation (including additional equipment, staff time) and failure-associated resource usage using previously established cost estimates; [33] and

M. Safety: Skin complications including skin rash, skin tears, blisters, pruritis, local or systemic allergic reaction.[34 35]

Study procedures

The research nurse (ReN) will screen patients daily, obtain written informed consent, and undertake randomisation. The ReN will have prepared study packs with securement and dressing products and will liaise closely with the CVAD insertion clinicians. Randomisation will be web-based via Griffith University https://www151.griffith.edu.au/random.This will ensure full compliance with best practice standards for randomisation generation and allocation concealment until study entry. Randomisation will be generated on a 1:1:1:1 (t-CASCADE Junior) or 1:1:1 (PICC- and nt-CASCADE Junior) ratio for the study groups. Block size will vary randomly. The Project Manager will undertake quality checks to ensure allocation integrity. CVAD securement and dressings are not amenable to blinding of patients, clinical staff or ReNs.

Data collection will be facilitated using REDCap (Research Electronic Data CAPture http://project-redcap.org/) by the ReN. The ReN will visit patients daily to inspect the CVAD and dressing securement products, view medical records and talk to staff, patients and caregivers. They will collect data until four weeks after insertion, study withdrawal, removal of the CVAD, or hospital discharge. CVADs still insitu at four weeks or discharge will be censored from the study at that time. ReN will collect data on primary and secondary outcomes. Demographic data will be collected to describe the participant group and enable comparisons to inform future generalisability. Data will also be collected regarding patient and device-related characteristics that are known to increase the risk of CVAD failure. [1 36-41] Variables to be collected include age, gender, diagnostic category, immunocompromise, existing infection, presence of stoma, parenteral nutrition, length of hospital stay, level of consciousness, diaphoresis, CVAD utilisation, insertion site and technique, experience of the CVAD inserter. ReN will inspect site and collect data on all adverse events. At CVAD removal (or within 24 hours), the ReN will ask the patient or caregivers, and healthcare staff about their

assessment of the acceptability and satisfaction with the dressing and securement product (numeric rating scale 0-10).

CVAD procedures

The pilot studies are pragmatic in order to maximise applicability to future efficacy trials and future generalisability, therefore ReNs will not be involved in CVAD insertion and will minimise their involvement in CVAD care. Standardised CVAD insertions include; a large sterile drape, sterile gloves, gown and mask. The CVAD inserter will select site (e.g. jugular, subclavian), CVAD type (e.g. number of lumens) and approach (tunnelled or non-tunnelled) based on clinical judgement of patient needs, and then apply the allocated products. [42] The ReNs will ask inserters to rate ease of application using an 11-point scale (0=very difficult, 10 = very easy).

Extensive education activities and user guides will be provided to hospital staff to ensure consistency and protocol adherence. Nursing staff will change study products weekly and as clinically indicated. Product replacements/reinforcements, including tape, and the reasons for these will be recorded.

Clinical staff will take blood and CVAD tip cultures on suspicion of infection, as per standard hospital and pathology protocols. [43 44] Diagnoses of CABSI and CVAD-related BSI will be made by an independent, blinded infectious diseases specialist. Similarly ultrasound for the identification of symptomatic venous thrombosis will be requested by the clinical team coordinating the participants' care, with diagnosis made by an independent, blinded radiologist using standard department protocols.

Reliability and validity

The reliability of the CASCADE junior trials will be ensured through the adherence to the *a priori* study protocol. [45] Internal validity will be maintained by following the study protocol monitored by the Project Manager, with adherence to reporting safeguards to minimise bias. Use of computer generated randomisation and allocation concealment will avoid risk of selection and allocation bias. The CVAD securement and dressing products being trialled are not amenable to blinding of patients,

family members, clinical staff or research staff. Radiological and laboratory staff assessing the CABSI and venous thrombosis outcomes will be blinded. With an intention to treat approach, all participants will be accounted for in the final analysis, following randomisation. [46] The CONSORT Guidelines,[47] including the checklist and diagram, will be used to report the CASCADE Junior trials findings.

Statistical methods

Each pilot study will be analysed separately. Descriptive statistics will be used to ascertain the primary outcome of feasibility for the larger trial. All randomised patients will be analysed on an Intention to Treat (ITT) basis. Comparability of groups at baseline will be assessed using clinical parameters. Incidence rates of CVAD device failure (per 1,000 device days) and CVAD complication (per 100 devices) will summarise the impact of each dressing regimen; group differences will be evaluated by calculating 95% confidence intervals and p-values. CVADs insitu after four weeks or at hospital discharge will be censored from analysis at this point. Kaplan-Meier survival curves (with log rank test) will compare CVAD failure and complication over time. Secondary endpoints including dwell-time, dislodgment, infection and safety will be compared between groups using parametric or nonparametric techniques as appropriate. In addition to group, multivariate regression (Cox) models will test the effect of patient and device variables associated with CVAD failure e.g. insertion site, dwell time, length of stay, diagnostic group, age, sex, mobility, co-morbidities and IV medications. Prior to analysis, data cleaning of outlying figures, missing, and implausible data will be undertaken, and a random 5% sample of source data re-entered and checked. All attempts will be made to collect the primary endpoint. A per-protocol analysis will assess the effect of protocol violations. P values of <0.1 will be evaluated as indicating some evidence against a null hypothesis, and values <0.05 will be considered statistically significant.

Estimating cost parameters

Trial costs will be collected as direct product costs (material costs) and healthcare resource utilisation (labour costs), including failure-associated costs using previously established cost estimates.[33].

Health resource utilisation will be measured by assessing the staff time and equipment associated with CVAD insertion (PICC, t and nt) and dressing changes.[44] Group differences will be tested using a non-parametric statistical test.

ETHICS AND DISSEMINATION

Ethics and safety considerations

Ethics approval for the CASCADE Junior trials has been gained from the Children's Health Services Queensland (HREC/13/QRCH/181) and Griffith University (NRS/10/14/HREC) Human Research Ethics Committees (HREC). The CASCADE Junior trials were also registered with the Australian and New Zealand Clinical Trial Registry (PICC-CASCADE ACTRN12614001327673; nt-CASCADE ACTRN12615000977572; t-CASCADE ACTRN12614000280606). Adverse events (e.g. skin irritation) will be recorded and Serious Adverse Events (e.g. death) will be reported to the HRECs.

Parents/legal guardians will be given an Information Sheet, time to read and fully understand it, and an opportunity to ask questions. Children will be provided a Youth Assent form if older than six years of age and developmentally appropriate. All children will be provided with information regarding the study and given the opportunity to provide assent for participation. Withdrawal from the study will, in no way, affect the care they receive from the hospitals. Participant confidentiality will be ensured and anonymity guaranteed. Only aggregate data will be published and data will be stored according to National Health & Medical Research Council guidelines [48].

Dissemination

In accordance with the primary outcome of feasibility, the results of this research will be used to inform the design of further efficacy RCTs of CVAD securement in paediatrics. The results of this

research will also be disseminated locally at the involved children's hospital, and at relevant local, national and international vascular access and paediatric scientific meetings. Each pilot study will be separately published in a relevant healthcare journal, presented in accordance with the CONSORT Statement recommendations[49]. Additionally, the results will be sent to the relevant organisations which lead CVAD focussed clinical practice guidelines development. The funding organisations will not be involved in the analysis or preparation of publications resulting from the research.

Trial status

Recruitment of patients to the PICC- and t-CASCADE Junior trials commenced in April 2014. Recruitment was paused from November 2014 to March 2015, due to the hospital merger, for the safety of all participants. Recruitment of patients to the nt-CASCADE Junior trial will commence in January 2016. It is expected that recruitment will be completed for all pilots by December 2016.

DISCUSSION

The risk of paediatric CVAD failure and complication varies between device types.[10] CVAD dressing and securement devices need to be evaluated for effectiveness and suitability across the CVAD range. A 'one size fits all' approach to CVAD securement is inappropriate and likely to be ineffective[35]. Depending upon insertion site and length, CVADs have different tensile strength requirements.[15] For example, tunnelled and cuffed devices, in comparison to other CVAD types, may have lower strength requirements after tissue engraftment. PICCs may have higher strength requirements due to limb movement and device length.

The contrasting external shapes of CVADs mean some securement products may not be suitable or vary in their effectiveness to prevent complication. For example, many of the SSD products anchor devices using the CVAD 'wings', which are absent in tunnelled cuffed CVADs such as Hickman® or Broviac® catheters. The limited skin space available to secure and dress jugular, non-tunnelled CVADs in infants and neonates can result in some securement devices also being impractical.

Individual testing of CVAD securement and dressing products in paediatrics between CVAD types is necessary.

CVAD securement and dressing products provide an important contribution to the prevention of CVAD failure and complication. The ideal CVAD securement and dressing should: 1) prevent accidental removal, micro-motion and pistoning; 2) block bacteria entering the wound; 3) have antimicrobial properties; 4) assist with haemostasis 5) be comfortable for patients; 6) be easy for staff to use; and 7) be cost-effective. Although many alternatives to suture and polyurethane dressings exist, how these meet the above criteria is largely unknown. Systematic and narrative reviews have highlighted the dearth of literature to support practice in this area.[15 50] The CASCADE Junior trials will contribute new knowledge to inform the individual efficacy of each dressing and securement type for each of the populations and devices utilising them.

Authors contributions

AJU conceived the study, wrote grant, developed protocol and funding applications, wrote the first draft of manuscript and approved the final draft. TK and DL assisted with proposal development, grant application, managed the study, reviewed manuscript and approved the final draft. CRM conceived the study, wrote grant, developed protocol, setting, reviewed manuscript and approved the final draft. GM contributed to statistical methods, proposal development, reviewed the manuscript and approved the final draft. VG and TW contributed in data collection, assistance with study management and primary end point assignment, reviewed the manuscript and approved the final draft. MC contributed in grant application, prepared and reviewed the manuscript, and approved the final draft. AH and CM contributed in grant application, oversight data collection, reviewed the manuscript and approved the final draft.

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Competing interests statement

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Legend for figures:

Figure 1: Illustration of products tested within the CASCADE junior trials:

a: Simple polyurethane and suture; b: Sutureless securement device with simple polyurethane; c: Integrated securement dressing product; d: Tissue adhesive

Figure 2: Medical Research Council framework for the evaluation of complex interventions [27]: reproduced with permission

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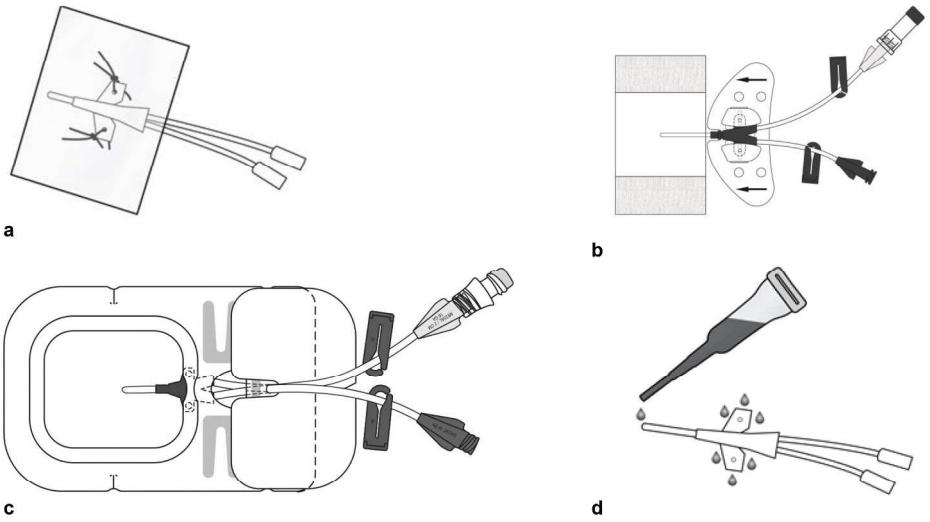

Figure 1: Illustration of products tested within the CASCADE junior trials:

a: Simple polyurethane and suture; b: Sutureless securement device with simple polyurethane; c: Integrated securement dressing product; d: Tissue adhesive
199x125mm (300 x 300 DPI)

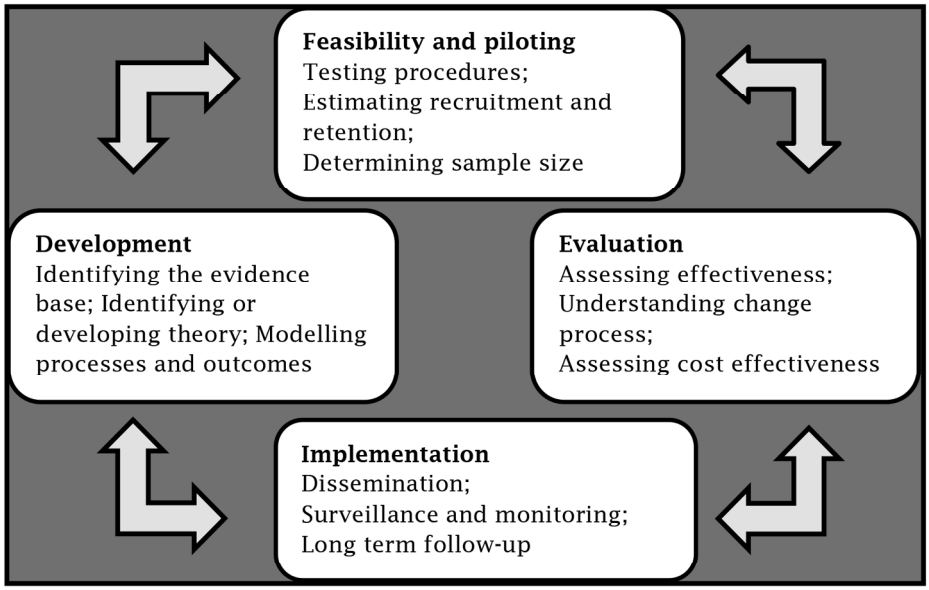

Figure 2: Medical Research Council framework for the evaluation of complex interventions [27]: reproduced with permission
166x108mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____Title page__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	____1_____
Funding	4	Sources and types of financial, material, and other support	_____17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____16_____
	5b	Name and contact information for the trial sponsor	___17_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___17_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___16_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	9-10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6,11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11,12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11,12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.