Annual report 2018
PedNet cohort studies

Data export January 2019

On behalf of the PedNet study group

Rolf Ljung, MD, PhD
Chairman of the management board

H. Marijke van den Berg, MD, PhD
Director of the PedNet Haemophilia Research Foundation
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**PedNet** (the European Paediatric Network for Haemophilia Management) began in 1996 as a collaboration of 22 paediatricians in 16 European countries. PedNet provides an infrastructure for clinical research on the management of children with haemophilia. Currently the PedNet study group consists of 31 haemophilia treatment centres in 18 countries.

The **PedNet Registry** started in 2003 and, in order to prevent selection bias, is set up as a birth cohort study. It collects real-life data from all newly diagnosed children treated in the participating centres. Data are collected through well-defined web-based 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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### Management Board

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<tr>
<td>Christoph Male, MD</td>
<td>Department of Paediatrics, Medical University of Vienna, Vienna, AUSTRIA</td>
</tr>
<tr>
<td>Gili Kenet, MD</td>
<td>The National Hemophilia Center, Ministry of Health, Sheba Medical Center, Tel Hashomer, Ramat Gan, ISRAEL</td>
</tr>
<tr>
<td>Rolf Ljung, MD, PhD</td>
<td>Lund University, Skånes Universitetssjukhus, Malmö, SWEDEN</td>
</tr>
<tr>
<td>Karin Kurnik, MD</td>
<td>Dr. v. Haunersches Kinderspital, University of Munich, Munich, GERMANY</td>
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### Scientific Advisory Council

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Manuel Carcao, MD</td>
<td>Hospital for Sick Children, Toronto, Ontario, CANADA</td>
</tr>
<tr>
<td>Johannes Oldenburg, MD, PhD</td>
<td>Universitätsklinikum Bonn, Bonn, GERMANY</td>
</tr>
<tr>
<td>Hervé Chambost, MD, PhD</td>
<td>CHU Timone, Marseille, FRANCE</td>
</tr>
<tr>
<td>Elena Santagostino, MD, PhD</td>
<td>IRCCS Ospedale Maggiore, Milano, ITALY</td>
</tr>
<tr>
<td>Kathelijn Fischer, MD, PhD</td>
<td>Van Creveld Kliniek, University Medical Center Utrecht, THE NETHERLANDS</td>
</tr>
<tr>
<td>Christel Van Geet, MD, PhD</td>
<td>Service of Pediatric Haematology, University Hospital Leuven, Campus Gasthuisberg, Leuven, BELGIUM</td>
</tr>
<tr>
<td>Christoph Königs, MD, PhD</td>
<td>Clinical and Molecular Hemostasis, Department of Pediatrics, University Hospital Frankfurt &amp; Goethe University, Frankfurt/Main, GERMANY</td>
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</table>
Included patients according to disease severity

- 1346 severe
- 312 moderate
- 484 mild

Key numbers

- In total, 2142 patients included in registry
  - 170 new patients included in 2018
- 1173 PUPS with severe haemophilia A
  - 90 new severe haemophilia A PUPS
- 173 PUPS with severe haemophilia B
  - 12 new severe haemophilia B PUPS
- 31 participating centers in 18 countries
- Gene mutations known in 85% of all patients
- Total number of follow up years: 15,515
### Key numbers

#### Follow up data

- **90%** of the severe haemophilia A patients reached 50 Exposure Days. 
  Lost to follow up before 50 EDs is only **2%**.

- **82%** of the severe haemophilia B patients reached 50 Exposure Days. 
  Lost to follow up before 50 EDs is only **3%**.

#### Inhibitors

- **391** Inhibitors diagnosed between 2000-2019.
- **351** severe haemophilia A.
- **16** severe haemophilia B.

- **2570** Follow up years for inhibitor patients.
- **2336** years for severe haemophilia A inhibitor patients.
- **89** years for severe haemophilia B inhibitor patients.

- **In total** **16,400** inhibitor test results are collected.
- **12,000** tests of the 391 inhibitor patients (Median of **23** tests per inhibitor patient (IQR 13-38,50))

### PedNet - Annual report 2018

**Contents**

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Participating countries and numbers of included patients

- Austria: 61
- Belgium: 55
- Canada: 136
- Denmark: 72
- Finland: 44
- France: 303
- Germany: 284
- Greece: 131
- Ireland: 111
- Israel: 69
- Italy: 92
- Norway: 29
- Portugal: 10
- Spain: 143
- Sweden: 151
- Switzerland: 27
- The Netherlands: 149
- United Kingdom: 275
Members list

Maria Teresa Alvarez Román
Unidad de Coagulopatías
Hospital Universitario La Paz
Madrid, SPAIN

Martina Bührlen
Klinik Bremen-Mitte.
Prof.-Hess-Kinderklinik
Bremen, GERMANY

Manuel Carcao
Division of Haematology/Oncology,
Hospital for Sick Children
Toronto, Ontario, CANADA

Manuela Carvalho
Centro Hospitalar São João, S.
Imuno-hemoterapia
Porto, PORTUGAL

Elizabeth Chalmers
Department of Haematology
Royal Hospital for Sick Children
Glasgow, SCOTLAND UK

Hervé Chambost
Service d’Hématologie Pédiatrique
CHU Timone
Marseille, FRANCE

Ana Rosa Cid
Unidad de Coagulopatías Congénitas
Hospital Universitario la Fe
Valencia, SPAIN

Ségolène Claeyssens
CHU Purpan
Centre de traitement des hémophiles
Toulouse, FRANCE

Carmen Escuriola
HZRM Hämophilie Zentrum Rhein Main GmbH
Mörfelden-Walldorf, GERMANY

Kathelijn Fischer
Van Creveldkliniek
University Medical Center Utrecht
Utrecht, THE NETHERLANDS

Christel Van Geet
Service of Pediatric Haematology
University Hospital Leuven
Campus Gasthuisberg
Leuven, BELGIUM

Heidi Glosli
Olso University Hospital
Oslo, NORWAY

Nadine Gretenkort Andersson
Department of Pediatrics
Lund University Hospital
Malmö, SWEDEN

Gili Kenet
The National Hemophilia Center
Ministry of Health
Sheba Medical Center
Tel Hashomer, ISRAEL

Rainer Kobelt
Hämophiliezentrum
Wabern, SWITZERLAND

Christoph Königs
Clinical and Molecular Hemostasis
Department of Pediatrics
University Hospital Frankfurt & Goethe University
Frankfurt/Main, GERMANY

Karin Kurnik
Dr. v. Haunersches Kinderspital
University of Munich
Munich, GERMANY

Ri Liesner
Haematology,
Great Ormond Street
Childrens Hospital
London, UNITED KINGDOM
## Members list

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anne Mäkipernaa</td>
<td>Hospital for Children and Adolescents, University of Helsinki, Helsinki, FINLAND</td>
</tr>
<tr>
<td>Christoph Male</td>
<td>Department of Paediatrics, Medical University of Vienna, Vienna, AUSTRIA</td>
</tr>
<tr>
<td>Angelo Claudio Molinari</td>
<td>Gaslini Hospital, Genova, ITALY</td>
</tr>
<tr>
<td>Jayashree Motwani</td>
<td>Department of Haematology, Birmingham Children’s Hospital NHS Trust, Birmingham, UNITED KINGDOM</td>
</tr>
<tr>
<td>Beatrice Nolan</td>
<td>Dept of Paediatric Haematology, Our Lady’s Children’s Hospital for Sick Children, Dublin, IRELAND</td>
</tr>
<tr>
<td>Johannes Oldenburg</td>
<td>Institut für Experimentelle Hämatologie und Transfusionsmedizin, Universitätsklinikum Bonn, Bonn, GERMANY</td>
</tr>
<tr>
<td>Helen Platokouki</td>
<td>St. Sophia Children’s Hospital, Haemophilia-Haemostasis Unit, Athens, GREECE</td>
</tr>
<tr>
<td>Anne Rafowicz</td>
<td>CRTH Bicetre, Service Hématoilogique, Le Kremlin Bicetre, FRANCE</td>
</tr>
<tr>
<td>Susanna Ranta</td>
<td>Dep. of Pediatrics, Clinic of Coag. Disorders, Karolinska Hospital, Stockholm, SWEDEN</td>
</tr>
<tr>
<td>George Rivard</td>
<td>Division of Hematology/Oncology, Hôpital St Justine, Montréal, CANADA</td>
</tr>
<tr>
<td>Elena Santagostino</td>
<td>A. Bianchi Bonomi Hemophilia and Thrombosis Centre, Institute of Internal Medicine, IRCCS Ospedale Maggiore, Milano, ITALY</td>
</tr>
<tr>
<td>Amparo Santamaria Ortiz</td>
<td>Unitat Hemofilia, Hospital Vall d’Hebron, Barcelona, SPAIN</td>
</tr>
<tr>
<td>Torben Stamm Mikkelsen</td>
<td>Dept of Pediatrics Århus Kommunehospital, Skejby Sygehus, Århus, DENMARK</td>
</tr>
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Introduction

The PedNet study group (the European Paediatric Network for Haemophilia Management) is a collaboration of now 31 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 stimulate international cooperation between centres specialised in the treatment of children with haemophilia. The foundation is not-for-profit and will publish an annual report on activities and a financial report. This report provides an overview of the status of the PedNet registry up to January 2019 and of the research activities performed by the PedNet study group in 2018. 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. New full analysis will be performed on all patients with severe haemophilia A and published.

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 2019, a total of 2142 previously untreated patients (PUPs) with haemophilia A or B are included in the study. Of these, 1373, have severe haemophilia A (90 more than last year) and 173 have severe haemophilia B (12 more than last year) (see Appendix 1). 1196 (89%) of the severe haemophilia patients (A plus B) have reached 50 exposure days. Data on gene defects are available for 1824 (85.2%) of all patients included in the study.
### Haemophilia A

<table>
<thead>
<tr>
<th></th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
<th>Total HA</th>
</tr>
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<tr>
<td>Baseline</td>
<td>1173</td>
<td>225</td>
<td>397</td>
<td>1795</td>
</tr>
<tr>
<td>Known gene mutations</td>
<td>1060</td>
<td>169</td>
<td>331</td>
<td>1530</td>
</tr>
<tr>
<td>At least 50 EDs</td>
<td>1054</td>
<td>90%</td>
<td>110</td>
<td>1205</td>
</tr>
<tr>
<td>Follow-up data</td>
<td>1116</td>
<td>214</td>
<td>371</td>
<td>1701</td>
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<tr>
<td>Total FU years</td>
<td>8608</td>
<td>1693</td>
<td>2880</td>
<td>13,181</td>
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<tr>
<td>Lost to follow-up</td>
<td>23</td>
<td>2%</td>
<td>14</td>
<td>41</td>
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<tr>
<td>during first 50 EDs</td>
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### Haemophilia B

<table>
<thead>
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<th>Mild</th>
<th>Total HB</th>
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<tr>
<td>Baseline</td>
<td>173</td>
<td>87</td>
<td>87</td>
<td>347</td>
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<tr>
<td>Known gene mutations</td>
<td>153</td>
<td>72</td>
<td>69</td>
<td>294</td>
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<tr>
<td>At least 50 EDs</td>
<td>142</td>
<td>82%</td>
<td>30</td>
<td>5</td>
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<tr>
<td>Follow-up data</td>
<td>165</td>
<td>84</td>
<td>79</td>
<td>328</td>
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<td>Total FU years</td>
<td>1200</td>
<td>574</td>
<td>560</td>
<td>2334</td>
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<tr>
<td>Lost to follow-up</td>
<td>6</td>
<td>3%</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>during first 50 EDs</td>
<td></td>
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### Display of PedNet Numbers

<table>
<thead>
<tr>
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<th>2017</th>
<th>2018</th>
<th>2019</th>
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<tr>
<td>Baseline</td>
<td>1,34</td>
<td>1,531</td>
<td>1,733</td>
<td>1,972</td>
<td>2,142</td>
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<tr>
<td>Known gene mutations</td>
<td>1,096</td>
<td>1,26</td>
<td>1,449</td>
<td>1,691</td>
<td>1,834</td>
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<tr>
<td>At least 50 EDs</td>
<td>851</td>
<td>950</td>
<td>1,094</td>
<td>1,235</td>
<td>1,382</td>
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<tr>
<td>Follow-up data</td>
<td>1,253</td>
<td>1,413</td>
<td>1,615</td>
<td>1,858</td>
<td>2,029</td>
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### Details on inhibitor patients in PedNet

<table>
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<th>All</th>
<th>Severe Haem A</th>
<th>Severe Haem B</th>
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<tbody>
<tr>
<td>N</td>
<td>391</td>
<td>351</td>
<td>16</td>
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<tr>
<td>Sum FU (yrs) after 1st positive sample</td>
<td>2570</td>
<td>2336</td>
<td>89</td>
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<tr>
<td>Median (yrs; IQR)</td>
<td>6</td>
<td>6,1</td>
<td>4,5</td>
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Data export January 2019
Studies performed in 2017/2018

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. Procedures for the implantation of CVADs vary between centres. Some centres insert central venous catheters in all children with severe haemophilia who start prophylaxis. Our group reported that intensive treatment is a risk factor for antibody formation. This caused concern and many physicians avoid CVADs or try to postpone the time of insertion to minimise this risk. Since bleeding during implantation of CVADs is a risk, investigating the different periods of haemostatic correction during CVADs will give insight into whether a short period is as effective to control haemostasis as a longer period. This study will provide information on overall risk/benefit ratio regarding both the timing and treatment with factor concentrates during and after surgery.

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

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 haemophilia in the 8 CTs and 617 PUPS with severe haemophilia 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 (Keipert et al., 2018).

REMAIN study (Real-life MAnagement of INhibitors among PUPs with severe haemophilia A)
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. The first article titled; Risk factors for the progression of low-titre to high-titre inhibitors in 260 children with severe haemophilia A and newly developed inhibitors. Described the cohort of inhibitor patients born between 1990-2009 has been published (Mancuso et al., 2017). Three papers are currently prepared;
1. During the last 20 years more patients with a low titre inhibitors have been diagnosed. This paper will describe the “Natural History of low titre inhibitors diagnosed between 1990-2009 in the PedNet study group.
2. Bleeding phenotype in boys with hemophilia and inhibitors before and during immune tolerance induction therapy –the REMAIN study. Using data from the multicenter PedNet cohort, this study aimed to assess bleeding in patients with low and high titer inhibitors before and during ITI.
3. The last article will focus on high titre inhibitor and response to ITI.
Neonatal working group
Mode of delivery in hemophilia: Vaginal delivery and cesarean section carry similar risks for intracranial hemorrhages and major bleeds (Andersson et al., Hematologica 2019; 104 :xxx)

The optimal mode of delivery for a pregnant hemophilia carrier is still a matter of debate. In this study we determined the incidence of intracranial hemorrhage and other major bleeds in neonates with moderate and severe hemophilia in relationship to mode of delivery and known family history. A total of 926 neonates, 786 with severe and 140 with moderate hemophilia were included in this PedNet multicentre study. Vaginal delivery was performed in 68.3% (n=633) and Cesarean section in 31.6% (n=293). Twenty intracranial hemorrhages (2.2%) and forty-four other major bleeds (4.8%) occurred. Intracranial hemorrhages occurred in 2.4% of neonates following vaginal delivery compared to 1.7% after Cesarean section (P=ns); other major bleeds occurred in 4.2% born by vaginal delivery and in 5.8% after Cesarean section (P=ns). Further analysis of subgroups (n=813) identified vaginal delivery with instruments being a significant risk factor for both intracranial hemorrhages and major bleeds (RR 4.78-7.39, p<0.01); no other significant differences were found between vaginal delivery without instruments, Cesarean section prior and during to labor. The frequency for intracranial hemorrhages and major bleeds for a planned Cesarean section and a planned vaginal delivery showed no significant difference. Children with a family history of haemophilia (n=466) were more likely born by Cesarean section (35.8% vs. 27.6%) but no difference in the rate of intracranial hemorrhages or major bleeds were found. In summary, vaginal delivery and Cesarean section carry similar risks of intracranial hemorrhages and major bleeds.

Haemophilia B projects.
Haemophilia B is very rare and this has hampered clinical studies. The first project in PedNet on haemophilia B included severe haemophilia B. Several publications are in preparation;
1. Inhibitor incidence in PUPs with severe haemophilia B is higher than usually reported; data from the PedNet registry
During EAHAD 2018 we reported the inhibitor incidence in severe haemophilia B. An unselected group of 161 patients with severe haemophilia B was included.
Of these 15 developed an inhibitor. The cumulative inhibitor incidence was 11.5% at 500 EDs. Detailed information on gene defects will give more insight into the effect on inhibitor development. These data will be submitted for publication in 2019. A separate article on all 15 patients with an inhibitor will follow and focus on allergic reactions and nephrotic syndrome during ITI.

Genetic project
The PedNet study group has collected detailed data on the FVIII and IX gene underlying the disease. These data have been used in several publications that adjusted for the high risk or low risk gene mutation in different studies. Many genetic studies have correlated a specific gene defect with an estimated risk for inhibitor. The strength of the PedNet registry is that all consecutively newly diagnosed patients with haemophilia A and B until FVIII/IX 25% were included. Large unselected study population give unique insight into the frequency of specific gene mutations. It is important to investigate the correlation with specific mutation effect on inhibitor development. This enables us to correlate unselected patients with a specific gene defect and compare our results with existing data bases such as EAHAD and CHAMPS databases.
Publications: PedNet study group 2017/2018


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

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<td>Oral</td>
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<td>EAHAD 2018, Madrid</td>
<td>Poster</td>
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<tr>
<td>WFH 2018, Glasgow</td>
<td>Oral</td>
</tr>
<tr>
<td>ASH 2018, San Diego</td>
<td>Poster</td>
</tr>
</tbody>
</table>
Study staff

Marijke van den Berg
Director

Ella van Hardeveld
Study coordinator

Marloes de Kovel
Research assistant
The PedNet foundation receives unrestricted funding from several pharmaceutical companies.

Current sponsors are:
- Bayer AG
- CSL Behring GmbH
- Grifols
- Novo Nordisk Health Care AG
- Pfizer SRL
- Swedish Orphan Biovitrium AB
- Takeda

Correspondence
PedNet Haemophilia Research Foundation
Mollerusstraat 1
3743 BW Baarn
The Netherlands
Participants PedNet Meeting Frankfurt, Germany September 2018
Appendix 1  Flowcharts January 2018

PedNet Birth Cohort 1 (2000 - 2009)
30 centres

N = 1208

Haemophilia A
1022

Haemophilia B
186

Severe
655
Moderate
126
Mild
241
Severe
85
Moderate
47
Mild
54

PedNet Birth Cohort 2 (2010 - 2019)
30 centres

N = 764

Haemophilia A
624

Haemophilia B
140

Severe
428
Moderate
77
Mild
119
Severe
76
Moderate
36
Mild
28

Appendix 2  Flowcharts January 2019

PedNet Birth Cohort 1 (2000 - 2009)
31 centres

N = 1231

Haemophilia A
1044

Haemophilia B
187

Severe
661
Moderate
125
Mild
258
Severe
87
Moderate
46
Mild
54

PedNet Birth Cohort 2 (2010 - 2019)
31 centres

N = 911

Haemophilia A
751

Haemophilia B
160

Severe
512
Moderate
100
Mild
139
Severe
86
Moderate
41
Mild
33