PedNet Haemophilia Research Foundation

PedNet

Research programme 2021-2023

On behalf of the PedNet study group:

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Contents

Definitions

PedNet (the European Paediatric Network for Haemophilia Management) began 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 **33** haemophilia treatment centres in **19 countries** (western 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 power of management of the Registry and represents the PedNet Haemophilia Foundation (Appendix 1).

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, thus enabling front-line research projects on inhibitor development, safety, efficacy and long-term outcome of replacement and non-replacement therapies.

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 (1-4%) or mild (5-25%). The current standard treatment is based on replacement of the missing coagulation factor to prevent (prophylaxis) or control bleeding episodes (on-demand treatment). In Europe, most children receive primary prophylaxis, which effectively prevents life-threatening haemorrhage, disabling joint arthropathy and muscle atrophy.[3]

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. Large international collaborative studies are needed to answer clinical research questions regarding natural history, 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 efficacy of various factor replacement concentrates as well as non-factor treatment options.

Inhibitors

The most important side-effect of haemophilia treatment is the development of neutralising alloantibodies (inhibitors) against factor VIII or IX. Inhibitors develop in 25-40% of children with severe haemophilia A mainly during the first 50 exposure days. The causes can be divided into endogenous (genetic) and exogenous (treatment-related) factors. An important exogenous factor is the type of replacement factor and controversial results have been published on the role of the source of FVIII, *i.e.* plasma-derived or from recombinant technology. Previous publications from the PedNet study group (RODIN study) showed that class recombinant products were comparable to class plasma products but also that treatment-related factors, such as intensive dosing of clotting factor, may have an impact on inhibitor risk. More knowledge on treatment-related factors may result in alternative treatment regimens reducing the overall inhibitor risk. 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 › 1100 Pups with severe haemophilia A. (See under working group on immunogenicity)

Safety or Pharmacovigilance studies

The safety and efficacy of several new-generation clotting products have been investigated in rather limited numbers of selected patients in the pre-licensure phase. In PUP (previously untreated patients) studies required by regulatory agencies, only a limited number of PUPs are required. Since many factors influence the risk of developing inhibitors, these studies 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 pharmacovigilance data.

Inhibitor patients

The PedNet Registry contains data on large number of children (› N=440) who have developed inhibitors. These patients are followed prospectively and collect detailed data on treatments. 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. (See under REMAIN)

The PedNet Registry - Protocol and design

The PedNet Registry is governed by the PedNet Registry protocol version 6.0 (2020) 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 01, 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 download is made on January 01 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.

The PedNet cohorts

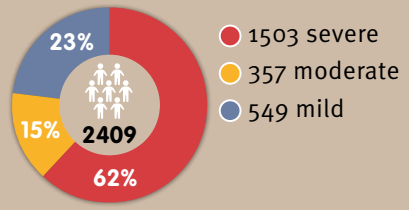
The PedNet registry is an observational study, to prevent selection bias participating centres agreed to include all newly diagnosed PUPS with haemophilia born after 1-1-2000.

Cohort I (2000-2009)	1253
Haemophilia A	1059
Haemophilia B	194

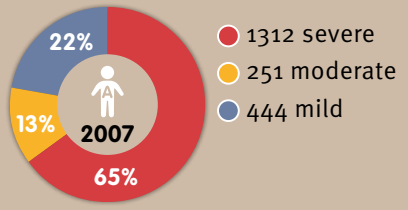
Cohort II (2010-2019)	1137
Haemophilia A	931
Haemophilia B	206

Cohort III (2020-2029)	Inclusion started
Haemophilia A	
Haemophilia B	

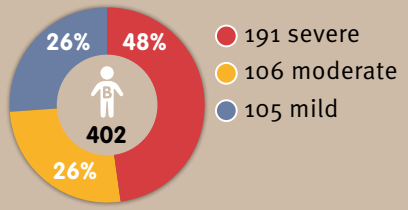
Total included patients



Haemophilia A patients



Haemophilia B patients



PedNet included patients		
Total patients included	2,409	
Known gene mutations (n/%)	2,071	86
Patients with ≥ED50* (n/%)	1,550	64
Patients with inhibitor (n/%)	441	18
Patients with follow up data (n/%)	2,314	96
Total years of follow-up (real vs expected)	19,956	23,033
Patients lost to follow-up at any time** (n/%)	298	12

* Including patients with Clinically Relevant Inhibitor (CRI)
** Patients who moved to adult treatment centres are not included in this number

Data export January 2021

The PedNet research infrastructure

The PedNet Haemophilia Research Foundation has its office in Baarn, the Netherlands. The staff employed, led by an executive director, consist of a senior study coordinator, a senior data manager, a data manager and a research assistant. The Registry is technically secured by the Julius Centre, University of Utrecht, the Netherlands. External monitors are employed by 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).

Research projects 2021-2023

The research projects for 2021–2023 have been structured into six working groups each with one chairperson, 5-10 members and administrative support from the study staff in the Netherlands.

The research focus of the six working groups are:

I. **Immunogenicity**
II. **Patients with inhibitors**
III. **Haemophilia B**
IV. **Gene mutations**
V. **Long-term outcome**
VI. **Novel therapies/Pharmacovigilance**

I Working group on immunogenicity (haemophilia A)

Objectives:

1. To study the incidence of inhibitors of type of and individual concentrates during the first 50 EDs in patients with severe haemophilia A;
2. To study the effect of early start of prophylaxis on the risk of inhibitor development in patients with severe haemophilia A.

Background: FVIII product type plays a dominant role in the development of inhibitors in previously untreated patients (PUPs) with severe haemophilia A. Studies with small numbers of patients and different study designs have limited the assessment of immunogenicity in single products. Products have usually been classified as recombinant (rFVIII) or plasma-derived (pdFVIII)[3-5].
This classification has limited clinical value since patients are treated with single products. PedNet published recently that the cut off for inhibitor development in PUPs with severe haemophilia A is 50-75 EDs and that after 75EDs patients can be defined as previously treated patients (PTPs)[5]. The large PedNet cohorts with ›90% detailed follow-up information at ED50 will make it possible to compare individual products and assess the risk of inhibitors. Vaccinations have previously been studied and were not found to be a risk factor for inhibitor development[7].

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, details of the individual product type (recombinant/plasma/ extended half-life products) and reason for treatment administration (bleed/prophylaxis), immunological 'danger signals' (according to each infusion for the first 50 treatment days), surgery, etc.

Working plan: Using the data download of January 2020, analysis will be performed for 1) risk factors for inhibitor development related to individual products (SHL, EHL, recombinant/ plasma derived) adjusted for potential confounding factors, and 2) the effect of early prophylaxis on immunogenicity.

II Working group on patients with haemophilia A and inhibitors

REMAIN study (Research on Management of Inhibitors)

Objectives:

1. To study the natural history of high-titre inhibitors and the effect of different ITI regimens;
2. To study the optimal management of patients with inhibitors;
3. To study the bleeding phenotype before, during and after ITI.

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. 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 may have given them a better outcome than previous generations of children who developed inhibitors before year 2000. The REMAIN study will increase our knowledge of the success rate of various ITI regimens as well as the long-term joint outcome. The first publications from the Remain study, on follow-up of inhibitors, have already been published[8,9].

Working plan: All patients born after January 01 2000 with haemophilia A who developed inhibitors are included. Data on ITI regimens (including the use of bypassing agents or bispecific antibodies), 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), mutation, peak titre etc.

III Working group on Haemophilia B

Objectives:

1. To study long-term outcome of patients >12 years of age with severe and moderate haemophilia B and compare them to patients with severe and moderate haemophilia A of the same age;
2. To study the outcome of patients with haemophilia B and inhibitors, treated or not treated with ITI.

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 include 297 (2021) 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[10].

Working plan: 1) To study the bleeding phenotype and long-term outcome of severe and/or moderate haemophilia B compared to age-matched controls with haemophilia A after the age of 12. 2) To study the bleeding phenotype and outcome of various ITI regimens given to children who developed inhibitors to FIX.

IV Working group on Gene mutations

Objectives:

1. To compare the spectrum of types of genetic variants (and phenotypes) in the cohort-based PedNet Registry with the spectrum of random reported variants in the international *F8* and *F9* gene databases (EAHAD and CHAMPS/CHBMPS);
2. To study the spectrum and frequencies of *F8* and *F9* gene variants in patients who have developed inhibitors and, conversely, the number of children who develop inhibitors (and if low/high titre) based on the different types of disease causing gene variants. Is the current view on estimated risk for a certain mutation to cause an inhibitor the same when calculated on a population-based PedNet cohort?

Background: The types of gene defect are associated with the disease severity and the risk of developing an inhibitor. The availability of a large number of unselected patients with known and centrally classified gene variant nomenclature makes it possible to, based on a population, study several important questions that previously have been studied in selected patients' populations often with an over-representation of inhibitors.

Working plan: Reported genetic data are continuously reviewed and classified according to HGVS nomenclature and the pathogenicity according to ACMG/AMP guidelines. Recently 88 new gene mutations were found in the PedNet cohorts[11] Spectrum of types and effects of mutations will be compared between the PedNet Registry and the EAHAD and CHAMPS/CHBMPS haemophilia variant databases. The risk of developing an inhibitor, either low- or high-titre, depending on the underlying gene defect will be evaluated and also the types of mutations present in those who do develop an inhibitor (reverse approach).

V Working group on Long-Term Outcome

Objectives:

1. 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.
   a. Can HJHS (Haemophilia Joint Health Score) or HEAD-US (Haemophilia Early Arthropathy Detection with Ultrasound) detect early changes already in puberty even though prophylaxis has been given?
   b. Do patients who have received prophylaxis have a normal QoL?
2. To compare the long-term outcome of patients with and without inhibitors ≥12 years.
   a. We hypothesise that the long-term outcome of patients with low-titre inhibitors is the same as for patients without inhibitors.

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 have been collected and enable studies that can provide valuable data in the discussion on trough levels, dosing, dosing frequency and alternative therapies for children in the future.

Working plan: A pilot study with five participating centres has started to explore the feasibility of several research questions on outcome of treatment as a platform for the planned studies.

VI Novel therapies/Pharmacovigilance

Background: Many new concentrates and alternative 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. In addition, it collects data on expected and unexpected adverse events. Regulatory authorities support the use of pharmacovigilance studies in Registry holders such as PedNet.

Working plan: During the research period, studies will be initiated with a focus on the pharmacovigilance of novel therapies such as EHL-FVIII and EHL-FIX and "non-factor" treatment options such as emicizumab with the aim of evaluating safety and efficacy using the large data-set on the traditional treatment regimens as potential comparators.

Significance PedNet

The PedNet Registry has a unique data collection with inclusion of >2400 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.

Recent publications

2020

- Inhibitor indicence in an unselected cohort of previously untreated patients with severe haemophilia B: A PedNet Study.
- ITI Treatment is not First-Choice Treatment in Children with Hemophilia A and Low-Responding Inhibitors: Evidence from a PedNet Study.
- Inhibitor development in previously untreated patients with severe haemophilia: A comparison of included patients and outcomes between a clinical study and a registry-based study.
- Long-term follow-up of neonatal intracranial haemorrhage in children with severe Haemophilia.
- Novel F8 and F9 gene variants from the PedNet hemophilia registry classified according to ACMG/AMP guidelines.

2019

- Mode of delivery in haemophilia: Vaginal delivery and cesarean section carry similar risk for intracranial hemorrhages and major bleeds.
- Recombinant factor VIII products and inhibitor development in previously untreated patients with severe haemophilia A: Combined analysis of three studies
- Timing of inhibitor development in >1000 previously untreated patients with severe hemophilia A.

For full publication list see https://pednet.eu/publications/

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Appendix

The PedNet Haemophilia Research Foundation

Management Board

Prof. Rolf Ljung, MD, PhD chair
Prof. Karin Kurnik, MD, PhD, vice-chair
Prof. Gili Kenet, MD secretary
Dr Christoph Male, MD, PhD, treasurer
Prof. Roseline d'Oiron, MD, member

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Dr Maria Teresa Alvarez Romàn, MD, PhD

Participating Centres

Aarhus, Denmark; Athens, Greece; Barcelona, Spain; Bern, Switzerland; Birmingham, UK; Bonn, Germany; Bremen, Germany; Brno, Czech; Dublin, Ireland; Frankfurt Goethe & Mörfelden-Walldorf Germany; Genova, Italy; Glasgow, Scotland, UK; Helsinki, Finland; Leuven, Belgium; London, UK; Madrid Spain; Malmö, Sweden; Marseille, France; Milan, Italy; Montreal, Canada; Le Kremlin-Bîcetre, France; Munich, Germany; Oslo, Norway; Porto, Portugal; Prague, Czech; Stockholm, Sweden; Tel Hashomer, Israel; Toronto, Canada; Toulouse, France; Utrecht, the Netherlands; Valencia, Spain; Vienna, Austria.

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