PedNet Haemophilia Research Foundation

# PedNet

# Annual report 2022
# PedNet cohort studies

Data export January 2023


**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 32 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.

In 2022 the first director of the foundation Marijke van den Berg retired. The position of director has been taken over by Gili Kenet. Christoph Male took over the position as chair of the board from Rolf Ljung, who remains board member.

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University Hospital Frankfurt &
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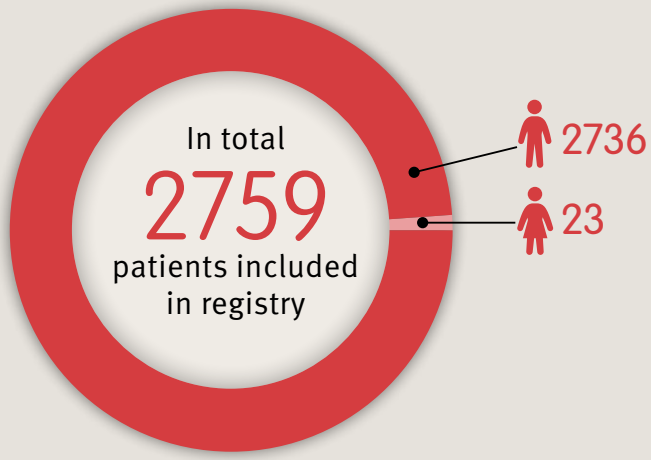
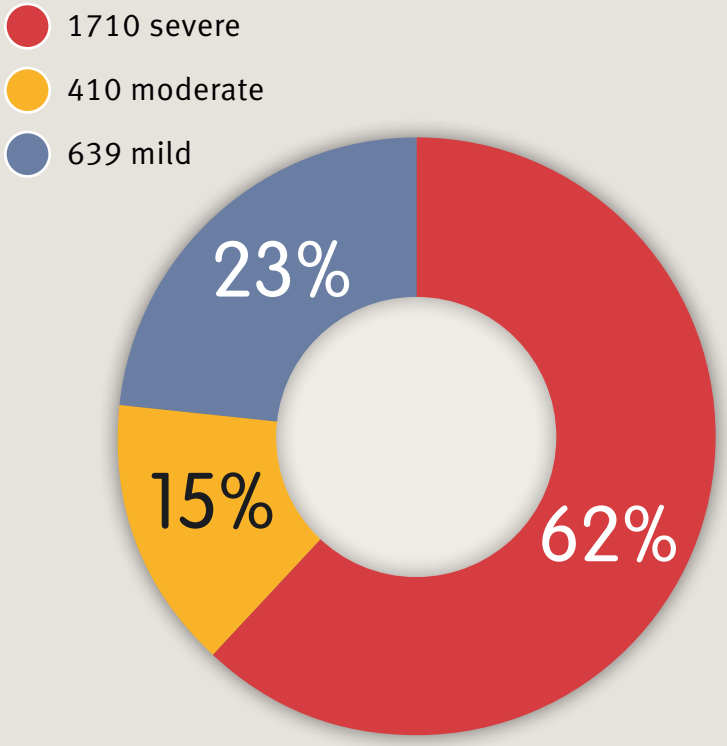
**Hervé Chambost, MD, PhD**
CHU Timone
Marseille, FRANCE

# Key numbers




183 new patients included in 2022

## Included patients according to disease severity




1491
PUPS with severe haemophilia A

80 new severe haemophilia A PUPS in 2022

219
PUPs with severe haemophilia B

12 new severe haemophilia B PUPS in 2022

32
participating centers in 19 countries

Detailed data on gene mutation available in
86%
of all patients

Total number of follow up years
24,394

Data export January 2023

# Key numbers

## Follow up data

**86%**

severe haemophilia A patients reached 50 exposure days.
Lost to follow up during first 50EDs is 3%

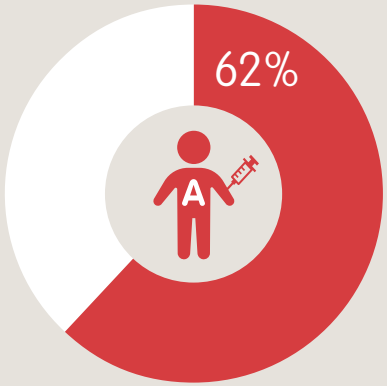
A

**82%**

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

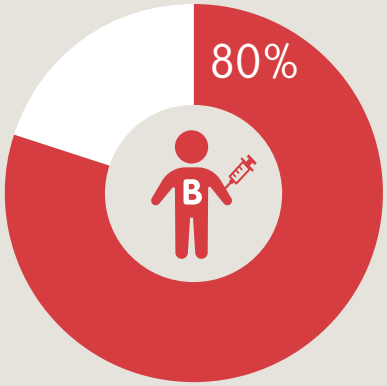
B

## Start Prophylaxis




**921**

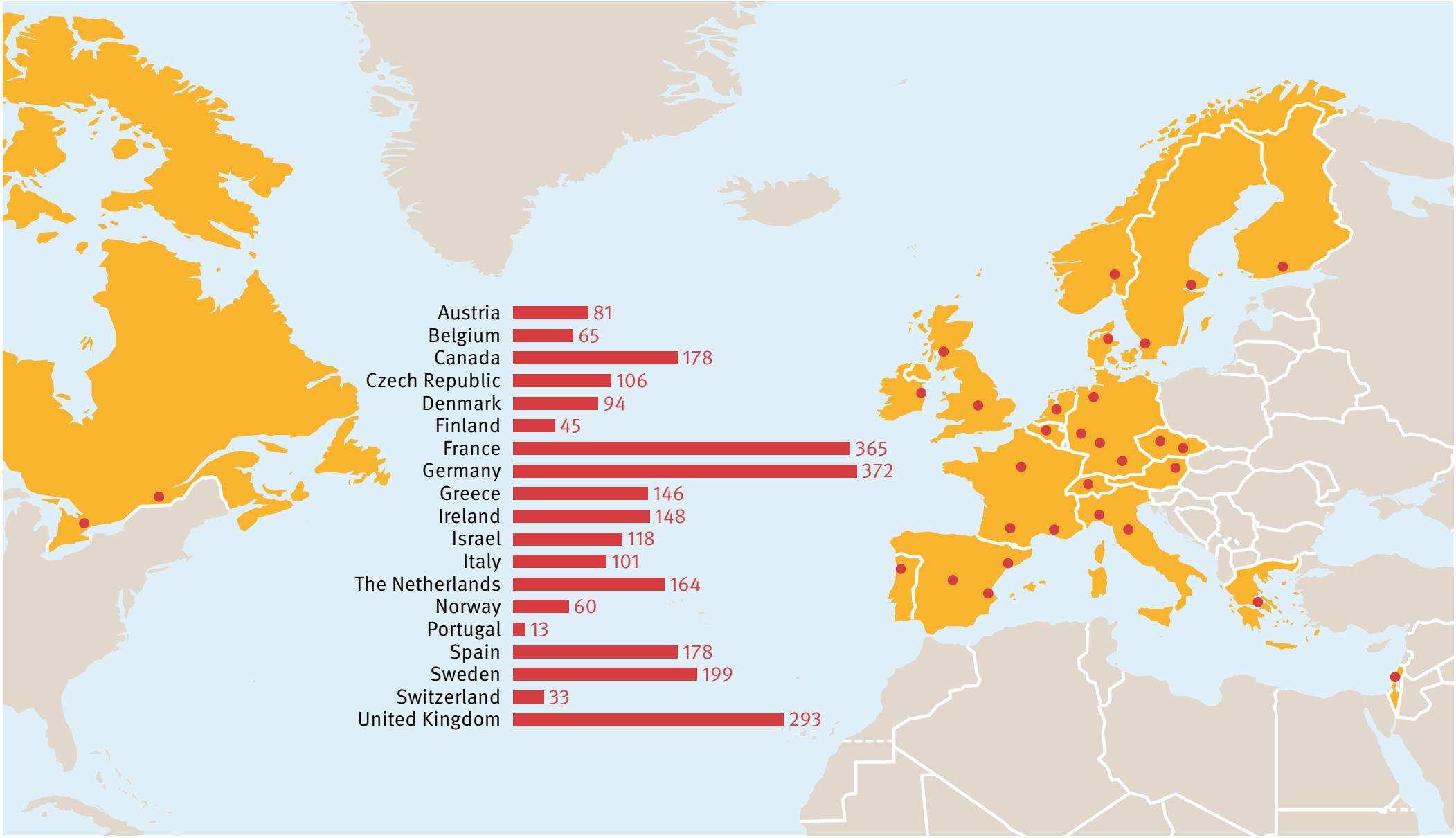
Severe haemophilia A patients started prophylaxis(CFC) before (‹) ED50.
Minimum of 2 consecutive months.
Median age at start in years is 1.3 (IQR 0.9–1.8)




**175**

Severe haemophilia B patients started prophylaxis (CFC) before (‹) ED50.
Minimum of 2 consecutive months.
Median age at start in years is 1.4 (IQR 0.9–2.1)

# Participating countries and numbers of included patients




Data export January 2023

# Introduction

The PedNet study group (the European Paediatric Network for Haemophilia Management) is a collaboration of now 32 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 2023 and of the research activities performed by the PedNet study group in 2022. More information on all research activities can be found in the Research programme 2021-2023.

**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 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 (Research Online). 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 2023, a total of **2759** previously untreated patients (PUPs) with haemophilia A or B are included in the registry. Of these, **1491** have severe haemophilia A (**80 more** than last year) and **219** have severe haemophilia B (**12 more** than last year) (see Appendix 1). **1461** (85%) of the severe haemophilia patients (A plus B) have reached 50 exposure days. Data on gene defects are available for **2373** (86%) patients included in the registry.

## Start prophylaxis

A total of **1245** patients started prophylactic treatment with clotting factor concentrate before ED50 and with a minimum duration of 2 months, **921** severe A and **175** severe B patients. The median age at start prophylaxis was 1.3 years for severe A and 1.4 for severe B patients.

# Key numbers

## Inhibitors

**501**
Inhibitors diagnosed between 2000-2022


445 severe haemophilia


18 severe haemophilia

**4306**
Follow up years for inhibitor patients


3938 years for severe haemophilia A inhibitor patients. Median of 8.6 years per severe haemophilia A inhibitor patient (IQR 4.4–13)

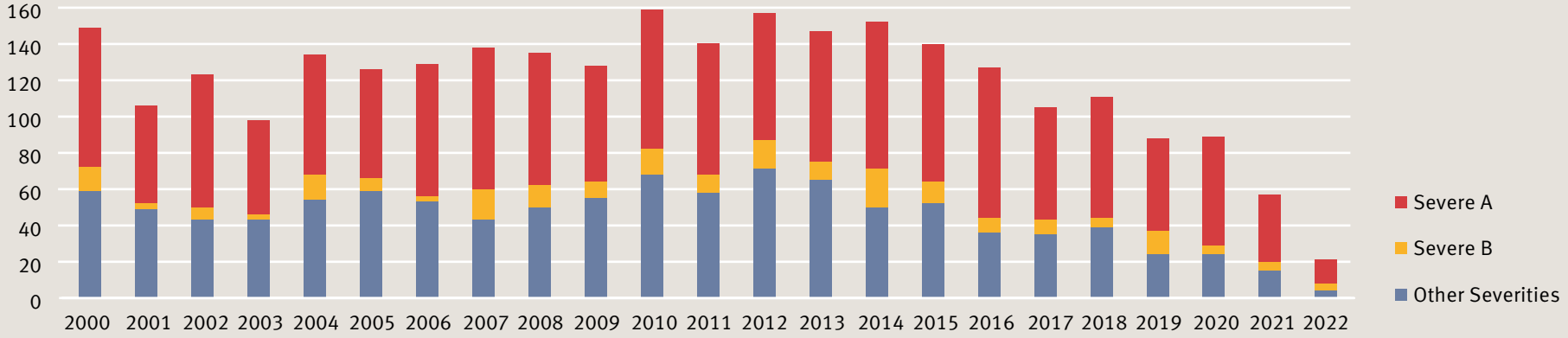

136 years for severe haemophilia B inhibitor patients. Median of 6.9 years per severe haemophilia B inhibitor patient (IQR 3–10.5)

In total
**23,494**
inhibitor test results are collected

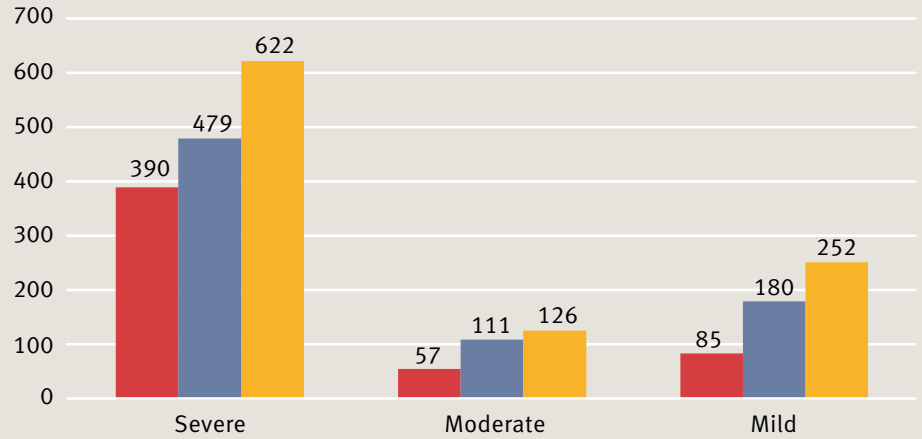
15,836 tests of the 501 inhibitor patients. Median of 23 tests per inhibitor patient (IQR 14–40)

# Tables & Figures

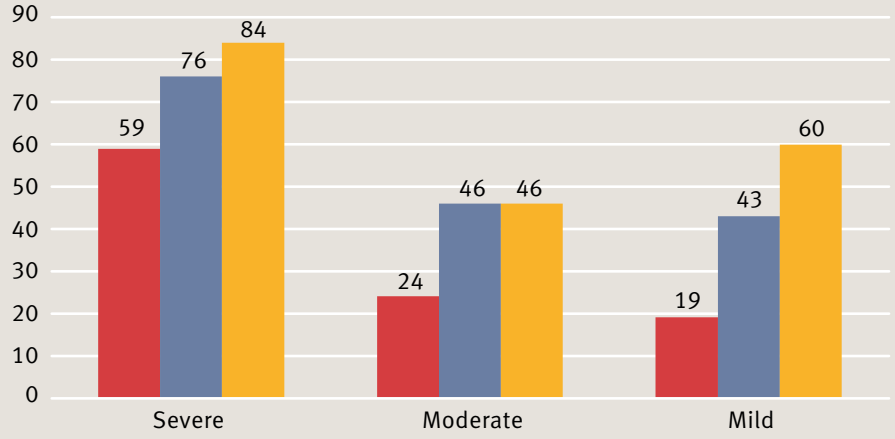
## N Patients per birth year

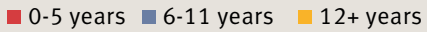



## Current age haemophilia A




## Current age haemophilia B



# Tables & Figures

## Haemophilia A

| | Severe | | Moderate | Mild | Total HA | |
|---|---|---|---|---|---|---|
| Baseline | 1,491 | | 294 | 517 | 2,302 | |
| Known gene mutations | 1,359 | | 235 | 394 | 1,988 | 86% |
| At least 50 EDs | 1,281 | 86% | 155 | 59 | 1,495 | |
| Follow-up data | 1,424 | | 280 | 495 | 2,199 | 96% |
| Total FU years | 13,574 | | 2,536 | 4,489 | 20,599 | |
| Lost to follow-up during first 50 EDs* | 45 | 3% | 26 | 98 | 169 | 7% |

* excl. Patients =›16 yrs

## Haemophilia B

| | Severe | | Moderate | Mild | Total HB | |
|---|---|---|---|---|---|---|
| Baseline | 219 | | 116 | 122 | 457 | |
| Known gene mutations | 193 | | 97 | 95 | 385 | 84% |
| At least 50 EDs | 180 | 82% | 50 | 12 | 242 | |
| Follow-up data | 209 | | 107 | 118 | 434 | 95% |
| Total FU years | 1,887 | | 923 | 984 | 3,794 | |
| Lost to follow-up during first 50 EDs* | 9 | 4% | 13 | 24 | 46) | 10% |

* excl. Patients =›16 yrs

## Display of PedNet Numbers

| | 2019 | 2020 | 2021 | 2022 | 2023 |
|---|---|---|---|---|---|
| Baseline | 2,142 | 2,304 | 2,409 | 2,576 | 2,759 |
| Known gene mutations | 1,834 | 1,958 | 2,071 | 2,219 | 2,373 |
| At least 50 exposure days | 1,382 | 1,483 | 1,550 | 1,653 | 1,737 |
| Patients with follow-up data | 2,029 | 2,203 | 2,314 | 2,472 | 2,633 |

## Inhibitors

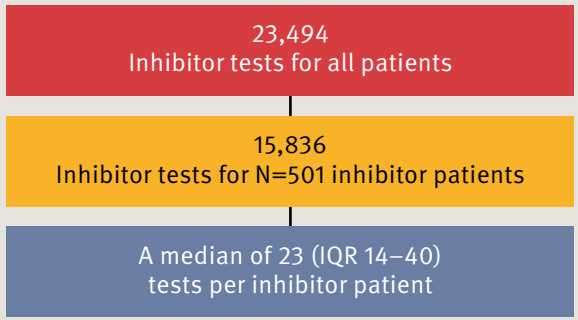
| | All | Severe Haem A | Severe Haem B |
|---|---|---|---|
| N | 501 | 445 | 18 |
| Sum FU (yrs) after 1st positive sample | 4306 | 3938 | 136 |
| Median (yrs; IQR) | 8.5 [4.3–12.8] | 8.6 [4.4–13] | 6.9 [3–10.5] |

## Adverse events in 2021 & 2022*

| | | Inhibitor | No inhibitor | Total |
|---|---|---|---|---|
| Total events | | 0 | 5 | 6 |
| Type of adverse event | Allergic reaction | 0 | 1 | 1 |
| | Thromboembolic event | 1 | 1 | 2 |
| | Thrombotic microangiopathy | 0 | 0 | 0 |
| | Neurological event (other than ICH) | 0 | 0 | 0 |
| | Local subcutaneous reaction | 0 | 1 | 2 |
| | Death | 0 | 0 | 0 |
| | Other | 0 | 1 | 1 |

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

## Inhibitor test results




Data export January 2023

# Activities of PedNet Working Groups

Research projects are been 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 2021-2023 https://pednet.eu/pednet-group/. For full publication list see www.pednet.eu/publications

## Genetic working group

New genetic reports are continuously reviewed according to the HGVS nomenclature and the pathogenicity according to ACMG/AMP guidelines. The group compared the spectrum of F8 and F9 variants in the PedNet data base with the spectrum of variants found in the "randomly reported" EAHAD and CHAMP/CHBMP databases. This comparison demonstrated a higher proportion of missense variants in severe HB in EAHAD (68%) compared to PedNet (48%) and CHBMP (46%). The F8 and F9 variants in the PedNet population based cohort offer a new frame of reference as an alternative to the established 'random-report" databases. The full article was accepted for publication by Research and Practice in Thrombosis and Haemostasis in 2022 and published in 2023.

The genetic group is currently working on a case series about patients with the HB Leyden mutation. Additional data is being collected, and a full draft is expected in 2023.

## Working group on immunogenicity

The working group analysed inhibitor incidence according to classes of concentrates as well as for individual FVIII concentrates in the PedNet cohort of SHA patients born between 2000 and 2018. The results show unchanged inhibitor rates compared to previous analyses, while multivariate regression analysis did not show a protective effect of pdFVIII. Due to the low numbers inhibitor incidence according to individual pdFVIII concentrates were not analysed. Of the rFVIII products only 5 were used in ›50 patients. Analysis of the these 5 products showed a higher inhibitor incidence in patients treated with Kogenate, which is in line with published results of the RODIN study. The authors conclude that samples of ›200 PUPs per concentrate may be needed to detect differences between individual FVIII concentrates. A letter has been published by JTH. Supplemental material can be found on the PedNet website https://pednet.eu/publications/2022_jth_fischer/.

The next manuscript on early prophylaxis and inhibitor development is in progress.

## Follow Up of SHA patients with inhibitors

***Previously REMAIN study (Real-life MAnagement of INhibitors among PUPs with severe haemophilia A)***

After the first two publications in 2017 and 2020, the working group decided to update the study population with patients from cohort II (born 2010-2019) and follow up beyond 3 years after inhibitor development. Analyses for the next two articles are performed on inhibitor patients born 2000-2019. The second article will focus on the results of ITI in patients with high titre inhibitors.

The first article evaluates the bleeding rates of all inhibitor patients before and during ITI, until the first negative titre. Results are under review and full articles are expected to be submitted in 2023/2024.

## 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., Hematologica 2020)*.

A manuscript on patients with severe haemophilia B and an inhibitor and their response to ITI will be submitted in 2023.

## 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 five 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 next 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 group is currently drafting a full article.

## 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 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 will be described in a letter, submission expected in 2023.
Data on bleeding control after switching to emicizumab in 251 children was accepted for a poster presentation on EAHAD 2023. Manuscript submission is expected in 2023.

## 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. A full manuscript is being finalized for submission.

***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 bleeds in real-world data 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.

## Prophylaxis

***Implementation of primary prophylaxis***

The prophylactic regimen in children with severe haemophilia has been discussed and suggested in various publications and guidelines. During the last decades, several studies have been published that may have influenced the regimens of primary prophylaxis. However, few data exist on its implementation in clinical practice. The study group investigated the implementation of prophylaxis based on real-life data from the PedNet registry during the last 20 years. The prophylaxis data (start, dose, regimen) of all children with severe haemophilia A or B born between 2000-2009 (Cohort I) and were compared with those born between 2010-2019 (Cohort II). The results show that primary prophylaxis nowadays starts at an earlier age. Approximately 70% of the patients in cohort II started on a weekly schedule with significantly reduced doses in SHA, but unchanged in SHB. The full article was published in Haemophilia in 2022.

# Publications PedNet study group since 2021

1. Koskenvuo M, Mäkipernaa A, Nolan B, Kobelt R, Ranta S. Correction of haemostasis can be reduced to four days for CVAD implantation in sever haemophilia A patients: Data from the PedNet study group https://onlinelibrary.wiley.com/doi/10.1111/hae.14231
2. Álvarez-Roman MT, Kurnik K, the PedNet study group. Care for children with haemophilia during COVID-19: Data of the PedNet study group https://onlinelibrary.wiley.com/doi/10.1111/hae.14286
3. Schmidt DE, Michalopoulou A, Fischer K, Motwani J, G. Andersson N, Pergantou H, Ranta S, the PedNet Study group. Long-term joint outcome in adolescents with moderate or severe haemophilia A https://onlinelibrary.wiley.com/doi/10.1111/hae.14636
4. Ljung R, de Kovel M, van den Berg HM, on behalf of the PedNet study group. 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 https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14729
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 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

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

## Abstracts & Presentations

| | | |
|---|---|---|
| ISTH 2021, Virtual | Oral presentation | Long-term outcome in adolescents with moderate or severe hemophilia A: a PedNet study |
| ISTH 2021, Virtual | ePoster | Spectrum of F8/F9 gene mutations in the PedNet cohort |
| ISTH 2021, Virtual | ePoster | Emicizumab treatment in paediatric haemophilia A patients: >1 year safety based on real-world data from the PedNet cohorts |
| ISTH 2022, London | Oral presentation | Bleeding in children with non-severe haemophilia A and B: data from the PedNet study group |
| ISTH 2022, London | Oral presentation | The type and frequency of bleeds in 870 children with severe haemophilia A & B on primary prophylaxis: data from the PedNet study group |

# Study staff

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Director

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**Marloes de Kovel MSc**
Research coordinator

**Elsbeth de Boer-Verdonk MSc**
Senior data manager

# Participants PedNet Meeting Amsterdam, The Netherlands September 2022

# Sponsor page

The PedNet foundation receives unrestricted funding from several pharmaceutical companies.

Current sponsors are:

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

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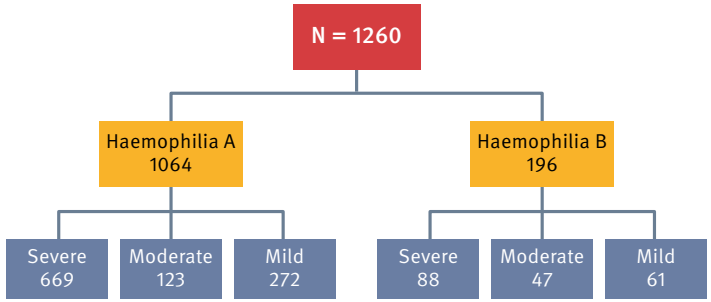
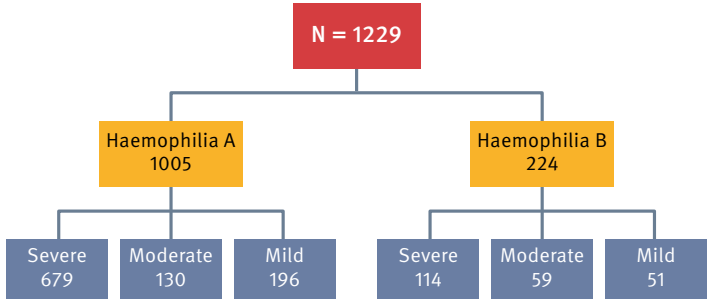
# Appendix 1 Flowcharts January 2022

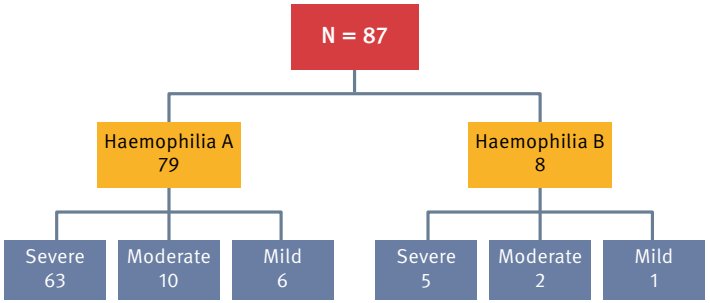
## PedNet Birth Cohort 1 (2000 - 2009) - 31 centres




## PedNet Birth Cohort 2 (2010 - 2019) - 31 centres

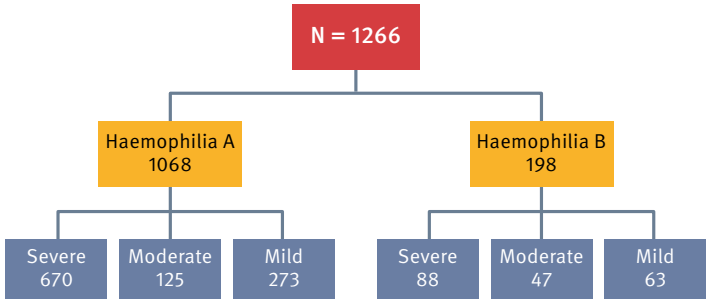



## PedNet Birth Cohort 3 (2020 - 2029) - 33 centres

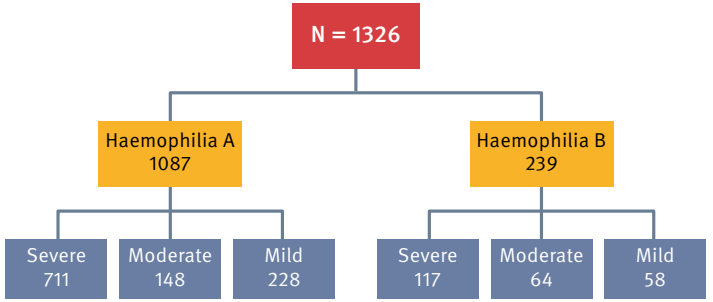



# Appendix 2 Flowcharts January 2023

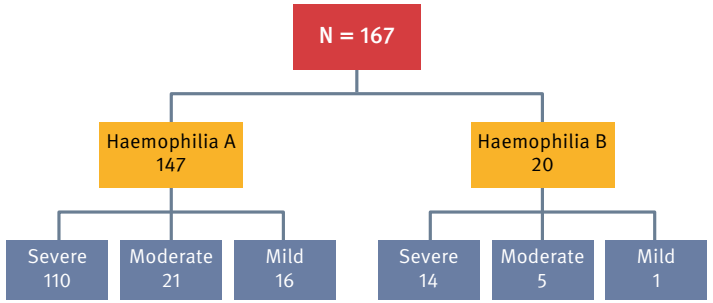
## PedNet Birth Cohort 1 (2000 - 2009) - 31 centres




## PedNet Birth Cohort 2 (2010 - 2019) - 33 centres




## PedNet Birth Cohort 3 (2020 - 2029) - 33 centres



PedNet Haemophilia Research Foundation

# PedNet

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