PedNet Haemophilia Research Foundation

# PedNet

# Annual report 2024
# PedNet cohort studies

Data export January 2025


**On behalf of the PedNet study group**

**Christoph Male, MD, MSc**
Chairman of the management board

**Gili Kenet, MD**
Director of the PedNet Haemophilia Research Foundation


# Contents

**PedNet** (the European Paediatric Network for Haemophilia Management) started in 1996 as a collaboration of 22 paediatricians in 16 European countries. PedNet was initiated to provide an infrastructure for clinical research on the management of children with haemophilia. Currently the PedNet study group consists of 34 haemophilia treatment centres in 19 countries.

**The PedNet Registry** started in 2003 and, in order to prevent selection bias, is set up as a birth cohort. It collects real-life data from all newly diagnosed children treated in the participating centres. Data are collected through well-defined e-CRF forms that contain details on all aspects of haemophilia from birth to adolescence and adulthood.
Patients with FVIII/IX levels up to 25%, born from January 1, 2000 are included in the PedNet Registry. Annual data exports are used for analysis of ongoing studies.

**The PedNet Haemophilia Research Foundation** was founded in December 2016 in The Netherlands and is the legal owner of the database and all its assets.

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Department of Paediatric
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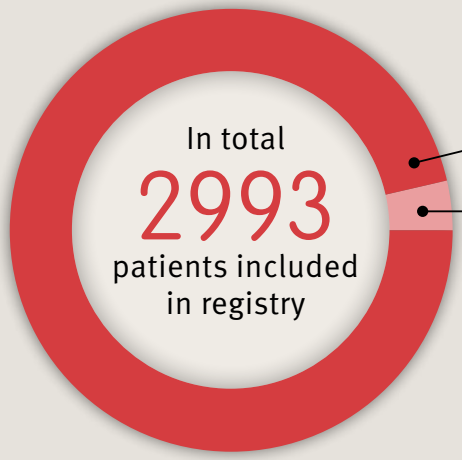
**Fernando Pinto, MD**
Department of Haematology,
Royal Hospital for Sick Children,
Yorkhill
Glasgow, UNITED KINGDOM

# Key numbers




2966 boys (1858 severe)

27 girls (4 severe)

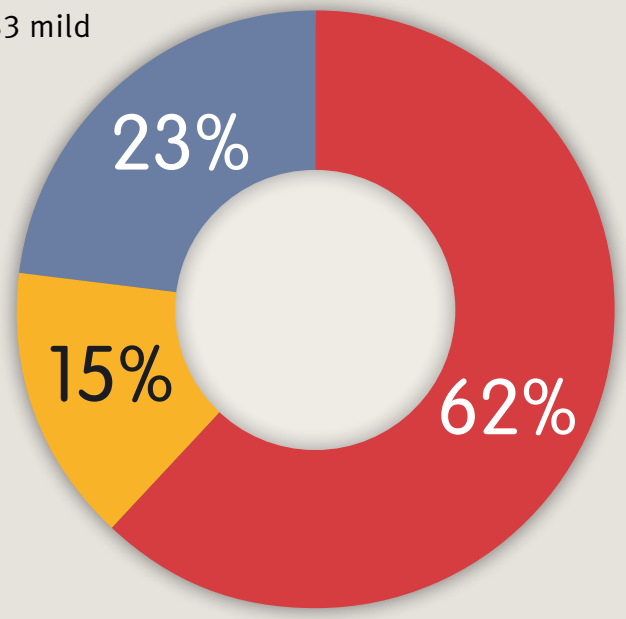
107 new patients included in 2024

## Included patients according to disease severity

1862 severe

448 moderate

683 mild




1625 PUPS with severe haemophilia A

68 new severe haemophilia A PUPs in 2024

237 PUPs with severe haemophilia B

5 new severe haemophilia B PUPs in 2024

34 participating centers in 19 countries

Detailed data on gene mutation available in 87% of all patients

Total number of follow up years 28,604

Data export January 2025

# Key numbers

## Follow up data

**84%**

severe haemophilia A patients reached 50 exposure days.
Lost to follow up during first 50EDs is 2%

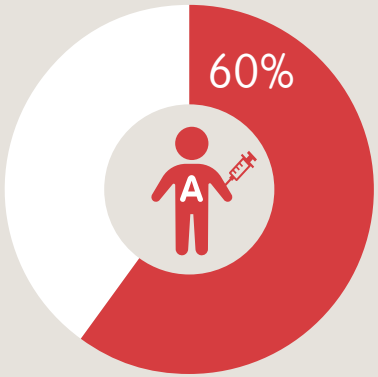
A

**86%**

severe haemophilia B patients reached 50 exposure days.
Lost to follow up during first 50EDs is 4%

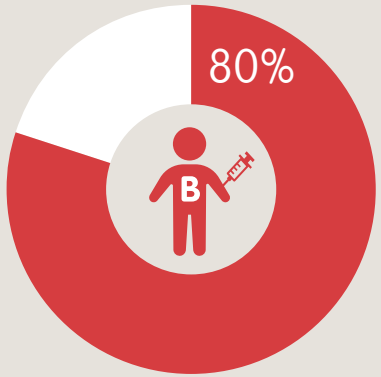
B

## Start prophylaxis




**982**

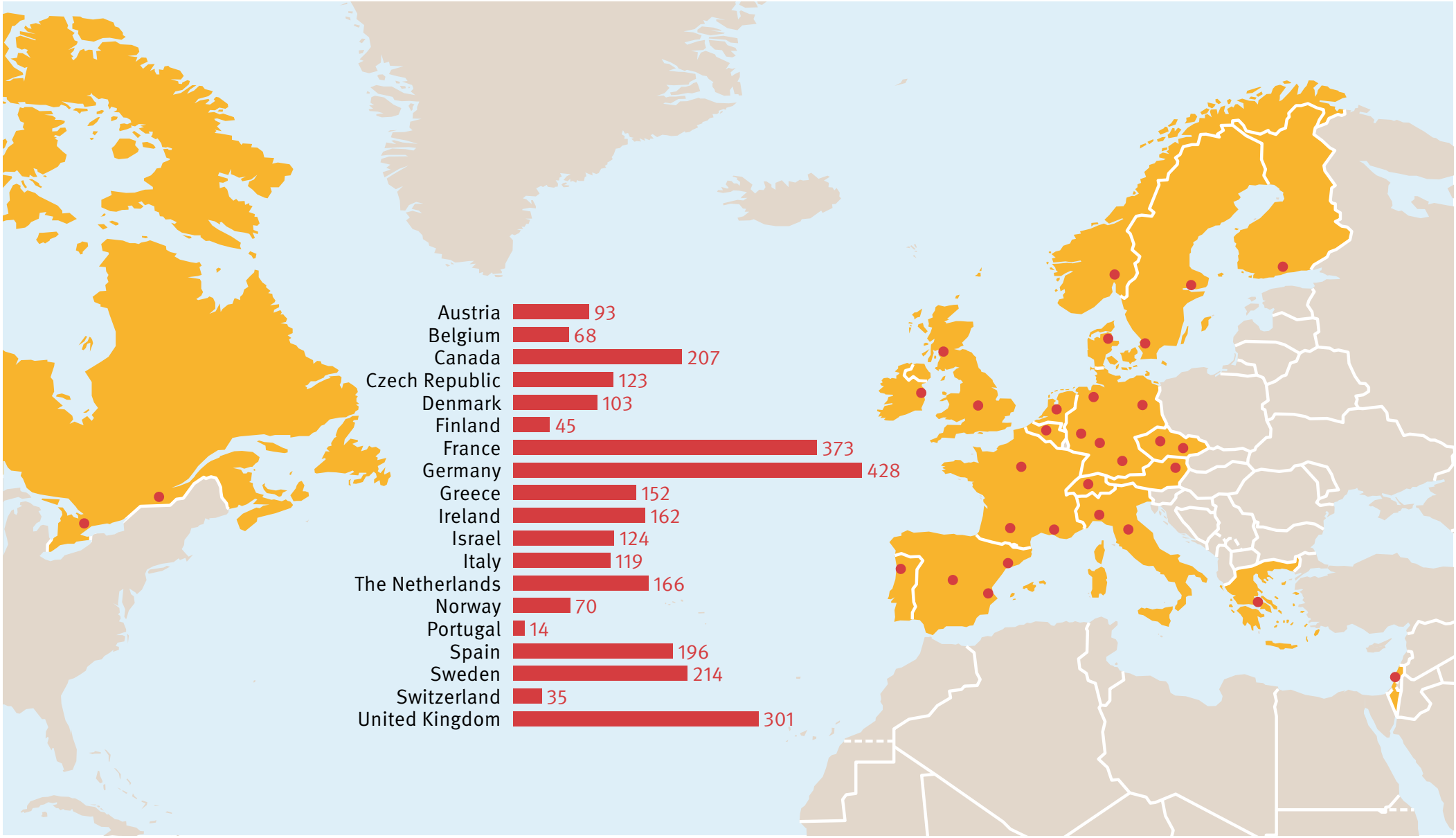
Severe haemophilia A patients started prophylaxis(CFC) before (‹) ED50.
Minimum of 2 consecutive months.
Median age at start in years is 1.2 (IQR 0.9–1.8)




**189**

Severe haemophilia B patients started prophylaxis (CFC) before (‹) ED50.
Minimum of 2 consecutive months.
Median age at start in years is 1.3 (IQR 0.9–2.0)

# Participating countries and numbers of included patients




Data export January 2025

# Introduction

The PedNet study group (the European Paediatric Network for Haemophilia Management) is a collaboration of now 34 haemophilia treatment centres (HTCs) in 19 countries, including Canada (Toronto and Montreal) and Israel. The PedNet cohort studies include all patients with FVIII/IX levels up to 25%, born from January 1, 2000 onwards and diagnosed in one of the participating HTCs.
On 16 December 2016, the PedNet Haemophilia Research Foundation was founded in Amsterdam. The Foundation was instituted to incorporate the PedNet study group and to ascertain that it can continue to function in the future. More information can be found on our website: www.pednet.eu.
This report provides an overview of the status of the PedNet registry up to January 2025 and of the research activities performed by the PedNet study group in 2024. More information on all research activities can be found in the Research programme 2024-2026.

**Mission of the PedNet Haemophilia Research Foundation**

The mission of the PedNet foundation is 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 of replacement and non-replacement therapies and long-term outcome. The foundation is not-for-profit and publishes annual reports on activities and financial reports. The reports can be found on www.pednet.eu.

## PedNet Registry

The protocol of the PedNet Registry follows the EMA guideline on registry based studies (EMA/426390/2021). Well-defined clinical parameters are collected through a secured data capture system (Castor EDC). For participating centres a minimum inclusion rate of 95% of all newly diagnosed patients is mandatory.

PedNet has consortium agreements with the participating centres and they are compensated for the new inclusions and follow-up reports.
Data of all included patients are regularly updated and they are checked for validity and completeness during the year. Yearly data exports are performed every January and used for new studies in that particular year.

## Monitoring

Data collected in the PedNet registry are monitored to improve data quality.
This is done by built-in checks on the e-CRF and regular data control on exports. Coordinators employed by the foundation are in frequent contact with centres and perform regular checks on the inclusion of new patients and follow up data entry. On-site monitoring of source data and informed consent is performed by an independent research organisation according to a predefined monitor plan. The PedNet centres agreed together that 100% of baseline data and informed consent forms are checked with the medical files in the centres. For 10% of the patients, all exposure days and follow-up data are checked.

## Current status

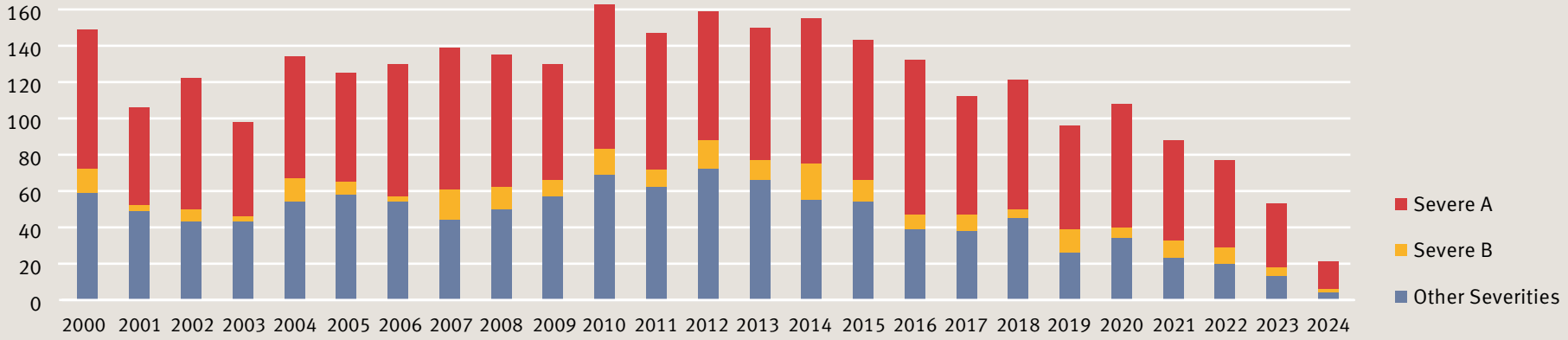
As of 1 January 2025, a total of **2993** previously untreated patients (PUPs) with haemophilia A or B are included in the registry. Of these, **1625** have severe haemophilia A (**68 more** than last year) and **237** have severe haemophilia B (**5 more** than last year) (see Appendix 1). **1566** (84%) of the severe haemophilia patients (A plus B) have reached 50 exposure days. Data on gene defects are available for **2601 (87%)** patients included in the registry.

## Start prophylaxis

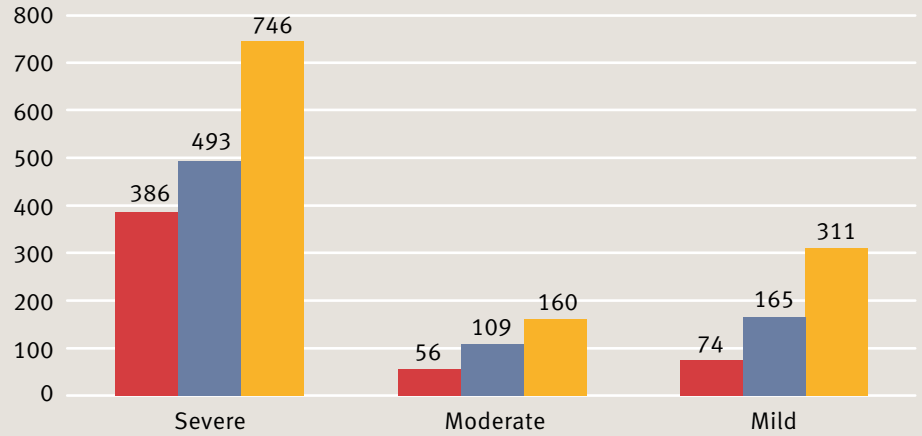
A total of **1353** patients started prophylactic treatment with clotting factor concentrate before ED50 and with a minimum duration of 2 months, **982** severe A and **189** severe B patients. The median age at start prophylaxis was 1.2 years for severe A and 1.3 for severe B patients.

# Tables & Figures

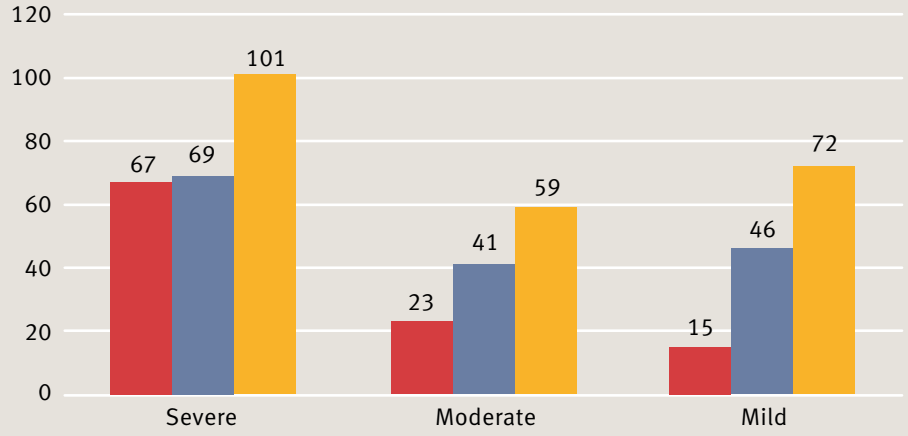
## N Patients per birth year

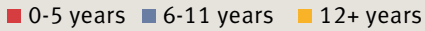



## Current age haemophilia A




## Current age haemophilia B



# Tables & Figures

## Haemophilia A

| | Severe | | Moderate | Mild | Total HA | |
|---|---|---|---|---|---|---|
| Baseline | 1,625 | | 325 | 550 | 2,500 | |
| Girls | 3 | | 3 | 12 | 18 | |
| Known gene mutations | 1,490 | | 263 | 427 | 2,180 | 87% |
| At least 50 EDs | 1,363 | 84% | 180 | 68 | 1,611 | |
| Inhibitors | 479 | | 31 | 11 | 521 | |
| Follow-up data | 1,580 | | 315 | 539 | 2,434 | 97% |
| Total FU years | 15,870 | | 3,057 | 5,176 | 24,103 | |
| Lost to follow-up during first 50 EDs* | 39 | 2% | 31 | 152 | 222 | 9% |

* excl. Patients =›16 yrs & discontinued centres

## Haemophilia B

| | Severe | | Moderate | Mild | Total HB | |
|---|---|---|---|---|---|---|
| Baseline | 237 | | 123 | 133 | 493 | |
| Girls | 1 | | 3 | 5 | 9 | |
| Known gene mutations | 211 | | 106 | 104 | 421 | 85% |
| At least 50 EDs | 203 | 86% | 66 | 13 | 282 | |
| Inhibitors | 20 | | 0 | 0 | 20 | |
| Follow-up data | 224 | | 121 | 130 | 475 | 96% |
| Total FU years | 2,181 | | 1,106 | 1,214 | 4,501 | |
| Lost to follow-up during first 50 EDs* | 9 | 4% | 19 | 33 | 61 | 12% |

* excl. Patients =›16 yrs & discontinued centres

## Display of PedNet Numbers

| | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 |
|---|---|---|---|---|---|---|
| Baseline | 2,304 | 2,409 | 2,576 | 2,759 | 2,886 | 2,933 |
| Known gene mutations | 1,958 | 2,071 | 2,219 | 2,373 | 2,479 | 2,601 |
| At least 50 exposure days | 1,483 | 1,550 | 1,653 | 1,737 | 1,844 | 1,893 |
| Patients with follow-up data | 2,203 | 2,314 | 2,472 | 2,633 | 2,790 | 2,909 |

## Adverse events in 2023 & 2024*

| | | Inhibitor | No inhibitor | Total |
|---|---|---|---|---|
| Total events | | 7 | 2 | 9 |
| Type of adverse event | Allergic reaction | 2 | 1 | 3 |
| | Thromboembolic event | 0 | 0 | 0 |
| | Thrombotic microangiopathy | 0 | 0 | 0 |
| | Neurological event (other than ICH) | 2 | 0 | 2 |
| | Local subcutaneous reaction | 3 | 1 | 4 |
| | Death | 0 | 0 | 0 |
| | Other | 0 | 0 | 0 |

* reporting of AE may be delayed, as centres first report to National and local authorities

# Activities of PedNet Working Groups

Research projects are structured into working groups each with one chair, 5-8 members, and analytic and administrative support from the study staff in the Netherlands. All planned research activities of the PedNet study group can be found in the Research Programme 2024-2026 https://pednet.eu/pednet-group/. For full publication list see www.pednet.eu/publications

## Genetic working group

Haemophilia B Leyden is a unique form of haemophilia B in which the endogenous factor IX levels rise over time. The genetic working group aimed to explore the natural history of these patients, assess the association between genetic variants, follow the rise in endogenous factor IX levels over time, and explore treatments and bleeding phenotype. Twenty four children with the HB Leyden phenotype were identified. The variant c.-36G>A was found in over 50% of the cases, FIX increase occurred at a very young age, and this variant was associated with low bleeding rates in contrast to children with a non-c.-35G>A variant. The manuscript has been accepted for publication in Journal of Thrombosis and Haemostasis (doi: 10.1016/j.jtha.2024.12.020).

## Haemophilia B working group.

In 2020 a paper on the inhibitor incidence in severe haemophilia B was published. Inhibitor incidence in an unselected cohort of previously untreated patients with severe haemophilia B: A PedNet Study *(Male et al., Haematologica 2020)*. A manuscript on patients with severe haemophilia B and an inhibitor and their response to ITI is underway.

## Working group on Long-term outcome

Patients in PedNet are followed from diagnosis until adulthood. The collection of data on validated outcome tools started in 2018. In 2021 a pilot project was performed on data of 141 patients (100 without inhibitors, and 41 with current/past inhibitors) from 5 PedNet centres with the aim to explore the feasibility to answer several research questions on long-term outcome. The results showed that most adolescents had a favourable joint health, while patients with inhibitors showed a two-fold increased proportion with joint deterioration by Haemophilia Joint Health Score. Project results are described in the article: *Long-term joint outcomes in adolescents with moderate or severe haemophilia A (Schmidt et al)*, which has been published in Haemophilia in 2022.
The succeeding project started in 2022: to compare treatment and joint health status in Greek and Swedish children with severe haemophilia on prophylactic treatment was accepted for a poster presentation on EAHAD 2023 in Manchester, UK. The manuscript is currently under review for publication.

## Working group on intracranial haemorrhage

Intracranial haemorrhage (ICH) is a major bleed causing morbidity and death. Children with haemophilia have a significantly higher risk of ICH compared to the normal population. Neonatal ICH has the highest known incidence for ICH. Prophylaxis with factor concentrate reduces the risk for ICH. New treatment options (non-replacement therapies such as emicizumab) have reached the market and could be given early in life. The aim of the study was to assess how many ICHs in children with haemophilia could be prevented by earlier start of prophylaxis. It has recently been accepted for publication by Haematologica (doi: 10.3324/haematol.2024.285874).

## Working group on novel therapies

As many new concentrates and alternative therapies are currently entering the market for haemophilia, the PedNet study group sees the need to study both the safety and the efficacy of these new therapies. The study group conducted a survey on the implementation of emicizumab in the PedNet centres. The results of the survey were accepted for publication in haemophilia (doi: 10.1111/hae.14847). Data on bleeding control after switching to emicizumab in 251 children was accepted for a poster presentation on EAHAD 2023. Manuscript has been accepted for publication in Haemophilia (doi: 10.1111/hae.15015).

## Working group on bleeding

***Bleeding in non-severe haemophilia***

Novel therapies, including modified replacement therapy and gene therapy, provide opportunity to substantially increase baseline FVIII activity levels, or (partially) correct haemostasis. Information on bleeding phenotype in non-severe haemophilia provides the best possible information regarding optimum target for prophylactic treatment. The aim of this project is to assess bleeding according to baseline FVIII activity in children with non-severe haemophilia A (HA). Data on comparing non-severe haemophilia A and B was presented at the ISTH in July 2022. At the same congress, a poster focused on bleeding in non-severe haemophilia A was presented. The manuscript has been accepted for publication by Journal of Thrombosis and Haemostasis (doi: 10.1016/j.jtha.2024.05.030).

***Bleeding pattern in severe haemophilia A and B on prophylaxis***

Few data exist on long-term follow-up of type and frequency of bleedings in children 0-18 years with severe haemophilia on primary prophylaxis with FVIII/FIX. The aim of this study is to compare real-world data of bleeds between different age groups in children with severe haemophilia A (SHA) or B (SHB) on primary prophylaxis. Data was presented at ISTH in July 2022. A full manuscript is in preparation.

# Publications PedNet study group 2023 & 2024

1. Kartal-Kaess K, Pinto F, Labarque V, de Kovel M, Nolan B, Carcao M, d'Oiron R, Stamm Mikkelsen T, Ljung R, G. Andersson N, the PedNet Study Group. Hemophilia B Leyden: Characteristics and natural history in the PedNet Registry. https://doi.org/10.1016/j.jtha.2024.12.020
2. G. Andersson N, de Kovel M, Castaman G, d'Oiron R, Kenet G, Königs C, Male C, Nolan B, Olivieri M, Pinto F, Sigurgisladottir S, Zapotocka E, Fischer, the PedNet Study Group. Intracranial hemorrhage before start of prophylaxis in children with hemophilia: incidence, timing, and potential for prevention. https://pubmed.ncbi.nlm.nih.gov/39605212/
3. de Kovel M, Escuriola-Ettingshausen C, Königs C, Ranta S, Fischer K, the PedNet Study Group. Bleeding phenotype according to factor level in 825 children with non-severe hemophilia; data from the PedNet cohort. https://doi.org/10.1016/j.jtha.2024.05.030
4. Van der Zwet K, de Kovel M, Motwani J, Van Geet C, Nolan B, Glosli H, Escuriola Ettingshausen C, Königs C, Kenet G, Fischer K, PedNet Study Group. Bleeding control improves after switching to emicizumab: Real-world experience of 177 children in the PedNet registry. https://onlinelibrary.wiley.com/doi/10.1111/hae.15015
5. Fischer K, Kenet G, Kurnik K, Carcao M, Oldenburg J, Stamm-Mikkelsen T, Cid Haro AR, Koskenvuo M, Blatny J, Königs C, PedNet Study Group. Determinants of bleeding before and during immune tolerance in 222 boys with severe hemophilia A and inhibitors ›5 BU. https://doi.org/10.1182/bloodadvances.2023011442
6. 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 PUPS with severe hemophilia A: data from the PedNet cohort. Supplemental material: https://pednet.eu/publications/2022_jth_fischer Letter: https://doi.org/10.1016/j.jtha.2022.11.020
7. Labarque V, Mancuso ME, Kartal-Kaess M, Ljung R, S. Mikkelsen T, G. Andersson N. F8/F9 variants in the population-based PedNet Registry cohort compared with locus-specific genetic databases of the European Association for Haemophilia and Allied Disorders and the Centers for Disease Control and Prevention Hemophilia A or Hemophilia B Mutation project. https://doi.org/10.1016/j.rpth.2023.100036
8. 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, G. Andersson N, Königs C. Dilemmas on emicizumab in children with haemophilia A: A survey of strategies from PedNet centres. https://onlinelibrary.wiley.com/doi/10.1111/hae.14847
9. G. Andersson N, Labarque V, Kartal-Kaess M, Pinto F, S. Mikkelsen T, Ljung R, PedNet Study Group. Factor VIII genotype and the risk of developing high-responding or low-responding inhibitors in severe hemophilia A: data from the PedNet Hemophilia Cohort of 1,202 children. https://doi.org/10.3324/haematol.2023.284095

For full publication list see www.pednet.eu/publications

## Abstracts & Presentations

| | | |
|---|---|---|
| EAHAD 2024, Frankfurt | Poster | Characteristics of girls with haemophilia A or B included in the PedNet registry |
| ISTH 2024, Bangkok | Oral presentation | Intracranial hemorrhage before initiation of prophylaxis in early age in haemophilia A – data from the PedNet registry |
| ISTH 2024, Bangkok | Poster | A survey on clinical practice in monitoring and management of bleeding in children on emicizumab prophylaxis in the PedNet centers |

# Sponsor page

The PedNet foundation receives unrestricted funding from several pharmaceutical companies.

Current sponsors are:

- Bayer AG
- CSL Behring GmbH
- Hoffmann-La Roche
- LFB Biotechnologies
- Novo Nordisk Health Care AG
- Pfizer SRL
- Sanofi
- Swedish Orphan Biovitrium AB
- Takeda

## Correspondence

PedNet Haemophilia Research Foundation
Mollerusstraat 1
3743 BW Baarn
The Netherlands
info@pednet.eu

# Study staff

**Gili Kenet, MD**
Director

**Angelique Hermeling**
Foundation Coordinator

**Marloes de Kovel, MSc**
Epidemiologist / Data Manager

**Marieke Blom-Smink, MSc**
Registry Coordinator

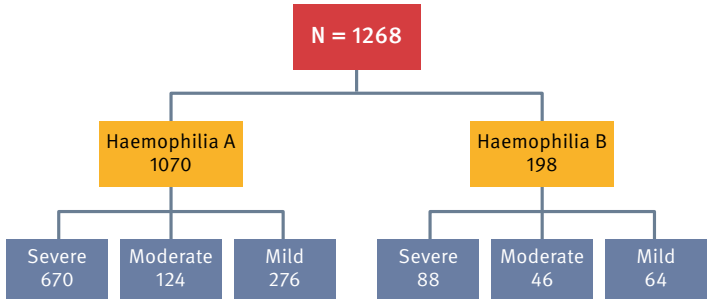
**Kathelijn Fischer MD, PhD**
Senior epidemiologist

**Marjolein Blits, MSc**
Data Manager / Junior Epidemiologist

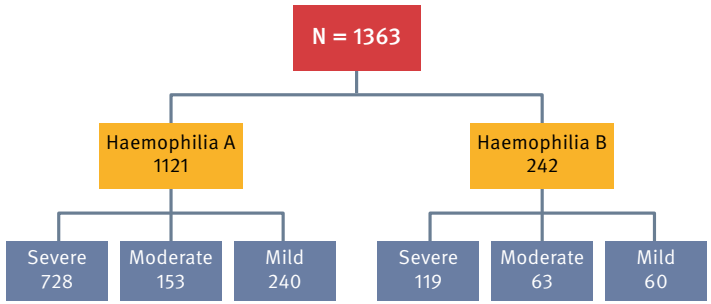
# Participants PedNet Meeting Prague, 2024

# Appendix 1 Flowcharts January 2024

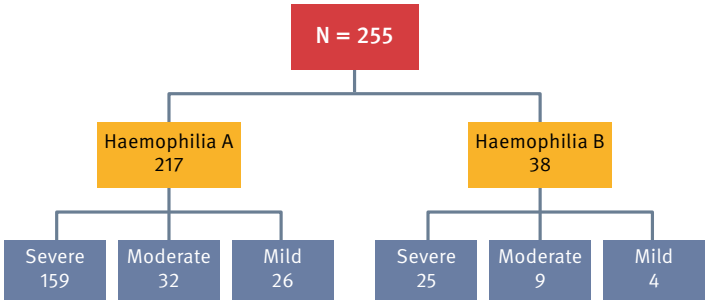
## PedNet Birth Cohort 1 (2000 - 2009)




## PedNet Birth Cohort 2 (2010 - 2019)

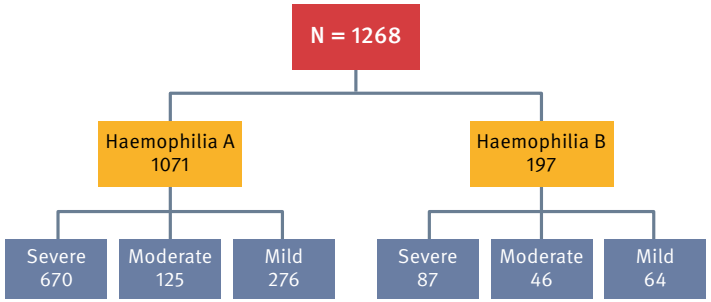



## PedNet Birth Cohort 3 (2020 - 2029)

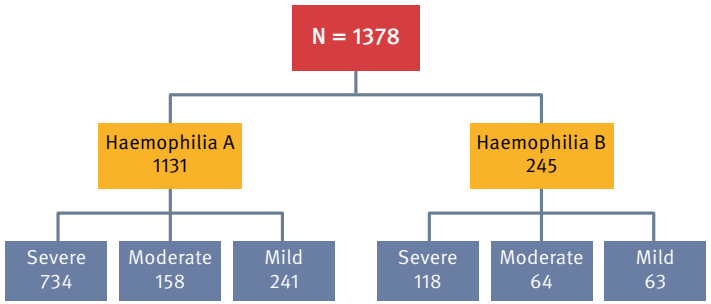



# Appendix 2 Flowcharts January 2025

## PedNet Birth Cohort 1 (2000 - 2009)




## PedNet Birth Cohort 2 (2010 - 2019)

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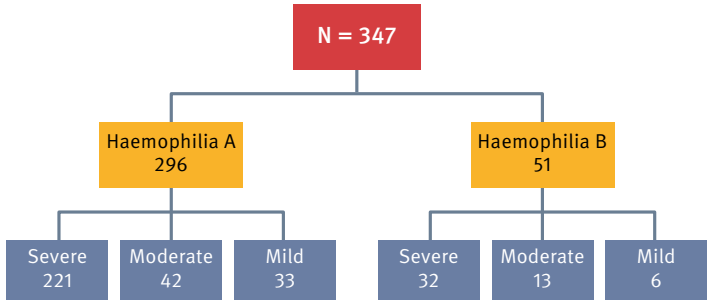

PedNet Haemophilia Research Foundation

# PedNet

www.pednet.eu

info@pednet.eu