SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT: PROSPECT: PROSpective evaluation of **P**ulmonary **E**mbolism in **C**hildren s**T**udy. Establishing a prospective registry of pediatric pulmonary embolism (PE) patients through the International Pediatric Thrombosis Network (IPTN) and the Throm-PED registry.

Subcommittee: Pediatric/Neonatal Thrombosis and Haemostasis

Person responsible (Chair / Principal Investigator):

Madhvi Rajpurkar, MD, Heleen Van Ommen, MD, Ernest Amankwah, PhD, Neil Goldenberg, MD, PhD.

Description/Abstract:

Pediatric pulmonary embolism (PPE), a disease with the potential for significant morbidity and mortality, is identified by the International Society of Haemostasis Thrombosis (ISTH) as a high priority area for actionable research. However, there is limited observational and no clinical trial derived evidence to guide current treatment decisions. There are several reasons for this knowledge gap: 1) PPE is rare at individual centers. Despite a 200% increase in incidence over a decade, PE constitutes approximately 10% of all thrombosis in children, and most centers manage a median of 8 new PE patients annually. This underscores the necessity for multicenter collaboration. 2) Pediatric PE has a complex phenotype distinct from PE in adults in its clinical evolution and response to treatment. Thus, treatment decisions from adult PE trials may not be applicable to children with PE. 3) In previous retrospective cohort studies, there has been considerable variability in assessing and defining early and long-term adverse outcomes. Consequently, prognostic risk factors that determine these outcomes have not been evaluated. 4) The duration of anticoagulation differs across countries and centers- thus, the accurate rate of recurrent thrombosis, anticoagulation related bleeding and other long-term outcomes are unknown.

Our long-term goals are to improve early and long-term outcomes after PPE. Our overall objective for PROSPECT, a prospective observational study, is to establish a multicenter, multinational cohort of PPE patients that will 1) Allow evaluation of the incidence and risk determinants associated with early and late outcomes after PPE. 2) Create PPE-specific common data elements that will be an initial step toward data harmonization for PE research across various registries in the future. We posit that data obtained from evaluating this cohort will inform the future design of randomized controlled trials.

We propose using the International Pediatric Thrombosis Network (IPTN) and developing PPE-specific data elements within the established Throm-PED registry to achieve this objective. The ISTH PPE-WG will act as the Scientific Advisory committee and members of Data Harmonization-Working group of the ISTH will advise the development of PPE-specific common data elements.

Design and methodology (Data expected to collect, sample size and statistical analysis):

Specific aim 1: Determine the incidence and prognostic factors for early adverse events (early AE, at 30 days post-diagnosis) after PPE: We will measure the incidence rate of early AE defined as a composite of intensive care stay, hemodynamic and ventilatory support, death, bleeding due

to thrombolytic therapy, and readmission to the hospital at 30 days. We hypothesize that the early AE will correlate with the type of clinical presentation of PE. To achieve this, we will correlate the early AE rate with the clinical presentation of PE categorized as low risk, intermediate risk/ high-risk PE according to the European Society of Cardiology (ESC) classification.

Specific aim 2: To compare the safety (bleeding) and efficacy (recurrent thrombosis) at 2 years of a conventional 12-week duration of anticoagulation to an extended duration of anticoagulation (>13 weeks) after the 1st episode of PPE. Currently, the optimal duration of anticoagulation and the implications on long-term outcomes after PPE are unknown. We will compare the development of a composite outcome of efficacy (recurrent thrombosis) and safety (bleeding) in patients who received conventional (</=12 weeks) and extended (>13 weeks) anticoagulation.

Exploratory aim 1: To characterize the frequency and type of functional limitations in patients who develop PPE: This aim will test the hypothesis that children with PE endure functional limitations that correlate with the clot burden at initial presentation and on residual thrombosis at the end of anticoagulation. For this aim, we will measure the symptoms, imaging and laboratory measures of cardio-respiratory compromise in children for two years following PE. We will correlate these findings with the initial CT angiography clot burden score (Quanadli score) and residual thrombosis.

Exploratory aim 2: Test the feasibility of standardizing pediatric PE specific common data elements (CDE) across thrombosis registries. This aim will test the hypothesis that it is feasible to establish consistent vocabulary and definitions for pediatric PE specific research across various registries [IPTN, PERT registry etc.,] which will allow cross-network data harmonization and will cement the future steps needed for pediatric PE-specific research. To achieve this goal, we will develop pediatric specific PE elements by developing a task force focused on modifying the current ISTH CDEs to encompass features unique to pediatric PE. During this process, we will coordinate with other pediatric thrombosis registries to ensure standardized definitions of such data elements.

At the conclusion of this study, we will establish 1) the incidence of early AE and associated risk factors 2) The rate of recurrent thrombosis and bleeding and risk factors after a first episode of PPE 3) the rate of long-term functional limitations after PPE 4) a platform for cross network data harmonization for conducting research in PPE.

Data collection:

a. Common data elements to be collected on all subjects:

1. Demographic information: Age, ethnicity, sex.2. Country, Center's name; contact information of site PI 3. Site of thrombus: main, left or right pulmonary artery, segmental or sub-segmental PA. 4. Underlying diagnosis: congenital heart disease, other provoking, and predisposing risk factors for thrombosis (ISTH Definitions), Laboratory risk factors. 5. Family history of thrombosis

b. For specific aim 1: Determine the incidence rate and prognostic factors for early adverse outcomes (early AE) after PPE.

1. Predictor variables: We will categorize the initial presentation of the subjects based on their clinical presentation and biomarker studies (when available). Patients will be classified as clinically unsuspected (surveillance and incidental) PE and symptomatic PE based on ISTH

definition. All symptomatic PE patients will be classified based on their clinical presentations into high risk, intermediate high and intermediate low, and low risk PE. Biomarker information (whenever available): EKG, ECHO, Troponin, B-Natriuretic peptide, Evidence of inter-ventricular septum deviation on imaging and Therapeutic interventions: Details on thrombolysis if any including dose, route andduration/ Thrombectomy will be collected.

We will also collect information on Supportive care: Intensive care unit stay, Hospital length of stay, ECMO (yes/no, number of days on ECMO), Pressors, Oxygen • Presence of PERTs or centers with specific PE diagnosis and management algorithms will be noted.

2. Outcomes of interest- Early Adverse outcome at 30 days: Composite outcome of ICU stay (yes/no), Length of ICU stay (days), Length on Ventilator (yes/no, days), Length of hospital stay (Days), Hemodynamic support (yes/no, Length on supportive care e.g., ECMO, Pressors), death

c. For Specific Aim 2: To compare the safety (bleeding) and efficacy (recurrent thrombosis) at 2 years of a conventional 12-week duration of anticoagulation to an extended duration of anticoagulation (>13 weeks) after the 1st episode of PPE. We will evaluate recurrent VTE rate and bleeding rate at 3 months, 6 months, 1 year and 2 years after the first PE episode.

1. Predictor variables: Duration of therapy: Conventional (</= 12 weeks) or extended (> 13 weeks), Type of anticoagulation (Vitamin K antagonist, Low molecular weight heparin or DOACs), D-dimer, if available, Resolution of thrombosis on follow-up scans

Outcomes of interest (a composite of): Recurrent VTE (PE and non-PE DVT)- as per ISTH definition and Anticoagulation related bleeding- as per ISTH definition

d. Exploratory aim 1- All enrolled subjects will be evaluated for long term outcomes (at 3 months, 6months, 1 year, 2 years after first episode of PE)

Outcomes of interest: Follow up ECHO/EKG/ other evaluations (6-minute walk test), Follow up imaging and resolution of PE on imaging.

e. Exploratory aim 2: Test the feasibility of standardizing pediatric PE specific common data elements (CDE) across thrombosis registries.

The Pediatric/Neonatal Thrombosis & Hemostasis Subcommittee of the ISTH SSC has unanimously endorsed a proposal to develop a Task Force on Cross-Network Data Harmonization in Pediatric Thrombosis Clinical Research. The goal of the work of this Task Force is to facilitate the feasibility and impact of future data sharing across networks, as well as provide a foundation for greater collaboration across networks, to accelerate and expand the knowledge gained through clinical research efforts in the field of pediatric thrombosis. The PPE-WG will collaborate with the Task Force to develop standardized definitions of PPE-specific common data elements across various registries such as the PERT (PI – Ayesha Zia), CHAT (PI- Julie Jaffray), ATHN (PI- Madhvi Rajpurkar), CPTHN (PI-Christine Sabapathy).

STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

A. SAMPLE SIZE CALCULATIONS:

As of April 2023, there were 1582 enrolled patients with VTE in the Throm-PED registry andapproximately 10% of these patients have PE(150 subjects). We anticipate a similar enrollment rate in PROSPECT.

For specific aim 1, early AE will be assessed at 30 days post-diagnosis of PE. Thus, we don't expect that patients will be lost to follow-up. For specific aim 2, we anticipate that 10% of patients will be lost to follow-up. Thus, to obtain an evaluable sample size of 150 subjects, we plan to enroll 168 patients.

Specific aim 1: A sample size of 150 will allow us to determine incidence of AE with the following two sided 95% confidence intervals: 1% (0.1%-4.2%), 2% (0.4%-5.7%), 5% (2.1%-9.8%), 10% (5.7%-16.0%) and 20% (13.9%-27.3%). This sample size will achieve 80% power to detect a risk ratio of 2.74 for the association between early AE and clinical presentation of PE and other factors.

Specific aim 2: Assuming 30% (n=45) of patients in IPTN received conventional 12-week duration of anticoagulation, a risk of recurrent thrombosis at 1 year of 2% and a rate of clinically significant bleeding of 2%, then a sample size of 150 patients achieves 80% power to conclude noninferiority if the absolute risk difference(ARD) in recurrent VTE as well as clinically relevant bleeding is 0.001.

For Exploratory Aim 1: No formal sample size calculation was performed. But all (150) subjects will be followed for the development of functional limitations.

For Exploratory Aim 2: No formal power/sample size calculation was performed but we will measure the rate of concordance in PPE specific data elements across previously mentioned registries.

ANALYSIS:

Descriptive statistics will be used to examine baseline characteristics. Continuous variables will be presented as mean ± standard deviation or median with interquartile range. Continuous variables will be compared between groups using Students T test (parametric variables) or Mann-Whitney test (for non-parametric variables). Categorical variables will be presented as counts and percentages and will be compared between groups using the Chi-square test or Fisher's exact test as appropriate.

Specific Aim 1: The incidence of AE at 30 days will be calculated as a percentage with the corresponding 95% confidence interval. Incidence will be reported for the composite AE outcome and separately for intensive care stay, hemodynamic and ventilatory support, death, and readmission to the hospital within 30 days, if there are sufficient numbers for each outcome. The association between early AE and clinical presentation of PE and other factors will be analyzed using multivariable mixed-effects log binomial regression model with study center as a random effect. Pertinent demographic and clinical variables will be adjusted as potential confounders. Missing data will be excluded from primary analyses and a sensitivity analysis using multiple imputation will be conducted as secondary analyses.

Specific Aim 2: We will use inverse probability of exposure weighting on propensity score analysis to balance the distribution of baseline covariates between the two groups (conventional 12-week and extended duration). Propensity scores will be derived from estimated probabilities obtained from group (conventional 12-week and extended duration) membership, using logistic regression modeling comprised of baseline covariates. Each patient will then be assigned a weight based on the propensity score. One-year risks and corresponding 95% confidence intervals (CI) of recurrent thrombosis and clinically-relevant bleeding for both groups will be calculated from weighted Kaplan-Meier curves. We will also estimate absolute risk differences (ARDs) for each, with corresponding exact 95% CI. These bivariate outcomes will be compared between the groups using the noninferiority boundary in a bivariate endpoint analysis with inference based on the 95% confidence rectangle (i.e., the rectangle defined by the 95% CI for recurrent thrombosis ARD and the 95% CI for bleeding ARD). Patterns of missing data will be examined, and depending on characterization of missingness, missingness will be handled via multiple imputation techniques or and/or its impact on study findings assessed via sensitivity analyses.

Exploratory aim 1: Descriptive statistics will be used to describe the number of patients who develop adverse functional outcomes at prespecified timelines (3 months, 6 months, 1 year and 2 years.). The types and frequency of functional limitations will be reported as proportions with the corresponding 95% confidence intervals.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Inclusion criteria:

1. All patients with PE will be identified by the local study PI. All new patients with the radiologically confirmed diagnosis of thrombo-embolic pulmonary embolism (TE-PE) or in-situ pulmonary artery thrombosis (ISPAT), less than 0-21 years of age will be included.

2. As this is an observational study, no patients will be excluded.

Expected timeline:

Project stage/set up:
Received seed funding from INVENT VTE Dragon's Den competition- last quarter of 2023
Launch: Jan 2024- December 2024
Duration: Anticipate starting data collection 2nd quarter, 2025, for 3-3.5 years
Finalization/analysis: 2028
Reporting: 2028-2029

Expected outcomes (ie. publications): Multiple publications are planned with involvement from the Early Career Working party members. 1. Primary publications will be on the incidence of early and late adverse outcomes. 2) Secondary publications will be guidance documents (based on data gathered during this study) to guide the duration of therapy and management and follow up of pediatric PE patients .

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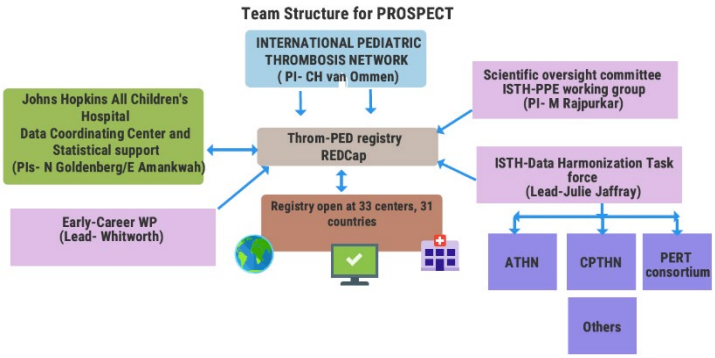
Description of project set/up and management, needed infrastructure and resources (summary):

We propose a prospective multi-center, multi-national observational study using the current framework of the International Pediatric Thrombosis Network (IPTN) and the REDcap Throm-PED registry as a platform for data collection. PROSPECT is a collaborative study between IPTN and the PPE- WP with Johns Hopkins All Children's Hospital acting as the data coordinating and statistical support center (Figure). The members of PPE-WP will provide scientific oversight. Additionally, members of the newly formed ISTH- Data Harmonization Task Force have provided advice regarding the development and harmonization of PPE-specific data elements in the Throm- PED registry and will continue to provide administrative oversight. Members from the Early Career- WP will be encouraged to take on leadership roles in study development and analysis of data.



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