PedNet Haemophilia Research Foundation

PedNet

Annual report 2017
PedNet cohort studies

Data export January 2018

On behalf of the PedNet study group

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Contents

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Key numbers

In total

1972

patients included in registry

239 new patients included in 2017

1083

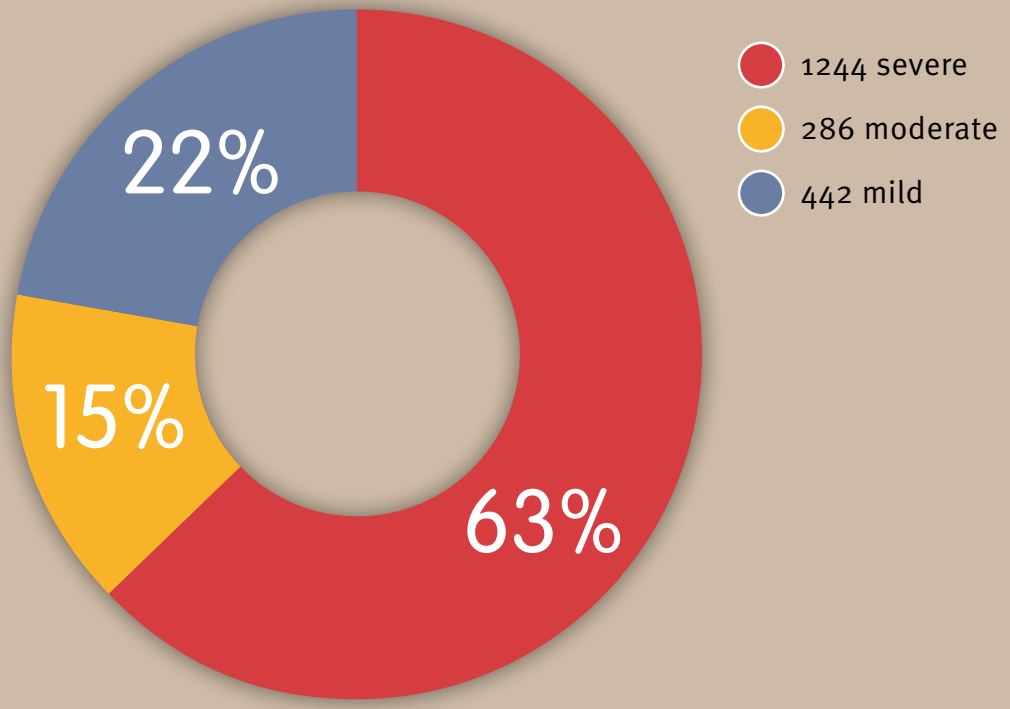
PUPS with severe haemophilia A

90 new severe haemophilia A PUPS included in 2017

161

PUPs with severe haemophilia B

Included patients according to disease severity



33

participating centers in **18** countries

Gene mutations known in

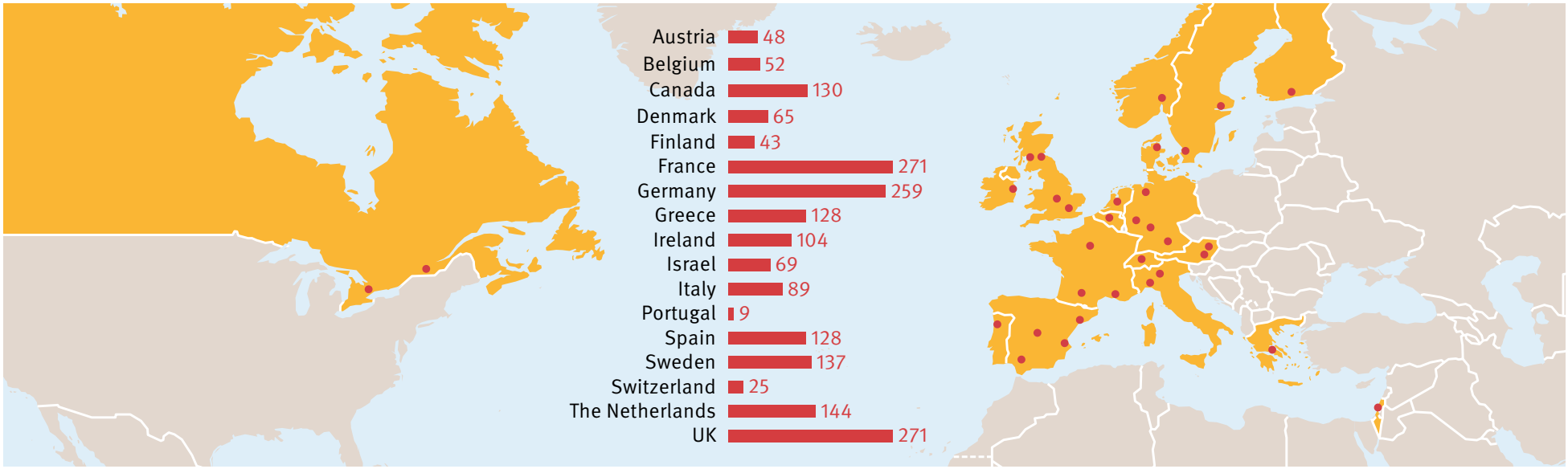
85.7%

of all patients

Total number of follow up years

13,499

Participating countries and numbers of included patients



Participating centres of the PedNet study group

Arhus (Torben Stamm Mikkelsen), Denmark
Athens (Helen Platokouki), Greece
Barcelona (Carmen Altisent), Spain
Birmingham (Mike Williams), UK
Bonn (Johannes Oldenburg), Germany
Bremen (Martina Bührlen), Germany
Dublin (Beatrice Nolan), Ireland
Edinburgh (Vacant), Scotland, UK
Frankfurt Goethe (Christoph Königs)
& Mörfelden-Walldorf (Carmen Escuriola), Germany
Genova (Claudio Molinari), Italy
Glasgow (Elizabeth Chalmers), Scotland, UK
Helsinki (Anne Mäkipernaa), Finland
Leuven (Christel Van Geet), Belgium
London (Ri Liesner), UK
Madrid (Maria Teresa Alvarez Romàn), Spain
Malmö (Nadine Gretenkort Andersson), Sweden
Marseille (Hervé Chambost), France
Milan (Elena Santagostino), Italy
Montreal (George Rivard), Canada
Munich (Karin Kurnik), Germany
Oslo (Heidi Glosli), Norway*
Porto (Manuela Carvalho), Portugal
Kremlin Bicêtre-Paris (Anne Rafowicz), France
Seville (Rosario Pérez Garrido), Spain
Stockholm (Susanna Ranta), Sweden
Tel Hashomer (Gili Kenet), Israel
Toronto (Manuel Carcao), Canada
Toulouse (Ségolène Claeyssens), France
Utrecht (Kathelijn Fischer), The Netherlands
Valencia (Ana Rosa Cid), Spain;
Vienna (Christoph Male), Austria
Wabern (Rainer Kobelt), Switzerland

* Norway starts inclusion in 2018

Introduction

The PedNet study group (the European Paediatric Network for Haemophilia Management) is a collaboration of now 33 haemophilia treatment centres (HTCs) in 18 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.
The objectives of the Foundation are to promote scientific research related to haemophilia and to promote international cooperation between centres specialised in the treatment of children with haemophilia. The foundation is not-for-profit and will publish the first annual report on activities and the first financial report in 2018.
This report provides an overview of the status of the PedNet registry in January 2018 and of the research activities performed by the PedNet study group in 2017.
More information on all research activities can be found in the Research program 2018-2020.

General aim

The general aim of the PedNet study group and of the foundation is to improve clinical research on inhibitors, phenotype and long-term outcome of different treatment regimens.

PedNet Registry

In the PedNet Registry prospective data of 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 contracts with the participating centres and they are reimbursed 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.
The first data export for analyses was performed in May 2011, 8 years after the start of the database in 2003. The data were used for the first satellite study of the PedNet registry, the RODIN study. In 2018 a new full analysis will be performed on all patients with severe haemophilia A.

Monitoring

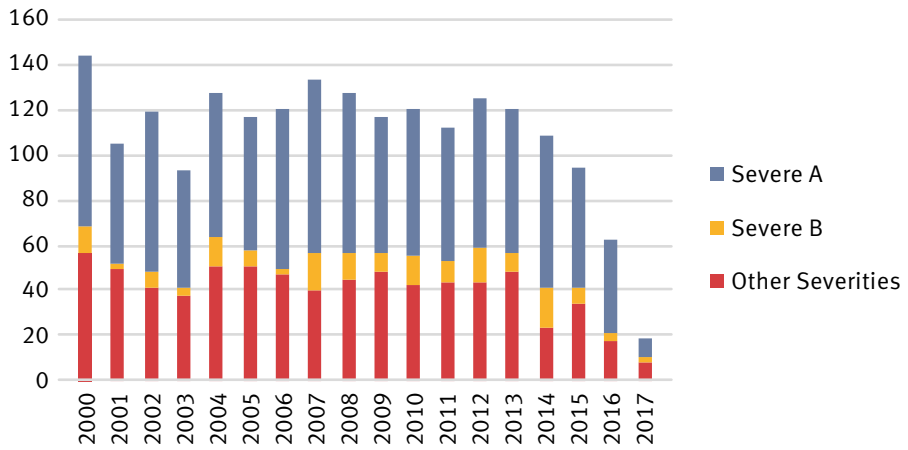
Data collected in the PedNet registry are monitored to improve data quality. This is done by built-in checks on the e-CRF and regular data control on exports. Study coordinators employed by the foundation are in frequent contact with centres and perform regular visits. On-site monitoring is performed by an independent research organisation according to a predefined monitor plan. The PedNet centres agreed together that 100% of all 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

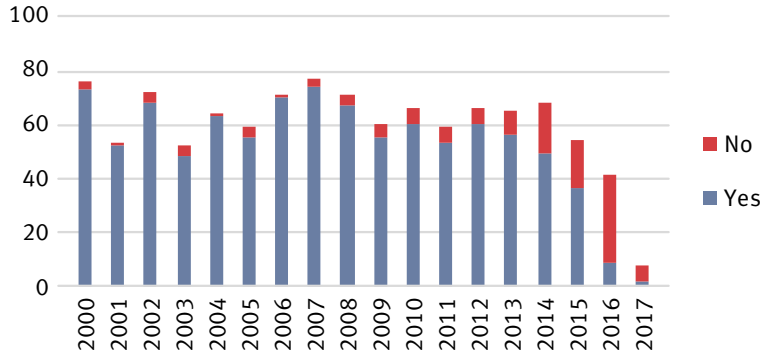
As of 1 January 2018, a total of **1972** previously untreated patients (PUPs) with haemophilia A or B are included in the study. Of these, **1083**, have severe haemophilia A **(90 more than last year)** and **161** have severe haemophilia B **(29 more than last year)** (see Appendix 1). **1069** (86%) of the severe haemophilia patients (A plus B) have reached 50 exposure days. Data on gene defects are available for **1691** (85.7%) of all patients included in the study.

Tables & Figures

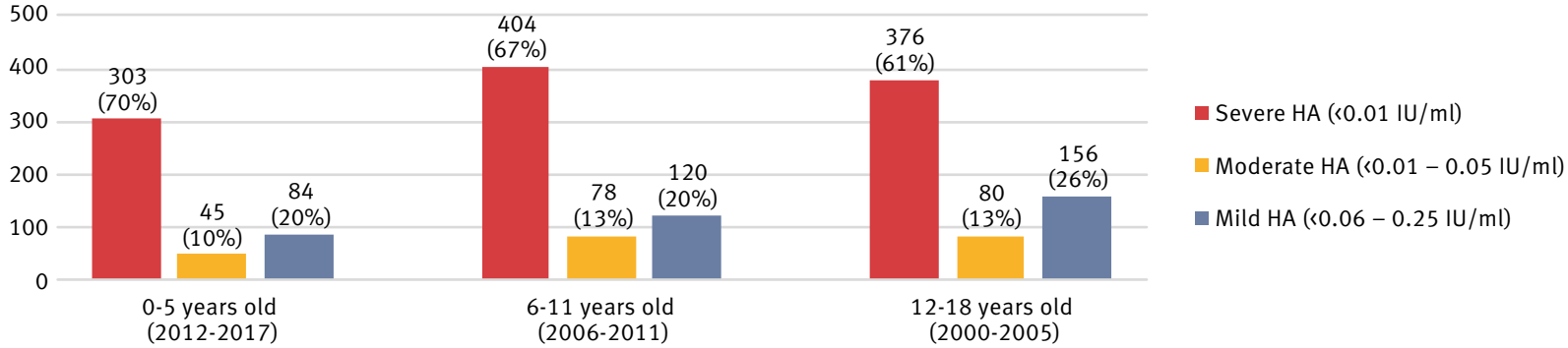
N Patients per birth year



N SHA ED50 Reached or INH development per birth year



Haemophilia A age distribution according to disease severity



Data export January 2018

Inclusions per birth cohort

Haemophilia A

	Severe HA	Moderate HA	Mild HA	Total HA	
N Baseline	1,083	203	360	1,646	
N Known gene mutations	993	153	271	1,417	86%
N ED =>50	943	100	36	1,079	66%
N PID with FU data	1,033	187	332	1,552	94%
Sum years FU	7,621	1,467	2,503	11,592	

N = number of patients, HA = Haemophilia A

Haemophilia B

	Severe HB	Moderate HB	Mild HB	Total HB	
N Baseline	161	83	82	326	
N Known gene mutations	145	67	62	274	84%
N ED =>50	126	26	4	156	48%
N PID with FU data	155	78	73	306	94%
Sum years FU	899	526	483	1,907	

N = number of patients, HB = Haemophilia B

Display of PedNet Numbers

	2015	2016	2017	2018
N Baseline	1,340	1,531	1,733	1,972
N Known gene mutations	1,096	1,260	1,449	1,691
N ED =>50	851	950	1,094	1,235
N PID with FU data	1,253	1,413	1,615	1,858

N = number of patients

Data export January 2018

Studies performed in 2017

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

The study started in 2012 and includes all patients diagnosed between 1990 and 2009 with a clinically relevant inhibitor. Detailed data were collected on all inhibitor titres, bleedings and treatment regimens (including product types and dosing) during the follow-up period. The data of 98% of all eligible patients are available and the first results were presented at the annual PedNet meeting. The first article has focussed on the description of the inhibitors during the 3-year follow-up after the first positive titre. This article has been published: Thromb Haemost 2017; 117:2274-82.

The PedNet study group will continue to collect follow up data of all (inhibitor and non-inhibitor) patients. This includes all information on treatment regimens, immune tolerance induction (ITI), bleedings and procedures. Laboratory samples are collected continuously after a single positive sample. It is expected that this will give more insight into the success rate of ITI and the impact of an inhibitor on bleeding and long-term outcome.

More information on the other projects of "REMAIN" can be found in the research program.

Effect of vaccinations on inhibitor development

As part of our research on factors influencing inhibitor development, we investigated whether vaccinations given in close proximity to FVIII infusion would increase inhibitor risk. Preliminary results were orally presented at EAHAD in 2017. We found no indication that vaccinations given in close proximity to FVIII exposure increase the risk of inhibitor development. Therefore, the results do not support separating vaccinations and FVIII exposure. The PedNet study group advises to give vaccinations according to the vaccination schedules in the individual countries for all children. Published in Haemophilia, Epub 2017; DOI: 10.1111/hae.13387.

CVAD working group

CVADs are important devices in the treatment of children with severe haemophilia; they allow for early good venous access and make home treatment a reality from a very young age onwards. The PedNet study group is collecting data on all CVADs implanted in the patients, both for inhibitor and non-inhibitor patients.

The PedNet study group performed a detailed analysis of the classification of centres that used different nursing practises. Three distinct home-care methods were described: 'aseptic non-touch technique' (ANTT), a technique that maintains asepsis in a non-touch manner rather than with sterile barriers such as gowns and gloves; 'sterile technique' (ST) using sterile gloves, sterile field and aseptic techniques; and 'fully sterile technique' (FST), in addition using gowns and masks. The first paper on the effect of nursing practises has been published: Haemophilia 2017;23:276-81.

More on CVAD studies can be found in the research program.

Intracranial haemorrhage in children and adolescents with severe haemophilia A or B – the impact of prophylactic treatment

An international study was performed by Andersson et al, aiming at investigating the incidence of intracranial hemorrhages (ICH). In total 33 haemophilia treatment centres in 20 countries participated. The reported ICH were correlated to the prophylactic regimens used. The incidence of ICH in the prophylaxis group was very low (0.00033 ICH cases per patient year), significantly lower as compared to the no-prophylaxis group (0.017 ICH cases per patient year). In the on-demand-group, 8% (2/24) children with ICH died while 33% had long-term sequelae, including intellectual and behavioural problems, paresis and epilepsy. It was concluded that children on regular, frequent prophylaxis have a low risk of ICH compared to those using non-frequent or no prophylaxis. Published: Br J Haematol 2017;179:298-307.

Clinical trials and registries in haemophilia: Opponents or collaborators? Comparison of PUP data derived from different data sources.

Christine Keipert of the Paul Ehrlich institute and Carla Jonker of the Dutch regulatory authorities investigated data from the historic PUP studies performed by companies collected in the framework of marketing authorisation and data of PUPS by the PedNet registry. The aim was to investigate relevant parameters as identified in the Clinical FVIII Guideline as well as inhibitor incidences in patients from both data sources. A total of eight controlled trials performed between 1987 and 2009, with 369 PUPs, were compared with 632 PUPs (born 2000-2009) from the PedNet registry. A direct comparison regarding inhibitors could only be performed in 198 PUPs with severe hemophilia in the 8 CTs and 617 PUPs with severe hemophilia A from the PedNet registry. The overall inhibitor incidences at ED 50 were 30.9% (CTs) and 30.6% (PedNet). Eighty-seven percent (47/54) of inhibitors in CTs developed before ED 20 as compared to was 81% in PedNet (151/186). High-titre inhibitors were detected at or before ED 20 in 12.8% (CTs) and 16.8% (PedNet) of patients. Inhibitor incidences for high-titre inhibitors at ED 50 were 14.9% (CTs) and 21.0% (PedNet). Comparison of survival curves of severe patients with high-titre inhibitors revealed no significant differences.

Conclusion: previously performed CTs in PUPs were divergent, preventing direct outcome comparison of individual products. However, this study demonstrated that data from CTs and carefully designed registries may complement each other in establishing sufficient safety information for single products in order to improve clinical insights and support regulatory decisions. Published: Haemophilia Epub 2018; DOI 10.1111/hae.13421.

Publications PedNet study group 2017

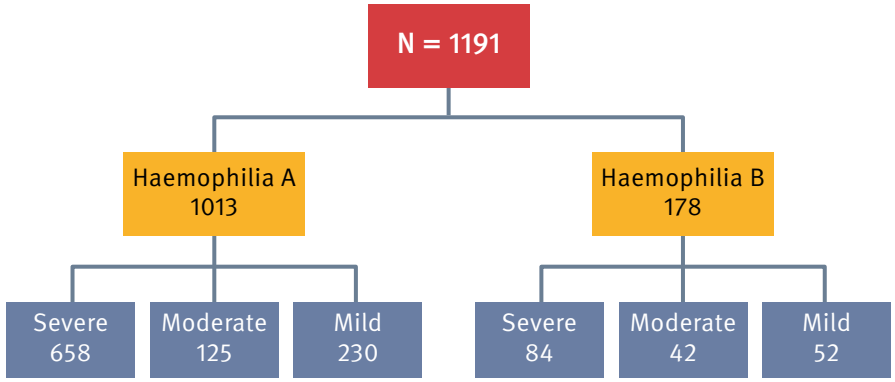
1. Khair K, Ranta S, Thomas A, Lindvall K; PedNet study group. The impact of clinical practice on the outcome of central venous access devices in children with haemophilia. Haemophilia 2017;23:276-81.
2. Mancuso et al. Risk factors for the progression from low- to high-titers in 260 children with severe haemophilia A and newly developed inhibitors. Thromb Haemost 2017;117:2274-82.
3. Andersson NG, Auerswald G, Barnes C, Carcao M, Dunn AL, Fijnvandraat K, Hoffmann M, Kavakli K, Kenet G, Kobelt R, Kurnik K, Liesner R, Mäkipernaa A, Manco-Johnson MK, Mancuso ME, Molinari AC, Nolan B, Perez Garrido R, Petrini P, Platokouki HE, Shapiro AD, Wu R, Ljung R. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B – the impact of prophylactic treatment. Br J Haematol 2017;179:298-307.
4. Andersson NG, Chalmers EA, Kenet G, Ljung R, Mäkipernaa A, Chambost H, on behalf of the PedNet group. Impact of mode of delivery on major bleeding and ICH in neonates with hemophilia. Vaginal delivery leads to less major bleeding than CS. Submitted.
5. 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 Epub 2017; DOI 10.1111/hae.13387.
6. Keipert C, Jonker CJ, van den Berg HM, Hilger, A. Clinical trials and registries in haemophilia: Opponents or collaborators? Comparison of PUP data derived from different data sources. Haemophilia Epub 2018; DOI 10.1111/hae.13421.

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

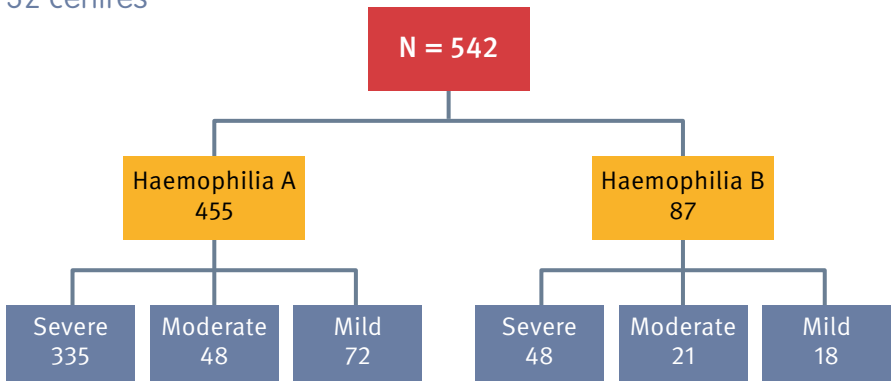
Participants PedNet Meeting Amsterdam, September 2017

Appendix 1 Flowcharts January 2017

PedNet Birth Cohort 1 (2000 - 2009)
30 centres

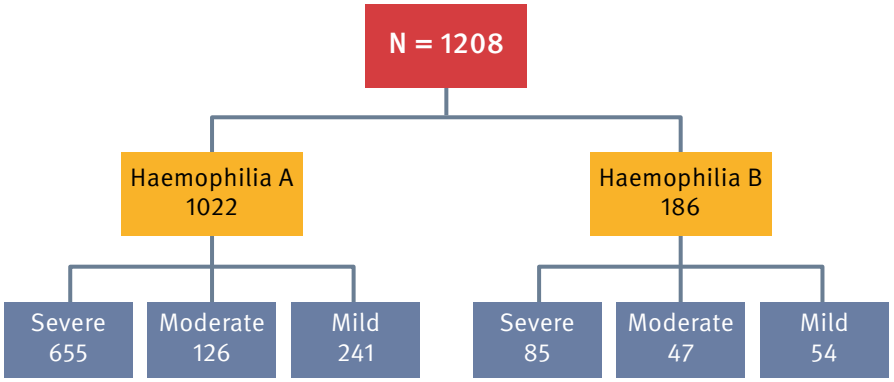


PedNet Birth Cohort 2 (2010 - 2019)
32 centres

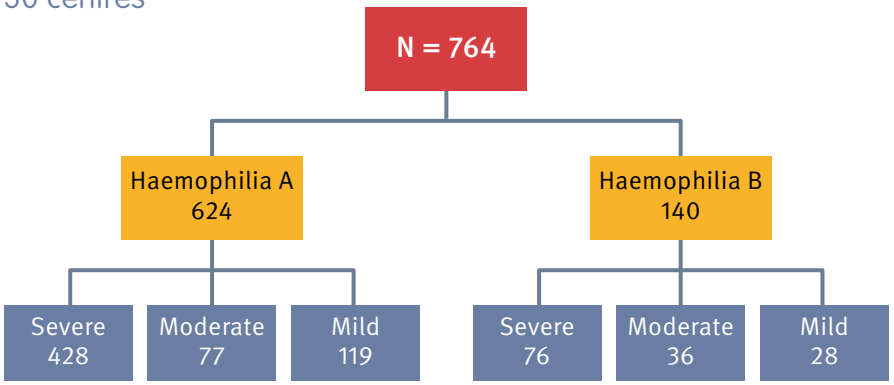


Appendix 2 Flowcharts January 2018

PedNet Birth Cohort 1 (2000 - 2009)
30 centres



PedNet Birth Cohort 2 (2010 - 2019)
30 centres



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