COMPARING PERIPHERALLY INSERTED CENTRAL CATHETERS TO LONG PERIPHERAL CATHETERS IN PEDIATRICS

Protocol 6/27/2022

NCT05346406

Protocol Summary/Submission Application

Instructions

- Providing a well-written and complete submission is a critical step toward ensuring an efficient IRB review and approval process. If you have any questions, contact the CW HRPP office at 414.337.7133 or CHWIRB@chw.org for assistance early in the submission process; however, the HRPP office is not able to offer consultation for protocol design issues.
- This document should be in your own words (NOT copy/pasted from the sponsor protocol) and must be understandable to individuals who do not have clinical expertise in the area being studied.
- Summarize the proposed study without substituting references to attached material, such as grant applications, multi-center or industry-sponsored protocols. The protocol summary should not read like a grant application.
- Reference GUIDANCE – Submission Documents Checklist (found under Forms and Templates in IRBNe or on the HRPP web site under Guidances) to determine what additional documents are required to be included in the submission package.
- If this is an update to a previous version, please track the changes made using the Review tab in Word.

Version date of this document (initial or revision): 6-27-2022
Study Title: **Com**paring **P**eripherally Inserted Central Catheters to **L**ong Peripheral Catheters for non-central vascular access indications – a Clinical **E**ffectiveness Pilot **T**rial in pediatrics (**ComPLET**)
Principal Investigator: Alina Burek, MD
Sponsor (if not sponsored, indicate that study is investigator-initiated): Investigator-initiated, funded by Children's Research Institute

Section 1 Regulatory Criterion for Approval: Risks are Minimized

Risks to subjects are minimized: (i) by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- Risks must be identified and classified as risks that would only be present if the subject participates in the research versus those risks that would happen as part of routine care or regardless of the subject's participation.
- ONLY evaluate the **research** risks and consider how to minimize those risks:
  - Is the question important scientifically/scholarly to answer?
  - Is the study designed so the question can be answered?
  - Can less risky procedures answer the question?
  - Can fewer procedures answer the question?
  - Are the procedures needed at all?
  - Can additional procedures reduce risk?
  - Can different eligibility criteria reduce risk?
  - Are investigators and key personnel adequately qualified relative to the activities being performed and are the activities within each individual's scope of practice?
  - Are procedures that will answer the scientific question being done anyway? If so, can the data from these procedures be used to reduce the likelihood or magnitude of harm?

Protocol Summary/Submission Application

Study Design

A. Has this proposal undergone separate formal review to determine appropriateness of study design (i.e. formal Scientific Review Committee)?

☒**No** If NO, the IRB is responsible for determining that scientific design is appropriate

☐**Yes** If YES, describe the entity and outcome of the review (provide minutes or supporting documents in the submission package, if available): Click here to enter text.

B. Purpose of the study:

The purpose of the proposed clinical effectiveness pilot trial is to test the feasibility of a full-scale effectiveness trial comparing Peripherally Inserted Central Catheters (PICCs) to Long Peripheral Catheters (LPCs) in hospitalized pediatric patients. We aim to identify a population in which LPCs are safe and effective alternatives to PICCs for medium-term (5-14 days), non-central vascular access; data that will inform the design of a full-scale effectiveness study. Over time, use of LPCs should result in decreased inappropriate PICC utilization with a concomitant decrease in serious complications such as central line associated blood stream infection (CLABSI) and venous thromboembolism (VTE). We also aim to include patient/family feedback about their experience with these devices in the hospital.

C. Hypothesis/specific aims:

The aims of this pilot, randomized controlled trial are:

Aim 1*:* To assess the feasibility of a full-scale effectiveness trial comparing PICCs to LPCs in hospitalized pediatric patients in need of non-central, medium-term vascular access (5-14 days anticipated need).
Hypothesis: Feasibility of a full-scale effectiveness trial will be established by demonstrating that > 70% of eligible patients agree to enrollment and randomization, > 80% of randomized patients receive the assigned intervention, > 80% of providers involved find the study acceptable, and < 5% of data are missing.

Aim 2**:** To identify a population in which a LPC is a safe and effective alternative to a PICC for vascular access in hospitalized pediatric patients age > 2 years, in need of non-central, medium-term access.
Hypothesis: We hypothesize that LPCs are non-inferior to PICCs for delivery of peripherally compatible infusate needed for 5-14 days in hospitalized pediatric patients. We plan to determine the time-to-removal of the vascular access device, both secondary to completion of therapy and secondary to complications. Safety will be assessed by measuring complication rate (e.g., VTE, CLABSI, occlusion, dislodgement, phlebitis). Cross over rate will be closely monitored as well.

Aim 3: To engage patients and families as advisors in vascular access device selection.
We will describe the patient and family experience with device placement and maintenance as well as perceived patient and parent insertion-related and sedation-related distress.

D. Background, significance, and rationale (including description of preliminary studies and any results):

Many hospitalized children require a vascular access device (VAD) for delivery of life saving interventions such as intravenous fluids and antibiotics.[1] With the broad range of VADs available, and their different profile of complications,[2] it is essential that clinicians have access to rigorous evidence to guide the selection of the most appropriate VAD. Appropriate VAD selection results in treatment efficiency and a decrease in catheter-related complications.[1] The problem is, even the most current and comprehensive guideline for VAD selection published in 2020, the Michigan Appropriateness Guide for Intravenous

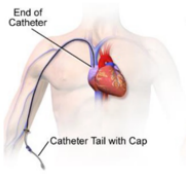
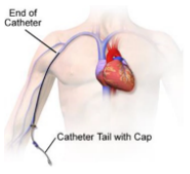
Catheters in Pediatrics (mini-MAGIC), has gaps in recommendations and relies on expert consensus recommendations, acknowledging the lack of effectiveness and safety data for some VADs.[1,3] Peripherally Inserted Central Catheters (PICCs, see ***Table 1***) are frequently used in hospitalized children for medium (5-14 days) and long-term access (> 14 days) and to administer solutions not compatible with peripheral infusion; however, concerns regarding potential inappropriate use (harm outweighing the benefits[4]) of PICCs were reported both in the adult and pediatric literature.[1,5,6] PICCs are central VADs associated with high rates of serious complications; Central Line Associated Blood Stream Infections (CLABSI) as high as 2-8.6% and Venous Thromboembolism (VTE) of 0-14% have been reported for PICCs.[2,7–11] At Children's Wisconsin, CLABSI was identified in 3.3% and VTE in 4.1% of PICCs during a 2012 to 2016 study period.[7] National collaboratives working to reduce hospital acquired conditions recognize CLABSI and VTE as 2 of the 9 *preventable* hospital-acquired conditions.[12]

One *critical* means of preventing PICC related complications and resultant patient harm is to prevent inappropriate placement of PICCs in cases when central venous access is not required (peripherally compatible infusate) and anticipated length of therapy is <14 days. Reducing inappropriate use of PICCs was shown to result in significant cost-savings over time, both in supplies, insertion and in cost reduction related to decrease in complications.[13,14] Attributable cost of CLABSI was reported to be $55,646 per patient[15], and that of VTE was $27,686.[16]

Need for feasible alternatives for medium-term non-central vascular access

To reduce inappropriate PICC utilization, feasible alternatives for medium-term, non-central venous access need to be identified and tested. Long Peripheral Catheters (LPCs, see ***Table 1***) have been recently adopted by some adult hospitals for short and medium-term venous access (<14 days) due to potential for fewer complications compared to PICCs.[17,18] Use of LPCs instead of PICCs for medium-term vascular access would benefit patients and healthcare organizations by reducing need for sedation [19] and lowering cost.[14,20] (***Table 1***) Unfortunately, there is a scarcity of literature evaluating the effectiveness of LPCs in pediatrics. The few published studies in this population generally describe program development and summarize retrospective data.[14,21,22] Prior studies are limited by small sample size [23–25], with poor generalization outside of specific populations, e.g., neonatal intensive care unit (NICU) [14,26] and cystic fibrosis [19,21,23]. Despite the low quality and quantity of published data, a few themes emerge. First, LPCs have longer dwell-time than the classic peripheral intravenous catheters (9.2+- 6 day vs 3.2+-2.1 days respectively; p<0.0001)[25], with an average LPC dwell-time of 4-12 days,[14,21–24,26,27] supporting their use for medium-term vascular access. Second, LPCs tend to have fewer significant complications compared to PICCs, aligning with findings in the adult literature. In one study, PICCs were associated with more complications during placement while LPCs had more complications during use.[22] A second study, a retrospective review of neonatal cases, showed that LPCs had no life-threatening complications while PICCs were associated with 4 life-threatening events during the study

Table 1: PICC versus LPC – Similarities and Differences

	PICC	LPC
		
Tip of the catheter	Central vein (e.g., superior vena cava)	Peripheral vein (e.g., basilic vein)
Type of infusate delivered	Vesicant and non-vesicant medications/solutions (e.g., chemotherapy)	Only non-vesicant medications/solutions (e.g., antibiotics)
Ultrasound guidance used	Yes	Yes
XR for tip location used	Yes	No
Sedation used	Commonly	No
Dwell-time	> 30 days	< 30 days
Used outside of the hospital setting	Yes	Variable (no at CW)
Blood-drawing abilities	Yes	Yes (but unclear for how long)
Complications	CLABSI and VTE Occlusion, dislodgement, leaking, phlebitis	Occlusion, dislodgment, leaking, phlebitis, infiltration
Estimated cost of supplies, labor, imaging *(Chenoweth et al)*	$590	$73

period.[14] Both studies were completed using retrospective analysis of electronic medical records (EMR), so more rigorous study designs comparing PICCs to LPCs are still needed. The feasibility of a randomized clinical trial comparing PICCs to LPCs in children with cystic fibrosis was proven possible in an Australian pediatric center, with a reduction of general anesthesia use for VAD placement (69% in PICCs vs 10% in LPCs).[19]

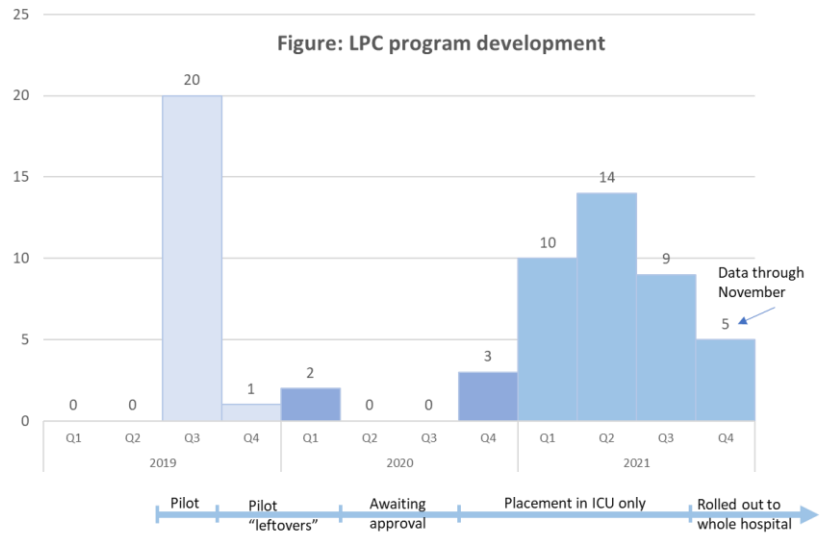
Preliminary work and results

We are one of the first few pediatric hospitals in the United States to implement and describe the development of an LPC program.[6] The LPC program was introduced at Children's Wisconsin (CW) in 2019 and was subsequently initiated in the intensive care units. In October 2021 the program expanded to the rest of the hospital. Our ability to place LPCs in hospitalized children gives us a significant advantage in obtaining high quality evidence regarding LPC use in pediatrics. In our initial test group of 20 successfully placed LPCs, there were no major complications such as VTE or CLABSI (***Table 2***). We did identify a 25% dislodgement rate that we are working to reduce by improving the LPC securement.

LPCs inserted (n)	20
Patients (n)	19
Age (years) median (IQR)	11 (7-15)
Male, n (%)	9 (45%)
Location, n (%)	
Acute Care unit	9 (45%)
Intensive Care unit	11 (55%)
Service, n (%)	
Critical Care	7 (35%)
Gastroenterology	6 (30%)
Hospital Medicine	4 (20%)
Oncology	3 (15%)
Anatomic Site, n (%)	
Cephalic vein	7 (35%)
Basilic vein	12 (60%)
Brachial vein	1 (5%)
Number of insertion attempts, n (%)	
1 attempt	19 (95%)
2 attempts	1 (5%)
Catheter size	
22 gauge	10 (50%)
20 gauge	10 (50%)
PIV insertion attempts prior to LPC,*n (%)	
0 attempts	12 (60%)
1 attempt	4 (20%)
2 attempts	3 (15%)
3 attempts	1(5%)
LPC Duration, days, median (IQR)	5.5 (1-9)
Remained until therapy completion, n (%)	11 (55%)
Complications, n (%)	
Occlusion	2 (10%)
Dislodgement	5 (25%)
Phlebitis	0 (0%)
Venous Thromboembolism	0 (0%)
Central Line Associated Blood Stream Infections	0 (0%)

Table 2: LPC data from prior study

Since the initial pilot of the LPC program, 43 LPCs have been placed at CW as standard of care (up until November 2021, see figure below). All LPCs were placed in the upper extremity (77% in the upper arm); 88% were placed in the PICU. The median (IQR) dwell-time was 6 (3-11) days; 14% remained in for > 14 days (max dwell-time 41 days), 19% for 7-14 days, and 58% for ≤7 days. Reason for removal was "no longer medically needed" in 70% (n=30) of the LPCs and complications in 21% (n=9). Most frequent complication was occlusion (n=3) and infiltration (n=2). These complications are similar to those of a peripheral IV. No clots or line infections identified.



E. Design and methods (including experimental design, technical details and laboratory methodology):

Study design:
Randomized clinical trial. We propose a parallel group, pragmatic randomized non-inferiority pilot trial design (*arm 1* and *arm 2*) (**Figure 1 below**) assessing the feasibility of a full-scale effectiveness trial comparing PICCs to LPCs for non-central, medium-term vascular access (5-14 days) in pediatrics.

Mixed methods (qualitative and quantitative data) will be used to determine patient/family experience.

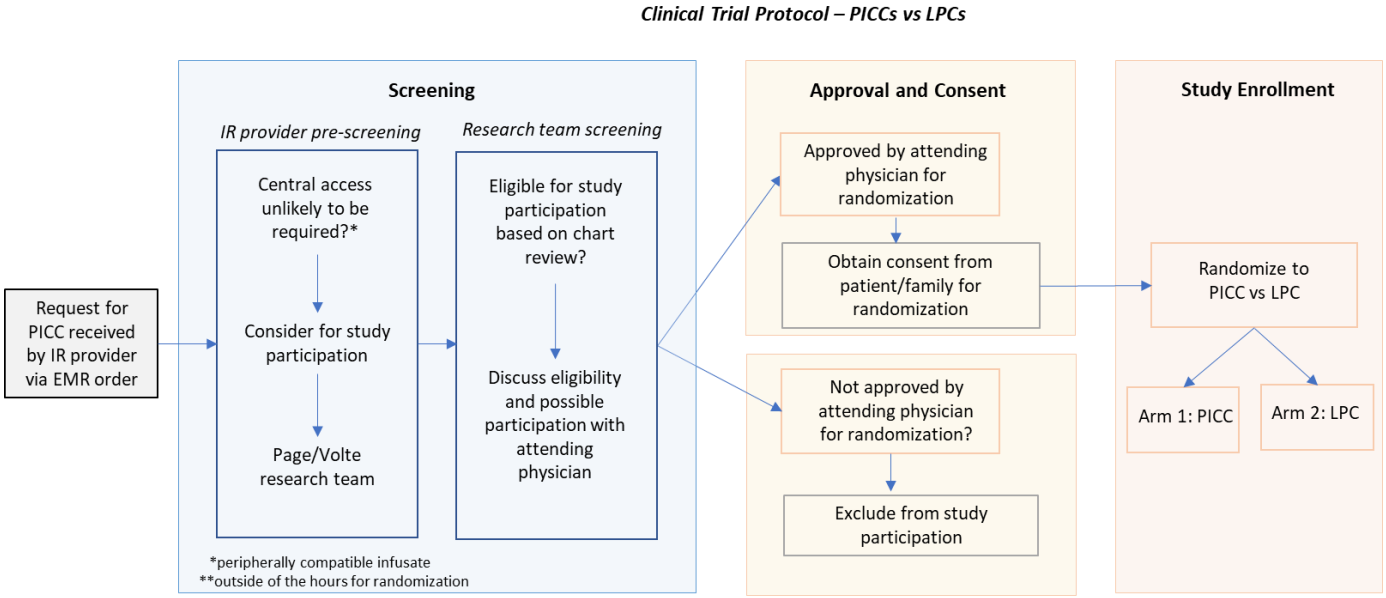
Setting and sample: This single center pilot study will take place at Children's Wisconsin main hospital in Milwaukee. We plan to use convenience sampling, enrolling Monday through Friday 8-5pm during the one-year timeline.

Inclusion criteria: patients age 2 to 17 years admitted to Children's Wisconsin and requesting placement of a PICC () for: (1) anticipated length of intravenous treatment of 5-14 days, (2) planning peripherally compatible infusates [28] (3) VAD not needed at discharge.
Exclusion criteria: non-English-speaking family, active bacteremia or VTE at site where device would be placed, urgent need of vascular access (within 4 hours), another central venous catheter already in place, device needed for any intervention requiring central access such as medications that cannot be given peripherally OR central monitoring. To be included in the study, the treating attending physician will need to give approval for participation and randomization.

Inclusion/Exclusion criteria for guardian participation in the semi-structured interviews: > 18 years old, English speaking.

Interventions:
After recruitment and consent, patients will be 1:1 randomized to receive:
1. **PICC:** Bard 3fr, 4fr or 6fr; Cook 4fr; or Medcomp 1.9fr and 2.6fr. (type and size to be selected based on interventional radiology standard protocol)
2. **LPC:** Bard Powerglide 8 cm, 20G and 22G. (size to be selected based on patient size)

Figure 1. Clinical Trial Protocol



Randomization:

Dr. Pan will generate the randomization numbers and they will available on RedCap to be accessed after consent. The randomization outcome will be conveyed to IR and to the attending physician.

F. **Research procedures such as lab draws (including volume of samples), ECG, imaging, clinical procedures, genetic testing, surveys (may attach activity table if available):**

The participants will enroll in the study prior to VAD placement; however, this procedure is based on clinical indications and part of routine care, so it is not a research procedure. The only research procedure for this study is the semi-structure interview and pain/anxiety assessments (see section on data analysis on section 6)

Describe what will happen to the subject solely for the purpose of this research study:

The **child participant** will undergo randomization, prospective health data collection, and pain/anxiety assessments related to VAD placement (1 anxiety survey before and 1 repeat anxiety survey with pain rating after VAD placement) solely for the purpose of this study.

The **adult participant (parent/guardian)** would complete anxiety assessments related to their child's VAD placement (1 survey before and 1 repeat survey after placement) and agreement to participate in a semi-structured interview after the VAD is removed. The child participant is welcome to contribute to the semi-structured interview responses with the parent as a child-parent dyad, but the child is not required to do so as part of the study.

The parent and child will be given the first survey to fill out prior to VAD placement. The study team member will distribute and collect the first survey. The repeat survey will be placed in the patient's binder. Following VAD placement (and once child is fully alert if sedation was used during placement), the study team member will either (1) return to distribute the repeat surveys to the family, or if unable (e.g. VAD is placed after business hours) (2) will Voalte the bedside nurse to hand the repeat survey papers to the guardian and child, and store them in the patient's binder upon completion. The study team member will collect the second completed surveys from the families. The study team member will enter the paper survey data into the REDCap database form associated with the participants, and then shred the paper versions.**Describe what is happening per protocol but is considered part of routine care (would happen even if the individual did not participate):**

VAD placement is part of the routine care for the population of interest (hospitalized children with given inclusion/exclusion criteria). All participants would receive a VAD (specifically a PICC) for vascular access even if they did not participate in the study. What the study offers is the opportunity to receive a different VAD (an LPC) that is also routine care just like the PICC, but may have a few benefits compared to PICCs This allows for comparison of those two VADs to determine which has the best effectiveness and safety profile making it the better option for vascular access. Per adult literature and a few studies in pediatrics (including our own local preliminary data), LPCs are safer than PICC regarding complications such as clots and line infections; however, they may not last as long as PICCs. Randomization to the LPC arm could pose the risk of early catheter failure (e.g., due to dislodgement) needing replacement of the VAD. Replacing the VAD will cause an additional poke for the patient (similar to replacing a peripheral IV).

Clinical Trial

A. Is this study a Clinical Trial/Clinical Investigation?

Clinical Trial *means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.* [45 CFR 46.102(b)]

Clinical Investigation *means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.* [21 CFR 56.102(c)]. Note: this also include biospecimens.

☐**No** If NO, skip questions B-H ☒ **Yes** If YES, answer the following questions B-H:

Protocol Summary/Submission Application

B. **What phase of clinical trial best describes this research?**

☐**Phase I** ☐ **Phase I/II** ☐ **Phase II** ☐ **Phase II/III** ☐ **Phase III** ☐ **Phase IV**
☒**Feasibility** ☐ **Pivotal (Feasibility vs Pivotal device studies)**

C. Is this trial "first-in-human" (in clinical trials, the first Phase-1 study in which a test product is administered to human beings)?

☒**No** ☐ **Yes**

If YES, the protocol must contain an adequate description of the pre-clinical research and/or other relevant data that supports the performance of the study.

D. Is this trial the first in a population (e.g., children)?

☒**No** ☐**Yes**

If YES, the protocol must contain an adequate description of the pre-clinical research and/or other relevant data that supports the performance of the study in the new population.

E. **Does this trial evaluate one or more** FDA-regulated products?

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) may be classified as drugs, devices, and/or biologics. Information on the classification of HCT/P's is available on this FDA website.

The 21st Century Cures Act excludes certain medical and decision support software from the definition of medical device meaning that such software is not subject to FDA regulations. Information regarding these exclusions is available on FDA's website for digital health. If uncertain whether a product under investigation is a medical device, contact the CW HRPP office.

☐**No** ☒ **Yes** If YES, indicate the following:

Product Type(s): Vascular access devices

Product Name(s):
1) Peripherally Inserted Central Catheters: Bard 3fr, 4fr or 6fr; Cook 4fr; or Medcomp 1.9fr and 2.6fr. (type and size to be selected based on interventional radiology standard protocol)

2) Long Peripheral Catheters: Bard Powerglide 8 cm, 20G and 22G. (size to be selected based on patient size)

If YES, also include in the submission package **IRB – Supplement Form – Drugs and Biologics** for studies of drugs and biologics and/or **IRB – Supplement Form – Devices** for medical device studies. These forms are found in IRBNet under Forms and Templates.

F. Will this trial enroll pregnant women or minors/women who are of child-bearing potential?

☐ **No** ☒ **Yes**

If YES, the protocol and consent must contain an adequate description of any known or anticipatable risks to pregnant women and fetuses and any measures to mitigate those risks. Birth control requirements, if applicable, must also be described. CW template pregnancy test language regarding disclosure of results must be included in parental permission/assent documents.

G. Does the sponsor intend to collect data on "pregnant partners" (sexual partners of clinical trial subjects who become pregnant while the subject is receiving investigational agents)?

☒**No** ☐**Yes**

If YES, review Children's Wisconsin IRB Position Statement Pregnant Subjects and Pregnant Partners found in IRBNet under Forms and Templates and on the HRPP web pages.

H. **Is this trial registered in** ClinicalTrials.gov?

Contact MCW CTSI if there are questions about what needs to be registered or visit their website for registration instructions.

☐**N/A, registration is not required for this trial (confirm with CTSI if uncertain)**

☐**No, but trial will be registered prior to enrolling any subjects**

☒**Yes, ClinicalTrials.gov #:** NCT05346406

For FDA-regulated and NIH funded clinical trials that are or will be registered in ClinicalTrials.gov, the following statement must be included verbatim in the consent/parental permission forms:

FDA: "A description of

this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

NIH: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Risks

A. Describe potential research-related risks and discomforts (consider physical, psychological, legal, social/economic/financial, loss of confidentiality, group harms); describe the probability, magnitude, and duration of the potential risks; do not address risks that would be present if the individual did not participate:

Physical risks: The subjects included in this study require VADs for medical treatment, which poses risks for complications and hospital-acquired conditions. Since it is not yet clearly known whether one VAD is more effective than the other in pediatric patients, the research randomization process could introduce physical risks that may not have occurred if the opposite VAD was selected by the medical team.

(1) Based on available literature, LPCs are safer than PICCs with fewer significant side effects (VTE, CLABSI) because they don't enter the central circulation. However, because LPCs are peripheral VADs (similar to a regular peripheral IV) they may not last as long as a PICC. Patients randomized to the LPC arm may be at higher risk for needing VAD replacement due to early catheter failure.

(2) VADs are sometimes used for lab draws to avoid extra poke to the patient. Both PICCs and LPCs can be used for lab draws; however, it is unknown if LPCs can sustain as many lab draws as PICCs before catheter failure.

(3) Most PICCs are placed under sedation while LPCs are placed awake. Randomization to the LPC arm would prevent the risks associated with sedation (e.g., nausea/vomiting, confusion). However, because the LPC will be placed in an awake patient (similar to a regular peripheral IV), there would be pain/discomfort with the placement, but this discomfort would be short lived (most discomfort is while the needle is inserted which takes a few seconds) and minimized using established comfort measures. Any other physical risks are expected to be comparable to ordinary medical care.

Psychosocial risks: Subjects and their guardians may feel discomfort participating in the structured interview about their experience with the VAD. Discomfort could arise from recalling stressful experiences during the child's hospitalization. These risks are expected to be comparable to ordinary life.

Privacy risks: Data security breaches could risk a loss of privacy for subjects included in this study.

B. Describe steps taken to minimize risks:

Physical risks: Subjects in this study will receive standard of care throughout their hospitalization, including monitoring and addressing complications. If a severe complication arises due to the randomly-assigned VAD, their medical treatment team will decide with the family whether to end participation in the randomized trial and choose alternative treatments. The study team will monitor data regularly during the course of the pilot study for early identification of unanticipated adverse outcomes related to VAD assignment, including cross over rate (LPC to PICC) Any reportable events will be disclosed to the Institutional Review Board within 24 hours and at time of continuing report. To reduce discomfort with VAD placement, VADs will be placed by trained professionals with prior experience. Child life specialists can be utilized to identify age specific technique for distraction and comfort. The participants will be offered comfort measure as per "CW Comfort Protocol for Needle Stick Pain" available on the Intranet.

Psychosocial risks: The study team member conducting surveys and interviews is not a part of the care team. The subject and guardian will be informed that their responses will not be shared with their medical team. If a subject reports significant distress answering research questions, the survey and interview will cease.

Privacy risks: A partial waiver of HIPAA authorization is being requested for PHI for screening and enrollment purposes, and this screening data PHI will be destroyed after patients have left the hospital. Only information authorized and consented by participating families will be collected and stored for research. Research data will be stored in a secure REDCap database on the Quantitative Health Sciences server.

Structured interview data will be audio-recorded with no identifiers and uploaded to a secure MCW-authorized transcription service. Transcripts will be stored in MAXQDA software on a password protected computer and audio files will be deleted after transcription. Members of the study team will have sole access to data collected for research purposes, and all have active CITI and HIPAA training. Participation in the randomization arm of the research study will be recorded in the electronic medical record according to CW procedures and will be safeguarded by the security features already established for medical records at CW. Signed copies of consent and authorization forms will be stored in a locked cabinet in the Hospital Medicine suite which is only accessible with CW badge access. When we prepare our reports or publications, we will summarize the results of the research in a manner that will not reveal the identities of children or their families.

Section 2 Regulatory Criterion for Approval: Benefits

Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

- If there is no benefit and no knowledge to be gained, there is no justification to expose subjects to risk.

A. Describe the potential benefits to science and/or society which may accrue as a result of this research:

Our pilot study will inform the future full-scale trial aimed to study the effectiveness and safety of LPCs in comparison to PICCs in the hospitalized pediatric population, a population in which effectiveness of LPCs has not been established in a rigorous matter. Use of LPCs in pediatric subgroups - neonates in the NICU and patients with cystic fibrosis - was studied [21,23], but even in these populations the quality of the evidence is low based on the retrospective nature of the study design. [29]Our cohort is novel in that it includes a large hospitalized pediatric population with varied disease processes that may include cystic fibrosis and perioperative care, but also patients treated for common pediatric conditions such as complicated community-acquired pneumonia, osteomyelitis, and appendicitis. Using comparative

effectiveness research design, [30] we aim to compare two VADs used in hospitalized pediatric patients (PICCs vs LPCs), both of which are currently available at CW. Based on preliminary data looking at LPC outcomes at CW, the complications seen with LPCs are similar to that of a regular peripheral IV. We anticipate that data from a well-designed clinical trial will benefit the field of hospital medicine by advancing clinical practice and supporting other pediatric institutions in implementing LPC programs targeted at reducing inappropriate use of PICCs. Over time, use of LPCs should result in decreased inappropriate PICC utilization with a concomitant decrease in serious complications such as central line associated blood stream infection (CLABSI) and venous thromboembolism (VTE).

B. Are there any benefits which may accrue to the individual subjects in this research (compensation is not considered a benefit)?

☐**No** ☒ **Yes**

If YES, describe: While this study hypothesizes non-inferiority of the LPC to the PICC VADs, it is likely that subjects randomized to the LPC will experience fewer serious complications (central catheter related infections and clots) based on data from the adult and pediatric literature.[14,31,32] Other benefits to the patient if randomized to interventional arm (LPC):
(1.) Because LPCs are placed awake similar to a traditional PIV, it avoids the use of sedation and, therefore, sedation-related complications (e.g. nausea/vomiting)[19]. (2). LPCs are more cost effective compared to PICCs,[14,19,23,24,33,34] 3. LPCs have higher rates of patient and family satisfaction based on 2 studies done in children with cystic fibrosis.[19,35]
Engaging subjects and guardians in the randomized groups for patient-reported outcomes research (survey and interview) may benefit them in that they are able to provide feedback from their experiences.

No other benefits to subjects are expected.

Section 3 Regulatory Criterion for Approval: Equitable Selection

Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

- No population is unfairly targeted
- No population is unfairly excluded
- Burdens are distributed fairly
- Benefits are distributed fairly

Protocol Summary/Submission Application

The research population includes the following:	Check all that apply:
Normal adults/health volunteers	☒
Inpatient population	☒
Outpatient population	☐
CW or MCW Employees/Staff	☐
Students of *(describe)* Click here to enter text.	☐
Residents/Fellows	☐
Prisoners	☐
Children	☒
Pregnant Women, Fetuses, Neonates (of uncertain viability or nonviable), after delivery, placenta, dead fetus, or fetal material	☐
Adults with Impaired Decision-Making Capacity (enrolled by legally authorized representative)	☐
Individuals with limited English proficiency *(specify anticipated primary language)*: Click here to enter text.	☐
Economically disadvantaged persons	☐
Educationally disadvantaged persons	☐
Other *(describe)*: Click here to enter text.	☐

A. Total number of human research subjects proposed:

Locally: We propose including 70 minors (patients) total in the randomization group (35 for LPC and 35 for PICC). We propose up to 70 adult guardians as participants in the surveys and structured interview.

/ Study-wide (if applicable): N/A

Describe what are these numbers are based on: In a prior study, we showed that 139 PICCs over a one-year period could have been avoided at our local hospital as they (1) delivered peripherally-compatible infusates, (2) stayed in for < 14 days and (3) were removed prior to discharge. This is the population that we target for our study. For this pilot trial, we plan to enroll 35 patients in each randomized study group (35 participants in arm 1 and 35 participants in arm 2 of the study). The study is not powered to detect statistical significance, but rather to assess the feasibility of this study protocol for a larger full-scale effectiveness trial and provide baseline estimates for the sample size calculations. With a **sample size of 60 or more** patient subjects, we will be able to estimate a participation rate of 70% (eligible patients agree to enrollment and randomization) within a 95% confidence interval of +/- 12%.

The decision to include up to 70 adult guardians in the semi-structured interview portion was made to reach thematic saturation in qualitative analysis. Selection criteria for the interviews will be based on the number needed to meet qualitative saturation of data. All parents who enroll in the study will be asked to participate in the structured interview until qualitative thematic saturation is met. As such, selection criteria in effect will be based on chronology of participation in the study and number of interviews obtained from participants who agreed.

Protocol Summary/Submission Application

B. How do you plan to identify subjects for recruitment or records for inclusion in the study?

The entry point into the study will be the interventional radiology (IR) team which currently places PICCs. Each patient who has an order for PICC placement entered in the electronic medical record will be pre-screened by the IR provider using the Research Subject Eligibility Checklist posted in the IR workroom. Then the research team will verify IR has used this checklist, and will also screen each potentially eligible participant. Then the research team will screen each potentially eligible participant to determine if the patient meets criteria for study participation.

When a potential participant is identified, the attending physician of record (primary physician) will have to give his/her approval for study participation and confirm that the VAD needed satisfies the inclusion criteria (e.g. assure the VAD is not needed for central monitoring). A research subject eligibility checklist has been created for this purpose. The checklist will be posted in the Interventional Radiology workroom and used by Interventional Radiology for pre-screening prior to contacting the study team. The study team will verify the Interventional Radiologist has used this checklist. One the Interventional Radiologist confirms subject eligibility, the checklist will be reviewed with the attending physician, either in person or via phone between the attending physician and study team member. Physician name, date/time, and person completing form (if study team member via phone) will be documented on the form in addition to the determination. The completed checklist form will be stored in the subject's research file. See attached document in this package for the form. Attending physician and IR provider determinations will be entered by the study team into the screening log and the full checklist forms will be kept in the subject's research record.

C. Eligibility Criteria (inclusion/exclusion criteria):

Inclusion criteria: patients age 2 to 17 years admitted to Children's Wisconsin with an order for placement of a PICC () for: (1) anticipated length of intravenous treatment of 5-14 days, (2) planning peripherally compatible infusates, (3) VAD not needed at discharge. Guardians of subjects enrolled in the randomization arm will be eligible for the structured interview study if > 18 year of age and English speaking. To be included in the study, the treating attending physician will need to give documented approval for participation and randomization using the research subject eligibility checklist, after Interventional Radiology and the PI have screened for eligibility.
Exclusion criteria: non-English-speaking family, active bacteremia or venous thromboembolism at site where device would be placed, central VAD already in place, urgent need of vascular access (within 4 hours), device needed for any intervention requiring central access such as medications that cannot be given peripherally OR central monitoring

D. Who will be responsible for determining whether potential subjects satisfy eligibility criteria and how will they do so?

Note: if the analysis of health information is necessary to determine eligibility, a medically-qualified person must be involved in the determination.

A provider will place an order for a medically-indicated vascular access device to Interventional Radiology (IR). IR will pre-screen the patient for potential eligibility in the study. IR will page/volte the research team to screen and apply the eligibility criteria for study participation. The PI Dr. Alina Burek will be responsible for making the final eligibility determination after approval by the primary attending physician of record and the interventional radiologist. If the attending physician, interventional radiologist, or PI determine the patient should not be approached, the patient will not be approached.

For the structured interviews in the randomized arms, the adult parent/guardian who signed the adult consent form to participate in the research study will be eligible.

E. Will recruitment materials be used?

☒**No** ☐ **Yes**

If YES, describe how and where materials will be posted/distributed: Click here to enter text.

Protocol Summary/Submission Application

Documents containing exact language to be used must be included in submission package for review and approval by the IRB. Review **Guidance – Recruitment for Human Subject Research** (found in IRBNet under Forms and Templates) for more information and instructions for logo use.

Section 4 Regulatory Criterion for Approval: Informed Consent Process

Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, §46.116./50.20.

- Circumstances of the consent process will provide the subject sufficient opportunity to consider whether to participate (this is an ongoing process and should be confirmed at the time of each interaction)
- Circumstances of the consent process will minimize the possibility of coercion or undue influence
- Information will be given in an understandable language
- Special issues that could present undue influence and need additional consideration: advertisements, payment for participation

Description of Process to Obtain Consent

Information regarding parental permission and assent is captured in Section 8: Vulnerable Populations.

A. WHO: List appropriately trained personnel *by role* rather than individual name (i.e., Investigators, Study Coordinators, etc.) who have been delegated authority by the PI to conduct the consent process, and indicate whether those individuals have an existing treating relationship with the potential subject:

Recruitment for the randomized arms will occur based on convenience sampling Mondays through Friday from 8am to 5pm. Subjects will first be pre-screened for eligibility by the interventional radiologist (IR) receiving an order for VAD placement. The IR will contact the study team to screen for eligibility. Since the randomization process may impact medical decision-making, the attending physician will be asked for permission by the study coordinator or the PI to approach the family. Documentation of the PI (Dr. Alina Burek)'s consultation with and approval by the attending physician will be recorded in a Research Note in the subject's EPIC medical chart. If approved, the attending physician will be asked to introduce the study team to the family, however if that is not possible he/she will be asked to identify a care team member with a treating relationship (e.g. resident, fellow, nurse) to introduce the study team to the family. The research coordinator will contact that care team member to accompany him/her to the patient room and perform the warm hand-off.

The research coordinator will then approach the subject and guardian to review the IRB-approved informed consent materials and invite them to participate in the randomization trial. After the guardian's written consent and authorization to collect PHI are obtained or declined, the research coordinator will contact the IR and attending physician to notify them of the decision and, if applicable, provide the VAD randomization assignment. For those who participate in the randomization arm, up to 70 families (up to 70 parents/guardians will be enrolled in a structured interview at the end of their hospitalization. This will be discussed with families during the initial informed consent process and if re-visited by the research coordinator for structured interview they will have the option to opt out at that time. Selection criteria for the interviews will be based on the number needed until qualitative thematic saturation is met. As such, selection criteria in effect will be based on chronology of participation in the study and number of interviews obtained from participants who agreed to be interviewed.

Consent and permission/assent to participate in the surveys before and after VAD placement will also be reviewed with the families during the consent discussion and details are included in the consent, assent, and permission forms.

B. WHEN: Describe when subjects are being informed of the research opportunity and how much time they are given to consider whether to participate:

Subjects will be informed of the research opportunity during their hospitalization, prior to VAD placement. This will occur if the order placement occurs between Monday through Friday from 8am to 5pm. Because urgent VAD placement need is an exclusion criteria (e.g. placement needed within 4 hours), subjects and guardians will be given time to consider whether to participate without undue time pressure. The consent discussion is estimated to take 30 minutes, but families may opt to take longer to decide including after the research coordinator makes first contact with them. Up to 1 hour from time of enrollment attempt will be given for families to decide.

C. WHERE and HOW: Describe the physical location of the consent discussion and how it will be conducted:

The consent discussion will occur in the patient room with the guardian(s) and patient. After approval from the attending physician and PI, the research coordinator will coordinate with an identified care team member who will introduce the study team member to the family as a warm hand-off. The research coordinator will then approach the family in the patient room with the appropriate documents. If parents are not present in the room, the research coordinator will not attempt recruitment. Treating physicians will not be present in the room during the consent discussion in order to mitigate perceived power dynamics. The research coordinator will re-introduce herself and her role and present the study using a script. If the family indicates they would like to learn more, the research coordinator will review all consent information and assent with the family via the printed form and verbally. Time will be given to answer any questions. If the subjects choose to enroll, the research coordinator will obtain 1) signed documentation of parental permission for minor's participation in the study, 2) signed documentation of assent from the patient (if patient is capable) on the assent form document for subjects aged 7-13 or an assent line on the parental permission form for subjects aged 14-17, and 3) adult consent from the parent who will participate in the surveys and agree to the interview. The family will be provided copies of all consent materials.

D. SPECIAL CONSIDERATIONS: Describe any subject compensation (reimbursement for expenses; compensation for time and effort):

Compensation will be provided to participants in appreciation for the time and effort taken to complete study survey and agreement to participate in semi-structured interview. A total of $75 will be provided to each family (parent/guardian-child dyad) enrolled who complete the surveys; completing the interview is not required for payment. The card will be handed to the parent/guardian.

E. If you are requesting to waive consent for some or all subjects, provide rationale:

We are requesting to waive consent for subjects who reach age of majority before study closure but are lost to follow-up. Lost to follow-up is defined in accordance with CW policy 'There is no longer regular contact with subjects and subjects are no longer reachable (lost to follow-up, contact information is not known or available).' A good faith effort (three contact attempts) will be made to reach each subject at age of majority.

Include **IRB – Request form for Alteration or Waiver of Assent, Consent, Parental Permission** (found in IRBNet under Forms and Templates) in the submission package.

Protocol Summary/Submission Application

Section 5 Regulatory Criterion for Approval: Documentation of Informed Consent

Informed consent will be appropriately documented or appropriately waived in accordance with §46.117/50.27.

A. Describe the plan for documentation of consent and process that is specific to the protocol and consistent with local requirements:

If you are requesting to waive documentation of consent/assent/parental permission, include **IRB – Request form for Alteration or Waiver of Assent, Consent, Parental Permission** (found in IRBNet under Forms and Templates) in the submission package.

Parental permission for minors' participation in the randomized study will be documented via signature on the informed consent-parental permission form. Minors who are capable of providing assent (age 7-17 years old, no documented developmental delay, not sedated) will a) sign a separate assent form if they are aged 7-13, or b) sign an assent signature line on the parental permission form if they are aged 14-17. Adult informed consent for the parents themselves as participants will be documented on a separate template with the adult participant signatures. Documents will be stored in a locked filing cabinet in the Pediatric Hospital Medicine suite in Children's Corporate Center, accessible only via CW Pediatric Hospital Medicine badge access.

Section 6 Regulatory Criterion for Approval: Safety Monitoring

When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

Considerations applicable to research that is deemed greater than minimal risk include:

- Who reviews safety data?
- What data are reviewed (safety and efficacy)?
- When/how often are data reviewed?

A. Is a Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) in Place?

☒No ☐ Yes ☐ N/A (study is not greater than minimal risk)

If YES, describe its members and how often they meet (you may include any DSMB/DMC charters in the submission package; once the study has been opened locally any DSMB/DMC reports should be submitted for review as reportable new information):

B. If there is no formal DSMB/DMC, describe the monitoring plan or indicate that the study involves no more than minimal risk (if the IRB disagrees and determines the study to be greater than minimal risk, the study will be deferred until an appropriate monitoring plan has been developed):

Dr. Burek (PI) will oversee the continuous monitoring of participant. She will accurately report any deviation from the protocol and identify adverse events. Monthly in person or zoom meeting with the research team will be conducted to discuss everything from the study enrollment to outcomes to safety monitoring and overall study progress.

Complications related to the two VADs will be monitored daily on-site while participants are hospitalized, and it is one of the main outcomes of the study. Safety assessment including analysis of complication rates, catheter failure

rate and cross-over rate will be conducted after enrolling 20 and then again after enrolling 40 out of the 70 participants. Participants' length of hospitalization is not dependent on the study participation and discharge criteria will be determined by their primary medical team. In case of a serious complication related to the VADs, the planned rescue intervention is to remove the VAD and treat the complication per routine clinical care. The primary attending physician will guide treatment of any catheter related complications in collaboration with the treating team. Treatment of catheter-related complications will not be the responsibility of the research team. Both VADs included in this study are regular standard of care at Children's Wisconsin, and treating their complication falls within the responsibility of the primary medical provider taking care of that patient. A comprehensive list of catheter related complications and their accepted definitions[36] are provided in the table below. Some of the complications (e.g., phlebitis and infiltration) are graded based on severity following established guidelines per the Infusion Therapy Standards of Practice.[36] Complications are divided into major (serious complications that generally require treatment) and minor complications (less serious complication that don't generally require treatment).

The proposed study is a feasibility pilot trial and not powered to detect a difference in efficacy between groups, therefore, efficacy stopping rules can't be established. See safety stopping rules below.

Complications	**Definition**
Major	
Central line associated bloodstream infection (CLABSI)	*NHSN surveillance definition: A laboratory confirmed infection where a CVC is in place for >2 calendar days prior to a positive blood culture and is also in place the day of or day prior to culture.*
Catheter-associated blood stream infection (CABSI)	*A bloodstream infection (BSIs) originating from either peripheral intravenous catheters (PIVCs) and/or central vascular access devices.*
Catheter-related blood stream infection (CR-BSI)	*It is diagnosed if the same organism is isolated from a blood culture and the tip culture, and the quantity of organisms isolated from the tip is greater than 15 colony forming units (CFUs). Alternatively, differential time to positivity (DTP) requires the same organism to be isolated from a peripheral vein and a catheter lumen blood culture, with growth detected 2 hours sooner (ie, 2 hours less incubation) in the sample drawn from the catheter.*
Catheter-related venous thromboembolism	*Positive clot on imaging (ultrasound) at catheter site.*
Minor	
Infiltration/Extravasation	*The fluid being infused leaks out into of the vein into the surrounding tissue ("tissuing"). Graded 1-4 on the bases of increased severity.*
Dislodgement	*Catheter accidentally comes out.*
Occlusion	*Inability to flush the catheter.*
Mechanical failure	*Catheter fracture, mispositioning, kinking.*
Leaking	*The fluid being infused leaks out of the exposed catheter part into the surrounding environment*
Phlebitis	*Pain and erythema/swelling at the site of catheter. Graded 1-5 on the basis of increased severity.*

Protocol Summary/Submission Application

C. Have stopping rules been established for the study (to evaluate whether the objectives have been met, or that the objectives cannot be met, or that the accumulated data indicates that the risks exceed the benefits of the study)?

☐**No** ☒ **Yes** ☐ **N/A (study is not greater than minimal risk)**

If YES, describe the stopping rules: The study will be stopped so the protocol can be re-evaluated for the following reasons: (1) catheter-related bloodstream infections identified in > 5 patients per arm (~15% of cohort), (2) catheter related venous thromboembolism identified in > 5 patients per arm (~15% of cohort), (3) catheter failure rate (meaning catheter had to be removed prior to completion of therapy intended for) > 50%, (4) cross-over rate > 30%. Those stopping rules will be assessed continuously from the time first patient is enrolled until study completion.

D. Describe procedures to be employed in analyzing data (including a power analysis):

Quantitative. Study data will be collected using REDCap. Feasibility outcomes will be collected from (1) screening logs maintained by the study team (rate of enrollment, assigned intervention), (2) ease/difficulty of VAD placement (scale 0=worse to 10=best) to determine VAD acceptability[19], and (3) REDCap datasheet for assessing missed data. Patient demographics (age, gender, race/ethnicity), clinical factors (reason for admission, co-morbidities, reason for PICC/LPC request, therapy to be infused, requesting service, hospital floor), VAD data (VAD type and size placed, insertion site/vessel, sedation, number of attempts, additional VADs), effectiveness data (time-to-removal of VAD, prolonged NPO, number of lab draws from VAD, number of non-VAD blood draws) and complications requiring medical intervention will be collected using the EMR and daily (Monday-Friday) check-ins with the bedside nurse. Procedural pain with non-sedated VAD placement will be assessed in patients age > 5 years by the RC within 24 hours of insertion using the Faces Pain Score (FPS) or the 0-10 pain scale depending on the developmental age of the patient. Patient/parent anxiety and overall experience with VAD placement will be assessed on a 0-10 scale (0= lowest, 10=highest) and using the short State-trait anxiety inventory (STAI) that is validated in children 5 and older.

Descriptive statistics will be used to report feasibility outcomes and explore clinical factors (see above). Cross over rate will be calculated as the proportion of the number of subjects who crosses from the randomized arm/line to a different arm/line. The exact Clopper-Pearson 95% confidence interval will be generated. Time-to-device removal for all reasons will be compared using a t-test. Non-inferiority of LPCs to PICCs will be demonstrated if the 95% confidence interval of the mean difference lies above -1 (non-inferiority margin: 1 day). The remaining outcomes will be compared using Chi-square test or Fisher's exact for categorical variables and t-test or Mann-Whitney-Wilcoxon test for continuous variables. Where necessary for parametric assumptions, appropriate transformations will be employed. Non-parametric tests will be used where parametric assumptions are not satisfied. Logistic regression or general linear model will be performed to control the potential confounders.

The study is not powered to detect statistical significance, but rather to assess the feasibility of this study protocol for a larger full-scale effectiveness trial and provide baseline estimates for the sample size calculations. With a sample size of 60 or more patient subjects, we will be able to estimate a participation rate of 70% (eligible patients agree to enrollment and randomization) within a 95% confidence interval of +/- 12%.

Qualitative. We will perform semi-structured interviews in a subgroup of the study participants; the adult guardians will be asked to participate as research subjects. We anticipate interviewing up to 35 participants from each randomized study group (70 total), but sample size will be determined by data saturation. Interviews will be completed by the research team within the week following completion of therapy, either in person (if the patient is still hospitalized) or via phone (if the patient was discharged). The main purpose of the interviews is to understand the patient's and family's lived experience with device insertion and ongoing maintenance during the time of participation in the study. The child is welcome to participate in the interview with their adult guardian but not required to. Their advice on ways to improve the process of insertion and/or maintenance will be collected as well. Interviews will be audio-recorded, transcribed verbatim, and uploaded into MAXQDA Qualitative Analysis software for coding. We will use a team-based inductive coding strategy, followed by theme identification.

Protocol Summary/Submission Application

Section 7 Regulatory Criterion for Approval: Privacy and Confidentiality

When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- Privacy refers to persons and their interest in controlling access to themselves
- Confidentiality refers to agreements with the subject about how data are to be handled

A. Provisions for the protection of privacy of subjects (having control over the extent, timing, and circumstances of sharing oneself [physically, behaviorally, or intellectually] with others):

Informed consent and enrollment discussions will occur in the private patient rooms within the hospital. Voluntariness of the study will be emphasized, including that subjects may select to enroll in the randomization arm (if pre-approved by the attending physician) or not to enroll at all. Subjects may choose whether or not to participate in the structured interviews after the vascular access device is removed, and if they do participate in the interview they may stop at any time. Subjects will be informed that they can stop participating in the project at any time during active involvement, and the consent form provides instructions for discontinuing participation after data is collected (i.e. removal of their health information from the study.) A HIPAA authorization is provided with the informed consent documentation, so subjects/families may choose whether to authorize access to health data as part of participation in the study. Privacy of subject data will be protected by using the Quantitative Health Sciences' secure REDCap server and only members of the study team will have permissions to access this database. Audio files for transcription will be deleted immediately following transcription, and transcripts will be de-identified and stored in the MAXQDA database on a password protected computer; MAXQDA does not use the Internet so it is not vulnerable to hacking.

B. Provisions to maintain the confidentiality of data (the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure, without permission):

Quantitative research data will be stored in REDCap hosted on Quantitative Health Sciences server within the Children's Research Institute. Qualitative data from the structured interviews will be audio-recorded and transcribed in de-identified form (i.e., any identifiers will be redacted from the transcripts). Only members of the study team will have access to the REDCap and transcripts.

C. If paper records are being maintained, indicate where paper documents will be kept and how secured (This includes hard copies of signed consent forms, as well as any other documents containing subject PHI):

Paper signed consent/assent forms will be stored in a locked filing cabinet in the Pediatric Hospital Medicine suite in Children's Corporate Center. The suite is also locked by badge access.

D. **Describe whether data will be shared outside MCW/CW, with whom (include outside collaborators and their institutions), and how (anonymous, identifiable, coded, de-identified [review OHRP guidance if uncertain]):**

If an investigator leaves MCW/CW during the study and the PI intends for the individual to continue to work on the study as a collaborator, this section must be updated and submitted as amendment package for IRB review. The CW HRPP will need to consider whether the investigator is conducting human subject research, whether data are appropriately protected, and whether a reliance agreement will need to be executed with the investigator's new institution.

No data will be shared outside MCW/CW.

Protocol Summary/Submission Application

E. Will a Certificate of Confidentiality (CoC) be obtained for this research or is one already in place?

Certificates of Confidentiality are issued automatically when:

- *Research is conducted or supported by NIH and falls within the scope of the NIH policy.*
- *Research is conducted or supported by the CDC and involves the collection of identifiable, sensitive information.*
- *Research is funded by the FDA in whole or in part and involves the collection or use of identifiable, sensitive information as defined in 42 U.S.C. 241(d).*

If you need help in making the determination, contact the HRPP office at 414.337.7133.

☐ **No** ☐**Yes** ☒ **N/A (study is not conducted, supported or funded by NIH/CDC/FDA)**

If YES, the required disclosure language must be included in the consent form(s) (see NIH website for suggested consent language).

Data Security Provisions

All research projects that collect electronic data must use appropriate security measures to ensure that data are protected from theft or loss in order to prevent breaches of confidentiality. You must indicate what encryption tools will be used from the options below, or indicate further below why they are not necessary.

The IRB will not review this protocol unless you indicate the encryption tools being used to secure your research data. If you do not have encryption in place on your systems, contact your Information Management Systems support team to arrange for one of the encryptions options listed below.

The following encryption products employ cryptographic modules that the National Institute of Standards and Technology has certified as meeting FIPS 140-2 requirements. Children's Hospital and Health System endorsed the use of these products made to encrypt hard drives and removable media. All electronic research data must be encrypted using one or more of these products.

This protocol summary/submission application must be kept current and revised via the amendment process for IRB approval if any security measures change during the course of the research study.

Indicate which encryption tools you are using to secure your research data:

Key: HD = Hard Drive; RS = Removable Storage (USB flash drive, CD, etc.); PD = Portable Device (iPod, iPhone, PDA, etc.)

☐	**Credent Mobile Guardian (RS, PD)**	☐	**McAfee Endpoint Encryption (HD, RS)**
☐	**GuardianEdge Hard Disk and GuardianEdge Removable Storage Encryption (HD, RS, PD)**	☐	**Seagate Secure Self-Encrypting Drives (HD when encryption option is enabled)**
☐	**IronKey encrypted flash drives (RS)**	☐	**Symantec Endpoint Encryption (HD, RS, PD)**
☐	**SafeNet Protect Disk and SafeNet Protect File (HD, RS)**	☐	**WinMagic SecureDoc encryption (HD) (for MCW owned computers)**
☐	**Microsoft Bitlocker (HD, RS when used with Windows 7 and FIPS compliant algorithms are enabled)**	☐	**PGP Whole Disk Encryption and PGP Portable (HD, RS)**
☒	**OTHER (describe):** REDCap hosted on Quantitative Health Sciences server		
NOTE: BOX is not a CW-approved tool for securing protected health information and cannot be used for research.			

Does not apply because:

☐	**Data are de-identified – no PHI collected (provide detailed information on data elements in the protocol summary/submission application)**	☐	**Data are stored on BOTH CW and MCW secured shared drives**

Protocol Summary/Submission Application

☐	**Data are stored on CW secured shared drives**	☐	**Data are stored on paper only**
☐	**Data are stored on MCW secured shared drives**	☐	**OTHER (describe):** Click here to enter text.

Section 8 Regulatory Criterion for Approval: Vulnerable Populations

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Additional steps to minimize coercion and undue influence:

- Assessment of capacity
- Permission of a representative
- Assent
- Witness to the consent process

Subpart D—Additional Protections for Children Involved as Subjects in Research (FDA: In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with 21 CFR part 50, subpart D.)

A. Do you intend to enroll children as subjects?

Yes

B. What is the age range of the children in this research?

2 years through 17 years old

C. Where will the children participate? (Check all that apply):

☒ **CW Hospital/Facility:** Children's Wisconsin-Milwaukee Hospital

☐ **CW Outpatient Clinic/Facility:** Click here to enter text.

☐ **Froedtert Facility:** Click here to enter text.

☐ **MCW lab/office:** Click here to enter text.

☐ **Home**

☐ **School**

If School is checked, have you obtained the necessary permission from the school district?

☐**No** ☐ **Yes** (if YES, include documentation of permission in submission package)

☐ **Other - Specify:** Click here to enter text.

If Other is checked, have you obtained the necessary permission?

☐**No** ☐ **Yes** (if YES, include documentation of permission in submission package)

D. Are any of the children Wards (46.409) of the State or any other agency, institution, or entity?

☒**No** ☐ **Yes**

If YES, contact the HRPP office prior to submission and provide protocol-specific details:

E. Risk Levels For Studies Involving Children

Check the category below that best represents the degree of risk and benefit to which the children in this study will be exposed.

More than one category may be indicated such as when a protocol involves both an experimental and a control group. In these cases, specify which category you believe applies to which group. The IRB will consider the Principal Investigator's assessment and rationale regarding the risk level for this study but it is ultimately the IRB's responsibility to determine appropriate risk levels.

☐ **Risk Level 1 (46.404/50.51):** (Research not involving greater than minimal risk.) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Provide protocol specific rationale (for each group):

☒ **Risk Level 2 (46.405/50.52):** (Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.) More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being.

Provide rationale for why/how:

(a) **the risk is justified by the anticipated benefit to the subjects (for each group):** Using comparative effectiveness research design, we aim to compare two VADs used in hospitalized pediatric patients (PICCs vs LPCs), both of which are currently available for routine care at CW. Even if not enrolled in the study, the study participants would require the placement of a VAD (PICC) for delivery of therapies such as IV fluids or antibiotics. (1)PICC (control) group: This group is receiving the VAD that the primary medical team planned to use for prolonged medical therapy (5-14 days). Because a PICC line is a central line, in rare situations (3-4% of cases)[7] a serious complication such as blood stream infection or clot can develop. Those complications require medical treatment (e.g., anticoagulation or antibiotics) and VAD removal. PICCs have other complications that are more minor such as occlusion, dislodgment, mechanical failure that if were to happen would require replacement of the VAD. PICCs generally are placed under sedation with the additional risk of sedation related complications (nausea/vomiting) and require an XR to confirm tip location. However, the anticipated benefits of using a PICC are many. The PICC stays in for weeks to months, so the medical therapy is not interrupted, in general no extra VADs are needed because PICCs have an 80-90% completion of therapy. By staying in longer, extra pokes for additional VADs are avoided. PICCs can also be used for blood draws, so additional pokes for blood draws are avoided. (2) LPC (interventional) group: LPCs are peripheral VADs similarly to a traditional PIV. Because they are longer (catheter length 8 cm vs traditional PIV < 4 cm) they last longer (>5 days LPC vs 2-3 days PIV). The most common complications for an LPC are dislodgment, occlusion, infiltration which would require the replacement of the VAD. LPCs stay in until completion of therapy in 70-80% of cases. LPCs are placed awake with topical anesthetic only. LPCs do not require a XR to confirm placement. Because LPCs tend to come out easier due to those minor complications, the patient may have extra pokes for replacement of the VAD. LPCs can be used for blood draws but it's unclear for how long they can withstand lab draws before they would clog. LPCs are more cost effective as compared to PICCs.
For the pain/anxiety scales assessing VAD placement experience, the risk of discomfort in answering these questions is the same as what is typically asked about in routine examination

during medical treatment and care.

For the structured interview following VAD removal, no more than minimal risk is anticipated; risks could include discomfort reflecting on the hospital experience, but this is not expected to be discomfort beyond that experienced in daily life.

(b) **the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches (for each group):** The most important potential benefit of the LPC over the PICC is reduced rate of serious complications such as central line related blood stream infections and clots. The anticipated reduction in central line related complications, sedation related complications, and healthcare costs outweigh the risk of early catheter failure in the LPC group due to minor complications.

The benefit of the PICC over the LPC is its known longevity for completion of therapy and reduction of potential additional pokes or replacement VADs.

☐ **Risk Level 3 (46.406/50.53):** (Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.) More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject.

Which intervention(s) or procedure(s) present more than minimal risk without offering the prospect of direct benefit to individual subjects (for each group):

Provide rationale for why/how:

(a) **the risk of the intervention(s) or procedure(s) represents a minor increase over minimal risk (for each group):** Click here to enter text.

(b) **the intervention(s) or procedure(s) presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations (for each group):** Click here to enter text.

(c) **the intervention(s) or procedure(s) is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition (for each group):** Click here to enter text.

☐ **Risk Level 4 (46.407/50.54):** (Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.) The proposed research does not meet the criteria of the above categories but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Provide justification for why this research of this risk level should be approved (for each group):

Protocol Summary/Submission Application

Parental Permission (46.408/50.55)

F. What permission will be obtained from the parents?

In general, permission from both parents is required for research involving children unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. However, for Categories 404/51 & 405/52, the IRB may find that the permission of one parent is sufficient. Permission from both parents should be obtained whenever possible regardless of risk level determination.

☐ **Permission will be obtained from both parents where possible**

☒ **Permission from only one parent is being requested**

☐ **A waiver of parental permission is being requested** (complete **IRB – Request form for Alteration or Waiver of Assent, Consent, Parental Permission** found in IRBNet under Forms and Templates)

☐ **A waiver of DOCUMENTATION of parental permission is being requested** (complete **IRB – Request form for Alteration or Waiver of Assent, Consent, Parental Permission** found in IRBNet under Forms and Templates)

G. If the research is being conducted in a group setting (e.g., a classroom), in which some children have permission to participation and some do not, what is the process to ensure that those children who do not have parental permission do not participate in the research.

N/a

Assent (46.408/50.55)

Adequate provisions must be made for soliciting the assent of children when in the judgment of the IRB the children are capable of providing assent and for soliciting the permission of their parents or guardians.

H. Indicate whether the children you intend to include in the research are generally capable of providing assent taking into account the ages, maturity and psychological state of the children proposed to be involved. Please be specific:

☐ **All are capable**

☐ **None are capable: Explain:** Click here to enter text.

☒ **Some are capable: Explain:** The age inclusion range for the study is 2 to 17 years old. Maturity level will differ by age and developmental status. The trial is for medically indicated vascular access devices during hospitalization; it is possible that some minors may be experiencing psychological or physical distress related to needing a device placed during their hospitalization. Assent will be sought for children aged 7 years or older, alert (not under sedation), and intellectually capable of providing assent (e.g. no developmental delay). An assent form is included with the submission package.

I. If children are capable of providing assent, are you planning to obtain assent from the children?

☒**Yes** ☐ **No** ☐ **N/A – none are capable**

If YES, describe the proposed process for obtaining assent, including who will be involved and the setting and circumstances under which it will be sought: Written assent will be obtained from minors who are capable of providing assent, on a signature line on the separate assent form. Minors' capability is defined as age 7 to 17 years old, no documented developmental delay, and not under sedation at time of recruitment attempt. For those capable, the research coordinator will ask the subject whether they are willing to participate in the research study.. The assent form at third-grade reading level will be reviewed with the capable child aged 7 years -13 years after

the full consent form is reviewed with the parents and child. For minors aged 14 years – 17 years, the research coordinator will review the parental permission form with the parents and for permission and assent. Signatures will be requested once both the guardians and minor aged 7 years or older and capable are fully informed of the study and agree to participate. Children aged 7-13 years old will sign the assent form, and children 14-17 years old will sign an assent signature line on the parental permission form.

If NO, a waiver of assent is being requested (complete IRB – **Request form for Alteration or Waiver of Assent, Consent, Parental Permission** found in IRBNet under Forms and Templates).

J. If assent will be obtained, describe the process and select how assent will be documented. Include in the submission package proposed assent forms or child information sheet, if any.

Describe the process:

☐ All minors will sign the assent signature line on the parental permission form

☐ All minors will sign a separate assent form

☒ Minors in the age range of **14 to 17 years will sign the assent signature line on the parental permission form, and minors in the age range of 7 years to 13 years** will sign a separate assent form

☐ Verbal assent will be obtained and discussion documented in research records

K. Describe the plan for obtaining legally effective informed consent and HIPAA Authorization at the age of majority [18] or describe why it is not applicable (review **Guidance – Consent for Continued Participation When a Child Reaches Age 18** found in IRBNet under Forms and Templates**):**

Since the randomized clinical trial arm is using FDA regulated devices, obtaining new consent at Age of Majority is required while the study is ongoing (i.e. not closed out, data still being accessed for analysis). We have attached a document to this package that will be mailed to subjects if they reach Age of Majority before the study is closed, including an updated legal consent and a HIPAA authorization. Subjects will be contacted by phone in addition to mail. In the assent form we have included standard age of majority language.

If a subject is lost to follow-up following their 18th birthday but their data is still being used in the study, we are requesting a consent and HIPAA waiver to use that data. Lost to follow-up is defined in accordance with CW policy 'There is no longer regular contact with subjects and subjects are no longer reachable (lost to follow-up, contact information is not known or available).' A good faith effort (three contact attempts) will be made to reach each subject.

If a subject's 18th birthday happens while they are still in the hospital, the study team will bring the clinical intervention consent from that their parent/guardian signed, review it with the subject, and ask them to sign that form as legally effective consent if they still want to be in the project.

Contact the CW HRPP office to obtain appropriate supplements if you intend to enroll other vulnerable populations such as pregnant women, fetuses and neonates, prisoners (including incarcerated minors), or cognitively impaired adults.

Protocol Summary/Submission Application

Section 9 Potential Conflicts of Interest

Relationships of all members of the research team: Do any research personnel or any of their family members (spouse or dependent children) have an incentive or interest, **financial or otherwise**, which may appear to affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity?

☒**No** ☐ **Yes** If YES, for each individual provide a description of each situation (including dollar values if applicable) as a separate document in the submission package which will be shared with the CW Conflict of Interest Committee.

It is the PI's responsibility to review applicable MCW/CW policies on conflict of interest with every study team member and determine whether any member has a Significant Financial Interest related to this project.

- ***For MCW faculty or staff, refer to MCW's Research Financial Conflicts of Interest Policy.***
- ***For employees of Children's, refer to Children's Research Conflict of Interest Policy.***
- ***For subcontractors or physicians/staff who are employed outside of Children's or MCW, contact Tom Twinem at 414-266-2215 for further guidance.***

FINANCIAL INTEREST includes any current **or anticipated** ownership interest or other financial relationship with any company or entity that sponsors, provides support, or otherwise has a financial interest in the conduct or outcome of this research protocol ("Financially Interested Organization"). This includes:

- ✓ Any related party who performed any work (not directly related to the costs of conducting research) within the past 12 months for a Financially Interested Organization.
- ✓ Any related party who received compensation (not directly related to the costs of conducting research) within the past 12 months from a Financially Interested Organization. This includes paid/reimbursed travel.
- ✓ Any related party who anticipates performing any work and/or receiving any compensation within the next 12 months (not directly related to the costs of conducting research) from a Financially Interested Organization. This includes paid/reimbursed travel.
- ✓ Any related party that maintained a board or executive relationship related to the research, regardless of compensation.
- ✓ Any related party who owns stock, stock options or other forms of ownership in a Financially Interested Organization. This does not include stock/stock options held in mutual, pension, or investment funds over which the investor has no control with regard to investment decisions.
- ✓ Any related party who has any intellectual property related to the proposed research (e.g., named as an inventor in an issued patent or patent application, license fees, technology transfers, current or future royalties from patents and copyrights).
- ✓ Your department/institution/organization has a financial interest in the agent under investigation or in a company that could benefit from the study findings, or receives significant financial support from such a company.

Section 10 Bibliography

List pertinent literature references:

[1] R.S. Paterson, V. Chopra, E. Brown, T.M. Kleidon, M. Cooke, C.M. Rickard, S.J. Bernstein, A.J. Ullman, Selection and insertion of vascular access devices in pediatrics: A systematic review, Pediatrics. 145 (2020) S243–S268. https://doi.org/10.1542/peds.2019-3474H.

[2] A.J. Ullman, N. Marsh, G. Mihala, M. Cooke, C.M. Rickard, Complications of central venous access devices: A systematic review, Pediatrics. 136 (2015) e1331–e1344. https://doi.org/10.1542/peds.2015-1507.

[3] A.J. Ullman, S.J. Bernstein, E. Brown, R. Aiyagari, D. Doellman, V.E.S. Faustino, B. Gore, J.P. Jacobs, J. Jaffray, T. Kleidon, P. V. Mahajan, C.A. McBride, K. Morton, S. Pitts, E. Prentice, D.C. Rivard, E. Shaughnessy, M. Stranz, J. Wolf, D.S. Cooper, M. Cooke, C.M. Rickard, V. Chopra, The Michigan appropriateness guide for intravenous catheters in pediatrics: miniMAGIC, Pediatrics. 145 (2020) S269–S284. https://doi.org/10.1542/peds.2019-3474I.

[4] K. Fitch, S.J. Bernstein, M.D. Aguilar, B. Burnand, J.R. LaCalle, P. Lazaro, M. Van Het Loo, J. Mcdonnell, J.P. Vader, J.P. Kahan, The RAND/UCLA Appropriateness Method User's Manual, 2001.

[5] C. Gibson, B.L. Connolly, R. Moineddin, S. Mahant, D. Filipescu, J.G. Amaral, Peripherally inserted central catheters: Use at a tertiary care pediatric center, J. Vasc. Interv. Radiol. 24 (2013). https://doi.org/10.1016/j.jvir.2013.04.010.

[6] A.G. Burek, J. Parker, R. Bentzien, L. Talbert, M. Havas, S.J. Hanson, The Development of a Long Peripheral Catheter Program at a Large Pediatric Academic Center: A Pilot Study., Hosp. Pediatr. 10 (2020) 897–901. https://doi.org/10.1542/hpeds.2020-0181.

[7] P.J. Noonan, S.J. Hanson, P.M. Simpson, M. Dasgupta, T.L. Petersen, Comparison of complication rates of central venous catheters versus peripherally inserted central venous catheters in pediatric patients, Pediatr. Crit. Care Med. 19 (2018). https://doi.org/10.1097/PCC.0000000000001707.

[8] D.G. Maki, D.M. Kluger, C.J. Crnich, The risk of bloodstream infection in adults with different intravascular devices: A systematic review of 200 published prospective studies, Mayo Clin. Proc. 81 (2006). https://doi.org/10.4065/81.9.1159.

[9] V. Chopra, S. Anand, A. Hickner, M. Buist, M.A.M. Rogers, S. Saint, S.A. Flanders, Risk of venous thromboembolism associated with peripherally inserted central catheters: A systematic review and meta-analysis, Lancet. 382 (2013) 311–325. https://doi.org/10.1016/S0140-6736(13)60592-9.

[10] T. Xu, L. Kingsley, S. DiNucci, G. Messer, J.H. Jeong, B. Morgan, K. Shutt, M.H. Yassin, Safety and utilization of peripherally inserted central catheters versus midline catheters at a large academic medical center, Am. J. Infect. Control. 44 (2016). https://doi.org/10.1016/j.ajic.2016.09.010.

[11] H. Seo, D. Altshuler, Y. Dubrovskaya, M.E. Nunnally, C. Nunn, N. Ello, J. Papadopoulos, X.J. Chen, The Safety of Midline Catheters for Intravenous Therapy at a Large Academic Medical Center, Ann. Pharmacother. 54 (2020). https://doi.org/10.1177/1060028019878794.

[12] A. Lyren, R.J. Brilli, K. Zieker, M. Marino, S. Muething, P.J. Sharek, Children's hospitals' solutions for patient safety collaborative impact on hospital-acquired harm, Pediatrics. 140 (2017). https://doi.org/10.1542/peds.2016-3494.

[13] L.I.M. Pernar, L.L. Wolf, A. Seshadri, V. Patel, Impact of a Surgeon-Led Peripherally Inserted Central Venous Catheter Team on Peripherally Inserted Central Venous Catheter-Related Complications and Costs, Surg. Infect. (Larchmt). 17 (2016) 352–356. https://doi.org/10.1089/sur.2015.093.

[14] K.B. Chenoweth, J.W. Guo, B. Chan, The Extended Dwell Peripheral Intravenous Catheter Is an Alternative Method of NICU Intravenous Access, Adv. Neonatal Care. 18 (2018) 295–301. https://doi.org/10.1097/ANC.0000000000000515.

[15] A. Goudie, L. Dynan, P.W. Brady, M. Rettiganti, Attributable cost and length of stay for central line-associated bloodstream infections, Pediatrics. 133 (2014). https://doi.org/10.1542/peds.2013-3795.

[16] A. Goudie, L. Dynan, P.W. Brady, E. Fieldston, R.J. Brilli, K.E. Walsh, Costs of venous thromboembolism, catheter-associated urinary tract infection, and pressure ulcer, Pediatrics. 136 (2015). https://doi.org/10.1542/peds.2015-1386.

[17] N. Moureau, G. Sigl, M. Hill, How to Establish an Effective Midline Program: A Case Study of 2 Hospitals, JAVA - J. Assoc. Vasc. Access. 20 (2015) 179–188. https://doi.org/10.1016/j.java.2015.05.001.

[18] M. DeVries, J. Lee, L. Hoffman, Infection free midline catheter implementation at a community hospital (2 years), Am. J. Infect. Control. 47 (2019). https://doi.org/10.1016/j.ajic.2019.03.001.

[19] T.M. Kleidon, J.A. Schults, C. Wainwright, G. Mihala, V. Gibson, M. Saiyed, J. Byrnes, P. Cattanach, F. Macfarlane, N. Graham, E. Shevill, A.J. Ullman, Comparison of midline catheters and peripherally inserted central catheters to reduce the need for general anesthesia in children with respiratory disease: A feasibility randomized controlled trial, Pediatr. Anesth. 31 (2021) 985–995. https://doi.org/10.1111/pan.14229.

[20] F. Tao, X. Wang, J. Liu, J. Li, F. Sui, Perioperative application of midline catheter and PICC in patients with gastrointestinal tumors, J. B.U.ON. 24 (2019) 2546–2552.

[21] M.A. Turner, V. Unsworth, T.J. David, Intravenous long-lines in children with cystic fibrosis: A multidisciplinary approach, in: J. R. Soc. Med. Suppl., 2002.

[22] J. Anderson, A. Greenwell, J. Louderback, B.J. Polivka, J.H. Behr, Comparison of Outcomes of Extended Dwell/Midline Peripheral Intravenous Catheters and Peripherally Inserted Central Catheters in Children, JAVA - J. Assoc. Vasc. Access. 21 (2016). https://doi.org/10.1016/j.java.2016.03.007.

[23] S.Y. Qian, M.T. Horn, R. Barnes, D. Armstrong, The use of 8-cm 22G Seldinger catheters for intravenous access in children with cystic fibrosis, J. Vasc. Access. 15 (2014) 415–417. https://doi.org/10.5301/jva.5000274.

[24] M. Pacilli, C.J. Bradshaw, S.A. Clarke, Use of 8-cm 22G-long peripheral cannulas in pediatric patients, J. Vasc. Access. 19 (2018). https://doi.org/10.1177/1129729818761278.

[25] A. Paladini, A. Chiaretti, K.W. Sellasie, M. Pittiruti, G. Vento, Ultrasound-guided placement of long peripheral cannulas in children over the age of 10 years admitted to the emergency department: A pilot study, BMJ Paediatr. Open. 2 (2018). https://doi.org/10.1136/bmjpo-2017-000244.

[26] M.M. Wyckoff, Midline Catheter Use in the Premature and Full-Term Infant, J. Vasc. Access Devices. 4 (1999). https://doi.org/10.2309/108300899775970737.

[27] L. Millar-Jones, M.C. Goodchild, Peripheral long lines in cystic fibrosis, J. Clin. Pharm. Ther. 22 (1997). https://doi.org/10.1046/j.1365-2710.1997.94075940.x.

[28] E. Clark, B.K. Giambra, J. Hingl, D. Doellman, B. Tofani, N. Johnson, Reducing risk of harm from extravasation: A 3-tiered evidence-based list of pediatric peripheral intravenous infusates, J. Infus. Nurs. 36 (2013). https://doi.org/10.1097/NAN.0b013e3182798844.

[29] H. Balshem, M. Helfand, H.J. Schünemann, A.D. Oxman, R. Kunz, J. Brozek, G.E. Vist, Y. Falck-Ytter, J. Meerpohl, S. Norris, G.H. Guyatt, GRADE guidelines: 3. Rating the quality of evidence, J. Clin. Epidemiol. 64 (2011) 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015.

[30] H.C. Sox, S.N. Goodman, The methods of comparative effectiveness research, Annu. Rev. Public Health. 33 (2012). https://doi.org/10.1146/annurev-publhealth-031811-124610.

[31] R. Pathak, S. Gangina, F. Jairam, K. Hinton, A vascular access and midlines program can decrease hospital-acquired central line-associated bloodstream infections and cost to a community-based hospital, Ther. Clin. Risk Manag. 14 (2018). https://doi.org/10.2147/TCRM.S171748.

[32] D.Z. Adams, A. Little, C. Vinsant, S. Khandelwal, The Midline Catheter: A Clinical Review, J. Emerg. Med. 51 (2016). https://doi.org/10.1016/j.jemermed.2016.05.029.

[33] A. Carr, J.R. Green, E. Benish, R. Lanham, T. Kleidon, L. Freeney, N. York, Midline venous catheters as an alternative to central line catheter placement: a product evaluation, Br. J. Nurs. 30 (2021).

[34] J. Glazner, K. Steinfort, Y.J. Hu, W. Browne, I. Smith, C. Brasher, Short midline catheters: High success rates for antibiotic therapy in children with cystic fibrosis, J. Vasc. Access. 00 (2021) 1–6. https://doi.org/10.1177/11297298211035310.

[35] J. Glazner, E. Prentice, B. Browne, I. Smith, B. Molloy, N. Reardon, Improving the venous access service and introducing midline catheters for children with cystic fibrosis, in: Cyst. Fibros. Conf., 2013: p. 394. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71321855%0Ahttp://dx.doi.org/10.1002/ppul.22898%0Ahttp://gr6md6ku7c.search.serialssolutions.com?sid=EMBASE&issn=87556863&id=doi:10.1002%2Fppul.22898&atitle=Improving+the+venous+acce.

[36] L.A. Gorski, L. Hadaway, M.E. Hagle, D. Broadhurst, S. Clare, T. Kleidon, B.M. Meyer, B. Nickel, S. Rowley, E.

Sharpe, M. Alexander, Infusion Therapy Standards of Practice, 8th Edition, J. Infus. Nurs. 44 (2021). https://doi.org/10.1097/NAN.0000000000000396.