Protocol of the PedNet Haemophilia Registry

Version: 6.5

June 2026

On behalf of the PedNet Haemophilia Research Foundation

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1. THE PEDNET HAEMOPHILIA RESEARCH FOUNDATION (www.pednet.eu)

The PedNet Haemophilia Research Foundation was established on December 2016 in the Netherlands and is recognized as a not-for-profit foundation by the tax authority of the Netherlands. The articles of the Foundation have been set up under Dutch Law.

The objectives of the foundation as described in the Deed of Incorporation are to;

- promote scientific research relating to haemophilia and allied inherited bleeding disorders;
- promote international cooperation between centres specialising in treating children with haemophilia;
- gain insight into all the factors influencing the course of the illness, including treatment with clotting products and the long-term effect of treatments;
- investigate the safety and efficacy of clotting products as well as non-replacement therapies; and
- publish and present the results of scientific research;
- to do anything which is, in the widest sense of the word, connected with or may be conducive to the attainment of these objectives.

The foundation achieves its objectives by:

- coordinating an independent, international network of centres specialised in haemophilia and participating in the PedNet Study Group (hereinafter: "**Participating Centres**");
- managing a database with clinical data of children with haemophilia born since the 1.1.2000 who are being treated at a Participating Centre (hereinafter: the "**PedNet Registry**");
- conducting scientific research in accordance with a research program approved by the Foundation
- intention to cooperate with regulatory authorities and pharmaceutical companies with respect to assessing the safety and effectiveness of medicines in post-marketing studies;

The foundation is the legal entity responsible for the protocol of the PedNet Haemophilia Registry. The foundation does not make profit. An annual financial report is published on www.pednet.eu.
The capital of the foundation consists of subsidies and other contributions; donations; and any other assets or income received. A regularly updated list of sponsors of the PedNet Haemophilia Research Foundation is published at https://pednet.eu/foundation/funding/.

2. INTRODUCTION

2.1 General overview of haemophilia

Haemophilia A is a rare disease, occurring in only 1 : 5.000 new-born males, with haemophilia B being about five times less common. Current treatment is still based on the replacement of the missing coagulation factor [1,2]. Recently new non-factor replacement therapies have become available and clinical trials with gene therapy for both haemophilia A and B are ongoing in adults [3-5]. In Europe, most children now receive primary prophylaxis, protecting them from potentially life-threatening bleeds, joint and muscle haemorrhages and long-term sequelae [6-8].

Presently, the most important adverse effect of haemophilia treatment during the first 50 exposure days is the occurrence of neutralizing antibodies (inhibitors) against factor VIII or IX. Inhibitors develop in 25-30% of all children with severe haemophilia A [9,10]. These antibodies bind to the infused coagulation factors and reduce factor VIII activity or block the effect of factor VIII completely. Currently the strongest predictive factor for inhibitor formation is the type of factor 8 gene mutation [11,12] . Patients with severe haemophilia A and large deletions or inversions have an increased risk of inhibitor development, while patients with missense mutations/low risk mutations that still allow for circulating factor VIII usually develop self-tolerance.

Of all patients with haemophilia, 15 % have haemophilia B. The reported inhibitor incidence is around 10% for severe haemophilia B. Some studies report that patients with severe haemophilia B have a less severe bleeding phenotype than those with severe haemophilia A [13,14]. These observations are based on limited data and there is a large need, also in haemophilia B, to design prospective studies of representative cohorts in order to improve the knowledge of this severe coagulation disorder. So far, data from the PedNet study group did not demonstrate a difference between haemophilia A and B with regards to the age of start of first joint bleed [15].

In the last years many new therapies for haemophilia have been developed [3]. Extended half-life products (EHL-FVIII/FIX) have become available and the first non-factor replacement therapy mimicking FVIII, Emicizumab, is now licensed for both inhibitor and non-inhibitor patients [16,17]. Other non-factor therapies, based on re-balancing coagulation by reducing anti-thrombin (AT) or inhibiting Tissue Factor Pathway Inhibitor (TFPI), are now in clinical studies. New safety aspects of non-factor replacement therapy, such as thrombotic events, have been observed in patients that used by-passing agents at the same time [18].

These new therapies are licensed for children but are based on very limited data in children. Independent registries need to collect data on patients using these products. The limited data from clinical trials needs to be extended by “real-life” data to assess the benefit-risk ratio. Registry holders such as PedNet have been requested by the Pharmacovigilance and Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) to perform post-marketing surveillance studies (PASS).

Gene therapy for haemophilia A and B has now reached the clinical stage. Trials showed that FVIII and FIX levels can be increased into the normal range [4,5]. Long-term follow-up data on safety and efficacy in adults is needed. Gene therapy for children will not be available at least for the next 5 years.

2.2 Rationale for the PedNet Haemophilia registry (PHR)

Large and representative study populations of unselected cohorts are needed to answer questions regarding determinants of inhibitor development, adverse effects of treatment, and the effect of various treatment regiments on long-term outcome. The European PedNet study group and the PedNet Haemophilia Registry provide an infrastructure for research with the aims to improve treatment and outcome [19].

2.3 Overview of current research topics (detailed in PedNet Research Programme)

The PedNet Haemophilia Research Foundation have structured the research work in several working groups each focused on a certain research area. The research is detailed in "The PedNet Research Programme" which is updated every third year. The latest version can be reviewed at www.pednet.eu.

2.3.1 Studies on risk factors for inhibitor development

Known risk factors for development of inhibitors in haemophilia A may be classified as genetic, treatment or product related.

Data of the PHR have been published on product type and inhibitor development in the RODIN study based on data available in May 2011 [20]. The study revealed different risks between single recombinant products and the results were later confirmed in two studies from the UK and France [21,22]. All recombinant products in these 3 studies have been evaluated by Paul Ehrlich Institute on request from the EMA (European Medicines Agency) using the individual patient data from Francecoag, UKCHDO and PedNet, which confirmed the results in the previous studies. [23]

There is an on-going debate whether recombinant FVIII products have a higher risk for inhibitor development than FVIII plasma products. [24-27,]. The results of the SIPPET study in which rcFVIII (4 different products) and pdFVIII (4 products) were compared in randomized fashion, reported a higher inhibitor risk for rcFVIII [28]. The PHR will be able to study and will focus interest on the inhibitor incidence of single products in on-going studies.

Other studies will focus on genetic risk factors. The PHR includes data on >85% of the disease-causing mutation which will enable a population based approach to study genetic risk factors in combination with treatment and product related risk factors.

2.3.2 Studies on patients with inhibitors

Most studies have focused on inhibitor development as and end point. In the PHR patients that develop an inhibitor are followed and detailed data on the inhibitor titres are collected over time in correlation with immune tolerance induction treatment (ITI). In the REMAIN (REal life MAnagement of INhibitors) study patients are followed for at least 3 years. This study will investigate the Natural History of low titre inhibitors and effect of

ITI, the outcome of ITI in unselected patients with high titre inhibitors and the bleeding phenotype before and during ITI.

2.3.3 Studies on prophylactic treatment

In the PHR data on start of prophylaxis and the number of bleeds before and during prophylaxis have been collected prospectively for 20 years. Primary prophylaxis is the preferred approach for the prevention of bleeding and arthropathy, but the optimal prophylactic regimen in an individual is unknown. Usual recommendations are to start prophylaxis, before or after the first joint bleed, in practice between 1 and 2 years of age [29]. Prophylaxis is very demanding, because it requires intravenous injections several times per week. The large numbers of patients in the PedNet registry who start prophylaxis at various ages and with different regimens, provide a unique opportunity to study the effects of different prophylactic regimens on long term outcome.

2.3.4 Studies on Haemophilia B

Inhibitor incidence in severe haemophilia B has usually been reported to be about 3-5%, much lower than the 25-30% rate reported in haemophilia A. Many studies combined severe and moderate haemophilia B. In a first study in data of the PHR we found that the inhibitor incidence was almost 10 % [30]. A large problem is the treatment of patients with inhibitors in haemophilia B. Our group will analyse all patients that developed an inhibitor and their response to ITI in a similar way as is done in our haemophilia A cohort.

2.3.5 Genetic studies

The PHR includes data on mutation on >85% of the included patients using a uniform nomenclature and classification. Existing large databases on molecular variants causing haemophilia A or B are based on random reports of data which may not be comparable to data based on a defined population. PHR enables studies on the spectrum of mutations causing disease, the relation between type of mutation and risk of inhibitor development and refined studies of prediction of variants with unknown pathogenicity.

3. OBJECTIVES of the PedNet registry

General objectives

To investigate natural history, safety and efficacy of replacement and non-replacement therapies in prospectively followed birth cohorts of all unselected previously untreated children with Haemophilia A and B in the respective participating centres.

Specific objectives

Research questions and subsequent projects are described in the PedNet Research Program 2018-2020 available on www.pednet.eu

4. DESIGN

Multicentre, observational birth cohort of patients with haemophilia A and B, followed in one of the participating Haemophilia treatment centres (HTC's).

5. POPULATION

5.1 Population (base)

Children with mild (FVIII/IX 6 to 25%), moderate (FVIII/IX 1 to 5%) or severe (FVIII/IX <1%) haemophilia A or B, born from January 1st 2000 onwards followed in one of the participating centres until 18 years of age.

According to the PedNet Regulations a "Participating centre" is on invitation by the PedNet Board and meets the following criteria:

- Centers should be recognized by EUHANET as a European Haemophilia Comprehensive Care Centers (EHCCCs)
- Centers need to care for children with haemophilia and have preferable a pediatrician or pediatric hematologist
- Centers need at least to include 2 or more new severe hemophilia patients per year (calculated over a 3-5 year period)

5.2 Inclusion criteria

In order to be eligible to participate in this registry, a subject must meet all of the following criteria:

- Diagnosed with Haemophilia A or B
- Factor VIII/ IX activity between <1 and 25%
- Complete records of coagulation factor replacement or administration of other non-factor replacement therapies (eg: Emicizumab; gene therapy) and bleeds
- Treated in one of the participating centres

5.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation:

- Referred with an inhibitor
- Informed consent not obtained

5.4 Sample size

The sample size of the registry is based on the patient numbers available at participating centres.

6. MATERIAL AND METHODS

6.1 Basic variables

The registry follows the guideline for FVIII/IX of the EMA [31] and contains the following recommended core data elements:

- Patient data: month and year of birth, gender, centre, family history, haemophilia related gene mutation, mode of delivery, natal- and postnatal bleeding
- Disease: haemophilia type & severity, date of diagnose, bleeding pattern, surgeries, joint status, quality of life
- Co-morbidities: other coagulation disorders or other diseases that might influence the prognose
- Haemophilia treatment: type of treatment, used product, start and end dates, regimen, reason for discontinuation, home treatment
- Disease or treatment related adverse events of special interest and serious suspected adverse reactions: start and end dates, treatment suspected to be associated, seriousness, outcome of adverse event;

Validated tools [32] for long term outcome such as the haemophilia joint score for children (HJHS 2.1) , the physical activity (PedHal) and QoL data (HemoQol and EQ-5D) are collected if performed routinely in the centre. In addition, results on MRI, Ultrasound (HEAD score) and X rays are collected as well.

The complete list of collected variables (CRF and codes) and used definitions can be found in Addendum 1 & 2.

6. 2 Laboratory variables and methods

PedNet collects the laboratory results obtained in the individual centres. PedNet centres are well-recognized haemophilia centres with specialized coagulation laboratories participating in external quality assessments.

Most participating laboratories use the Nijmegen modification of the Bethesda assay with local cut off values varying between < 0.3 and < 0.6 BU/ml. Centres are encouraged to use the cut of level for positivity proposed by the ISTH of 0.6 BU/ml [33].

All centres routinely perform testing for inhibitors as advised by PedNet guidelines, *i.e.* at least every 5th exposure day during the first 20 exposure days and thereafter at least every 3 months until 50 exposure days are reached. After 50 exposure days inhibitors are tested at least once per year.

For children treated with non-factor replacement therapies, it is advised to test inhibitors prior to therapy initiation and retest them at least once per year using the relevant laboratory tests. Additional assays in line with recommendations of ISTH are implemented by the centres.

Analysis of variants in the *F8* and *F9* genes are done according to local routines. The reported genetic results are revised into a uniform HGVS based nomenclature and stratified to defined groups according to type of mutation and effect of mutation. The deleterious effects of missense variants are (since 2020) assessed with ALAMUT VISUAL (http://www.interactive-biosoftware.com/alamut-visual/). The effects of variants at splice junctions are evaluated with ALAMUT VISUAL v.2.8.1 (http://www.interactive-biosoftware.com/alamut-visual/).

6.3 Procedures

- As observational study, the PedNet protocol allows patients to be treated according to the local guidelines for medical treatment in the participating centres. After the IC form has been signed, every patient is added to the centre's patient list.
- Data are collected and updated on each regular visit to the centre. The data capture system is web based and secured by personal login and password.
- Access to the data capture system is restricted to:
    - Personnel working for a participating centre that is added to the Delegation of Duties log, which is signed by the SPI (read & write for specific centre only)
    - Members of the PedNet study staff who are appointed by the director of the PedNet foundation
    - Monitors employed by a trusted third party (CRO) in the Netherlands for the purpose of on-site monitoring (read only rights)
- A unique PID number is generated by the data capture system for each included patient . E-CRF forms will be filled in and submitted to the data capture system which is hosted by the Julius Centre of Health Sciences and Primary Care of the University Medical Centre Utrecht, The Netherlands. The data capture system meets GCP guidelines (ISO 27001) and is FDA compliant (21 CFR part 11).

6.4 Safety reporting

Local investigators notify the National authorities according to local legal obligations and data are collected in PedNet for all inhibitors, allergic responses, thromboembolic complications and thrombotic micro angiopathic complications and death suspected of being related to haemophilia treatment. Details can be found in Addendum 2. Reports on non-replacement therapies will include data on any other adverse events, as applicable.

Annual reports are prepared of all reported inhibitors correlated with the products. Data reports are sent to all participating centres and to the sponsors concerning their products.

Safety reporting for registered products is performed by participating centres according to National regulations issued by to the national authorities.

6.5 Statistical analysis

Statistical Considerations

The PedNet database provides a large set of data including parameters measured only once (such as baseline data) as well as repeatedly, i.e. concerning treatment and bleeding

collected during the first 50 EDs and during annual follow up until the patients reach the age of 18 years. Bleeds are rare events and therefore their frequency has a skewed distribution requiring special statistical techniques; it has been established that the negative binomial distribution is most appropriate [34]. Prophylaxis influences bleeding frequency and phenotype. Therefore, statistical analyses of bleeding data always include adjustment for prophylactic treatment.

As follow-up in the registry is continuing for years and inclusion is on-going, not all patients have the same length of follow-up in the database. Usually, data are analysed up to the last visit available. To account for differences in follow-up, survival analyses or multivariable Cox regression analysis is used. For analyses on the outcome of prophylactic treatment, data are only used until last follow-up or inhibitor development (censoring), as inhibitors interfere with normal effective treatment.

For analysis of the endogenous and exogenous determinants of inhibitor development, it is important to account for differences in follow up as well as for changes in inhibitor risk in relation with the number of exposure days. Therefore, multivariable Cox regression analysis or conditional logistic analysis is used for the estimation of the risk of developing inhibitors according to individual risk factors.

7. ETHICAL CONSIDERATIONS

Regulation statement

The registry is conducted according to:

- the principles of the Declaration of Helsinki (7th version, October 2013) and
- the principle of the Declaration of Taipei (revised October 2016) [35]

Recruitment and consent

Parents/caretakers of the patients receive written and verbal information about the registry, its aims and the consequences of their participation according the national regulations in the respective participating countries

Written informed consent of the parents/caregivers is obtained.

From the age of 12 years, a patient will be able to reconsider his/her participation in the registry. The child will receive written and verbal information about the registry. The age when patients have to sign consent follows local regulations.

Patients and parents/caretakers may withdraw or change their initial informed consent. Upon withdrawal of consent the data collected until that timepoint is included in analysis. In that case, the collected data are irreversibly anonymized after data analysis, so that tracking of the patient is no longer possible.

Benefit and risk assessment

No risk for patients arising from participation in the study is expected.

General benefits are increased knowledge of this rare disease and its treatment and side effects, which will have an impact on current and future generation of patients. The registry concerns young children with haemophilia and cannot be applied to older patients, as over 90% of inhibitors against FVIII or FIX develop during the first 50 exposure days, and the results of prophylactic replacement therapy are highly dependent on the early initiation of this treatment.

8. DATA PROTECTION, DATA HANDLING AND DATA QUALITY

8.1 Data protection, handling and storage of data

The PedNet Haemophilia Registry is designed to ensure that participants' data are secure and processed in accordance with the General Data Protection Regulation GDPR. Data are collected under the responsibility of the Representatives in each of the participating centres in accordance with the study protocol and the written instructions of the PedNet Board and all applicable laws, regulations and procedures at the time of Data collection initiation, including but not limited to the GDPR and applicable national implementation legislation. PedNet and the Participating Centres will process personal data in accordance with the GDPR and any other applicable laws or regulations covering the protection of personal data in their respective roles as either controller, joint controller or processor, as the case may be.

Towards these ends the storage and handling of data is organized as followed:

- The database meets all requirements according to GCP and GPDR standards for electronic data entry with respect to safeguarding data integrity and data security regulations.
- Data handling and -storage is performed by the University Medical Centre Utrecht (UMCU). For this purpose, a data processing agreement in line with the provisions of the European GDPR is entered into between the UMCU and the PedNet Haemophilia Research Foundation.
- Access to source data is limited to the study staff employed by the PedNet Haemophilia Research Foundation and the employed data managers at the University Medical Centre Utrecht (UMCU), The Netherlands and to a monitor employed by a trusted third party in the Netherlands for the purpose of on-site monitoring.
- Password protection and encryption codes to maintain data integrity will be used by all parties that have access to the source data or the data capture system
- Patient identifiers, consisting of (i) a unique pseudonymized patient identification number known only to individual haemophilia treatment centres to ensure confidentiality and (ii) a centre code. Participation in the Registry will be clearly marked by centres in the patient file.
- Help line is available Monday through Friday, 9.00 to 17.00 hr CET.

8.2 **Data Quality Assurance**

To ensure the highest data quality possible the followings steps are taken:

- Work instructions and manual for data collection and -entry are in place and are regularly updated
- Regular training of data registrars in the centres by members of the PedNet study staff, both individual and on a group level
- The E-CRF contains:
    - Built-in validations to avoid incorrect data entry
    - Mandatory fields to avoid missing data
- Regular visits to all centres by a member of the PedNet study staff depending on timeliness of enrolment and data entry
- Quarterly data checks performed by the PedNet study staff according to a specified set of rules
- Weekly processing of queries in the data capture system by the PedNet study staff
- Regular on-site monitoring by a CRA employed by a trusted third party to perform source data verification (SDV) of 100% of baseline and 10% of follow up data, according to a specified set of checks

9. **GOVERNANCE, PUBLIC DISCLOSUE AND PUBLICATION POLICY**

Governance, public disclosure and publication are in accordance with the Regulations of the PedNet Haemophilia Research Foundation. The Regulations can be found on www.pednet.eu. Definitions used in this clause 9 have the meaning described in the Regulations. Data are collected under the responsibility of the PedNet Study Group representative in each of the participating centres in accordance with the protocol and all applicable laws, regulations and procedures at the time of Data collection initiation. Should such regulatory requirements be changed, participating centres and representatives will comply with the new regulations. In the event that compliance with any such new regulations necessitates a change in the protocol or regulations, participating centres will obtain written consent to such change from the PedNet Board prior to implementation.

1. Participating centres will receive a patient fee for reported patients according to the Regulations and obligations and rights will be arranged in the separate consortium-agreement(s) with the PedNet Haemophilia Research Foundation as legal representative of the PedNet Registry and the participating Centre(s) in question.
2. The data, which are entered in the PedNet Registry (PHR) by the PedNet Partner shall remain the property of the PedNet Partner and no use will be made of them other than for the purpose stated in the Protocol and Research Program.
3. Regulatory authorities and sponsors may receive excerpts of aggregated data from the PHR for continuous reports on safety, efficacy and adverse events on (their) products. These data can be used for post-marketing surveillance studies (PASS) required by regulatory authorities if: (i) a contract between the stakeholder and

PedNet has been granted by the management board, (ii) the data is fully anonymized; and (iii) the data is only used for research into and registration of the safety, safety and efficacy and adverse events of medicinal products used by the patients concerned.

4. The PHR Database generated and obtained by the PedNet Partner in the course of the Data collection shall be owned by the PedNet Haemophilia Research Foundation, The Netherlands
5. Except as provided for in section 9.3, use of the Data is limited to Representatives, Participating Centres and PedNet. The Data will be used for scientific research and/or regulatory purposes only. Each PHR Study has to be approved by the PedNet Board. The Parties shall acknowledge, in accordance with academic standards, each other's contribution to the Data and results derived from a PHR Study in any research publication arising from the PHR.
6. Sponsors shall be acknowledged for their support of the PHR in all publications. Other conditions for publication of the results of a new Study will be inserted in the separate -agreement with the Sponsor(s).
7. All data and results derived from a PHR Study and any inventions or discoveries made as a result of a PHR Study are the property of the PedNet Haemophilia Research Foundation.
8. The PedNet Board appoints a Scientific Advisory Board with 7 members who will have an advisory function to the PedNet Board concerning publication plans, authorship and study protocols.

10. REGULATION STATEMENT

The Regulations of the PedNet Haemophilia Foundation, version 2.1, has been accepted at the PedNet annual meeting held in Frankfurt am Main, Germany in September 2018. The latest version of Regulations can be found on www.pednet.eu.

11. SUMMARY

Rationale:

Haemophilia is a rare disease; to improve knowledge international collaboration is needed. Large study populations are needed to study variables related to the aetiology of inhibitor development, side effects of treatment, and the correlation of treatment and outcome. The European PedNet study group and the PedNet Haemophilia Registry aim to provide a network of collaboration and research.

Objective:

To investigate natural history, safety and efficacy of replacement and non-replacement therapies in prospectively followed age cohorts of all unselected previously untreated children (PUP) with Haemophilia A and B

Design & Population:

Multicentre, observational birth cohort of patients with haemophilia A and B , followed in one of the participating Haemophilia treatment centres (HTC's). Children with mild (FVIII/IX 6 to 25%), moderate (FVIII/IX 1 to 5%) or severe (FVIII/IX <1%) haemophilia A or B, born from January 1st 2000 onwards followed in one of the participating centres. Data are collected from diagnosis until 18 years.

Material & Methods:

The registry contains the core elements recommended by the European Medicines Agency (EMA) [31] for a disease registry: patient data, date on the disease, co-morbidity, haemophilia treatment, disease or treatment related adverse events. Working groups focus on specific areas of research – risk factors for inhibitors, prophylactic treatment and outcome, haemophilia B studies on patients with inhibitors and genetic studies.

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13. PARTICIPATING CENTRES

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The Netherlands	Utrecht	Van Creveld Kliniek, University Medical Centre Utrecht	C Eckhardt

ADDENDUM 1

Definitions and abbreviations used in PedNet

Outcome		
Clinically relevant inhibitors		at least two positive inhibitor titres on different time points combined with a reduced recovery; cut-off values for positive tests according to the local laboratory
Reduced recovery		FVIII or FIX recovery of < 66% of expected
Low responding inhibitor		inhibitor level is <=5 BU/ml at any time
High responding inhibitor		inhibitor level is > 5 BU/ml at any time
Joint bleed		any complaint requiring treatment located in a joint
Soft tissue bleed		any complaint requiring treatment located outside the joints
Minor bleed		bleed characterised by mild pain, minimal swelling, minimal restriction of motion, resolving within 24 hours of treatment
Major bleed		bleed characterised by pain, swelling, limitation of motion and failure to respond within 24 hours of treatment
Treatment		
First treatment		first infusion with clotting factor concentrate or other products to correct coagulation
First infusion of clotting factor concentrate		first infusion with FVIII or FIX concentrate
Reason for infusion during first 50 ED is defined as:		
	Bleed	primary infusion of FVIII/IX concentrate for treatment of a bleed
	Follow up treatment	subsequent infusions for continued treatment of a bleed or surgery
	Short-term prophylaxis	one or several infusions given to prevent bleeding in special circumstances, such as a fall or head trauma
	Long-term prophylaxis	infusions given with regular intervals to prevent bleeding (see definition of prophylaxis)
	Surgery	primary infusion to cover surgical procedure
Long-term prophylaxis		the use of clotting factor product in the absence of bleeding, with regular intervals, at least once a week, for at least two consecutive months.
The start of long term prophylaxis		As start of long-term prophylaxis is not explicitly specified in the CRF, frequencies of prophylactic infusions will be calculated from individual ED data. Using the definition of prophylaxis, two independent researchers assess the start date, frequency and dose of prophylaxis for each patient. Discrepancies are solved by group discussion
Immune Tolerance Induction		Regular infusions of CFC with a minimum dose of 50 IU/kg per day given at least three times weekly for at least 3 consecutive months
Prophylaxis bypassing agents		Any regular schedule of aPCC or rFVIIa infusions for at least 1 month
First injection of bispecific antibodies		First injection with bispecific antibodies for bleeding prophylaxis

Long-term prophylaxis with bispecific antibodies	the use of a non-replacement coagulation product, with regular intervals, at least once every 4 weeks, for at least two consecutive months.
Adverse Events	
	An adverse event (AE) or reaction (AR) is considered serious (SAE) if: • It is life-threatening or has a fatal outcome • It requires in-patient hospitalisation or extended existing hospitalisation • It results in persistent or significant disability or incapacity

Abbreviations	
EMA	European Medicines Agency
ESF	European Science Foundation
GCP	Good Clinical Practice
HTC	Haemophilia Treatment Centre
IC	Informed Consent
PASS	Post marketing Surveillance Studies
PHR	PedNet Haemophilia Registry
PRAC	Pharmacovigilance Risk Assessment Committee
RODIN study	Research On Determinants of Inhibitor development
GDPR	General Data Protection Regulation (EU 2016/679)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-Wetenschappelijk Onderzoek met Mensen)

ADDENDUM 2 Variables

Baseline Characteristics

General Characteristics		
Date of baseline data collection		
Date of birth		
Sex		male female
Haemophilia type		A B
Severity		severe (<1%) moderate (1-5%) mild (>5%)
Measured activity of clotting factor	% FVIII/IX:C	0-25
Measured activity date		
Used assay		one stage chromogenic
FVIII antigen	% FVIII:Ag or or	0-150 not tested unknown
Pair of twin with same deficiency		yes no
Blood group		A B O AB not tested
Mutation known		yes planned/ waiting for result tested, but unknown mutation not tested no
Intron22 inversion		yes no *(mutation results are collected)*
Mutation comment		free text

Medical History	
Mode of delivery	vaginal caesarean unknown
Instruments used during delivery	yes no unknown
Specification of used instruments	forceps

	vacuum
	other
	unknown
Specification other used instrument	free text
Caesarean section performed	prior to onset of labour
	during labour
	unknown
Planned CS due to	haemophilia carrier status of mother
	maternal condition unrelated to haemophilia
	fetal condition
	combination
	other, specification
CS during labour due to an emergency situation?	yes
	no
	unknown
If yes, please specify	maternal reason
	fetal condition
	combination
	other
	unknown
Specification other	free text
If no, please specify	planned CS, but labor started before
Specification other	free text
Gestational age at delivery	15-43
	unknown
Date of diagnosis of haemophilia	
Prenatal diagnosis	yes
	no
Reason for diagnosis	family history
	bleed
	other
	invasive intervention (circumcision)
	pre-operative screening
	family history + bleed
	family history + invasive intervention
	family history + pre-operative screening
	unknown
Reason for diagnosis comment	free text
Major, abnormal or unexpected bleeds before diagnosis	yes, treated
	yes, untreated
	both treated and untreated
	no
	unknown
Location of untreated bleeds before diagnosis	intracranial
	muscle
	soft tissue

	circumcision
	heel prick/ stick/ puncture
	other
	joint
	intracranial + soft tissue
	joint + soft tissue
	unknown
Other location of untreated bleeds before diagnosis	free text
Additional bleeding disorder	no
	VWD
	FVL
	other
	unknown
Additional bleeding disorder comment	free text
Other disease that may interfere with prognosis	no
	yes, specify
	unknown
Specification other disease	free text

Family history of haemophilia

Family history of haemophilia at time of diagnosis	yes
	no
	unknown
Number of siblings with haemophilia at time of diagnosis	0-10
	unknown
Number of family members with inhibitor at time of diagnosis	0-10
	unknown
Related to PID number	0-20000000
Remarks	free text

First 50 Exposure Days to clotting factor

Date of treatment	
Number of exposure days	0-50
Reason for treatment #	bleed
	trauma capitis
	follow up
	Surgery
	prophylaxis long term
	prophylaxis short term
	ITI
	unknown
In case of a bleed:	
Location of bleed	location list *
	or other
Other location of bleed	free text
Side of bleed	right

	left
	not applicable
	unknown
Severity of bleed	minor
	major
	unknown
Number of units given	0,1 - 9999,9
Product name	product list
Other product name	free text
Remarks on this exposure day	free text

Second & Third infusion can be added to this form

Predefined location of bleeds	*location list
	ankle
	elbow
	hip
	intra cranial
	knee
	muceous membrane
	muscle
	shoulder
	soft tissue
	wrist
	other
	m. iliopsoas
	unknown

Follow Up Treatment & Bleeds

Treatment & bleeds per period *(after ED 50 or switch to bispecific antibodies)*	
Date start treatment	
Date stop treatment	
Type of treatment	prophylaxis FVlll/ FlX ITI prophylaxis bypassing agent prophylaxis bispecific antibody other no regular treatment unknown
Dose of treatment	0 - 9999,9
Frequency of treatment	frequency list
Frequency of other treatment	free text
Name of product given during this treatment	product list
Name of other product given during this treatment	free text
Remarks treatment	free text
Date start treatment where bleeds occurred	
Date stop treatment where bleeds occurred	
Number of major joint bleeds during this treatment	0-100
Number of minor joint bleeds during this treatment	0-100
Number of major other bleeds during this treatment	0-100
Number of minor other bleeds during this treatment	0-100
Life threatening bleeds during this treatment	no ICH iliopsoas muscle other

Extra treatment (or on demand treatment)	
Date start extra treatment	
Date stop extra treatment	
Reason for extra treatment	surgery major bleed minor bleed* trauma unknown

*Only applicable during treatment with bispecific antibodies

In case of a bleed:

Location of bleed	location list *
Approximate total number of units/ mg given on demand for this reason	0,1-10000
Total number of ED treated on demand for this reason	1-999

Name of product used for this demand treatment	product list
Other product name used for this on demand treatment	free text
Remarks on demand treatment	free text

Venous Access

Substitutions were performed by	Peripheral venous access
	Porth-a-cath
	Broviac
	Hickman
	AV-fistula
	Sub-cutaneous injection
	Other (to be specified)
	Unknown
Venous access was judged as	Easy
	Acceptable
	Difficult (to be specified)
	Not applicable
	Unknown
Complications CVAD	No
	Infection
	Thrombosis
	Other (to be specified)
	Not applicable
	Unknown
Remarks on venous access	free text

Additional parameters

Inhibitor Development	
Positive inhibitor in this period	yes *(all results are collected until negative for at least 6 months)* no *(all results are collected for severe and moderate patients during First 50 Exposure days)* waiting for result
Date 1st positive inhibitor in period	01-01-2000
Recovery measured	yes, normal recovery yes, decreased recovery no unknown

Other adverse events	
	yes no unknown
If yes, specify	allergic reaction thrombo embolic event (TE) thrombotic microangiopathy (TMA) local subcutaneous reactions neurological event death other
Comment if other and any relevant remark to event	free text
Date event	
Event related to administered coagulation product?	yes no unknown
Related product	productlist
Remarks	free text

Additional blood tests	
Abnormal results on ASAT, ALAT, Creatinine	yes *(if yes, lab results should be uploaded)* no not tested unknown

Weight	
Weight	0,5-200
Date weight measured	

Surgery	
Date of surgery	
Type of surgery	surgery list
Other type of surgery	free tekst

Correction for haemostasis for this surgery?	Yes *(if yes, details should be filled in in Extra Treatment table*) no unknown
Hospitalized for this surgery	yes no unknown

Hospitalization

Number of days in hospital during this period	0-50

Home Treatment

Start or change of home treatment	yes no
Date of start or change of home treatment	
Situation of home treatment after change	no home treatment by nurse by parent/guardian by patient
Reason for start or change of home treatment	free text

Update Family History

New sibling born with haemophilia	yes no
Date of birth new sibling	
New family member with inhibitor	yes no unknown

Participates in other studies

Name other study participating in this period	free text

Long Term Outcome

Joint status

Date of routine joint status score	
Joint score used	HJHS Petterson Score MRI Score HEAD US Score other
Specification other	free text

Joint outcome HJHS or Petterson Score		
	elbow left	1-20
	elbow right	1-20
	knee left	1-20
	knee right	1-20
	ankle left	1-20
	ankle right	1-20
HJHS global gait		1-4
MRI or HEAD US		
Per examined joint		normal
		abnormal
In case of abnormal findings per examined joint		bone changes y/n
		synovial changes y/n
		cartilage changes
Does patient have a target joint?		yes (if yes, which joint?)
		no
		unknown

Patient Reported Outcome	
Date of PRO questionnaire	
List completed	patient list
	parent list
Which Questionnaire was used?	PedHal
	HaemoQol
	EQ-5D
If PedHal	score per domain
	total score
If HaemoQol	score per domain
	total score
If EQ-5D	score per domain
	total score

End of Follow Up	
Date end of follow up	
Reason end of follow up	withdrew informed consent
	patient treated in other center
	death
	lost to follow up
	insufficient follow up data
	moved to adult centre
	other

Date of death	
Death related to haemophilia	yes no unknown
Other reason end of follow up	free text

ADDENDUM 3

Board members (since September 2025)

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ADDENDUM 4

Investigator Signature

I have read the:

"Protocol of the PedNet Haemophilia Registry" (Version: 6.5, June 2026)

and agree to conduct this protocol as it is described here.

Centre code _____

Name Investigator _____

Department _____

Investigator Signature

Hospital _____

City _____

Country _____

Date _____