UK National Haemophilia Research Registry

Key members

National Haemophilia Database

Prof Charles RM Hay Director, National Haemophilia Database Custodian of UK NHR Consultant haematologist and Centre director Manchester Haemophilia Comprehensive Care Centre, Manchester Foundation Trust GRO-C Charles.Hay@ GRO-C	
Lynne Dewhurst Administrator / Analyst NHD GRO-C Lynne.Dewhurst@GRO-C	Ben Palmer Medical Statistician GRO-C Ben.Palmer@ GRO-C
Dr Hua Xiang Statistician GRO-C Hua.Xiang@ GRO-C	

UKHCDO Charity Executive Board

Dr Ri Liesner – Chair	Prof Peter Collins – Vice Chair
Dr Kate Talks – Secretary	Dr Pratima Chowdary - Treasurer

UKHCDO Limited

Dr Pratima Chowdary	Prof Peter Collins
Prof Charles Hay	Dr Ri Liesner
Prof Christopher Ludlam	Dr Andrew Will

Protocol Authors

Dr Pratima Chowdary	Prof Peter Collins
Prof Charles Hay	Prof Mike Laffan
Dr Keith Gomez	

Abbreviations

UKHCDO	**United Kingdom Haemophilia Centre Doctors Organisation**
NHD	**National Haemophilia Database**
UK-NHR	**United Kingdom National Haemophilia Research Registry**
PIS	**Patient Information Sheet**
ICF	**Informed Consent Form**
HRA	**Health Research Authority**
NIHR	**National Institute of Health**
GDPR	**General Data Protection Regulation, 2018**
DPA	**Data Protection Act, 1998**

Contents

1 Background

1.1 Bleeding disorders

The term 'bleeding disorder' refers to diseases of the blood that impair the ability of the blood to clot. Patients can have a variety of symptoms such as unexpected bruising, nosebleeds, heavy periods and bleeding after surgery or childbirth or spontaneous bleeding into internal organs, including brain with attendant fatality.

There are more than 30,000 people in the UK with a bleeding disorder, of whom 4,000 are children (UKHCDO, 2017). These diseases can be severe, with bleeding occurring spontaneously from birth, or milder, with bleeding only occurring with injury, surgery or childbirth. There are at least 35 different types of bleeding disorder (Colman, 2006). These include deficiencies of blood clotting factors and abnormalities platelet number or function. Correct diagnosis and recognition of the severity of the disease is key to ensuring that patients get the best treatment whenever and wherever they need it.

Bleeding disorders often present with variable severity. In the most severe forms, bleeding is seen in the first few years of life. Symptoms include bleeding from umbilical stump after birth, intracranial bleeding, easy bruising and bleeding into joints and muscles. Intracranial bleeding and internal bleeding may be fata l(Darby et al., 2007). The long-term consequences of musculoskeletal bleeding include joint and muscle damage with subsequent disability. Milder disorders can present at any age often with bleeding in the context of trauma or surgery. This can result in poor outcomes and on occasions can be fatal or result in severe disability (Mannucci & Tuddenham, 2001).

Many bleeding disorders are very rare with fewer than a hundred cases in the UK at any time. Due to their rarity, clinical management is generally provided through specialist haemophilia centres and all people with a bleeding disorder in the UK should be registered with a haemophilia centre. Even with expertise focused in this way, there will only be a few patients with some of the rarest disorders in each centre (Mumford et al., 2014). Pooling of data and clinical experience is critical to improved understanding of these conditions and their management. In this the UK this has been achieved by the UK-wide registry (the National Haemophilia Database or NHD). All patients with bleeding disorders in the UK are registered on the NHD. This allows the knowledge gained all over the UK to be centralised for the benefit of all patients and their treaters, no matter where they live. The database facilitates highest standards of care are delivered uniformly across the UK.

1.2 Bleeding disorders – Classification

1. Coagulation factor deficiency or dysfunction
    a. Haemophilia A and B
    b. von Willebrand disease
    c. Rare congenital coagulation disorders
    d. other rare disorders
2. Platelet disorders
    a. Congenital thrombocytopenia's
    b. Congenital platelet function defects
    c. other rare conditions
3. Disorders of fibrinolysis
    a. Plasminogen deficiency
    b. other rare conditions
4. Vascular disorders
5. Acquired inhibitors of coagulation factors
6. Unclassified bleeding disorders

The disorders can be inherited or acquired and are due either to single gene defects, an auto-antibody to a coagulation factor or specific mechanism that results in the decrease of a single coagulation factor. Where bleeding is secondary to known and well-established acquired disorder(s) such as liver disease, they are not recorded by the NHD.

A list of the disorders currently registered by NHD is provided as an appendix.

1.3 Management of bleeding disorders – General principles

Effective treatment for bleeding disorders requires accurate diagnosis in specialist centres. Specific treatment is available in most cases and coordinated by haemophilia centres. For most of the last century patients with severe disease died from bleeding or complications before reaching adulthood. Through intensive research the outlook for patients has improved dramatically. Now patients have the same life expectancy as the rest of the population in the UK. Due to the rarity of the conditions and the potential long term consequence of bleeding, sharing of clinical experience and expertise is critical for improving the care of this group of patients. This is a key aim of the NHD.

Treatment of bleeding disorders usually requires replacement of the missing coagulation factor, called replacement therapy, or substitution with blood components that as in the case of platelet

disorders. Treatment can be given at the time of a bleed to stop bleeding or prior to planned procedure to prevent bleeding, this is called on-demand or episodic treatment. In severe disorders, treatment is often given to prevent bleeding, this is called prophylaxis. Therapeutic agents and frequency of administration are determined by the disorder in question.

Therapeutic agents used for management of bleeding disorders include single coagulation factor concentrates that are either plasma derived or made with recombinant technology, platelets, desmopressin and tranexamic acid. Some patients who are treated with coagulation factors develop antibodies to these proteins which inhibitor their function. These antibodies are called inhibitors and prevent the use of standard treatment.

Procoagulant therapies have been developed that activate the coagulation system despite the presence of an inhibitor, these include recombinant activated FVII, factor eight bypassing therapy (FEIBA). Recently a number of novel treatments for bleeding disorders have been introduced or in clinicla trial, these include emicizumab, concizumab and other anti-TFPI antibodies, fitusiran. Further, gene therapy currently in clinical trials has the potential to become the new standard of care.

The core dataset collected by NHD is provided as an appendix.

2 Challenges in the management of bleeding disorders

The UK has been at the forefront of global research into bleeding disorders for many years. Many of the ground-breaking changes have been achieved in this country through the combined efforts of patients and clinicians. The advances that we have seen and excellent clinical outcomes that we now achieve would not be possible without the National Haemophilia Database. Worldwide the picture is very different with many patients in the developing world facing an uncertain future. There is still a lot of work to be done to make treatments more effective and easier for patients and their families both in the UK and abroad.

Major challenges in the management include

1. Limited evidence base for current treatment strategies due to small patient numbers
2. Long term consequences of the disease
3. Treatment complications including loss of effectiveness exposing patient to risk of mortality and severe morbidity.

4. Clinical pathways that may not be conducive to optimal outcomes

5. Lack of agreed outcomes and monitoring strategies for the various bleeding disorders

6. Need for improved understanding between genotype and phenotype to avoid treatment where not indicated.

3 United Kingdom Haemophilia Centres Doctors Organisation (UKHCDO) and National Haemophilia Database

Haemophilia centres were first designated by the UK Ministry of Health in 1968. The directors of the then 36 haemophilia centres first met in 1968 and subsequently agreed in 1969 to establish a register of all patients with bleeding disorders. The United Kingdom Haemophilia Centre Doctors' Organisation charity is an association of medical practitioners who work within the Haemophilia Centre's of England, Scotland, Northern Ireland or Wales and have an interest in the care of people with Haemophilia or other inherited bleeding disorders. UKHCDO was established in 1968 to improve haemophilia care, research into bleeding disorders, their treatment epidemiology and complications and to facilitate healthcare planning. It is registered with the charity commission and the registration number is 1032606.

3.1 UKHCDO objectives

a. to preserve, protect and relieve persons suffering from haemophilia and other inherited bleeding disorders;

b. to advance the education of the medical profession, the nursing profession, professions allied to medicine and the general public in the knowledge of haemophilia and other inherited bleeding disorders and their treatment

c. to promote or assist in the promotion of audit and research into the causes, prevention, alleviation and management of haemophilia and other inherited bleeding disorders and to disseminate the useful results of such research.

3.2 National haemophilia database (NHD)

UKHCDO established the National Haemophilia Database in 1969 and has managed the database since that time. As well as patient numbers and diagnosis, the register included details of the type and quantity of treatment used for therapy and the complications of treatment. This register forms

the basis of what is now the National Haemophilia Database (NHD). Although the quantity and extent of detail has increased over the intervening years, the original aim is unchanged in principle. Following another health service directive in 1976 the National Haemophilia Database is obliged to supply the NHS every quarter with data on the quantities of therapeutic products used to treat haemophilia and other inherited, and some acquired, bleeding disorders.

Originally, only total amounts of therapeutic products were recorded but the depth of detail demanded by the NHS and government has steadily increased. This has included surveillance for complications of treatments such as infectious disease and development of resistance to treatment called inhibitors. Individual patient joints scores are performed on a regular basis by haemophilia centre physiotherapists and these are also uploaded into the NHD. Patients who undergo genetic testing are asked whether they agree to their genetic data being uploaded to the NHD and if they agree to this and have signed a consent form the genetic information is added to their record.

More recently ditial technology has been implemented that allows patients to report individual treatments and the reasons for those treatments (Hay et al., 2017). Patients record this information via the haemtrack application either via mobile apps or home computers. Many haemophilia treatment products are bar coded to facility this process. The information uploaded by patients on their individual treatment episodes can be viewed by staff at their own haemophilia centre and treatment may be adjusted according to this information. Therefore the Haemtrack record is an important part of direct patient care. NHSE has made it a required for patients to complete a Haemtrack to receive specific types of treatment and reports of aggregate data derived from Haemtrack is used by the NHS for health care planning.

The data collected by NHD are important for NHS budgeting and governance purposes, but also increasingly to establish that the funding for these disorders is spent appropriately and with demonstrable benefit. The benefit of treating haemophilia may seem obvious but all treatments in the NHS are now subject to review in which the benefits achieved by the expenditure are closely scrutinised and compared. The annual budget for inherited bleeding disorders in 2017 to 2018 was in excess of 90 Million pounds. It is clearly essential we have these data available for haemophilia to ensure continued funding.

Collecting and organising the vast quantities of data that are now collected requires a substantial number of staff, in the haemophilia centres themselves, and also in the National Database where it is collated, organised and analysed before despatch to the DoH.

4 Databases, Registries and Outcomes

Patient registries are being increasingly recognised as powerful tools for systematic data collection, that enable iterative learning and quality improvement (Skovron, 2006). A registry is defined as " A systematic collection of defined events or product exposures in a defined patient population for a defined period of time"(Arlett P, 2005).

Registries are ideally placed to define the characteristics of the target population for new drugs, understand the clinical course of the disease, treatment patterns and frequency of adverse events in addition to analysis of efficacy (Skovron, 2006). They are particularly valuable for monitoring long term outcomes in rare disorders and can have multiple objectives and importantly are not restricted to the most compliant patients. EURORDIS (EUROpean Rare DISeases) a non-governmental patient-driven alliance of patient organisations and individuals active in the field of rare diseases actively promotes patient registries as key tools for increasing knowledge with the pooled data contributing to basic, clinical and epidemiological research, and real life post marketing studies (EURODIS, 2013).

Early in the registry life cycle a cross sectional analysis of patient characteristics, and practice patterns is typically undertaken, and progressively the relationship between patients and treatment characteristics and outcomes are explored. Subsequently in long running registries, the influence of change in practice on outcomes can be analysed. Through the entire period, adverse event monitoring is undertaken as standard (Skovron, 2006). National databases in addition to pharmacovigilance data are also geared towards collection of consumption data. Additionally, consistent longitudinal collection of patient data facilitates the development of standards of care and dramatically improves patient outcomes (EURODIS, 2013).

5 Rationale for establishing NHD as Research Database

The data held in NHD in addition to direct patient care and health care planning offers major opportunities for research and indeed publications have been undertaken on aggregate data over the last 50 years,. In keeping with general data protection regulation an application is being made to register the NHD as a research database.

5.1 Research database

HRA defines a research database as a database that has a collection of personal data on human subjects for use in research (Departments & Service, 2017). HRA further defines research as an attempt to derive generalisable or transferable new knowledge to answer questions with

scientifically sound methods including studies that aim to generate hypotheses as well as studies that aim to test them, in addition to simply descriptive studies.

Research databases may have their origins in one of the three ways as detailed by HRA.

1. Databases originally established for research purposes, including those:
    a. Originally supporting one or more specific research projects but now used for other research purposes.
    b. Intended to establish a baseline for further research generating and directly supporting future research studies
    c. Designed to support meta-analysis through collation of other databases.
2. Databases established for purposes other than research, where there is now an intention to use that database for research purposes, for example databases originally established to support:
    a. Delivery of care
    b. Audit or service evaluation
    c. Population or health care planning
3. Databases established for multiple purposes, such as disease registers, where research is one of the intended purposes.

5.2 NHD – core functions

National haemophilia database is a mixed database and has the following core functions. The core functions represent the legitimate interest of the database and are also of public interest. The core functions are listed below.

1. Direct patient care.
2. Health care planning including audit
3. Research

5.3 NHD for Direct patient care and health care planning

For the purposes of direct patient care and health care planning NHD consent is presumed and all patients are registered and data are submitted on total treatment issued, side effects in relation to the treatment and other complications of bleeding such as joint scores. This information is linked to the patients name and NHS number. The name is necessary so that the NHD can issue individuals with a Bleeding Disorder Card which the states the patients name, diagnosis, usually treatment and haemophilia centre. Patients can show this card to any health care provider as required.

In addition, patients give informed signed consent at their local haemophilia centre to have genetic information uploaded. When a patient signs up to Haemtrack they agree to their data being included in the NHD. This consent for genetic data and Haemtrack covers direct patient care and health care planning. Patients are informed about the NHD and the use of their data by the NHD is covered in the NHD patient information leaflet provided in appendix. In this leaflet they are informed of their right to opt out of the having some or all of their data held on the NHD. Patients are provided the leaflet at the time of registration onto NHD.

5.4 NHD as research database and UK National Haemophilia Research Registry

Establishing the NHD as research database allows the data held by the NHD to be used for research purposes and ensures that the conduct of this research is in line with current principles on management of personal information. Patients who are registered on the NHD will be offered the opportunity to participate in research. Patients will be provided with a research information sheet and given the opportunity to ask questions. If they wish to have their data used for they will be asked to sign a consent form. Age appropriate procedures will be used for children.

Patients who consent to participation into research will registered onto the UK National Haemophilia Research Registry (UK – NHR) a subsection of the NHD.

In addition to conduct of research on existing data, it will allow new data collections that additional to routine patient care.

5.5 Patient groups in NHD based on consent

Patients in NHD will be allocated to one the three groups based on their consent for research and participation in the UK-NHR. Depending upon the consent for research.

A. Patients registered and consented for UK-NHR
B. Patients registered and declined consent for UK-NHR
C. Patients registered and with no data available on consent for UK-NHR. Typically the patient is not in regular contact with the centre and the opportunity to seek consent has not presented.

5.6 Time scale for consent

The research conducted by NHD involves analysis and reporting of aggregate data. Currently patients are informed about the purpose of data collection including research but have not been explicitly consented for research. It is proposed to seek consent from all patients registered on NHD. As the number of patients registered currently is >28,000 we propose prospective accrual of consent as the opportunity presents over the next 5 years, acknowledging the difficulties in obtaining consent from patients now lost to follow up.

For patients with severe bleeding disorders reviewed 6-12 monthly y we expect to obtain consent from most (at least 90%)within 12 months and obtain consent from most patients with mild bleeding disorders over a period of three or 4 yearsgiven their longer review intervals and intermittent contact with the Haemophilia Centre.

We propose to consent 20% in the first year and 10-25%each subsequent year, to maximum of 100% and a minimum of 50% at 5 years.

During this process of approaching patients for consent, it is proposed that the NHD continues to undertake research including all patients except for those who have declined participation in UK-NHR.

6 Aim

Establish and develop the UK-NHR as a resource for research, to further our understanding of coagulation disorders and their management.

7 Scope of the Planned Research

Research conducted on data held by NHD has the important aim of understanding disease natural history, mechanisms, epidemiology, current treatment options and outcomes, complications and health economics. The NHD and UKHCDO do not undertake interventional studies and studies of this type are run through individual haemophilia centres. The NHD undertakes observational research in which the outcomes of treatment agreed between the patients and the haemophilia centre is analysed.

Broad areas of research include:

7.1 Natural history of disease and its complication

Examples include:

1. Understanding natural history of mild disorders and correlation to the genotype to ascertain need for intervention and complication in relation to intervention.
2. Joint disease progression in patients with severe and moderate haemophilia
3. Development of target joints in severe and moderate haemophilia patients on prophylaxis
4. Prevalence of joint disease in mild and moderate haemophilia patients
5. Correlation between bleeding symptoms and genotype in rare bleeding disorders

7.2 Epidemiological research

Examples include:

1. Longitudinal study of mortality and cause of death in patients with bleeding disorders
2. Prevalence of bleeding disorders across UK
3. Correlation between outcomes and dose and frequency of treatment
4. Comparative audits of care across centre including the use of validated tools

7.3 Treatment outcomes

Examples include:

1. Outcomes of replacement therapy given as preventative treatment
2. Surgical outcomes including replacement therapy
3. Musculoskeletal morbidity and progression
4. Health economic analysis of care and coagulation factor concentrate provision

8 Activities to be undertaken by or within the National Haemophilia Research Registry

1. Collection of new data from the living
    a. New clinical data
    b. New laboratory data
2. Collection of pre-existing data
    a. Hospital patient records
    b. Hospital Episode statistics

c. Data derived from other national databases

3. Other research procedures involving contact with participants
    d. Validated questionnaires
4. Conduct research studies using the data
5. Release of pseudonymised data to other researchers for conduct of research within UK and outside of UK
6. Release of pseudonymised data to regulatory agencies for conduct of research within UK and outside of the UK
7. Produce reports of aggregate anonymised data to for industry partners

9 Study design

9.1 General Design

Data held within the NHD will be used for both prospective and retrospective observational studies. Where required, data additional to those for routine care can be collected. This includes information related to treatment, investigations or outcome assessments additional to routine care.

9.2 Study Group

All patients registered with National Haemophilia Database with an inherited or acquired haemostatic abnormality for routine clinical care.

9.3 Inclusion Criteria

1. Patients registered with National Haemophilia Database
2. Patients or parents or guardians able to provide informed consent

9.4 Exclusion Criteria

1. Patients or parents or guardians who decline to give permission for data to be used for research

9.5 Recruitment and consent

All patients registered with NHD with an inherited or acquired coagulation disorder are eligible for participation. Eligible patients will be provided with the information sheet and given the opportunity to discuss any issues with a member of the haemophilia centre. Patients will be given adequate time to consider participation. The decision on whether or not to participate will be recorded locally and

in the national haemophilia database. Formal reconsent will be undertaken when the child reaches the age of 16 or where are there are significant changes to the PIS and ICF.

9.6 Study visits

No additional visits or blood tests over and above those performed routinely are envisaged in relation to participation in this registry. Additional data or investigations may be instituted locally as part of enhanced care, in these instances the utility of these will be discussed by the committee responsible for providing oversight of the UK-NHR.

9.7 Study related procedures

In certain patient groups to assess outcomes, validated questionnaires may be collected on an adhoc basis following review and approval by the data management working party. Similarly, where data additional to current fields are collected the purpose of the collection will be reviewed and authorised by the DMWP. Where additional laboratory data is collected the investigations will standard investigations available in local laboratories.

9.8 Data collection fields

Information gathered will be part of routine clinical care collected during the visits. Data from laboratory tests may be collected during these visits, but no biological fluids will be stored as part of the database.

In addition, data is also provide by the patients on their usage of clotting factors and disease symptoms (bleeding) via haemtrak. Data in relation to mutation analysis will also be collected and stored and released appropriately.

10 Study duration

As patients are diagnosed with lifetime conditions, consent will be sought for use of data for research indefinitely.

11 Patient contact

A percentage of the patients will be under regular follow up for their inherited disorders or chronic disorders and will be seen regularly. Where results of research are clinically relevant, i.e. information that has an impact on the immediate management of a patient's coagulation disorder, the patient's

local direct health care team will be informed. The local health care team will be offered the patient an appropriate appointment to review and discuss the findings. Their GPs will be informed of relevant findings following consultation with the patient.

12 Database – Management

The NHD is administered by UKHCDO Ltd which was established 4th April 2006 as the commercial arm of UKHCDO, a registered Charity, which has a registered address at City View House, Union Street Ardwick, Manchester, M12 4JD.

UKHCDO Ltd is overseen by a Board including NHD director, UKHCDO charity executive and other agreed members as listed under key members. The Database is overseen by a Data Management working Party, Chaired by vice chair of the UKCHDO executive and including working party chairs, NHD director, a patient representative, a representative of The Haemophilia Society, representatives of the Haemophilia Nurses Association and the Haemophilia Physiotherapist Association a representative of NHS England and Database staff.

The Datbase is hosted By Central Manchester Healthcare Foundation Trust. All communications are encrypted and within the NHS Net on the N3 network. The servers are held within a NHS server hotel at a Mancheter Health Authority Facility based in Leigh Infirmary. The trust undertakes regular inspection through a review by the hospital Caldicott Guardian.

12.1 Data Controllers and research sponsor

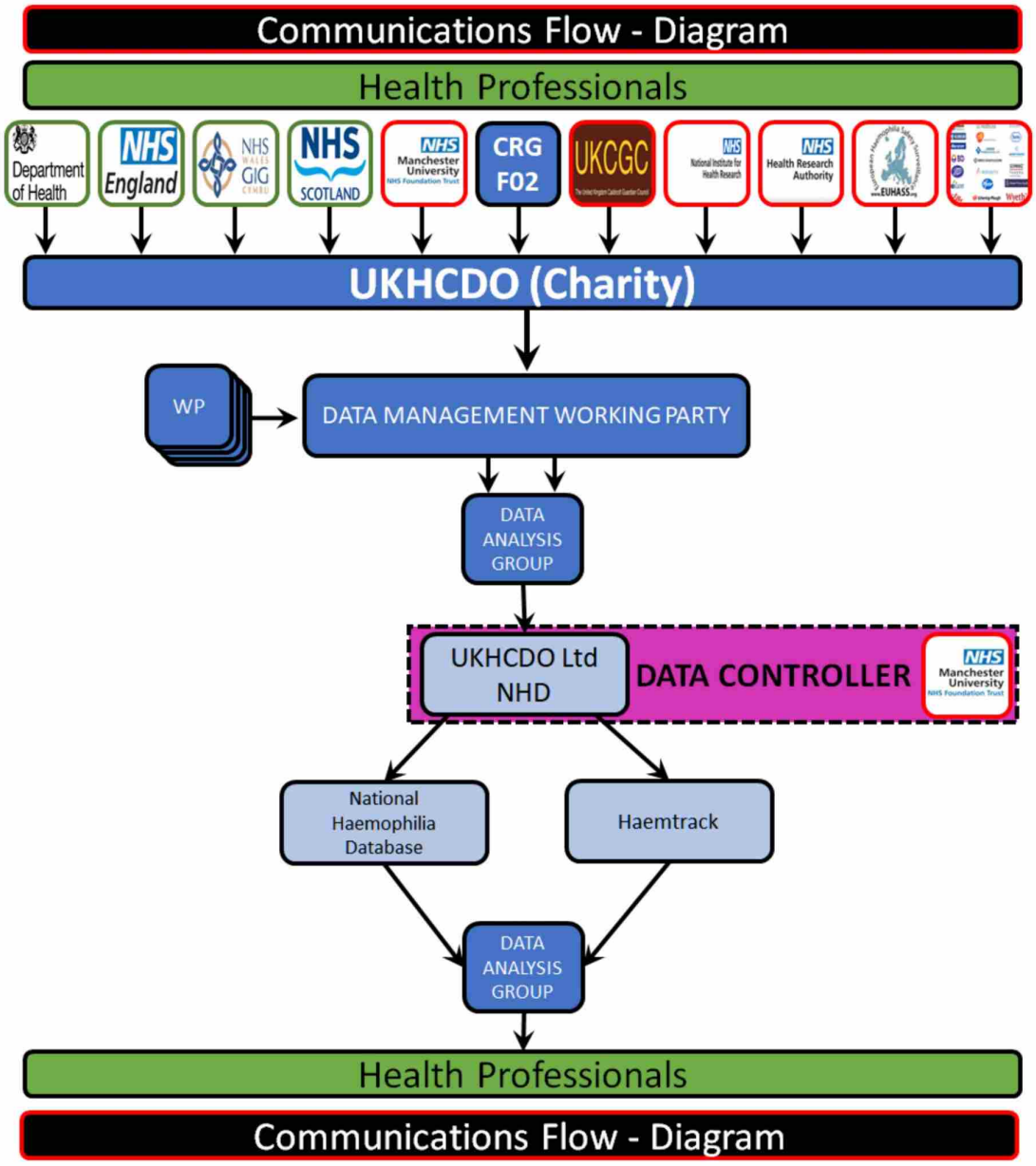
For the purposes of direct health care and health care planning, the NHD and UKHCDO ltd are the data controllers. For the purposes of research Central Manchester Healthcare Foundation Trust is the data controller and sponsor of the study.

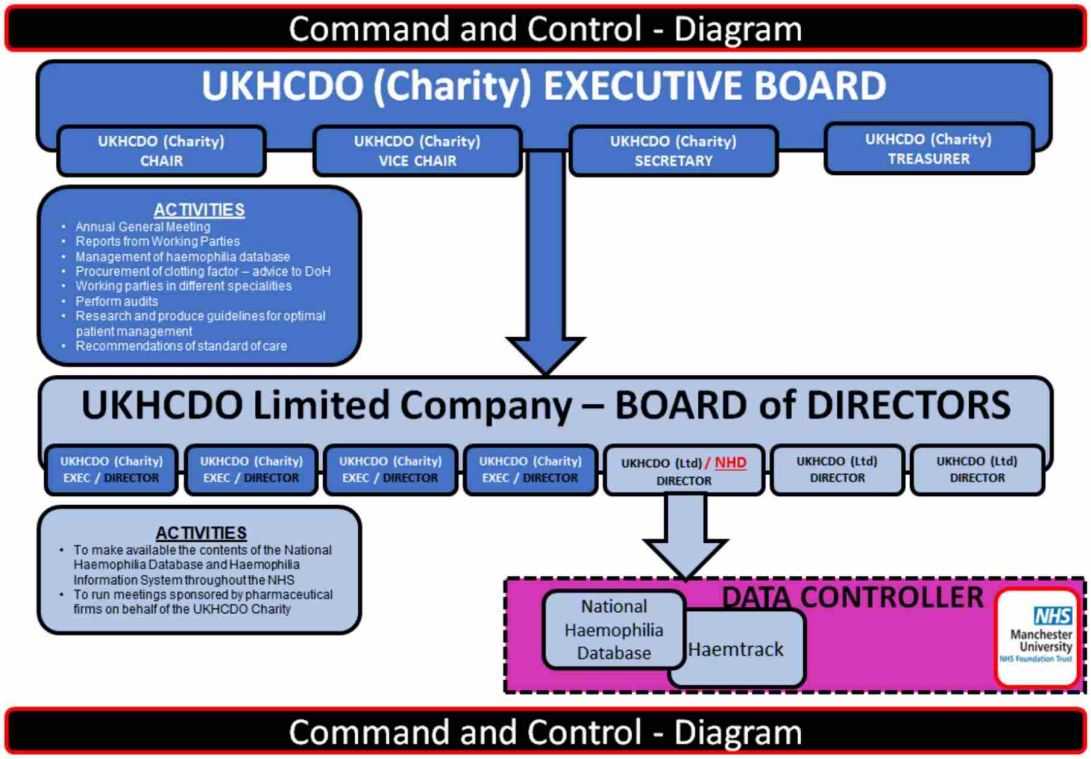
12.2 Data processors

Data collection centres who submit the data are included in the appendix.

12.3 Organogram

Diagram of the proposed relationship between NHD, Manchester, UKHCDO limited, UKHCDO charity.





13 Data protection

In running this research database, the Sponsor and NHD shall comply with all laws and statutes as amended from time to time, applicable to the conduct of research including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- General Data Protection Regulation and Data Protection Act 2018
- Freedom of Information Act 2000
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments

- The Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

Information about study subjects will be kept confidential and managed in accordance with each trust's data protection guidance, which incorporates the Data Protection Act of 2018. As the results have the potential to impact patient management they will be integrated into the patients' medical record where appropriate.

The study staff will ensure that the participants' anonymity is maintained. All patients identifiable Data will be stored on NHS computers and encrypted devices in accordance with Trust Data Protection guidance. The study will comply with the Data Protection Act 2018 which requires data to be anonymised as soon as it is practical to do so. Access to patient identifiable data will be restricted to the investigators and members of the direct health care team. Electronic data will be stored on the main server and will be password protected. Data in the electronic database will be pseudoanonymised as information of clinical significance may be obtained.

13.1.1 What systems will be in place to ensure the confidentiality of personal data?

- Data can only be audited by through VPN logs.
- Annual NHS Information Governance training as per IGSOC requirements

13.1.2 What security and audit measures will be in place to secure access to identifiable data held by the Database

- The database is hosted by Central Manchester Healthcare Foundation Trust, our fileservers are housed in a secure facility in the North-West Commissioning Support Unit of the NHS at Leigh Infirmary. All our data communications are paperless, within the NHS N3 network using a 256-bit Advanced Encryption Standard and a variety of other security features. The data is stored on mirrored secure N3 servers hosted in an NHS data centre. Access to the data centre server rooms are restricted through card key access with external building security measures including CCTV, alarms, security fencing and door/window locks.
-
- The systems, PC's and servers are protected by passwords and firewalls restricting IP, port and application access. Access to the servers is via an encrypted VPN network link to the N3 server available to authorised users only, across a restricted IP range.

- NHS Staff within UKHCDO Ltd are the only people who can have full access to identifiable data held by the database and there are three members of staff with that access.

13.2 Data collection, storage and transmission

Data will be collected on an ongoing basis for routine care and financial management. Additional data will be collected on an ad hoc basis. All Data is collated by Haemophilia Centres and transmitted, encrypted, within the NHS net using the N3 network. None of the data is transmitted on paper or by post. There are several additional security features such as timed automatic logouts, security usernames and passwords for all users etc. Data is stored on NHD fileservers stored in a secure Health authority server hotel in Leigh Infirmary.

The database operates a paperless office. Paper records from periods prior to 2000 are securely archived off-site. There are no paper records for periods after 2000.

14 Management of Research

The management of the research activity undertaken on data collected through the bleeding disorder registry will be carried out under the auspices of the Data Management Working Party (DMWP) and its sub group the Data Analysis Group (DAG) and, in the case of a project originating and conducted under the auspices of an individual working Party, also under the direction of the working party in question.

14.1 DMWP and DAG

DMWP has the responsibility for overseeing the management of all patient data collected by National Haemophilia Database in accordance with the protocol and recommendation of the ethic committee and GDPR. The role of day to day management of research analyses is delegated to the Data Analysis Group.

The membership of the DMWP includes the Vice Chair of UKHCDO (Chair), the chairmen of all the UKHCDO Working Parties or Task Forces, statisticians from NHD, NHD/UK-NHR coordinator, director of the NHD, representatives of NHS England, Haemophilia nurses association (HNA), Haemophilia physiotherapy group (HCPA), the Haemophilia Society and a patient representative.

The DMWP/DAG remit includes a critical review of the research question to ensure scientific validity, clinical utility and address areas of potential overlap between projects. In addition, it also will

consider the workload capacity of the database and prioritise studies or data collection exercise's as required.

The DMWP/DAG will review all applications for use of data from UK-NHR to ensure that the research is in keeping with donor consent and the aims of the registry. It will also review the results of to ensure that clinically relevant information is forwarded to the direct health care team for further contact with the patient.

The DMWP meets twice a year in face to face meeting and its subgroup the DAG meets once a month by teleconference. Discussions will be minuted for future reference. The DMWP/DAG will ensure that all projects are registered with the UK-NHR coordinator for updates on progress and publications.

The DAG is co-Chaired by the Chair of DMWP and the Director of NHD and its membership includes the statisticians from NHD, Working Party Chairs and two patient representatives.

Terms of reference for the DMWP and DAG are included as appendices

14.2 Requesting access to stored data for research

1.1.1 Responsible persons: NHD Manager

The UK-NHR is committed to sharing data for scientific gain and will consider requests for release of data which is in keeping with aim of the registry and donor consent. Applicants wishing to use data for a specific project will be asked to complete the Data Request form and send it to the NHD manager for distribution to the DMWP.

The data request form has been included in the appendicies.

14.3 Review of applications for release of NHR data

1.1.2 Responsible persons: DMWP

Applications to use data held by the UK-NHR for research purposes are made to the DMWP. The DMWP usually delegates review of these applications to the DAG. Members of the DAG review the application and either agree to proceed with the analysis, recommend changes to the analysis and re-submission or decline the analysis. If the DAG cannot reach a consensus the application is reviewed by the DMWP.

Following a review, the DMWP/DAG will approve eligible projects and data requests. All projects being carried out in will be registered with R&D in the Cental Manchester University Foundation Trust. Prior to release all results are reviewed by the Data Analysis Group to ensure coherence of results and to identify if any patient identifiable data is present. Where anonymised results are provided and the number of patients is below five (5) this is also reviewed to ensure that the data cannot be combined with other sets of data to reveal patient identities.

14.4 Release of data to researchers contributing to data in NHR

The policy of the UK-NHR is to release data to investigators in keeping with the following principles;

1. The aim is scientifically valid, and in keeping with aim of the NHD and donor consent
2. The results of the study will be presented at national and/or international meetings, and/or sent for publication. A copy will be provided to the DMWP
3. NHR will remind all investigators receiving data of their ethical and regulatory responsibilities concerning the use of these samples

14.5 Release of data to external researchers

Where data are released to external investigators, no personal identifiable information will be released and all research will be done on a collaborative basis with UKHCDO. In addition to the above principles, the other prerequisites are;

1. The release of data is more efficient than conducting analyses in house
2. Where pseudo-anonymised or anonymised data are appropriate
3. A summary of the data generated must be presented to the research committee to assess the possible impact on the management of individual patients.

14.6 Psedoanonymisation and anonymisation

Patient identifiable information is needed to write back to patients in the event of a clinically significant finding becoming available later. Where sub-databases are created for analysis of data, anonymization will be carried out at the earliest possible stage of the analysis.

14.7 Annual report to ethics committee & trust R&D department

1.1.3 Responsible person: NHD Director

The responsible person will ensure that all projects agreed by the DMWP/ DAG in relation to the NHR are registered with R&D office of the Central Manchester University Foundation Trust This person will also be responsible for preparation of an annual report for submission to the ethics committee and an annual progress report summarizing the consent status for subjects registered on the NHD.

15 Funding of National Haemophilia Database

The funding for the NHD comes primarily from the NHS commissioners in England, Scotland and Wales. This pays for the staffing and infrastructure of the NHD and the data collection costs at local haemophilia centres. In addition funding is generated by performing analyses and writing reports that are commissioned by research groups, institutions and the pharmaceutical companies that manufacture products for haemophilia care.

16 Publication policy

Numerous publications from UKHCDO based on data from NHD have contributed to change in clinical practice and improved outcomes. It is expected that the results of all research from UK-NHR a subgroup of the NHD will be presented at national and international meetings and that NHD/ UKHCDO will be acknowledged in the presentation. Ideally, all research results should be sent for peer reviewed publications with a copy of the presentation or publication being sent to the research committee.

The publication policy is provided as appendix to the protocol.

17 Ethics

The proposed study is a non-interventional study and will not require additional visits to the hospital. All efforts will be made to reduce burden to the participants.

18 Stakeholder consultation

The proposal has been discussed at the UKHCDO advisory committee meeting and was agreed unanimously. The proposal has also been reviewed by UK Haemophilia society.

19 Arlett P, M. J., Seligman PJ. (2005). A View from Regulatory Agencies. In S. BL (Ed.), *Pharmacoepidemiology* (4th ed., pp. 119).

Colman, R. W. (2006). *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*: Lippincott Williams & Wilkins.

Darby, S. C., Kan, S. W., Spooner, R. J., Giangrande, P. L., Hill, F. G., Hay, C. R., . . . Williams, M. (2007). Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood, 110*(3), 815-825. doi:10.1182/blood-2006-10-050435

Departments, U. H., & Service, R. E. (2017). *Standard Operating Procedures for Research Ethics Committees; Version 7.2*. Retrieved from https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-tissue-banks-and-research-databases/

EURODIS. (2013). Eurordis (European Rare Diseases) policy fact sheet - rare disease patient registries. In.

Hay, C. R. M., Xiang, H., Scott, M., Collins, P. W., Liesner, R., Dolan, G., & Hollingsworth, R. (2017). The haemtrack home therapy reporting system: Design, implementation, strengths and weaknesses: A report from UK Haemophilia Centre Doctors Organisation. *Haemophilia, 23*(5), 728-735. doi:10.1111/hae.13287

Mannucci, P. M., & Tuddenham, E. G. (2001). The hemophilias--from royal genes to gene therapy. *N Engl J Med, 344*(23), 1773-1779. doi:10.1056/nejm200106073442307

Mumford, A. D., Ackroyd, S., Alikhan, R., Bowles, L., Chowdary, P., Grainger, J., . . . O'Connell, N. (2014). Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol, 167*(3), 304-326. doi:10.1111/bjh.13058

Skovron, M. L. (2006). *Databases or Registries? Points to Consider.* Paper presented at the FDA/Industry Statistics Workshop. September 29, 2006.

UKHCDO. (2017). *UK National Haemophilia Database Bleeding Disorder Statistics for 2016-2017.* Retrieved from http://www.ukhcdo.org/annual-reports/