PedNet Haemophilia Research Foundation

Research program 2018-2020

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INTRODUCTION

PedNet, the PedNet Registry and the PedNet Haemophilia Research Foundation

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 and management of children with haemophilia. The members of the group do not represent their respective countries or any national organisation, but they are responsible for the care of a substantial number of children with haemophilia in (mainly) Western Europe. Annual workshops serve as a platform for informal discussion on important topics to improve quality of care by promoting information exchange about clinical practice and research. Currently the PedNet study group consists of 32 haemophilia treatment centres in 18 countries.

The PedNet Registry started in 2003 and, in order to prevent selection bias, is set up as an age cohort study. It collects real-life data from all newly diagnosed children born in the participating centres. Data are collected through well-defined web-based U-CRF forms that contain details on all aspects of haemophilia from birth to adolescence and adulthood. Data on long-term joint and patient-reported outcomes will be added in the near future. In the PedNet Registry patients with FVIII/IX levels up to 25%, born between January 1, 2000 and January 1, 2020, and diagnosed and treated in one of the participating haemophilia treatment centres (HTCs) are included. Annual data downloads are used for analysis of ongoing studies. The RODIN study, based on the first data download in 2011, was the first satellite study in the PedNet Registry.

The PedNet Haemophilia Research Foundation was founded in December 2016 in order to secure long-term continuation of the Registry. The Foundation is the legal owner of the database and all its assets.

Background

Haemophilia A and B are hereditary, X-chromosomal recessive disorders caused by absent, deficient or dysfunctional factor VIII (FVIII) and factor IX (FIX), respectively. Patients with haemophilia develop a bleeding phenotype which, depending on the concentration of FVIII or FIX coagulant activity in blood, may be classified as severe (<1% of normal activity), moderate (1-4%) or mild (5-25%). Haemophilia A affects approximately 1:5000 males, haemophilia B approximately 1: 20,000 males. The current treatment is based on replacement of the missing coagulation factor, either from early age (primary prophylaxis) or only when bleeds occur (on-demand treatment).

Over the last decades, much progress in therapy has been made.[1,2] In Europe, most children receive primary prophylaxis, which effectively prevents life-threatening haemorrhage, disabling joint arthropathy and muscle atrophy.[3,4] Nowadays, optimal treatment can convert severe haemophilia from a condition with a life expectancy of only 20 years into a condition with a normal life expectancy and without significantly limited physical health.[5,6] The cost of treatment is a major issue, however, limiting treatment options in many countries. Although prophylactic treatment is generally considered to be the optimal mode of treatment, the optimal prophylactic treatment regimen is still a matter of debate; guidelines are often based on opinion rather than scientific data. Large international collaborative studies are needed to answer clinical questions regarding treatment outcome, inhibitor development, etc. The PedNet centres have introduced primary prophylaxis and the follow up of these patients will give new information on whether classic factor replacement therapy can prevent joint disease.

The PedNet study cohorts are complete and unselected age-cohorts, including all newly diagnosed patients treated in one of the participating centres. Children will be followed until adulthood.

Currently, 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. More than 90% of all inhibitors emerge during the first 50 exposure days and 50% of these within the first 15 exposure days. These antibodies bind to the infused coagulation factor and reduce or neutralise the coagulant activity of factor VIII or IX. In the last decades, the understanding of the pathophysiology of factor VIII and IX inhibitor development has greatly increased. The causes can be divided into endogenous (genetic) and exogenous (treatment-related) factors. Besides mutations in the gene for factor VIII, factors related to immune modulator genes may also influence the occurrence of inhibitors.[6-13] An important exogenous factor is the type of replacement factor VIII or IX and much research has been focused on the establishment of risk profiles. There is an ongoing debate on whether recombinant factors have a higher risk for inhibitor development than plasma products.[14-18]

There is new evidence that other treatment-related factors, such as the dosing of clotting factor, have an impact on inhibitor risk. This also holds true for large bleeds and intensive therapy, which can be seen as danger signals and cause higher inhibitor risks.[19-21] On the other hand, early start of prophylaxis without the presence of a 'danger' signal seems to prevent inhibitors.[22] Knowledge of treatment-related factors may result in alternative treatment regimens reducing the overall inhibitor risk. Individual patients will benefit from this improvement of treatment results.

The RODIN study investigated genetic and non-genetic aspects of haemophilia in over 600 previously untreated patients (PUPs) with severe haemophilia A.[1,3] Important new insights have been obtained regarding genetic factors, importance of dosing and intensive treatment on inhibitor incidence, as well as with respect to the various products. No difference was demonstrated between plasma-derived and recombinant products. However, unexpectedly, one second-generation recombinant product was found to have a higher risk of inhibitor development as compared to plasma products and other recombinant products.[1] These findings highlight the need for large collaborative studies in children. Since several new generation clotting products are in the registration phase, the collection of data in large unselected cohorts continues to be important. In the

regulatory PUP studies required by the European Medicine Agency (EMA), the inclusion of only a limited number of PUPs is needed before marketing authorisation is granted. Since there are many factors that influence inhibitor risk, these studies are largely underpowered and will not be able to determine differences between products with regard to both safety and efficacy. The quality of the data collected by the PedNet Haemophilia Research Foundation has 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 used by the pharmaceutical companies for the collection of additional pharmacovigilance data.

General aim

The general aim of the PedNet Haemophilia Research Foundation is to collect prospective data of full birth/age cohorts on children with haemophilia A and B in order to facilitate scientific work and clinical management. The PedNet study group and the PedNet Haemophilia Research Foundation provide a network for collaboration and research.

Significance

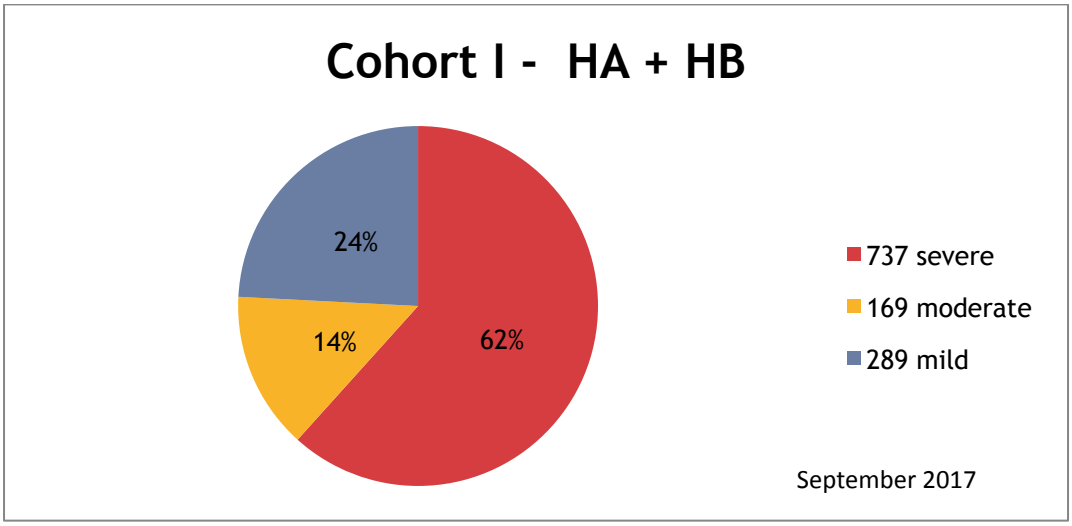
The PedNet Registry has been the origin of several publications in medical journals with high impact factors, demonstrating its scientific and clinical value and its potential for the future. Many clinical and scientific questions in haemophilia can only be addressed by large collaborative studies with carefully monitored data sampling.

The PedNet Registry cohorts and methods

The data collection in the PedNet Registry is according to defined study protocol, clearly defined clinical parameters are the basis of the web-based CRF forms. The PedNet protocol can be found at www.pednet.eu. All centres have ethical approval for the PedNet protocol and information on external monitors, inclusion and exclusion criteria are subject to protocol.
The number of participating centres has changed over time; initially, in 2003, only 22 centres participated in the PedNet study group. Another eight centres participated in the RODIN study, but only for patients with severe haemophilia A. Both groups merged after the publications of the RODIN study and all centres became part of the PedNet study group. Overall the PedNet Registry includes no patients with FVIII/IX levels > 25% and as a consequence the collection of patients with mild haemophilia is lower.

Cohort I, born between 2000 and 2009 (29 centres participated)
Children with mild (5-25%), moderate (1-4%) and severe (<1%) haemophilia A or B, born between January 1, 2000 and December 31, 2009, who are diagnosed and treated in one of the centres participating in the PedNet Registry. Patients will be followed until adulthood.

Figure 1. Cohort I, 2000-2009, according to severity



Cohort II, born between 2010 and 2020 (34 centres participate)

Children with mild (5-25%), moderate (1-4%) and severe (<1%) haemophilia A or B, born between January 1, 2010 and December 31, 2019 who are treated in one of the participating centres. Eight of the 21 centres in cohort I included only patients with severe haemophilia A, leading to an overrepresentation of these patients. For all patients detailed data will be collected for the first 50 exposure days; thereafter at least annual follow-up will take place with data on bleedings, treatment regimens and side-effects such as inhibitors and long-term outcome of treatment.

Figure 2. Cohort II, 2010-2019

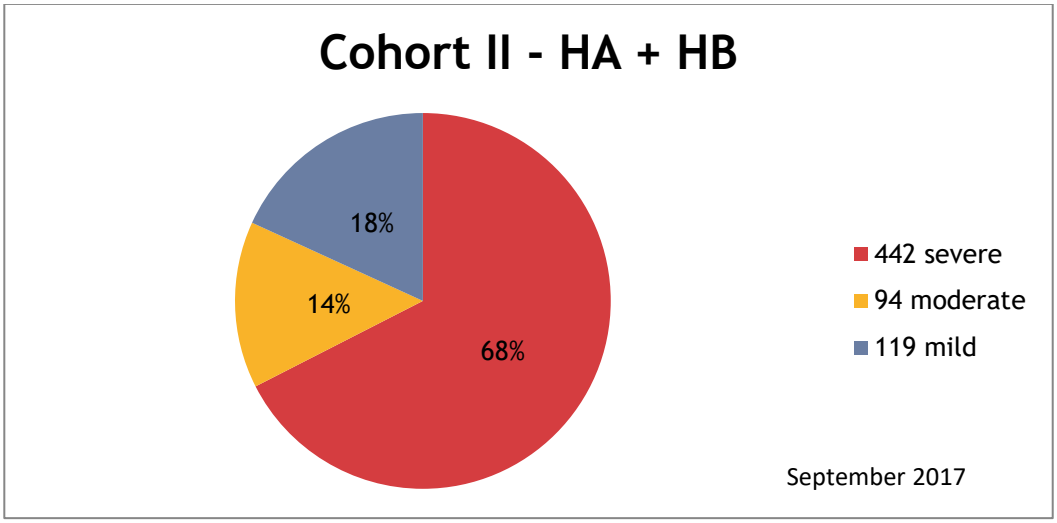


Figure 3. New inclusions per birth year, 2000-2017

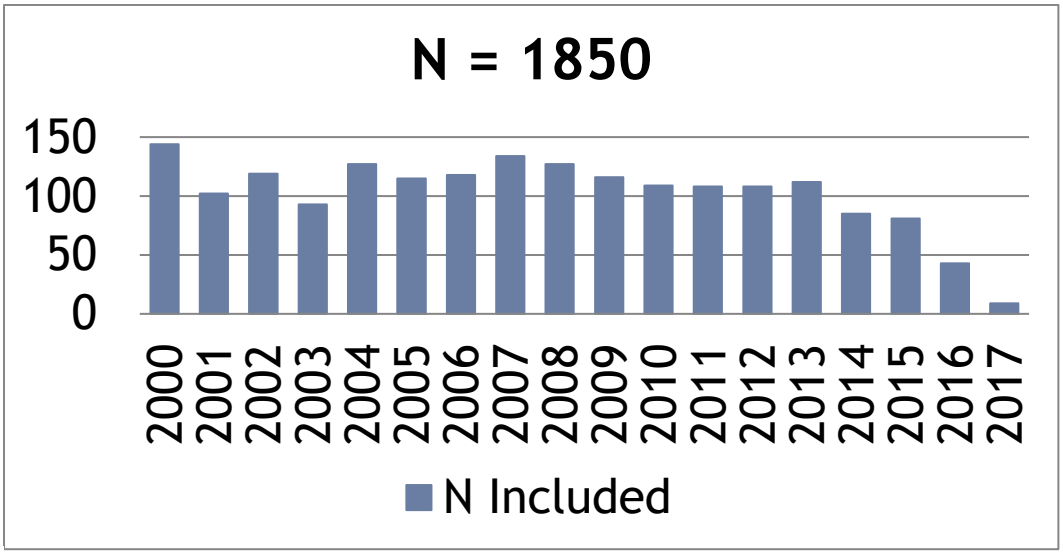


Figure 4. Patients with severe haemophilia A with and without 50 or more exposure days; new inclusions per birth year, 2000-2017

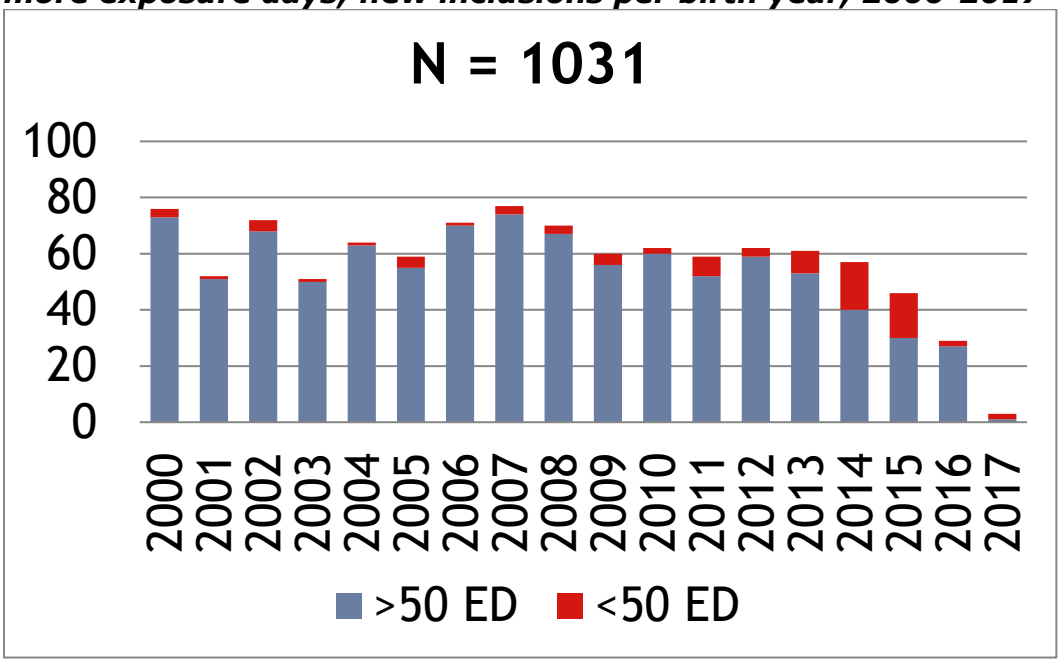


Figure 5. Total number of included patients 2000-2017

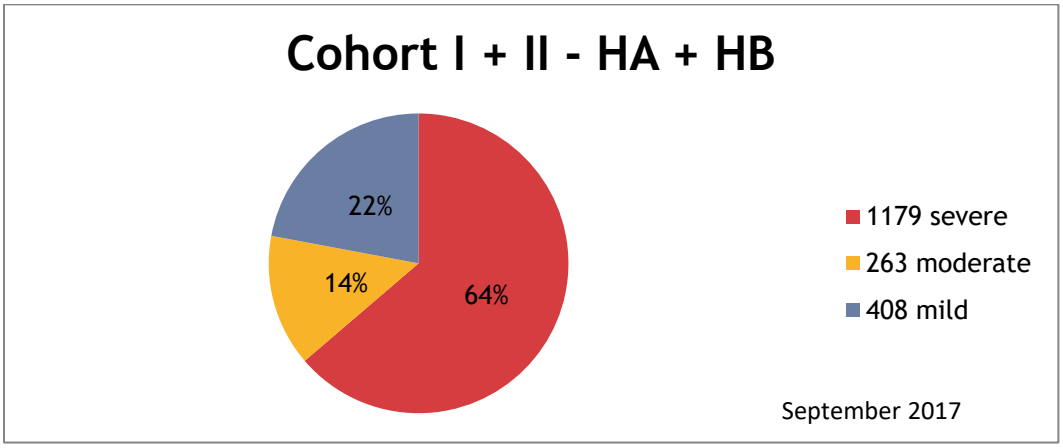


Table 1. PedNet Cohorts I and II, data download September 2017

	Haemophilia A & B
Total number of patients	1850
Number with known gene mutations	1582 (86%)
Number with >50 exposure days	1206 (65%)
Number of patient identifiers (PID) with follow-up data	1775 (96%)
Sum years of follow-up	12498 (16421)
Number lost to follow-up at any time	167 (9%)

SATELLITE STUDIES AND WORKING GROUPS

Working groups have been initiated that are responsible for the various satellite studies using the PedNet Registry data. Every member of the PedNet group participates in at least one working group; these groups may also include some non-members affiliated with a member centre. All results produced by the working groups are the property of the PedNet Haemophilia Research Foundation.

Studies 2018-2020

I. Working group on immunogenicity

Endogenous (genetic) and exogenous (treatment-related) determinants of inhibitor development.

Investigators: all members.

Objective: To study the effect of different risk genetic and non-genetic risk factors on inhibitor development. New analysis, which will lead to two original articles.

Background: Analysis of the effect of different risk genetic and non-genetic risk factors for inhibitor development need large and complete follow-up data until at least 50 EDs. The > 1000 unselected PUPs with severe haemophilia A in the PedNet Registry will give a unique opportunity to describe the effect of different genetic and non-genetic risk factors over time. The strength of the Registry is the completeness of follow-up data. For the 2018 analysis we expect that > 90% of the patients with severe haemophilia will have follow-up data until 50 EDs.

Endpoints: clinically relevant inhibitors, defined as two positive samples above the cut-off value of each participating centre's laboratory. All centres perform testing for inhibitors as advised by the study protocol, which means at least every 5 exposure days during the first 20 exposure days and thereafter at least every 3 months until 50 exposure days. All participating laboratories use the Nijmegen modification of the Bethesda assay with cut-off values of between 0.3 and 0.6 BU/ml.

Determinants: baseline FVIII/IX levels, family history for inhibitors, FVIII/IX gene mutation, details of the product type (recombinant/plasma/ various recombinant) and administration (on demand/prophylaxis/ prophylaxis model) of replacement therapy, immunological 'danger signals' (according to each infusion for the first 75 treatment days), surgery, etc.
Working plan: Using the data download of January 2018, a new analysis will be performed regarding risk factors for inhibitor development. Two articles will be prepared for submission in 2018. One article will present the results of the individual products. Confounding factors such as start of prophylaxis, dosing, intensive treatment, etc will be adjusted for. The second paper will describe non-genetic risk factors/treatment-related risk factors other than concentrate.

II. REMAIN study (Research on Management of Inhibitors)

Objective: To study the natural history and optimal management of inhibitors.
Background: Inhibitor development is still a major side-effect of haemophilia treatment. Few studies have focused on the impact of inhibitors on bleeding and the clinical management of a large group of unselected patients. All patients who develop an inhibitor in the PedNet Registry are followed for detailed data on bleeding, immune tolerance induction treatment and outcome of treatment. The first group of patients who developed an inhibitor in the CANAL or the RODIN study with at least 3 years of follow up after inhibitor follow up were included in the REMAIN study. The REMAIN study was initiated in 2012 and the data that are now analysed are based on the January 2016 data download.

Risk factors for the progression of low-titre to high-titre inhibitors in 260 children with severe haemophilia A and newly developed inhibitors.
Investigators: Maria Elisa Mancuso, Kathelijn Fischer, Elena Santagostino, Johannes Oldenburg, Helen Platokouki, Cristoph Königs, Carmen Escuriola-Ettingshausen, George E. Rivard, Ana Cid, Manuel Carcao, Rolf Ljung, Pia Petrini, Anne Rafowicz, Carmen Altisent, Gili Kenet, Ri Liesner, Christel van Geet, Maria Teresa Álvarez-Román, H. Marijke van den Berg.
Funding: Initial study supported by a grant from NOVO Nordisk.
Time line: Article accepted for publication in *Thrombosis and Haemostasis.*

Bleeding phenotypes pre-ITI and during ITI

Investigators: Kathelijn Fischer, Christoph Königs, Karin Kurnik and others.

Objective: to investigate the bleeding rate of patients with inhibitors during a 3-year follow-up period.

Time line: first draft August 2017, to be submitted at the end of 2017.

Natural history of low titre inhibitors

Investigators: Elena Santagostino, Niels Clausen, Anne Rafowicz, H. Marijke van den Berg.

Objective: to investigate the clinical course of low-titre inhibitors during a 3-year follow-up period.

Time line: to be finished in 2018.

High titre inhibitors and response to ITI

Investigators: Chris Van Geet, Mike Williams, Maria Elisa Mancuso, Segolene Clayessens.

Objectives: 1) to investigate the response of high-titre inhibitors to different ITI regimens; 2) to establish cost and outcome of different treatment regimens; 3) to develop a prediction model for the outcome of ITI.

Time line: to be finished in 2018.

III. Neonatal working group

Investigators: Hervé Chambost, Rolf Ljung, Nadine Gretenkort, Gili Kenet, Liz Chalmers.

Objective: to compare the outcomes of vaginal delivery and Caesarean section in children with severe haemophilia A and B.

Background: The PedNet Registry has collected detailed data on the mode of delivery and the bleedings in the neonatal period. For clinical practice in haemophilia it is important to have real-life data to investigate whether vaginal delivery, which is still most often practised in Europe, results in more bleeding and intracranial haemorrhages in the newborn than Caesarean sectios. The data will potentially lead to new recommendations on how to deliver children with bleeding disorders.

Working plan: A study was performed on the data download of January 2015 on 825 children with moderate and severe haemophilia A and B. More than 50% of children with severe haemophilia are born with a negative family history; these data are part of the analysis.
Time line: An article on the effect of mode of delivery on bleeding in the neonatal period will be submitted in 2018.

IV. Working group on CVAD management

Investigators: Susanna Ranta, Beatrice Nolan, Anne Makiperna, Minna Koskenvuo.
Background: The use of central venous access devices (CVADs) is still needed in many children with haemophilia who receive primary prophylaxis or are in need of ITI. Centres participating in the PedNet Registry have different practises, which might vary between the implantation of a CVAD in every child with severe haemophilia or using very few CVADs. This gives the opportunity to investigate different aspects of CVADs. A study on nursing practices was published recently.[14]

Safety and outcome of different duration of clotting factor coverage during implantation of CVAD in children without an inhibitor
Investigators: Susanna Ranta, Beatrice Nolan, Anne Makiperna, Minna Koskenvuo.
Objectives: 1) To investigate the efficacy of different treatment regimens with coagulation factor concentrates in the prevention of surgery-related bleeding, in particular short haemostatic coverage of 3 days compared with longer time of over 5 days and the effect on inhibitor development; 2) To compare consumption and cost of the different treatment modalities.
Time line: analysis 2018, article to be submitted in 2018.

V. Collaborative work of regulators and PedNet

Direct comparison of clinical parameters between regulatory clinical trials and registry data in severe haemophilia A previously untreated patients
Investigators: Carla Jonker, Christine Keipert, H. Marijke van den Berg, Anneliese Hilger.
Objective: to investigate whether data from regulatory clinical PUP trials are comparable with data from the PedNet Registry.
Methods: The clinical trial (CT) database, established as part of the ABIRISK project and located at the Paul-Ehrlich-Institut, with PUPs and minimally treated patients from CTs performed before the new clinical guideline came into effect in 2012, and the first cohort of the PedNet Registry (patients born 2000-2009 and followed until January 2016) as data sources. Comparability of data collection systems investigated based on study concepts of CTs and PedNet.
Time line: manuscript submitted in 2017.

New studies in PedNet to be initiated 2018-2020

VI. Long-term outcome studies

Investigators; All PedNet members
Objectives: 1) To compare long-term outcome of different pre-defined treatment regimens for starting prophylaxis/prophylactic regimens; 2) To compare outcome according to history of inhibitory antibodies.
Working plan: from the PedNet Registry, structured and independent joint assessment and patient-reported outcome will be used to assess differences between treatment regimens, inhibitor status, haemophilia type and haemophilia severity. This will result in:
- Determination of long-term outcome of children with severe and moderate haemophilia (imaging, physical function, patient-reported outcomes on activities, neurological situation/academic achievements.

- Comparison of long-term outcome of children with severe and moderate haemophilia A versus B (imaging, physical function, patient-reported outcomes on activities, neurological situation/academic achievements.
- Determination of long-term outcome of children with moderate haemophilia regarding the same parameters and time points will serve as comparison.
Time line: Start in 2018.

VII. Impact of switching to EHL concentrates in children

Investigators: Maria Teresa Alvarez-Roman, Segelene Claeyssens.
Objective: To investigate whether the introduction of extended half-life products (EHL) has changed the frequency and dosing of children on prophylaxis. 1) Have patients on EHL and reduced frequency got adequate bleeding control? 2) Can we define criteria to select patients in whom the frequency of infusions can be reduced?
Inclusion criteria: Children aged < 12 years with severe haemophilia A (FVIII activity <1%), on prophylactic treatment with standard or EHL.
Time line: To be defined.

VIII. Project on genotype

Investigators: Rolf Ljung, Johannes Oldenburg, Chris van Geet, Marijke van den Berg. Publication on behalf of all members.
Objectives: To describe the spectrum of mutations in the PedNet population cohort in comparison with existing mutation databases, to study the genotypes at risk for development of inhibitors and to report previously unreported mutations causing haemophilia and the prediction of the mutations being deleterious.
Background: The PedNet Registry contains information on the causative mutation in almost 90% of the patients. Several mutations have not been published previously in the international databases on FVIII or FIX mutations. The PedNet Registry offers a possibility to study the spectrum of mutations in a population-based cohort in comparison to the existing databases of mutations which are dependent on single reported cases from various laboratories/centres.

Methods: descriptive analysis of mutations according to inhibitor development, unadjusted and analyses adjusted for other risk factors.
Time line: start 2018.

IX. Project on Haemophilia B

Investigators: to be defined.
Objective: Comparison of onset of bleeding and bleeding phenotype between haemophilia A and B.
Background: Haemophilia B is even more rare than haemophilia A. Therefore, specific analyses of haemophilia B are scant. The PedNet Registry includes >120 patients with severe haemophilia B with full treatment history. This provides a unique opportunity for studying the natural history of this condition, including a comparison with haemophilia A.
Methods/time line: to be discussed.

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