NAME OF PROJECT:

International Pediatric Thrombosis Network: working together to advance the field of pediatric thrombosis

Subcommittee: Pediatric and Neonatal Hemostasis and Thrombosis
Person responsible (Chair/PI): Dr CH van Ommen (PI), Prof Dr C Male (Chair SSC)

Description Abstract

State the application’s broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Suggested length is 2-3 paragraphs.

In 1994, Maureen Andrew was the first to publish a prospective registry of children with thromboembolic events (TEs). (1) Since then, pediatric TE have been increasingly recognized as secondary complications of severe underlying diseases and their treatment. (2) Compared to adults, TE in children are rare and differ significantly in epidemiology: they are heterogeneous with regards to patient age, comorbidity, risk factors, and anatomical location, including all kinds of thrombi such as (neonatal) catheter-related thrombosis and renal vein thrombosis, asparaginase-associated sino-venous thrombosis, and oral contraceptive–associated pulmonary embolism (PE) in teenagers. These TE have their unique pathophysiology, short and long-term consequences, and treatment benefit-risk balance. Thus, one could consider each type of paediatric TE an individual rare disease. (3)

Because of the scarcity of the disease, little progress has been made in generating systematic evidence for the management of pediatric thrombosis. (4, 5) Only a few randomized treatment trials have been executed, but most of them closed early due to slow recruitment. (6-10) Thus, current guidelines for clinical care of pediatric TE are based on low level evidence and mainly extrapolated from adult studies. (5) Many important questions remain regarding the pathophysiology, risk profile, optimal diagnostic modalities, the natural history of pediatric arterial and venous TE, and effective and safe anticoagulant prophylaxis or treatment in different age categories and individual TE types. Because of the rarity and heterogeneity of pediatric TE and the limited the number of patients per center, international collaboration is essential to enable high-quality research to improve the evidence for management of TE in children.

Development of drugs, such as anticoagulants, is particularly challenging in children. Recent regulatory legislations in the US and Europe now oblige pharmaceutical companies to develop new medicines also for children. However, such regulatory studies face methodological and logistical difficulties due to the specificities of TE in children, and a historical lack of experience with anticoagulant trials in children. To address these challenges and to optimize the planning and effective execution of anticoagulant trials in children, there is a need for collaboration between pediatric thrombosis centers to bundle and expand experience and infrastructure for conducting clinical trials. Moreover, many important questions will not be answered by regulatory trials, such long-term efficacy and safety, including effects on growth and development, use in rare types of TE, specific age-groups (e.g. prematurity), or co-morbidities, treatment combinations, drug interactions, optimal treatment duration, etc. Such questions can only be addressed by international collaborative academic studies.
To empower international research collaboration, the **International Pediatric Thrombosis Network (IPTN)** has been initiated at the SSC on Pediatric/Neonatal Hemostasis and Thrombosis in 2017. This Network consists of pediatric thrombosis expert centers across the world whose ultimate goal is to bring the best treatment to pediatric patients with thrombosis.

The components and objectives of the IPTN are

(i) **Throm-PED Registry**: prospective disease-based registry as a basis for conducting epidemiological research on frequency, risk factors, diagnosis, treatment and short- and long-term outcome of pediatric TE in general, but of specific TE subtypes in particular. Moreover, data on TE frequency in participating centers will allow for feasibility assessment for interventional studies in the clinical trial network (below). ([https://www.isth.org/page/ThromPEDreadmore](https://www.isth.org/page/ThromPEDreadmore))

(ii) **Clinical Trial Network**: network of pediatric thrombosis centers with clinical trial experience and infrastructure to effectively conduct interventional studies in pediatric thrombosis. The network will act as platform to conduct industry-sponsored regulatory trials as well as investigator-initiated academic trials on anticoagulation management.

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

Describe concisely the research design and methods for achieving these goals. Suggested length 2-3 paragraphs

**Methods:**

1. **Executive committee of IPTN**
   The executive committee (EC) of the IPTN has been formed at the SSC on Pediatric/Neonatal Thrombosis and Hemostasis meeting in Berlin 2017 (for details see project structure below).

2. **Participating centers of IPTN**
   Any center worldwide taking care of neonates and children with TE is eligible to participate in the IPTN. To reach these centers, newsletters are sent regularly by email to all members of the SSC on Pediatric/Neonatal Thrombosis and Hemostasis to inform them about the IPTN, the Throm-PED registry and other substudies. Members of the IPTN are encouraged to send information about the IPTN to colleagues in their country to recruit further centers. Additionally, meetings are organized at the ISTH congress and other conferences, to provide public information about the IPTN and to recruit further centers.

3. **Organizational structure of the IPTN**
   The IPTN serves as platform for the Throm-PED registry and its sub-studies, and for the Clinical Trial Network. The following structures have been established and will be further developed:
   - A consortium charter and agreement ([https://www.ISTH.org/IPTN](https://www.ISTH.org/IPTN))
   - Annual meeting at each ISTH congress for all members, to discuss ongoing and new research projects, study manuscripts, position papers, etc.
   - Teleconferences for the EC (twice a year) and for all members (twice a year)
   - Any member may propose new research projects using a special application form which will be reviewed and prioritized by the EC and then offered to all centers for participation.
   - Reports on each ongoing studies every 6 months
   - Study material: including study protocols, patient information sheets, and other material for ERB submission
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- Administrative support for centers for setting up and running individual sub-studies
- Continuous development and update of the IPTN website (https://www.ISTH.org/IPTN)

4. **Collaborative clinical research:**

4.1. The **Throm-Ped registry** is the backbone of epidemiological research in the IPTN. The protocol is available on the IPTN website. [https://www.isth.org/page/ThromPEDreadmore](https://www.isth.org/page/ThromPEDreadmore) The Throm-PED registry is established to increase knowledge about the epidemiology, risk factors, diagnosis, and treatment of **thrombosis in children in general.** The following data are being collected: age at diagnosis of TE, type of TE (venous or arterial), location, risk factors, and treatment. Once a patient is registered, there is the possibility to collect follow-up data on disease course and treatment outcome.

This basic database can flexibly be supplemented with datasheets for additional sub-studies. The first ongoing dedicated **substudy** is on **neonatal renal vein thrombosis.** If a new patient is entered into Throm-PED, and the location of TE is renal vein in a neonate, an additional datasheet appears with specific questions about neonatal renal vein thrombosis. In that way, important information can be collected about specific types of TE in childhood.

To date, the IPTN has 27 members and 18 patients have been entered into the Throm-PED registry (Appendix).

Further studies currently planned are:

1. **Portal vein thrombosis**
2. The short-term and long-term consequences of **asymptomatic thrombosis**
3. **Use of DOACs in children in real life:** collection of data on current off-label use in children; after licensure in children, collection of complementary information from use in specific atypical pediatric indications (eg. prematurity and other co-morbidities, special TE locations).

Early career researchers are encouraged to propose and take on the responsibility for projects in the Throm-PED registry, each of which is mentored by a senior member.

4.2. **A Clinical Trial Network** is currently being developed within the IPTN to conduct collaborative interventional studies in paediatric thrombosis. The Clinical Trial Network will be steered by the **Task Force for Paediatric Anticoagulant Development** which has recently been founded by the Pediatric SSC. The objective of the task force is to provide guidance to regulatory agencies and the pharmaceutical industry to optimize and harmonize paediatric anticoagulant developments globally. Specific aims are to:

- define therapeutic needs and priorities in paediatric thrombosis
- provide methodologic guidance for paediatric anticoagulant trials (position papers),(11-13)
- provide input into the design of industry trials to generate clinically relevant and feasible protocols
- assess the feasibility of running these trials among members of the Throm-PED Clinical Trial Network
- provide a contact point for industry to roll-out these trials in the Network
- provide a platform for developing and performing academic collaborative trials.

In principle, any member of the IPTN with an interest in contributing to a clinical trial can register with the Throm-PED Clinical Trial Network. Pragmatically, these will initially be mostly centers which have experience from previous or ongoing industry trials or academic trials in this therapeutic area. While the network is further developed, we will define criteria for trial experience, infrastructure, and capacity, as
well as track performance characteristics of centers in actual trials. These quality criteria are not intended to exclude any centers from trial participation but to allow for realistic feasibility estimates for future trials. While practical experience from trial participation is important, the network will also provide educational material and training to centers.

Ideally, the network will be developed along a concrete model trial. A best-practice example is the Kids-DOTT trial (coordinated by N. Goldenberg, former co-chair of the Pediatric SSC), an ongoing academic trial on the optimal duration of anticoagulation in children that involves multiple centers from the US, the EU, Israel, Australia, many of which are members of the Pediatric SSC and the IPTN. (14)

The Task Force for Paediatric Anticoagulant Development has established a cooperation with generic paediatric clinical trial platforms in the US and EU (I-ACT and C4C, respectively), which will allow to collaborate with other disease-specific paediatric networks (e.g. Pediatric Heart Network), to exchange methodological expertise, to develop template study protocols, to interact with the regulatory agencies, and will facilitate joint applications for funding of trials.

We have recently performed a survey among the members of the Pediatric SSC regarding their interest for participating in the planned Clinical Trial Network. To date, 69 members have responded of whom 67 expressed an interest in the Network. Of these, 93% represent tertiary care pediatric centres; 68% treat up to 50 children with TE/year, 16% between 50-100 children, and 16% more than 100 children with TE/year. 90% of centers are already participating in anticoagulant trials; not participating centers had either not been approached (67%) or insufficient personnel capacity (17%). 93% of centers indicated they have a dedicated clinical research team, including study coordinator or nurse, data manager, statistical support, trial pharmacy and trial laboratory.

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

Suggested length 2-3 paragraphs

**Study population:**
All children with TE aged 0 to less than 18 years can be included in the Throm-PED registry and depending on the type of TE or treatment in additional prospective observational cohort studies.

Ethical approval: Study protocols are submitted to National Medical Ethics Review Committees for approval to collect data in both the general Throm-PED registry and additional substudies of the IPTN. For any study protocols going beyond the data collection in the registry, including laboratory testing, biobanking, diagnostic or therapeutic study procedures, or interventional trials, separate ethical approval will be sought in every center. All study patients and/or their legal representatives have to provide written informed consent as per local legal requirements.

**Expected timeline:**

The Throm-PED registry is an ongoing registry, which serves as a backbone for future observational studies. The Clinical Trial Network is currently being developed building up on existing study collaborations and is intended as a permanent infrastructure. For a sustainable registry and clinical trials network, further funding will need to be obtained in the future based on several individual study projects.
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**Expected outcomes (ie. publications):**

- Original article about the international survey on the epidemiology of pediatric thrombosis worldwide (Throm-PED registry).
- Original articles about further additional studies, including neonatal renal vein thrombosis, surveys, etc. performed by the IPTN.
- Original articles reporting the results of interventional trials performed in the Throm-PED Clinical Trials Network
- Methodological articles and position papers regarding diagnostic and therapeutic trials in paediatric TE.

All manuscripts arising from the IPTN will have the name of the group in the title (Pediatric Thrombosis Network). Author’s list will include as a suffix “on behalf of the Pediatric Thrombosis Network”.

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

**Project set up and management**
The IPTN was founded during the SSC Pediatric/Neonatal Thrombosis and Hemostasis in Berlin 2017. The executive committee of the IPTN consists of the pediatric hematologists/experts in paediatric coagulation: C. van Ommen (Netherlands, chair IPTN), C. Male (Austria, chair task force), S. Holzhauer (Germany), B. Branchford (USA), P. Monagle (Australia), U. Nowak-Gottl (Germany), M. Albisetti (Switzerland), E. Chalmers (UK), S. Revel-Vilk (Israel), M. Bonduel (Argentina), M. Bhatt (Canada). A. Chan (Canada) is senior advisor. Membership of the executive committee is for 5 years. Each future committee member will be elected by secret ballot. The EC meets at least twice a year, once at the annual ISTH congress, once by telephone conference.

**Needed infrastructure and resources**
For the start-up of the IPTN and the Clinical Trial Network, a trial coordinator is needed, and funding is applied for the first 2 years. The tasks of the trial coordinator are to encourage centers and pediatric thrombosis experts to participate in the IPTN, and to provide support to set-up centers; to manage the communication between the IPTN chair, the EC, principal investigators of individual sub-studies, and participating members; to organize the annual meeting at the ISTH congress, the teleconferences, generate study progress reports, manage the correspondence to the IPTN email ([IPTN@erasmusmc.nl](mailto:IPTN@erasmusmc.nl)); to develop and update the website; to support early career researchers with the development new projects (study protocol, submission material, setting up datasheets, information to centers, etc.). Initially, the coordinator will also monitor data entry, and prepare data outputs and interim analyses. In the future, these tasks shall be taken over by a data manager and/or statistical expert.

Therefore, the budget for the current grant application is mainly intended for the personnel costs of the trial coordinator for the first 2 years. With the IPTN growing, we will apply for additional grants in the future, to finance an overarching IPTN study center with a secretary, trial coordinator and statistical experts.

**References:**


### APPENDIX
List of centers currently participating in the IPTN

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<thead>
<tr>
<th>Institute</th>
<th>Country</th>
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<tbody>
<tr>
<td>AMC</td>
<td>the Netherlands</td>
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<tr>
<td>University of Colorado School of Medicine/Children's Hospital Colorado</td>
<td>USA</td>
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<tr>
<td>Starship Blood and Cancer Centre, Starship Children's Health, Auckland 1142</td>
<td>New Zealand</td>
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<tr>
<td>Children's Hospital of Michigan/Wayne State University, Detroit</td>
<td>USA</td>
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<tr>
<td>Saint Louis University</td>
<td>USA</td>
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<tr>
<td>Children's Hospital of Philadelphia</td>
<td>USA</td>
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<tr>
<td>U of Iowa</td>
<td>USA</td>
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<tr>
<td>Shiraz Hematology Research Center</td>
<td>Iran</td>
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<tr>
<td>North Carolina State University and University of North Carolina at Chapel Hill</td>
<td>USA</td>
</tr>
<tr>
<td>Department for Thrombosis and Haemostasis, Skåne University Hospital, Malmo</td>
<td>Sweden</td>
</tr>
<tr>
<td>Rush University Medical Center</td>
<td>USA</td>
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<tr>
<td>Sant Joan de Déu Hospital</td>
<td>Spain</td>
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<tr>
<td>Hematology Center after R. Yeolyan</td>
<td>Armenia</td>
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<tr>
<td>Sophia Children's Hospital ErasmusMC</td>
<td>the Netherlands</td>
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<tr>
<td>Sheba Medical Center</td>
<td>Israel</td>
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<tr>
<td>The University of Texas Southwestern</td>
<td>USA</td>
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<tr>
<td>Instituto nacional de pediatria</td>
<td>Mexico</td>
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<tr>
<td>Universitätskinderklinik des Saarlandes, Klinik für pädiatrische Hämatologie</td>
<td>Germany</td>
</tr>
<tr>
<td>Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University</td>
<td>Thailand</td>
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<tr>
<th>Institution</th>
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<tr>
<td>Penn State Hershey Children’s Hospital/Penn State University College of Medicine</td>
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<tr>
<td>Karolinska Institutet, Karolinska University Hospital</td>
<td>Sweden</td>
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<tr>
<td>The Hospital for Sick Children</td>
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<tr>
<td>Hospital Vall d’ Hebrón</td>
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<td>Rady Children’s Hospital San Diego</td>
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<td>Fakultní nemocnice Ostrava</td>
<td>Czech Republic</td>
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