Regulations of the PedNet Haemophilia Research Foundation and the PedNet Haemophilia Registry

Additional to the articles nos. 1-15 of the Articles of Association of the PedNet Haemophilia Research Foundation (see Annex A).

Version 3.2

Article 1: The PedNet Foundation

The PedNet Haemophilia Research Foundation (“PedNet”) coordinates an independent, international collaboration framework consisting of health centres and physicians treating haemophilia and allied disorders. It is used as a forum to exchange experiences and to encourage international collaboration on care of paediatric haemophilia. It aims to facilitate basic and clinical research endeavours specific to haemophilia and related coagulation disorders and to publish and present the results of such scientific research. PedNet is the legal body that coordinates the activities of the PedNet Study Group and manages the PedNet Haemophilia Registry. PedNet is a non-for-profit organisation.

The mission of the PedNet Haemophilia Research Foundation is to improve the current and future care of children with haemophilia by collection of high-quality data from a large cohort of unselected previously untreated children with haemophilia A and B, thus enabling front-line research projects on inhibitor development, safety, efficacy and long-term outcome of replacement and non-replacement therapies.

The objectives of the PedNet Haemophilia Research Foundation are to:

- promote scientific research relating to haemophilia and allied 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 effect of treatments.
- present and publish the results of scientific research.
- investigate the safety and effectiveness of replacement and non-replacement therapies.

Article 2: Terminology and role descriptions

Articles of Association: the Dutch legal document that governs the PedNet Haemophilia Research Foundation (“Statuten PedNet Haemophilia Research Stichting”) when it was established in 2016. The document (see Annex A) lays out how processes are to be accomplished within the organization, including the process for appointing directors and the handling of financial records. These rules are recorded with a notary and therefore not quickly adjusted to daily practice.

Regulations: PedNet’s Regulations are the translation of the Articles of Association to daily practice and extended with necessary regulations not covered by the formal “Statuten”. These are created by the PedNet Board and not registered at the notary.

PedNet Study Group (“PSG”): a study group consisting of physicians treating haemophilia and allied disorders where each Participating Centre is represented by one Representative.

Representative: a physician who treats haemophilia and allied disorders (Health Care Professional, “HCP”) and who represents a Participating Centre.

Participating Centre: a treatment centre, admitted to the PedNet Study Group by the PedNet Board, where the Representative works and where he or she treats patients with haemophilia and allied disorders.

PedNet Haemophilia Registry ("PHR"): a database owned and administered by The PedNet Haemophilia Research Foundation containing coded data of all children with haemophilia born from 01-01-2000 onwards, who are treated at a Participating Centres. The PHR records and makes available data sets for Participating Centres. The PHR database is physically located at the University Medical Centre Utrecht (UMCU).

The Management Board of the Haemophilia Research Foundation ("PedNet Board"): the management board of PedNet which is authorised to manage and represent PedNet.

The PedNet study staff: consists of staff employed by PedNet. Full job descriptions are determined by the Board and documented separately. In short, the study staff consists of the following:

- The Executive Director of the PedNet Haemophilia Research Foundation ("PedNet Director") is appointed by and reports to the PedNet Board. The PedNet Director is responsible for execution of administrative matters of PedNet such as the infrastructure of the database, preparation and negotiation of legal and economic matters, oversight and coordination of PHR studies, day-to-day matters. The PedNet Director is the contact point for requesting information on Data and Data access conditions, and supervisor of the study staff of PedNet. The PedNet Director is also appointed as "Data protection supervisor" and responsible for the protection of the Data in accordance with applicable regulations.
- The Senior Coordinator provides scientific and administrative support to the PedNet Board and Director, is responsible for the general coordination of PedNet and day to day management of the PedNet Office in close collaboration with the PedNet Director.
- The Senior Epidemiologist is an adjunct member of the Scientific Advisory Council (see below) who gives advice to working groups and individual members of the PedNet Study Group on research design, methodology and statistics to support the design, execution and publication of medical research within the PedNet Study Group. The Senior Epidemiologist also advices and supports the (junior) Epidemiologist.
- The Epidemiologist/Data Manager performs data management to secure the quality of the collected research data. The Epidemiologist/ Data Manager monitors, coordinates and reports on progress of research projects to SAC, Board and involved study group(s) for the support of the execution and publication of this medical research within the PedNet Study Group.
- The Senior Data Manager coordinates and performs complex data management tasks to secure the quality of the collected research data and supports medical research.
- The PedNet Haemophilia Registry (PHR) Coordinator is responsible for the coordination of the PHR and Participating Centres and works to achieve high quality of the collected research data.

The Scientific Advisory Council ("SAC"): is tasked with setting up the rules for authorship, supervision and advising on new protocols and assisting the PedNet Board with scientific advice on the annual research programme, manuscripts and new Participating Centres.

Data: coded information of data, according to the PedNet protocol, in the PHR on patients with congenital haemophilia A and B collected by the Participating Centres or during a PHR Study.

PedNet Research Program: a multi-year research program of ongoing and planned PHR Studies, compiled by the PedNet Director and established by the PedNet Board after advice from the SAC.

PedNet Protocol: a document which contains a detailed description of the PedNet Haemophilia Registry (PHR).

PHR Study: a study approved by the PedNet Board after advice from the SAC, based on data from the PHR.

Sponsor: a third party, being a pharmaceutical company or other interested party, that financially supports PedNet.

Article 3: PedNet Board - Organisation and Tasks

The PedNet Board consists of a minimum of three and a maximum of seven members, who will be elected from the PedNet Study Group. One board member, the "Board member finance", will reside in the Netherlands and primarily be responsible for local banking matters and implementation of decisions of the board regarding financial matters. All Board members are elected for a term of three years in accordance with PedNet's Articles of Association. A member of the Board can be directly re-elected once only for a new 3-year period. One year after leaving the Board, any representative is electable again to the Board.

1. The PedNet Board will appoint a PedNet Director to execute the tasks as indicated in Article 2.

2. The PedNet Board is responsible for the annual budget of PedNet.

3. The PedNet Board will report annually to the Participating Centres and the PedNet Sponsors ("Annual Report").

4. After formal application by a Participating Centre, the PedNet Board approves proposals for studies using Data of the PHR. Data cannot be used without such permission from the PedNet Board.

5. The PedNet Board will approve the PedNet Protocol and the PedNet Research Program or amendments of the PedNet Research Program and PHR Studies.

6. The PedNet Board will also decide on the following subjects:
    - Organisation of the Data collection (IT-infrastructure).
    - Content of the PHR.

  - Permission to submit manuscripts of PHR Study results.
  - Payment to the Participating Centres for collecting data.
  - Admission of new Participating Centres in PedNet (invitation and withdrawal).

7. The PedNet Board endeavours to have a minimum of one face-to-face meeting per year and regular virtual conferences once every month or at the reasonable demand of a Participating Centre. The Chairpersons of the Scientific Advisory Council will be invited to the annual face-to-face PedNet Board meeting and to virtual meetings every 3 months.

8. More details regulating the PedNet Board can be found in the Articles of Association of the PedNet Haemophilia Research Foundation:
   - constitution and operation of the PedNet Board is arranged for in article 4.
   - the PedNet Board meetings and resolutions are arranged for in article 5.
   - the powers of the PedNet Board and representation are arranged for in article 6 and article 7.
   - the termination of PedNet Board membership is arranged for in article 8.
   - the constitution and operation of the PedNet Study Group is arranged for in article 10.

Article 4: Scientific Advisory Council (SAC)

1. The constitution and operation of the SAC is arranged for in article 11 of the Articles of Association.

2. The SAC consists of seven representatives who will be chosen by and from the PedNet representatives. From the seven SAC representatives, a maximum of two can be alternates instead of full members. A member of the SAC may not be a member of the PedNet Board at the same time.

3. The SAC will internally elect a chairperson.

4. All SAC members are elected for a term of three years. A member of the SAC can be directly re-elected once only for a new 3-year period. One year after leaving the SAC, any representative is electable again to the SAC.

Article 5: PedNet Study Group (PSG) and Representatives

1. A haemophilia treatment centre may be invited to participate in the PSG as a Participating Centre by the PedNet Board if it fulfils the following criteria:

   - Centres should preferably be recognised by EUHANET as European Haemophilia Comprehensive Care Centres (EHCCCs).
   - Centres should care for children with haemophilia and preferably have a paediatrician or paediatric haematologist.
   - Centres should include at least 2 new severe haemophilia patients per year (averaged over a 3–5-year period).

2. Participating Centres will receive a compensation for reported patients. The model for financial compensation is determined by the PedNet Board after

consultation with the PedNet Study Group. PedNet's and Participating Centres' obligations and rights will be arranged in consortium agreement(s) with PedNet as legal representative of the PHR and the Participating Centre in question.

3. Participating Centres will be evaluated by the study staff and may be excluded from the PedNet Haemophilia Research Foundation if they do not fulfil their obligations (see Annex B). Final decisions regarding participation/ exclusion of any centre are made by the PedNet Board.

4. Representatives agree to the Regulations of PedNet and to collect Data, according to the PedNet protocol, from patients with congenital haemophilia A and B (severe, moderate and mild, factor VIII or IX up to 25%) born from 01 January 2000 onwards. From 2020 onwards (Cohort III), data will be collected from boys with haemophilia with factor VIII/IX activity level up to 15%. And from girls with factor VIII/IX activity level up to 25%. The Participating Centres and Representatives agree to participate in quality control of data according to the Monitor Plan (Annex D).

5. Representatives meet annually at the annual PedNet Haemophilia Research Foundation meeting. Representatives agree to participate in the activities of PedNet. If a representative is unable to participate over the course of two consecutive calendar years, representative should inform the Director about an acceptable reason for a lack of participation. Decisions about continuing membership of the Centre will then be made by PedNet Board.

6. A Representative ends their position in the PedNet Study Group:
   - when the Representative stops working at a Participating Centre, or the Centre is discontinued;
   - a PedNet Representative may elect to withdraw from PedNet at any time with thirty (30) days' prior written notice to the PedNet Office. Termination of membership will not affect the rights and obligations of the representative that accrued prior to the effective date of the termination. The right to authorship, depending on the contribution to PedNet projects before withdrawal, will be suggested by the SAC and put forward to the Board for decision.

7. PedNet's scientific work is conducted in research working groups on specific topics/projects. All representatives are expected to be participants in at least one research group. A working group chair, elected by the working group, is responsible for leading the work of the group, initiating regular meetings and stimulating planned scientific production. Working group chairs will be notified to the PedNet office and SAC.

Article 6: Data: collection, ownership, use and publication

1. Data will be collected under the responsibility of the Representatives in each of the Participating Centres in accordance with the PedNet Protocol, 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 General Data Protection Regulation (GDPR) and applicable national implementation legislation.

2. Representatives, researchers and other staff employed by a Participating Centre for the execution of a PHR Study must sign a confidentiality statement before they are allowed to use data for analysis.

3. The data entered to the PHR by the Participating Centres will remain the property of the Participating Centres and no use will be made of them other than for the purpose stated in the PedNet Research Program.

4. Use of the Data collection is limited to Participating Centres. The PHR will be used for scientific research. Each study using the Data in the PHR must be approved by the PedNet Board with the advice of the SAC. The flowchart for new research projects can be found in Annex C.

5. All results and inventions or discoveries with the potential to be patented or commercialised generated from a PHR Study or PedNet activity will be the intellectual property of PedNet.

Article 7: Research Grants

1. Proposals for a new research project/study to be supported by a PedNet grant should be sent to the SAC chairs to discuss the feasibility of research, scientific merit and budget demands.

2. The SAC will have an advisory function to the PedNet Board to decide on the winner(s) for that year. The winning PI/ Centre will be announced at the annual PedNet meeting.

3. The financial model for the research grant consists of the following:
    a. upon notification of the winning project, the winning PI/Centre will receive 50% of the grant, to enable research initiation.
    b. a further 25% of the grant will be transferred once interim report of the study results are delivered to SAC.
    c. the final 25% of the grant will be delivered upon submission of a final study report to SAC and/or with proof of submission for publication of a manuscript based upon study results or proof of international congress abstract acceptance.

Article 8: Author Guidelines

1. Publications in the name of PedNet must follow all ICMJE (International Committee of Medical Journal Editors) recommended four criteria for authorship:
    a. Substantial contribution to the concept or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
    b. Drafting the work or revising it critically for important intellectual content; AND
    c. Final approval of the version to be published; AND
    d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2. All PedNet Members named as authors must meet all four criteria for authorship. Members of a PedNet working group who have participated in the group's activity should normally fulfil the criteria. The corresponding author is the one individual who takes primary responsibility for the integrity of the work and communication with the journal during the manuscript submission, peer review, and publication process.

3. PedNet members do not need to be members of a specific PedNet working group to be author of a PedNet publication if they fulfil the four criteria above and such persons can be either first or senior author if they fulfil the ICMJE expected criteria for these two roles. Authorship by non-PedNet members will be decided by the PedNet Board after advice from the SAC.

4. Proposals for a new PedNet research project/study must include the names of the proposed authors and timelines of a future manuscript. Suggested authorship may be revised before submission depending on how the proposed authors have fulfilled ICMJE criteria at the time of submission. Revised authorship must then be re-approved by all remaining authors and in the case of conflicting views, authorship will be decided by the PedNet Board with advice from the SAC, guided by the more detailed ICMJE Guidelines.

5. The SAC will have an advisory function to the PedNet Board on publication plans, authorship and study protocols. The SAC can object to the submission of a manuscript and provide comments for consideration if data are not presented in a scientifically correct manner or if ethical issues are raised, and the authors will consider all such comments. In the event of conflicting views, the detailed ICMJE guidelines will be consulted for guidance.

6. While the PedNet Board and SAC will not impose authorship on a manuscript from a working group, they have the authority to suggest authorship for a member of a PedNet Participating Centre which has made significant contributions to the PHR , and which are important for the study under discussion. Such a suggested author must agree to be an author and fulfil the ICMJE author criteria.

7. All PedNet members and respective affiliations will always be listed in "Contributor/Collaborator", "Acknowledgement", "Addendum", "Supplement" or similar depending on applicability in the relevant journal. All PedNet members will be sent all manuscripts written "on behalf of PedNet" before submission and allowed 14 days for comments.

8. Funders will be acknowledged for their support of PedNet in all publications.

9. Publications from PedNet must comply with ICMJ regulations, not only those regarding authorship.

Article 9: Funding and Sponsorship

1. PedNet, PHR and satellite studies can be funded by:
    a. Industry Grants.
    b. Standard research grants.
    c. Gifts and legacies.

   Funding will be unrestricted.

2. PedNet may be financially supported by third parties, including pharmaceutical companies. Sponsorship benefits are limited to receipt of aggregated anonymous data concerning the Sponsor's products. Sponsorship will be governed by special written agreements with the Sponsor.

3. All Sponsorship will be transparent and public. Sponsor names are disclosed in the PedNet Research Foundation website. PedNet always retains ownership of the information shared with its Sponsors.

4. Requests for Sponsorship will be managed and negotiated by the PedNet Director and approved by the PedNet Board.

5. Sponsors will be acknowledged for their support of PedNet/PHR in publications.

Article 10: Termination

1. Termination of the PedNet Haemophilia Research Foundation is arranged for in article 15 of the of the Articles of Association ('Statuten') of PedNet. The future ownership or cancellation of the PHR will be determined at the final meeting of the PedNet Board.

These revised regulations were accepted by the PedNet board on 05 September 2023 and by the PedNet members as final agreed at the PedNet annual meeting on 06 October 2023.

The English version of the Articles of Association ('Statuten') of the PedNet Haemophilia Research Foundation, established on 16 December 2016 is attached hereto as Annex A.

Annex A: Articles of Association of the PedNet Haemophilia Research Foundation.
Annex B: Evaluation of Participating Centres.
Annex C: Flowchart new research project.
Annex D: Monitor Plan for on-site monitoring.