Research projects 2024-2026

The research projects for 2024–2026 have been structured into several working groups each with one chairperson, 5-10 members and administrative support from the study staff.

The research focus of the working groups (WG) are:

I. Immunogenicity
II. Patients with inhibitors
III. Haemophilia B
IV. Intracerebral haemorrhages
V. Gene variants
VI. Efficacy of treatment (& long-term outcome)
VII. Novel therapies
VIII. Girls with haemophilia
IX. Rare bleeding disorders

I. Working group on immunogenicity

Objectives:

a. To study the association of family history of haemophilia with inhibitor development.
b. To study the association of blood group O with inhibitor development-manuscript submitted.
c. To provide an updated analysis of inhibitor development according to FVIII/IX concentrate.

Background: The risk factors for FVIII inhibitor development have been extensively studied by PedNet in the last years. Family history of haemophilia and/or inhibitors affects diagnosis and early treatment. Choice of factor VIII/IX concentrate may affect risk of inhibitor development. Blood group O affects half-life of factor VIII concentrates. PedNet's recent analysis suggests that inhibitor development in PUPs peaks before 50-75 exposure days (EDs), yet timing of inhibitor evolution may change in the new era. Data regarding FVIII tolerance and inhibitor evolution in children treated by emicizumab prophylaxis with or without additional FVIII are currently scarce.
For haemophilia B- potential immunogenicity of various clotting products, especially EHL, deserves attention as real world data addressing this issue are limited.
For new clotting factor concentrates, and new therapy modes, PedNet's extensive cohort with >90% follow-up at ED50 will enable comparisons and inhibitor risk assessment

Endpoints: clinically relevant inhibitors, defined as two positive samples above the cut-off value of each participating centre's laboratory (Nijmegen modification of the Bethesda assay

with cut-off values of between 0.3 and 0.6 BU/ml). All centres perform testing at least every 5th ED during the first 20 EDs and thereafter at least every 3 months until 50 EDs.

Determinants: baseline FVIII/IX levels, family history for inhibitors, FVIII/IX gene mutation, blood group type, details of the individual prophylaxis regimen (recombinant/plasma/ extended half-life products/ emicizumab) and reason for treatment administration (bleed/prophylaxis), immunological 'danger signals' (according to each infusion for the first 50 treatment days), surgery, etc.

Working plan: Analyses will be performed for risk factors for inhibitor development related to family history, blood group O, individual products (SHL, EHL, recombinant/plasma derived) adjusted for potential confounding factors, and the effect of early prophylaxis on immunogenicity. (See also WG on novel therapies)

II. Working group on patients with haemophilia A and inhibitors

Objectives:

To study the natural history of high-titre inhibitors and the effect of different ITI regimens; and to evaluate the optimal management of patients with inhibitors
The following projects will be pursued:

a. Predictors of ITI success in 231 children with severe haemophilia A with high titre inhibitors against FVIII. Manuscript in preparation.
b. Association of genotype and disappearance of inhibitors with and without ITI.
c. Novel therapies and results of ITI
d. Novel therapies and recurrence of inhibitors

Background: Development of inhibitors is still a major side-effect of haemophilia treatment. Few studies have focused on the impact of inhibitors on bleeding phenotype and the clinical management of a large group of unselected children of comparable age. PedNet recently published the results regarding bleeding phenotype of 222 children with high responding inhibitors before and after ITI. All patients who develop an inhibitor in the PedNet Registry are followed by detailed data on bleeds and regimens and outcomes of immune tolerance induction (ITI). Children in PedNet have developed inhibitors at an early age before established joint disease. More frequent ITI and prophylaxis with by-passing agents, and recently with emicizumab, may have given them a better outcome than previous generations of children who developed inhibitors before year 2000. The REMAIN study, whose first analyses were already published, will increase our knowledge of the success rate of various ITI regimens as well as the long-term joint outcome.

Working plan: All patients born after January 1st, 2000 with haemophilia A who developed inhibitors are included. Data on ITI regimens (including the use of bypassing agents or NRT prophylaxis), type of concentrates, dose and frequency of dosing are registered as well as bleeds and long-term outcome.

Endpoints: Success, partial success or failure of ITI. Time to success and bleeds.

Determinants: ITI regimen (low/high dose, frequency), mutation, historical/peak titre, etc.

III. Working group on Haemophilia B

Objectives:

1) To study the outcome of patients with haemophilia B and inhibitors, treated or not treated with ITI.
2) Genetic markers of inhibitor development in hem B (see genetics)
3) To study HB Leyden- see genetics

Background: Haemophilia B is diagnosed in about 15% of all patients with haemophilia and clinical studies are thus hampered by the small number of patients eligible for studies over a long time period. The effect of modern haemophilia treatment on long-term outcome can only be studied if patients are followed from diagnosis and onwards with complete data on treatment and outcome parameters. The PedNet cohorts includes a large cohort of children with severe or moderate haemophilia B which enables such studies. In a first report, published in 2020, a higher than previously reported incidence of inhibitors (10%) was found for patients with severe haemophilia B.

The genetic variants of F9 gene and their impact upon Haemophilia B phenotype as well as upon inhibitor risk are being studied by the WG of genetics.

Working plan: To study the outcome of various ITI regimens given to children who developed inhibitors to FIX.

IV. Working group on intracranial haemorrhage

Objectives: To study Intracranial haemorrhages (ICH) before start of prophylaxis in children with haemophilia: incidence, timing, and potential for prevention.

Background: ICH is one of the most devastating complications of haemophilia and may be associated with high morbidity and mortality. The epidemiology of ICH in children and adolescents with haemophilia was previously studies by PedNet. While the use of prophylaxis with FVIII and FIX concentrates has reduced the risk of ICH markedly, the incidence of neonatal ICH remains high: in a study from the PedNet group, it was 2.2% for children with severe HA or HB.

Working plan:

a. To study ICH risk, epidemiology and risk factors in infants with haemophilia beyond the neonatal period (first 4 weeks of life) and assess the possible impact of early prophylaxis upon ICH occurrence. Manuscript submitted.
b. To study ICH in infants with haemophilia during the neonatal period.

V. Working group on gene variants

Objectives:

1) To describe the natural history of haemophilia B Leyden. Manuscript submitted.
2) To study the outcome of ITI by genotype.
3) To study the association of genetic *F8 and F9* variants with inhibitor development.

Background: Today, genetic markers provide the only established endogenous risk factor for inhibitor development in haemophilia. Reported genetic data are continuously reviewed and classified in PedNet according to HGVS nomenclature and the pathogenicity according to ACMG/AMP guidelines. Recently 88 new gene mutations were found in the PedNet cohorts, and risks for inhibitors were studied. The group now intends to study the outcome of ITI by genotype.

Working plan: Reported genetic data are continuously reviewed and classified according to HGVS nomenclature and the pathogenicity according to ACMG/AMP guidelines. The genetic group studies the association of F8 and F9 variants with inhibitor development, A study that describes the natural history was recently submitted. The outcome of ITI by genotype will be evaluated both in high-responder and low-responder inhibitors.

VI. Working group on efficacy of treatment (including long-term outcome)

Objectives:

a. To study the long-term outcome of primary prophylaxis on bleeds, patient-reported activities, quality of life and joint status in moderate and severe haemophilia ≥ 12 years. Differences in joint health status of adolescents with severe haemophilia A and B on prophylaxis between Sweden and Greece are assessed. Manuscript in preparation.
b. To provide reference data on bleeding during factor VIII/IX prophylaxis in severe HA and HB
c. To study pathways to prophylaxis in non-severe HA

Background: The treatment for children with haemophilia has changed dramatically over the last 20 years. Prophylaxis was first implemented in a small group of patients and often practised as secondary prophylaxis. Centres in the PedNet study group have been early adopters of primary prophylaxis. Many children followed from diagnosis onwards have complete data regarding the start of treatment and life-long bleeding records. Many of our

patients have now reached adulthood. Data on validated outcome tools, such as HJHS score or HEAD- US have been collected and enabled studies that can provide valuable data in the discussion on trough levels, dosing, dosing frequency and alternative therapies for children in the future. In a recent publication PedNet data supported the conclusion that most adolescents with severe or moderate HA show favourable joint health, and ultrasound paired with physical examination increases sensitivity for detection of joint damage

Endpoints: Annual bleeding rate (ABR) and annual joint bleeding rate (AjBR) clinically relevant major bleeds, prophylaxis- defined as at least once weekly IV administration of clotting concentrate, inhibitors, defined as two positive samples above the cut-off value of each participating centre's laboratory, HJHS /HEAD-US scores for joint status evaluation

Working plan: A pilot multicentre study involving five centres has been initiated to evaluate the feasibility of various research questions concerning long term treatment outcomes, serving as a foundation for future studies. During the research period, studies will be initiated with a focus on the pharmacovigilance of novel therapies such as EHL-FVIII , EHL-FIX, XHL, and "non-factor" treatment options such as emicizumab (see below) with the aim of evaluating safety and efficacy using the large dataset on the traditional treatment regimens as potential comparators.

VII. Novel therapies/Pharmacovigilance

Objectives:

a. Survey on inhibitor monitoring during emicizumab. Manuscript in preparation.
b. To study the association of concomitant / on demand treatment with FVIII with inhibitor development in children receiving emicizumab prophylaxis
c. To assess safety and efficacy of emicizumab in PUPs and MTPs in severe haemophilia A.
d. To address risk of inhibitor recurrence in emicizumab treated patients after ITI who stopped FVIII prophylaxis

Background: Many new concentrates and non-replacement therapies are currently entering the market for haemophilia. At the time of marketing authorisation, data on immunogenicity and safety in children are limited. As a disease Registry, PedNet follows all included patients and documents the effect of new therapies on bleed protection.
A survey addressing management and monitoring of emicizumab treated patients in PedNet centres was recently published[12] and a study comparing bleeding patterns before and after emicizumab prophylaxis showed results favouring emicizumab.
In addition, PedNet collects data on expected and unexpected adverse events. Regulatory authorities support the use of pharmacovigilance studies in Registry holders such as PedNet. Since 2020 PedNet has started to systematically collect other adverse events related to haemophilia treatment in addition to inhibitor development and life-threatening bleeding.

Determinants: baseline FVIII/IX levels, inhibitors, FVIII/IX gene mutation, details of the individual prophylaxis regimen/ITI and reason for treatment administration (bleed/prophylaxis), immunological 'danger signals' (according to each infusion for the first 50 treatment days), adverse events

Working plan: During the research period, studies will be initiated with the aim of evaluating safety and efficacy, the natural history of inhibitor occurrence and treatment strategies using the large dataset on the traditional treatment regimens as potential comparators.

VIII. Working group on girls with haemophilia

Objectives: to evaluate the bleeding phenotype of girls with mild, moderate or severe haemophilia

Background: Although haemophilia in females has gained increased recognition, diagnosing and managing it remains challenging. While severe and moderate factor VIII/IX deficiencies are uncommon among female carriers, mild deficiency is frequently overlooked. Carriers of haemophilia tend to experience bleeding symptoms, eg: heavy menstrual bleeding, oral bleeding, and even joint bleeds. Recent studies emphasize the need to test factor levels and evaluate bleeding patterns early in life for potential carriers, ideally before menarche. In the PedNet registry real world data are collected about girls with haemophilia (up to 25% factor activity levels), genetically analysed and longitudinally followed.

Working plan: Data collection addressing genetic mutations, bleeding phenotype and treatment of girls included in all PedNet registry cohorts. Perform a survey on the management of girls with haemophilia.

IX. Working group on rare bleeding disorders (RBD)

Objectives: to evaluate the bleeding phenotype, genetic background and natural history of infants and children with severe rare bleeding disorders

Background: the incidence of congenital rare bleeding disorders (RBD) varies from 1:5,000 (Haemophilia A), 1:30,000 (Haemophilia B) to considerably less frequent (1:500,000 for FVII deficiency, 1:1-3 million for prothrombin or FXIII deficiencies). Most RBDs are inherited as autosomal recessive, and bleeding symptoms may occur in infancy or childhood. Bleeding symptoms among girls with RBD may present along with menarche. Currently, haemostatic control is largely based upon replacement of the missing coagulation factors, unless presence of inhibitors renders it impossible. Real world studies of various RBDs are limited and the specific knowledge regarding symptoms, treatment, complications and outcomes among paediatric populations is not well addressed in the currently available publications.

The special design of the PedNet registry provides an excellent opportunity to prospectively study and follow such bleeding disorders.

Working plan: A specific “task force” was formed within PedNet to adopt registry’s structure and initiate disease specific data collection, aiming at outcomes addressing genetic variants, bleeding phenotype, prophylactic treatment and long term impact upon joint as well as general health.

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