Research programme 2024-2026

PedNet Haemophilia Research Foundation

On behalf of the PedNet study group:

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1. Definitions

PedNet (the European Paediatric Network for Haemophilia Management) started in 1996 as a collaboration of 22 paediatricians in 16 European countries treating haemophilia in children. The members of the group are physicians who do not represent their respective countries or any national organisation but are responsible for the care of children at a Haemophilia Treatment Centre (HTC) in their respective countries. Currently the **PedNet study group** consists of **32** haemophilia treatment centres in **19 countries** (Europe, Israel and Canada) – see Appendix 1.
The PedNet Registry started in 2003 and collects real-life data from all children born after January 01, 2000, diagnosed with haemophilia A or B, and treated in one of the participating HTCs.

The PedNet Haemophilia Research Foundation was founded in December 2016 to secure long-term continuation of the basic and clinical research using the Registry and is the legal, not-for-profit, body that coordinates the activities in the PedNet study group and manages the PedNet Haemophilia Registry. The "Management Board" has the responsibility of management of the Registry and represents the PedNet Haemophilia Foundation (Appendix 1).
The data of the Registry is stored and secured by the Julius Centre, Utrecht University Medical Center, the Netherlands. External monitors are employed by the CRO company Julius Clinical, Zeist, the Netherlands.
The members of the PedNet study group have initiated working groups on specific research projects. All members participate in at least one working group and the projects are supervised by the chairperson of the individual working group and the Scientific Advisory Council (SAC).

2. Mission of the PedNet Haemophilia Research Foundation

To improve the current and future care of children with haemophilia by collection of high-quality data from a large cohort of unselected previously untreated children with haemophilia A and B followed from start of therapy, thus enabling front-line research projects on inhibitor development, safety, efficacy and long-term outcome of replacement and non-replacement therapies (NRT)[1,2].

3. Significance

The PedNet Registry has a unique data collection with inclusion of >2700 children with haemophilia A or B, many of whom have been followed prospectively for more than 12 years and several for 18 years. The quality of the data is assured by regular monitoring as well as the low percentage of missing data or patients lost to follow-up. Several papers in high-ranked medical journals have been published based on data from the PedNet Registry, demonstrating its scientific and clinical value and its potential for the future management of children with haemophilia A or B.

4. Overview of research field

Haemophilia A and B are hereditary, X-chromosomal recessive disorders caused by deficiency or dysfunction of, respectively, plasma coagulation factor VIII (FVIII) or factor IX (FIX). The bleeding phenotype may, depending on the concentration of FVIII or FIX coagulant activity, be classified as severe (<1% of normal activity), moderate (1-5%) or mild (>5-25%). The current standard treatment for severe forms is prophylaxis to avoid bleeding episodes, either by replacing the missing clotting factor or by non-replacement therapies, such as FVIII mimetic agents or rebalancing therapies, targeting the natural coagulation inhibitors. In Europe, most children receive primary prophylaxis, which effectively prevents life-threatening haemorrhage, disabling joint arthropathy and muscle atrophy[1]. Among patients treated by non-replacement therapies, clotting factor concentrates are used to control breakthrough bleeding episodes or any surgical interventions.

1) Prophylaxis

Although prophylactic treatment is the standard treatment regimen for the more severe forms of the disease, the optimal prophylactic regimen is still a matter of debate. Recent new options for prophylaxis have added more complexity to this debate. Large international collaborative studies are needed to answer clinical research questions regarding natural history, efficacy, complications including inhibitor development, and long-term maintenance of joint health. The PedNet centres have used primary prophylaxis on a large scale and the long-term follow-up of these children has the potential to provide new information on different prophylactic regimens, the short- and long- term efficacy of various factor replacement concentrates as well as non-factor treatment options[3].

2) Evaluation of new treatment modalities (safety and efficacy)

The PedNet Registry includes a large body of data on bleeding (efficacy) and side-effects (safety) of treatment with clotting factor concentrates, and of patients treated by currently registered non-replacement therapies. As such, PedNet is able to provide an important comparator for the evaluation of efficacy and safety of new clotting factor concentrates and/or treatment modalities.

3) Input for post-licencing safety studies

The safety and efficacy of new generation clotting products have been investigated in limited numbers of selected patients in the pre-licensure phase. In PUP (previously untreated patients) studies mandated by regulatory agencies until recently, only a limited number of PUPs were required. Since many factors influence the risk of developing inhibitors, these studies are likely to be selected and are underpowered to determine the relative impact of various risk factors or to enable comparisons between products regarding both safety and efficacy. The quantity and quality of the data collected by the PedNet Haemophilia Research Foundation have been recognised by the Pharmacovigilance Risk Assessment Committee (PRAC), the European Medicines Agency's (EMA) committee responsible for assessing and monitoring the safety of human medicines.

The PedNet data are based on an unselected cohort and are used by pharmaceutical companies for the collection of additional safety data.

4) Inhibitors

The most important adverse effect of haemophilia treatment with clotting factor concentrates (CFC) is the development of neutralising alloantibodies (inhibitors) against factor VIII or IX. Inhibitors develop in ±30% of children with severe haemophilia A mainly during the first 50 exposures to CFC.
The rarity of the disease highlights the need for collaborative studies to investigate all potential risk factors in a large cohort such as the PedNet Registry. PedNet is currently analysing the data on >1500 Pups with severe haemophilia A. (See under working group on immunogenicity). The PedNet group has provided important insights in the effects of risk factors (Gouw NEJM 2013[4]; Fischer JTH 2024[5]) and research on additional exogenous and endogenous risk factors and treatment of inhibitors is ongoing[4-7]. In the era of non-replacement therapy (NRT) prophylaxis, where children receive FVIII therapy as needed for breakthrough bleeds, the epidemiology of inhibitors and the timing of their development may shift. Thus, specific factors and "danger signals" should be further investigated.
The PedNet Registry contains data on large number of children (N>500) who have developed inhibitors. These patients are followed prospectively and detailed data on treatment and bleeding are collected. The Registry allows studies on the bleeding phenotype and the efficacy of various ITI (immune tolerance induction) regimens as well as various prophylactic or treatment options[8-12].

5) Exploration of gene mutations

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 Registry, and risks for inhibitors were studied. The group now intends to study the outcome of ITI by genotype.

6) Exploration of additional Rare Bleeding Disorders (RBDs)

The PedNet foundation is investigating the viability of including additional RBDs in the Registry. The unique design of the PedNet Registry provides an excellent opportunity to prospectively study and follow such bleeding disorders in the paediatric population.

A specific "task force" was formed within the PedNet study group to adopt the Registry's structure and initiate disease specific data collection, aiming at outcomes addressing genetic mutations, bleeding phenotype, prophylactic treatment, and long-term impact upon joint as well as general health.

5. The PedNet Registry - Protocol and design

The PedNet Registry is governed by the PedNet Registry protocol version 6.4 (2022) which details all methodological, legal and ethical issues of the collection of data (www.pednet.eu). The PedNet Registry is registered on http://ClinicalTrials.gov under the number NCT02979119.

The PedNet Registry collects data prospectively from all children diagnosed with severe, moderate and mild haemophilia A and B born from January 1st, 2000 and who are being treated from diagnosis at a participating HTC[1]. Web-based Case Report Forms (CRFs) register basic parameters at inclusion and then regular prospective follow-ups until the age of 18 years, more frequent during the first 50 exposure days (ED). The CRFs have been harmonised to the recommendations from an EMA workshop in June 2018. By regular internal and external monitoring and frequent direct contacts with the centres, data are continuously confirmed, cleaned, and improved to ensure high quality and completeness. Informed consent is obtained according to each participant's national ethical review regulations and the coded identity (PID) is kept at the HTC. Since the aim is to collect prospective data on complete birth/age cohorts, a data export is performed on January 1st every year to be used for annual reports and to prepare working files for on-going projects. A statistical analysis plan is prepared for each single research project based on the research question and available data.

6. Research projects 2024-2026

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

The current working groups are:

I. Immunogenicity of FVIII and FIX
II. Patients with inhibitors
III. Haemophilia B
IV. Gene mutations
V. Intracerebral haemorrhages
VI. Efficacy of treatment
VII. Novel therapies
VIII. Girls with haemophilia
IX. Rare bleeding disorders

I. Working group on immunogenicity of FVIII and FIX

a. Family history of haemophilia and/or inhibitors affects diagnosis and early treatment. The aim is to study the association of family history of haemophilia with inhibitor development.
b. Blood group O affects half-life of factor VIII concentrates. The aim of the study is the association of blood group O with inhibitor development.
c. Choice of factor VIII/IX concentrate may affect risk of inhibitor development. The aim of the study is to provide an updated analysis of inhibitor development according to FVIII/IX concentrate (Ref Fischer JTH 2024- containing data until 2020).

II. Working group on patients with haemophilia A and inhibitors

a. Predictors of ITI success in 231 children with Severe haemophilia A children 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

III. Working group on Haemophilia B

a. To study the outcome of patients with haemophilia B and inhibitors, treated or not treated with ITI.
b. Clinical phenotype and progression of factor IX levels according to mutation type in patients with a HB Leyden variant.

IV. Working group on gene mutations

a. To describe the natural history of haemophilia B Leyden. *Manuscript submitted.*
b. To study the outcome of ITI by genotype
c. To study the association of genetic F8 and F9 variants with inhibitor development

V. Working group on intracranial haemorrhage

a. Intracranial haemorrhages (ICH) before start of prophylaxis in children with haemophilia: incidence, timing, and potential for prevention. *Manuscript submitted.*
b. ICH in infants with haemophilia during the neonatal period

VI. Working group on efficacy of treatment

a. Differences in joint health status of adolescents with severe haemophilia A and B on prophylaxis between Sweden and Greece. *Manuscript in preparation.*
b. Reference data on bleeding during factor VIII/IX prophylaxis in severe HA and HB
c. Pathways to prophylaxis in non-severe HA

VII. Novel therapies

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. Safety and efficacy of emicizumab in PUPs and MTPs in severe haemophilia A.

VIII. Working group on girls with haemophilia

a. To evaluate the bleeding phenotype of girls with mild, moderate, or severe haemophilia
b. Survey on management of girls with haemophilia.

IX. Working group on rare bleeding disorders

a. To evaluate the bleeding phenotype, genetic background and natural history of infants and children with severe rare bleeding disorders

7. References

1. Fischer, K., Ljung, R., Platokouki, H., Liesner, R., Claeyssens, S., Smink, E. and van den Berg, H.M. (2014), Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. Haemophilia, 20: e280-e286. https://doi.org/10.1111/hae.12448
2. Report on Haemophilia Registries, Workshop 8 June 2018, EMA/487643/2018
3. Ljung R, de Kovel M, van den Berg HM. Primary prophylaxis in children with severe haemophilia A and B—Implementation over the last 20 years as illustrated in real-world data in the PedNet cohorts. Haemophilia. 2023; 29: 498–504. https://doi.org/10.1111/hae.14729
4. Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S, van Geet C, Kenet G, Mäkipernaa A, Molinari AC, Muntean W, Kobelt R, Rivard G, Santagostino E, Thomas A, van den Berg HM. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med 2013; 368: 231-9. https://doi.org/10.1056/NEJMoa1208024
5. Fischer K, Carcao M, Male C, Ranta S, Pergantou H, Kenet G, Kartal-Kaess M, Königs C, Carvalho M, Alvarez MT, Brakenhoff T, Chambost H, van den Berg HM. Different inhibitor incidence for individual factor VIII concentrates in 1076 previously untreated patients with severe hemophilia A: data from the PedNet cohort. J Thromb Haemost. 2023 Mar;21(3):700-703. https://doi.org/10.1016/j.jtha.2022.11.020
6. Gouw SC, van den Berg HM, Fischer K, Auerswald G, Carcao M, Chalmers E, Chambost H, Kurnik K, Liesner R, Petrini P, Platokouki H, Altisent C, Oldenburg J, Nolan B, Garrido RP, Mancuso ME, Rafowicz A, Williams M, Clausen N, Middelburg RA, Ljung R, van der Bom JG; PedNet and Research of Determinants of INhibitor development (RODIN) Study Group. Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. Blood. 2013 May 16;121(20):4046-55. https://doi.org10.1182/blood-2012-09-457036.
7. Platokouki H, Fischer K, Gouw SC, Rafowicz A, Carcao M, Kenet G, Liesner R, Kurnik, K, Rivard GE, van den Berg HM. Vaccinations are not associated with inhibitor development in boys with severe haemophilia A. Haemophilia. 2018; 24: 283–290. https://doi.org/10.1111/hae.13387
8. van den Berg HM, Fischer K, Carcao M, Chambost H, Kenet G, Kurnik K, Königs C, Male C, Santagostino E, Ljung R; PedNet Study Group. Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A. Blood. 2019 Jul 18;134(3):317-320 https://doi.org/10.1182/blood.2019000658
9. van den Berg HM, Mancuso ME, Königs C, D'Oiron R, Platokouki H, Mikkelsen TS, Motwani J, Nolan B, Santagostino E; European Pediatric Network for Haemophilia Management (PedNet). ITI Treatment is not First-Choice Treatment in Children with Hemophilia A and Low-Responding Inhibitors: Evidence from a PedNet Study. Thromb Haemost. 2020 Aug;120(8):1166-1172. https://doi.org/10.1055/s-0040-1713097
10. Mancuso ME, Fischer K, Santagostino E, Oldenburg J, Platokouki H, Königs C, Escuriola-Ettingshausen C, Rivard GE, Cid AR, Carcao M, Ljung R, Petrini P, Altisent C, Kenet G, Liesner R, Kurnik K, Auerswald G, Chambost H, Mäkipernaa A, Molinari AC, Williams M, van den Berg HM; European Pediatric Network for Haemophilia Management (PedNet) the REMAIN (REal life MAnagement of children with

INhibitors) Study Group. Risk Factors for the Progression from Low to High Titres in 260 Children with Severe Haemophilia A and Newly Developed Inhibitors. Thromb Haemost. 2017 Dec;117(12):2274-2282. https://doi.org/10.1160/TH17-01-0059
11. Male C, Andersson NG, Rafowicz A, Liesner R, Kurnik K, Fischer K, Platokouki H, Santagostino E, Chambost H, Nolan B, Königs C, Kenet G, Ljung R, Van den Berg M. Inhibitor incidence in an unselected cohort of previously untreated patients with severe haemophilia B: a PedNet study. Haematologica. 2021 Jan 1;106(1):123-129. https://doi.org/10.3324/haematol.2019.239160
12. Ranta S, Motwani J, Blatny J, Bührlen M, Carcao M, Chambost H, Escuriola C, Fischer K, Kartal-Kaess M, de Kovel M, Kenet G, Male C, Nolan B, d'Oiron R, Olivieri M, Zapotocka E, Andersson NG, Königs C. Dilemmas on emicizumab in children with haemophilia A: A survey of strategies from PedNet centres. Haemophilia. 2023 Sep;29(5):1291-1298. https://doi.org/10.1111/hae.14847

8. Appendix 1

The PedNet Haemophilia Research Foundation

Management Board
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Toronto, M Carcao
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Utrecht, C Eckhardt
Valencia, A Cid
Vienna, C Male