Protocol for the Catheter-Related Early Thromboprophylaxis With Enoxaparin (CRETE) Studies

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OBJECTIVES: In post hoc analyses of our previous phase 2b Bayesian randomized clinical trial (RCT), prophylaxis with enoxaparin reduced central venous catheter (CVC)-associated deep venous thrombosis (CADVT) in critically ill older children but not in infants. The goal of the Catheter-Related Early Thromboprophylaxis with Enoxaparin (CRETE) Studies is to investigate this newly identified age-dependent heterogeneity in the efficacy of prophylaxis with enoxaparin against CADVT in critically ill children.

DESIGN: Two parallel, multicenter Bayesian superiority explanatory RCTs, that is, phase 3 for older children and phase 2b for infants, and an exploratory mechanistic nested case-control study (Trial Registration ClinicalTrials.gov NCT04924322, June 7, 2021).

SETTING: At least 15 PICUs across the United States.

PATIENTS: Older children 1–17 years old ($n = 90$) and infants older than 36 weeks corrected gestational age younger than 1 year old ($n = 168$) admitted to the PICU with an untunneled CVC inserted in the prior 24 hours. Subjects with or at high risk of clinically relevant bleeding will be excluded.

INTERVENTIONS: Prophylactic dose of enoxaparin starting at 0.5 mg/kg then adjusted to anti-Xa range of 0.2–0.5 international units (IU)/mL for older children and therapeutic dose of enoxaparin starting at 1.5 mg/kg then adjusted to anti-Xa range of greater than 0.5–1.0 IU/mL or 0.2–0.5 IU/mL for infants while CVC is in situ.

MEASUREMENTS AND MAIN RESULTS: Randomization is 2:1 to enoxaparin or usual care (no enoxaparin) for older children and 1:1:1 to either of 2 anti-Xa ranges of enoxaparin or usual care for infants. Ultrasonography will be performed after removal of CVC to assess for CADVT. Subjects will be monitored for bleeding. Platelet poor plasma will be analyzed for markers of thrombin generation. Samples from subjects with CADVT will be counter-matched 1:1 to subjects without CADVT from the opposite trial arm. Institutional Review Board approved the "CRETE Studies" on July 1, 2021. Enrollment is ongoing with planned completion in July 2025 for older children and July 2026 for infants.

KEYWORDS: anticoagulants; biomarker; pediatrics; treatment effect heterogeneity; venous thromboembolism

Pediatric venous thromboembolism (VTE), primarily deep venous thrombosis (DVT), is a serious safety concern in hospitalized children. The rate of clinically apparent VTE in children in the United States increased by greater than 150% in the past 2 decades to its current rate of 106 cases per 10,000 hospitalizations (1, 2). Critical illness and presence of central venous catheter (CVC) are the most important risk factors for DVT in children (3). Risk of CVC-associated DVT (CADVT) in critically ill children is as high as 54% (4). Clinically apparent CADVT is

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RESEARCH IN CONTEXT

- Untunneled central venous catheters are typically inserted when children are critically ill and may be hypercoagulable.
- The risk of deep venous thrombosis is low within 24 hours after insertion of an untunneled central venous catheter in critically ill children, but the risk increases thereafter and peaks on day 4 after insertion.
- Development of deep venous thrombosis from a central venous catheter is a complex interplay of various mechanisms with thrombin generation playing a central role.

associated with 5 excess days on mechanical ventilation, 8 excess days in the PICU, and 6 excess days in the hospital (5, 6). Clinically unsuspected CADVT may also be important as CVC is associated with 18–58% of children with pulmonary embolism (7–12). Pharmacologic prophylaxis is effective in preventing lower extremity DVT in adults (13). Yet due to paucity of pediatric evidence, only 12% of children in the PICU receive pharmacologic prophylaxis (14).

We completed a Bayesian phase 2b multicenter randomized clinical trial (RCT) in seven children's hospitals in the United States (4). We showed that prophylactic dose of enoxaparin, the most common agent in children, given within 24 hours after insertion of an untunneled CVC then adjusted to an anti-Xa range of 0.2–0.5 international units (IU)/mL, resulted in a risk ratio of CADVT of 0.55 (95% credible interval [CrI], 0.24–1.11) in critically ill children. In post hoc analyses, reduction in CADVT was observed in older children 1–17 years old, but not in infants younger than 1 year old, which has not been previously reported (15). Risk ratio of CADVT was 0.24 (95% CrI, 0.04–0.82; n = 27) in older children and 0.98 (95% CrI, 0.37–2.44; n = 24) in infants. To validate these findings, the goal of the Catheter-Related Early Thromboprophylaxis with Enoxaparin (CRETE) Studies is to investigate this newly identified age-dependent heterogeneity in the efficacy of prophylaxis with enoxaparin against CADVT in critically ill children.

METHODS

"CRETE Studies" are composed of two parallel multicenter Bayesian superiority explanatory RCTs and an exploratory mechanistic nested case-control study. The phase 3 "CRETE in Older Children Trial" aims to confirm the efficacy and safety of early administration of prophylactic dose of enoxaparin in reducing the risk of CADVT in critically ill older children (15). The phase 2b "CRETE in Infants Trial" aims to determine the efficacy and safety of early administration of the higher therapeutic dose of enoxaparin in reducing the risk of CADVT in critically ill infants. The nested case-control "CRETE Biomarker Study" aims to probe thrombin generation and other mechanisms that may underlie the age-dependent heterogeneity in the efficacy of enoxaparin in reducing the risk of CADVT in critically ill children. "CRETE Studies" are funded by the National Institutes of Health and regulated by the Food and Drug Administration (Investigational New Drug number 133096). They have no roles in designing the studies. "CRETE Studies" were registered in ClinicalTrials.gov (NCT04924322) on June 7, 2021. Biomedical Research Alliance of New York Institutional Review Board (IRB) approved the study on July 1, 2021 (IRB Number 2000030683). Procedures will be conducted in accordance with ethical standards of responsible committees on human experimentation and Helsinki Declaration of 1975. "CRETE Studies" will be conducted in at least 15 children's hospitals in the United States.

Subjects

"CRETE in Older Children Trial" and "CRETE in Infants Trial" will enroll subjects 1–17 years old and older than 36 weeks corrected gestational age younger than 1 year old, respectively, who are admitted to the PICU with untunneled CVC inserted in the prior 24 hours (**Table 1**). Those with or at high risk of clinically relevant bleeding, as defined by the International Society on Thrombosis and Haemostasis, will be excluded (16). Research teams will screen the PICU daily and approach parents or legal guardians for informed consent before study-related procedures (**Table S1**, http://links.lww.com/PCC/C561). Assent will be obtained from children 7 years old or older at any time from informed consent to end of study but deferred for those with limited decision-making capacity (**Appendix S1**, http://links.lww.com/PCC/C561).

TABLE 1.
Eligibility Criteria for the Catheter-Related Early Thromboprophylaxis With Enoxaparin Studies

Inclusion criteria
1) 1–17 yr old (CRETE in Older Children Trial) or > 36 wk corrected gestational age < 1 yr old (CRETE in Infants Trial)
2) < 24 hr after insertion of an untunneled CVC
3) CVC inserted in the internal jugular or femoral vein
Exclusion criteria
1) Radiologic diagnosis of CVC-associated deep venous thrombosis in the site of insertion in prior 6 wk
2) Currently receiving an antithrombotic agent, e.g., low-molecular-weight heparin, UFH, warfarin, and aspirin but not UFH at dose to maintain patency of a vascular catheter
3) Presence of clinically relevant bleeding, i.e., hemoglobin decreased ≥ 2 g/dL in 24 hr, required medical or surgical intervention to restore hemostasis, or in the retroperitoneum, pulmonary, intracranial, or CNS in the prior 60 d
4) Surgery in the prior 7 d
5) Major trauma in the prior 7 d
6) Presence of coagulopathy, i.e., international normalized ratio > 2.0, activated partial thromboplastin time > 50 s, or platelet count < 50 × 10^3/mL
7) Presence of renal failure, i.e., creatinine clearance < 30 mL/min/1.73 m^2
8) Known hypersensitivity to heparin or pork products
9) Laboratory confirmed heparin-induced thrombocytopenia
10) Current pregnancy or lactation
11) Presence of an epidural catheter
12) Limitation of care
13) Previous enrollment in the "CRETE Studies"

CRETE = Catheter-Related Early Thromboprophylaxis with Enoxaparin, CVC = central venous catheter, UFH = unfractionated heparin.

Assignment of Intervention

Randomization will be stratified by age to minimize imbalance on the risks of CADVT and bleeding between trial arms (**Fig. 1**). For "CRETE in Older Children Trial," we will stratify subjects to 1–13 years old or older than 13 years old, as we did in our previous RCT, then randomize 2:1 to enoxaparin (intervention) or usual care (no enoxaparin). Unequal allocation will provide more data to monitor the safety of enoxaparin, while allowing more subjects to receive a potentially beneficial therapy (17). For "CRETE in Infants Trial," we will stratify subjects to 2 months old or older or older than 2 months chronologic age to minimize confounding due to potential age-related differences in response to enoxaparin (18). Given the lack of efficacy of prophylactic dose of enoxaparin in infants in our previous RCT, subjects will be randomized 1:1:1 to therapeutic dose of enoxaparin adjusted to either of two target anti-Xa ranges or usual care. For "CRETE Biomarker Study," each case with CADVT will be counter-matched 1:1 to a randomly selected unique control without CADVT from the opposite trial arm. This sampling strategy accounts for randomization in the RCTs, allows assessment of the effect of age and increases statistical power for the primary analysis (19, 20). Permuted block randomization will be performed in Research Electronic Data Capture (REDCap) (21, 22). Trial arm assignment will only be known after informed consent is obtained and subject is registered and randomized in REDCap. Randomization will not be stratified within PICU because of the anticipated small number of enrolled subjects per PICU. "CRETE Studies" are open label because subjects cannot be given placebo due to ethical concerns of inducing pain from subcutaneous injection without potential for direct benefit (23).

Intervention and Other Study Procedures

Similar to our previous RCT, prophylactic dose of enoxaparin in "CRETE in Older Children Trial" will

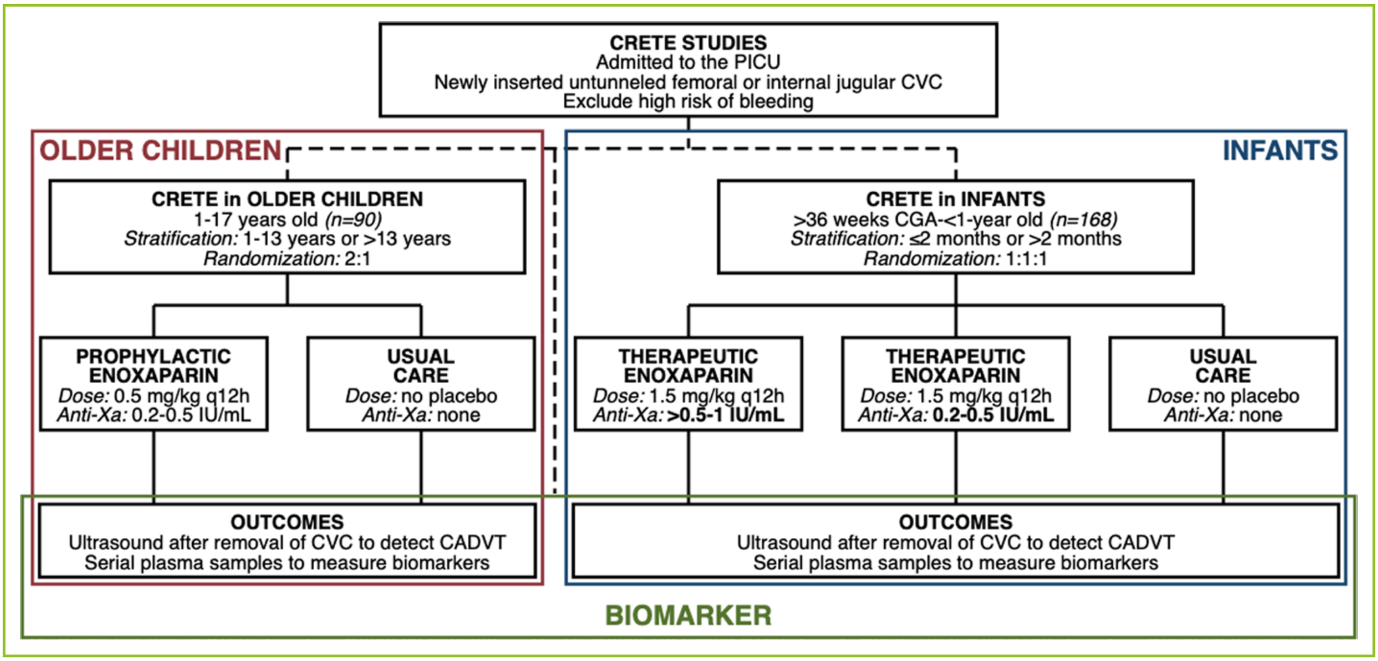

Figure 1. Flow chart of the Catheter-Related Early Thromboprophylaxis with Enoxaparin (CRETE) Studies. CADVT = central venous catheter-associated deep venous thrombosis, CGA = corrected gestational age, CVC = central venous catheter, IU = international units, q12h = every 12 hr.

start at 0.5 mg/kg but doubled for obesity, halved for renal insufficiency to maximize safety, and capped at 30 mg, which is the dose in adults (4). Obesity is defined as greater than 95th percentile of sex-specific weight-for-length for subjects 1–2 years old and greater than 95th percentile of sex-specific body mass index-for-age for subjects older than 2 years old (24). Renal insufficiency is defined as creatinine clearance less than 75 mL/min/1.73 m^2. Subsequent doses will be adjusted to anti-Xa range of 0.2–0.5 IU/mL to a maximum dose of 30 mg (**Table 2**) (4). In "CRETE in Infants Trial," therapeutic dose of enoxaparin will start at 1.5 mg/kg but halved for renal insufficiency (25). Subsequent doses will be adjusted to an anti-Xa range of greater than 0.5–1.0 or 0.2–0.5 IU/mL (4, 26). Doses will be given subcutaneously every 12 hours with the first dose at less than 24 hours after insertion of CVC. Anti-Xa level will be measured locally 4–6 hours after the third dose until target anti-Xa range is reached, then weekly to ensure that anti-Xa level remains within target range (**Fig. 2**).

Enoxaparin will be stopped upon removal of the CVC, or earlier upon discharge from the PICU, radiologic diagnosis of CADVT by the clinical team, development of clinically relevant bleeding, antithrombotic therapy is started by the clinical team, or 28 days after insertion of CVC. It will be held temporarily, but not replaced with another agent, if coagulopathy develops, 24 hours before surgery or invasive procedure, renal failure develops, or clinical team suspects heparin-induced thrombocytopenia (HIT), that is, unexplained drop in platelet count to less than 50 × 10^3/mL or by 50% of baseline platelet count in the ICU within 21 days after exposure to heparin when risk is highest (27). Renal failure is defined as creatinine clearance less than 30 mL/min/1.73 m^2. Enoxaparin will be resumed 24 hours after coagulopathy is corrected, that is, does not meet our criteria for coagulopathy, 24 hours after surgery or invasive procedure, 24 hours after renal failure is resolved, and HIT is excluded with negative anti-platelet factor 4 antibody.

The research teams will monitor each subject daily for adverse events (AEs), particularly bleeds, querying the clinical team and reviewing the medical records. The site investigator or their designee will conduct prompt investigations of AEs. Bleeds will be communicated to the project manager as soon as possible.

Blood will be drawn from the CVC on the day of, day after and day 4 after insertion of the CVC, and at the end of study before CVC is removed. Blood will be drawn into commercially available citrated tubes, processed to obtain platelet poor plasma, then frozen. Samples will be shipped and stored at the Yale School of Medicine Biobank.

TABLE 2.
Titration of Enoxaparin Dose to Achieve Target Anti-Xa Range

Anti-Xa Level	Enoxaparin Dose Titration	Next Anti-Xa Level Check
a) Target anti-Xa range of **0.20–0.50 IU/mL**		
< 0.10 IU/mL	Increase dose by 20%	After third dose
0.10–0.19 IU/mL	Increase dose by 10%	After third dose
0.20–0.50 IU/mL	Keep same dose	Weekly or when renal insufficiency develops or is resolved
0.51–1.00 IU/mL	Decrease dose by 10%	After third dose
> 1.00 IU/mL	Hold dose until anti-Xa is < 0.20 IU/mL, then decrease last administered dose by 20%	2 hr before next dose and every 12 hr, until anti-Xa < 0.20 IU/mL
b) Target anti-Xa range of > **0.50–1.00 IU/mL**		
< 0.35 IU/mL	Increase dose by 25%	After third dose
0.35–0.50 IU/mL	Increase dose by 10%	After third dose
0.51–1.00 IU/mL	Keep same dose	Weekly or when renal insufficiency develops or is resolved
1.01–1.50 IU/mL	Decrease dose by 20%	After third dose
> 1.51 IU/mL	Hold dose until anti-Xa is < 0.50 IU/mL, then decrease last administered dose by 30%	2 hr before next dose and every 12 hr, until anti-Xa < 0.50 IU/mL

IU = international units.
Boldface entries are the target ranges.

Systematic ultrasonographic surveillance will be performed by blinded technicians using standardized procedures at the end of study. The vein where the CVC is inserted will be scanned proximally and distally (28). Images in the transverse and longitudinal planes, with and without compression, and with and without color Doppler will be acquired.

We will maintain a high level of protocol adherence. Research teams will be trained on the study protocol before site activation. The Project Management Team will review weekly site-based summaries of subject enrollment, enrolled subject visits completed, missing data forms, number of queries made, number of outstanding queries, protocol deviations, and average times between visit and data entry, and between query and query resolution.

Outcome Measures

Primary outcome is development of CADVT diagnosed by systematic ultrasonographic surveillance (**Table 3**). A valid, reliable and unbiased determination of the primary outcome is essential, particularly for explanatory RCTs and mechanistic studies, such as "CRETE Studies" (29, 30). The Outcomes Committee, which is composed of three pediatric radiologists, will centrally, blindly, and independently adjudicate CADVT for purposes of the "CRETE Studies." CADVT will be diagnosed if greater than or equal to 2 of IV echogenic material adherent to venous wall, non-compressibility of vein or abnormal venous Doppler are present on ultrasound (28). At least two concurring members of the Outcomes Committee are needed to diagnose CADVT. Secondary outcomes characterize the other measures of the burden of VTE and AEs from enoxaparin. Any VTE diagnosed while on study reflects the overall burden of disease. Clinically apparent VTE will include any event suspected clinically then confirmed radiologically (31). We will use the definition of the International Society on Thrombosis and Haemostasis to ascertain clinically relevant bleeding, our AE of special interest (16). Bleeding will be adjudicated by the site investigator with assistance from the safety monitor, as needed.

Biomarkers will be measured in duplicate from platelet poor plasma using commercially available assays at Yale School of Medicine (15, 32). Primary biomarker is endogenous thrombin potential (ETP) from plasma obtained on the day after insertion of CVC, that is, when early administration of enoxaparin is first assessed with

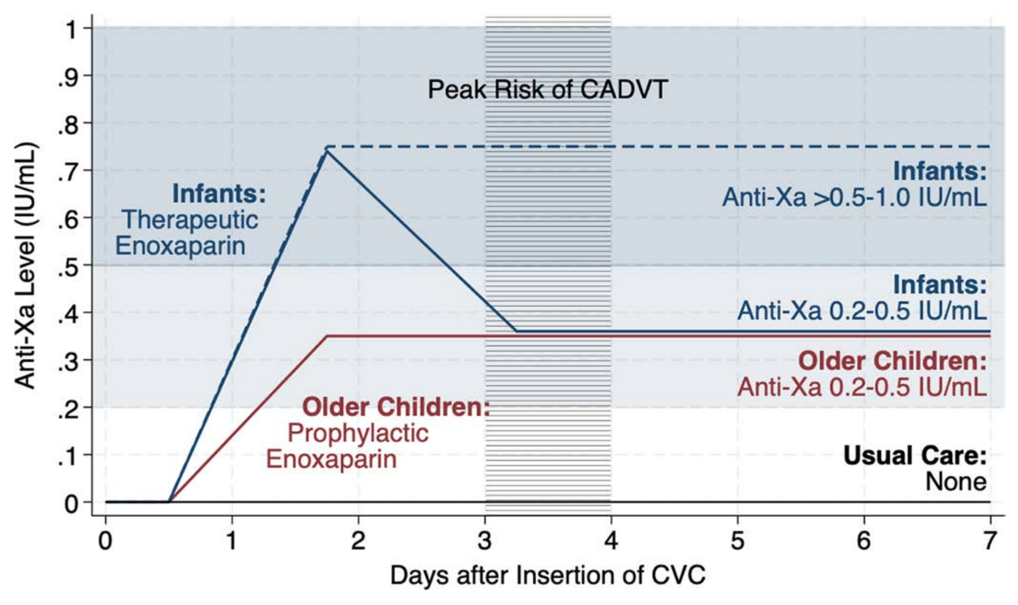

Figure 2. Anticipated profile of anti-Xa levels per trial arm in the Catheter-Related Early Thromboprophylaxis with Enoxaparin (CRETE) Studies. CADVT = central venous catheter-associated deep venous thrombosis, CVC = central venous catheter, IU = international units.

anti-Xa level. ETP directly measures thrombin generation over time and captures the effects of natural and pharmacologic pro- and anticoagulants (15, 32). We will measure ETP with ST Genesia Thrombin Generation System (Diagnostica Stago, Parsippany, NJ). Secondary biomarkers are plasma biomarkers of thrombin generation (prothrombin fragment 1 + 2, thrombin-antithrombin complex, factor VIII, and antithrombin), platelet (P-selectin, beta-thromboglobulin, thromboxane B_2, and glycoprotein VI), contact (factors XI and XII) and endothelial (thrombomodulin, von Willebrand factor, and endocan) activation, and fibrinolysis (D-dimer and plasmin-antiplasmin complex).

Data Management

Patient-related information will be collected from electronic health records. REDCap will be used to manage electronic data capture (21, 22). Sample-related information will be entered in Freezerworks (Dataworks Development, Mountlake Terrace, WA).

Statistical Considerations

Bayesian methods will be used to mitigate the effect of limited sample size (33). Primary analyses will be conducted under intent to treat principle whereby outcomes in all randomized subjects will be included, regardless of treatment compliance. A per protocol analysis is also planned. For "CRETE in Older Children Trial," posterior distribution of the log-risk ratio of CADVT with enoxaparin will be used for making statistical inference. The hypothesis is one-sided, that is, posterior probability that log-risk ratio of CADVT with enoxaparin is less than 0, which is equivalent to risk ratio less than 1.0. The implication of futility or enoxaparin being worse than usual care is the same and that enoxaparin should not be prescribed. We will conservatively define success as greater than 0.975 posterior probability of log-risk ratio being less than 0. In the primary analysis, we will incorporate historical data from our previous RCT through a power prior of 0.1, which was used to justify sample size (34). Normalized power prior and Bayesian hierarchical models will be used in sensitivity analyses to incorporate historical data from of our previous RCT and account for stratifying variable and PICU of admission (35–37). Type I error and power of the "CRETE in Older Children Trial" was estimated using simulation (**Appendix S2**, http://links.lww.com/PCC/C561). A sample size of 90, 2:1 allocation and a power prior of 0.1 have a type I error of 0.01 and power of 0.90.

For "CRETE in Infants Trial," posterior distribution of log-risk ratio of CADVT with therapeutic dose of enoxaparin will be estimated using Bayesian statistics with informative priors from our previous RCT. If therapeutic dose, regardless of target anti-Xa range, is efficacious against CADVT in critically ill infants, we anticipate the effect size to be at least a risk ratio of 0.55, as in our previous RCT (15). We will then estimate the posterior distribution of log-risk ratio of CADVT between target anti-Xa ranges to assess equivalence (38, 39). A sample size of 168, 1:1:1 allocation and a power prior of 0.1 have a type I error of 0.025 and power of 0.80.

For "CRETE Biomarker Study," we will compare ETP and other biomarkers between presence and

TABLE 3.
Definitions of Outcome Measures for the Catheter-Related Early Thromboprophylaxis With Enoxaparin Studies

Primary outcome
CADVT—thrombus in the central vein where the CVC was inserted that is diagnosed with systematic ultrasonographic surveillance
Secondary outcomes
1) Any VTE—thrombus in the deep vein of any extremity or pulmonary embolism that is confirmed radiologically
2) Clinically apparent CADVT—any CADVT, except one that is only diagnosed with the systematic ultrasonographic surveillance
3) Clinically apparent VTE—any VTE, except one that is only diagnosed with the systematic ultrasonographic surveillance
4) Clinically relevant bleeding—bleeding that is fatal, with drop in hemoglobin by ≥ 2 g/dL in 24 hr, requires medical or surgical intervention to restore hemostasis, or in the retroperitoneum, pulmonary, or CNS
5) Any bleeding—any overt or macroscopic evidence of bleeding
6) Heparin-induced thrombocytopenia—unexplained drop in platelet count to < 50 × 10^3/mL or by 50% of baseline platelet count in the PICU within 21 d following exposure to heparin, and with a positive anti-platelet factor 4 antibody
Exploratory outcomes
1) CVC-associated bloodstream infection as determined clinically
2) Duration of mechanical ventilation from enrolment
3) Duration of stay in the PICU from enrolment
4) Duration of stay in the hospital from enrolment
5) Mortality during current hospitalization

CADVT = central venous catheter-associated deep venous thrombosis, CVC = central venous catheter, VTE = venous thromboembolism.

absence of CADVT, infants and older children, and trial arms. We will estimate the posterior distribution of the modifying effect of infants in a conditional logistic regression model fitted in the Bayesian setting. Using informative priors from our previous RCT, absence of CADVT will be regressed on ETP, infants (vs. older children) and their interaction accounting for matching strategy. The posterior probability that the coefficient of the interaction term is less than 0 will quantify the probability that the log-odds of absence of CADVT is lower in infants than in older children for every level increase in ETP. Based on our previous RCT, we anticipate ~170 subjects with equal numbers of subjects with and without CADVT (15).

On an ongoing basis, the occurrence of clinically relevant bleeding will be summarized after complete data is available from greater than or equal to ten subjects per trial arm, and monthly, thereafter, for each trial (40). A safety signal will be defined as greater than or equal to 90% posterior probability that the risk ratio of clinically relevant bleeding with enoxaparin is greater than or equal to 1.5.

Missing data will not be imputed for our primary analyses, which should be valid under the assumption that data is missing completely at random or missing at random (41). To examine the robustness of these assumptions, sensitivity analyses will be implemented using a fully Bayesian approach of treating the missing values as parameters and assigning priors to them, and multiple imputation (42).

Study Oversight

The Project Management Team, composed of the principal investigator, lead biostatistician, and project manager, serves as point of coordination, provides administrative and fiscal oversight, and streamlines communication, decision-making and data sharing among Clinical and Data Coordinating Centers, sites, and regulatory agencies (**Fig. S1**, http://links.lww.com/PCC/C561). The site monitor will visit each site after the second, fifth and every fifth enrollment, thereafter. They will review and 100% source verify the informed consent, eligibility criteria, AEs, protocol compliance,

WHAT THIS STUDY MEANS

- Catheter-Related Early Thromboprophylaxis with Enoxaparin (CRETE) Studies aims to confirm whether prophylactic dose of enoxaparin is efficacious and safe in preventing catheter-associated thrombosis in critically ill older children.
- “CRETE Studies” aims to determine whether therapeutic dose of enoxaparin is potentially efficacious and safe in preventing catheter-associated thrombosis in critically ill infants.
- “CRETE Studies” aims to probe the role of thrombin generation in the age-dependent heterogeneity in the efficacy of enoxaparin in preventing catheter-associated thrombosis in critically ill children.

protocol deviation, reasons for study discontinuation, outcome measures, regulatory documents, and training and qualifications of staff. Monitoring will be done remotely, unless findings dictate the need for an onsite visit, or the site does not allow remote monitoring. The Data and Safety Monitoring Board will assess performance with respect to recruitment, retention, follow-up, protocol adherence, and data quality, monitor interim safety data, consider protocol modifications, and advise as to whether the study should continue. It will be composed of a pediatric intensivist (chair), pediatric hematologist, and biostatistician.

Patient and Public Involvement

A parent advisory group assisted in developing recruitment strategies, including consenting scripts and recruitment materials. We will involve them in summarizing our findings in lay language, identifying target audience and eliciting novel ways to share our results.

DISCUSSION

We present the design and rationale of the “CRETE Studies.” Protocol publication increases research transparency, facilitates future publication of results, avoids research duplication and informs the community (43, 44). We briefly described our statistical analytical plan. Given its novelty and complexity, a separate article with technical details will be forthcoming.

Previous RCTs failed to demonstrate the efficacy of pharmacologic prophylaxis in reducing the risk of CADVT in children (45–47). We surmised that this was in part due to delays in starting prophylaxis and inadequate reduction in thrombin generation. Our previous RCT suggested that early prophylaxis may be needed to prevent CADVT in critically ill children (4). It also suggested that the magnitude in the reduction in thrombin generation may be age dependent (15). “CRETE Studies” will address these hypotheses. However, we are only enrolling in the United States. While do not expect the efficacy of early prophylaxis with enoxaparin to be different for children outside the United States, the baseline risk of CADVT without prophylaxis may be different (48, 49). For example, Asians have lower risks of VTE (50). Therefore, the generalizability of our findings should be assessed relative to the baseline risk of CADVT.

Other limitations should be considered. We do not stratify by site. While this may result in confounding, we will adjust for site in the analysis. The significance of clinically unsuspected CADVT remains unsettled (30, 51). Based on our results, a pragmatic RCT with clinically apparent CADVT as outcome may be needed.

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Drs. Faustino, Kandil, Spinella, Raffini, Taylor, McPartland, and Shabanova conceived the idea and developed the study methods. Drs. Faustino, Kandil, Leroue, Glau, Kolmar, Schreiber, Kong, Cholette., Ramirez, Sochet, Pinto, Nellis, Muisyo, Kerris, and Chegondi are conducting the study, including enrollment and data collection. Drs. Sharathkumar, Polikoff, Silva, Ehrlich, and Navarro are adjudicating the outcome measures. Dr. Shabanova wrote the codes and will perform the data curation and statistical analyses. Drs. Faustino, McPartland, and Shabanova wrote the protocol. Dr. Faustino wrote the initial draft of this article. All authors reviewed and revised this article for intellectual content. Drs. Faustino and Shabanova are providing oversight and leadership responsibility. Dr. McPartland is managing the committees and coordinating with the regulatory agencies and enrolling sites. Dr. Faustino acquired funding.

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This article presents Version 1.0 (May 10, 2021) of the protocol for the Catheter-Related Early Thromboprophylaxis with Enoxaparin (CRETE) Studies, which has not been amended. The first site was activated on May 11, 2022. The first older child was randomized on August 16, 2022, while the first infant was randomized on September 19, 2022. Enrollment is ongoing with planned completion in July 2025 for "CRETE Studies in Older Children Trial" and July 2026 for "CRETE Studies in Infants Trial." We will disseminate the results through publications in peer-reviewed medical journals, conferences, social media, newsletters, institutional websites, webinars and press releases.

The list of study investigators is given in the ***Appendix S3*** *(http://links.lww.com/PCC/C561).*

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