BLEEDING DISORDERS STATISTICS FOR THE INFECTED BLOOD INQUIRY 2022

NATIONAL HAEMOPHILIA DATABASE AND UK HAEMOPHILIA CENTRE DOCTORS' ORGANISATION

Contents

Abbreviations

AIDS	Acquired immune deficiency syndrome
ATIII	Antithrombin
BPL	Bio Products Ltd., Elstree (previously Blood Products limited)
CCC	Comprehensive Care Centre
CDSC	Communicable Disease Surveillance Centre
CFC	Clotting factor concentrate
CJD	Creutzfeldt-Jakob disease
CJDIP	CJD Incidents Panel
DDAVP	1-deamino-8-D-arginine vasopressin
DH	Department of Health
dL	Decilitre
EACA	Epsilon-aminocaproic acid
FEIBA	Factor Eight Inhibitor Bypassing Activity
FFP	Fresh frozen plasma
FII	Factor Two (Prothrombin)
FIX	Factor Nine
FV	Factor Five
FVII	Factor Seven
FVIII	Factor Eight
FX	Factor Ten
FXI	Factor Eleven
FXII	Factor Twelve
FXIII	Factor Thirteen
GP	General Practitioner
HA	Haemophilia A
HB	Haemophilia B
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HP	High purity
HPA	Health Protection Agency
HPPF	Human plasma protein fraction
HT	Heat treated
the Inquiry	Infected Blood Inquiry
IU	International units
LTR	Liver transplant registry
Mcg	Microgram

mL	Millilitre
MRC	Medical Research Council
NHD	National Haemophilia Database
NHS	National Health Service
NHSBT	National Health Service Blood Transfusion
ONS	Office for National Statistics
PCR	Polymerase chain reaction
pd	Plasma-derived
PFC	Protein Fractionation Centre, Edinburgh
PFL	Plasma Fractionation Laboratory, Oxford
PwBD	People/person with a bleeding disorder(s)
PWH	People/person with haemophilia
r	Recombinant
rFIX	Recombinant Factor Nine
rFVIIa	Recombinant Activated Factor Seven
rFVIII	Recombinant Factor Eight
rFXIII	Recombinant Factor Thirteen
RNA	Ribonucleic acid
rVWF	Recombinant Von Willebrand Factor
SCIEH	Scottish Centre for Infection and Environmental Health
TFPI	Tissue factor pathway inhibitor
U	Units
UK	United Kingdom
UKHCDO	UK Haemophilia Centre Doctors' Organisation
US	United States
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor

1 Background

The National Haemophilia Database (NHD), run by the United Kingdom Haemophilia Centre Doctors' Organisation, received a request dated 6th April 2020 from the Infected Blood Inquiry for analysis of data held by the NHD ("Rule 9 request"). The request was entitled 'Amended request for a written statement and the production of documents and information under Rules 9 (1), (2) and (4) of the Inquiry Rules 2006' and was addressed to Professor Pratima Chowdary, Co-Director of the NHD.

1.1 NHD and data collection

In the UK, the systematic collection of data about people with bleeding disorders (PwBD) and their treatment started in the late 1960s. It was initiated in 1969 by the Medical Research Council (MRC) cryoprecipitate working party established by a group of Haemophilia Centre Directors, following a grant from the MRC. The working party's remit was to document the incidence of hepatitis and antibodies to blood clotting factors (inhibitors) following transfusion, the two most important complications observed during the treatment of PwBD at that time.

Subsequently, the UK Haemophilia Centre Directors Organisation (now, UK Haemophilia Centre *Doctors'* Organisation) was established as a group of doctors with an interest in the care of PwBD. The data collections initiated by the MRC working party evolved into the NHD to improve understanding of the epidemiology and treatment of haemophilia and related conditions. In the early years, Dr Rosemary Biggs directed the NHD from The Churchill Hospital in Oxford with administrative support from Miss Rosemary Spooner and Mrs Pat Wallace (part-time secretary). In 1977, Dr Charles Rizza succeeded as Centre Director for the Oxford Haemophilia Centre and Director of the NHD. In 1993, Dr Paul Giangrande took over as Director of the NHD. In 2002, following Miss Spooner's retirement, the NHD was relocated to Manchester, and directorship was handed over to Prof. Charles Hay. Prof. Pratima Chowdary joined as co-director in April 2020.

An important aim of UKHCDO is to improve the care of PwBD supported by data about bleeding disorders. Over the last five decades, committees and working parties of the UKHCDO have used data collected by NHD to support the development of clinical treatment guidelines and document the natural history of disease and treatment complications, i.e. observational research. Although the data collection was started as a research project, it evolved to become a voluntary data collection exercise to address topical issues aimed at improving the care of PwBD. On occasions, specific NHD data collection exercises have been initiated to facilitate this aim or at the request of other bodies, such as the Department of Health, for health care planning.

The scope of the information collected by NHD changed regularly in the early years, along with the number of centres contributing to the data collection. The first survey in 1969 established by the MRC cryoprecipitate working party requested information about the number of people with haemophilia (PwH), the treatment used by each affected individual and any treatment related complications from the small number of centres that existed. For the first three years (1969 - 1971), individual PwBD level data were collected, encompassing exposure to different products, amount of product used and treatment related complications. Centre level summary data were collected for the next few years,

including the number of people per diagnosis, consumption per diagnosis, and product type. During this period, some individual PwBD level data were also submitted, limited to the type of product used but not the quantities. From 1971, Centres were also asked to provide a list of PwH who had died that year, and their cause of death, if known. Information about VWD and haemophilia carriers was collected from 1976 onwards. From 1977, in addition to centre level data, individual PwBD level information about exposure to various products in a calendar year was also requested.

Following these initial surveys, the UKHCDO/NHD sought annual voluntary data submissions from all UK haemophilia centres. Some centres submitted data annually, and others every couple of years. Data collection was through an annual return form, which included a pre-printed list of products. The list of products was determined by local availability and updated regularly based on the information provided by the centres. The data collected included information about new registrations of PwH (and later, other bleeding disorders); development of an inhibitor or jaundice; the type of treatment used (and in some years, volumes of treatment used); and whether treatment was administered in the home setting. Additional data was collected as required to address new queries.

Initially, data was collected from a limited number of centres that were large in size. In 1976 data collection was expanded to include smaller centres. Information about the treatment given to PwBDs at hospitals that were not haemophilia centres was not submitted to NHD. However, in some instances, the treating hospitals provided this information to their local haemophilia centre, with subsequent submission to NHD.

From 2005 onwards, the individual PwBD level data collected included both the type of product and the amount of product dispensed to the person for home and hospital treatment. Since 2007 the NHD has collected treatment usage data quarterly. Although batch numbers of concentrates were collected for a limited number of projects, they were not routinely collected, and the database has limited data in relation to this.

Evolving technology has had a significant impact on data collection methods over time. From 1995, the annual paper submissions or returns were entered into an electronic database upon receipt by the NHD. The 'annual return' of data became a fully electronic submission in 2003, facilitated by the development and implementation of the Haemophilia Centre Information System (HCIS). At the beginning of computerisation, some historical records were also entered into the database. However, it is important to note that only summary data and information thought to be significant at the time were transcribed from historical paper records onto the electronic database. Demographics and treatment usage data were transcribed from the historical paper records into the electronic record if a data field was available. As part of the NHD's work to answer the Rule 9 request from the Inquiry, considerable effort has been devoted to transcribing the available historical paper returns into the electronic database. Therefore, the data in this report and attached spreadsheets represent the data from electronic annual returns and the historical annual paper returns.

The quality of data submitted to NHD improved significantly with the computerisation of submissions. Submissions became more timely and comprehensive once reporting to the NHD became mandatory in

2007/08 to comply with NHS commissioning contracts. There have also been intermittent initiatives by the Department of Health to encourage data submission. Similarly, reminders were sent by NHD to ensure a comprehensive view of treatment use across the country.

As improvements or upgrades to the electronic NHD were implemented, data fields were added, and others became redundant. During the early years of the database, changes to the data collection template were frequent. The changes in data fields make the comparison of data collected in the first few years challenging. Further, if centres reported data two to three years in arrears, only the years relevant to the following annual report were transcribed into the database. In preparing this report, data verification checks have been performed. Where gaps existed or anomalous data was found, a review of the archived paper return records was undertaken, and some data gaps were resolved. Technological advances with migration onto new databases created additional challenges. Due to the longitudinal nature of data collection, duplicate records of PwBD were not uncommon, impacting data quality. Errors in the submission were not always easily identifiable.

The NHD data has never been used to direct individual person care; therefore, individual PwBD level data in the NHD is not comparable to the information in a person's records held by hospitals or haemophilia centres.

1.2 Response to Rule 9 Request

Following the receipt of the initial Request from the Infected Blood Inquiry, a working group was established consisting of the membership below:

National Haemophilia Database members

- Professor Pratima Chowdary, Royal Free Hospital, London, and Co-Director of NHD and UKHCDO Chair (November 2021 onwards)
- Professor Charles Hay, Manchester Royal Infirmary and Co-Director of NHD
- Andrew McNally, NHD Manager
- Ben Palmer, Statistician, NHD
- Hua Xiang, Statistician, NHD
- Lynne Dewhurst, Analyst and Administrative Assistant, NHD until 2021
- Mike Grove, Data Manager, NHD until 2021

UKHCDO Executive members (2019-2021)

- Dr Ri Liesner, Great Ormond Street Hospital, London; UKHCDO Chair (2015-2021)
- Professor Peter Collins, Cardiff and Vale University Health Board, Cardiff; UKHCDO Vice-Chair (2016-2020)
- Dr Kate Talks, Royal Victoria Infirmary, Newcastle-upon-Tyne; UKHCDO Secretary until 2020, Vice-Chair since 2020

1.3 Working group and methods

The group communicated by email and met virtually to develop a response to each of the questions in the Rule 9 Request. Wherever possible, the questions were interpreted within the broader context of the Terms of Reference of the Inquiry. As a result, additional data has been provided in certain instances to aid analysis and subsequent interpretation, particularly of patterns and trends. Confounders identified by the working group and potential weaknesses of the data have been described where applicable.

The Rule 9 Request has been interpreted to cover all information held by NHD, including information held on the electronic database and in paper records. The paper records were scanned and uploaded into the database by the end of December 2020 to enable a comprehensive analysis of all information held by NHD.

Following data extraction, preliminary analysis and reconciliation were undertaken to identify redundancies, inconsistencies, and data gaps. Iterative data checks were undertaken; most questions required three or more rounds of extraction and checking. In some instances, assumptions were made due to data gaps and quality issues. These are described in the relevant sections.

Sections 2, 3 and 4 describe the data held in the NHD, namely diagnosis and clotting factor concentrates used in the UK and a list of the haemophilia centres that provide (or have provided) information to NHD about PwBD care.

Sections 5 -15 and the relevant pivot tables provide the responses to the questions posed in the Inquiry's Rule 9 Request. Where appropriate, the data for each question are presented as an Excel pivot table attachment with an explanation of the field labels provided in this document. Detailed methodology is provided in each section.

2 NHD – Bleeding disorder diagnoses

Bleeding disorders are caused by a partial or complete deficiency of clotting factors, platelets or a platelet component, or abnormalities of fibrinolysis. Following investigation and confirmation of the diagnosis, centres register the person on the NHD using the diagnostic categories available. The diagnostic categories on the NHD are related to the deficient component and are detailed in tables 2.1 to 2.5. In some instances where no laboratory explanation has been found, persons with bleeding symptoms can be diagnosed and registered as having an unclassified bleeding disorder.

A new bleeding disorder diagnosis is added to the database when a centre reports it for the first time or following a recommendation from national or international societies. Where possible, the severity of the deficiency is also quantified as it predicts the clinical picture and potential complications of the disorder.

Advances in scientific understanding have resulted both in new diagnoses and changes to existing disease classification and severity categorisation. The diagnosis at registration reflects the then prevailing nomenclature. Further, changes to existing registrations following updated nomenclature can

be slow, and centres may not implement minor changes if there is no immediate impact on a person's care. In addition, the registrations of deceased people are not updated.

The concentration of coagulation factors is measured in international units (IU) per decilitre (dL) or millilitre (mL). Normal coagulation factor activity is considered 100%, 100 IU/dL or 1.0 IU/mL with a reference range provided for the population. Before 2001, a factor level of 1% in persons with haemophilia A or B was variably defined as severe or moderately severe. The definitions used in the tables in this section for categorising the severity of haemophilia A and B were formalised in 2001 following international guidance (White, Rosendaal et al., 2001*). Before this, centres used contemporaneous criteria for categorisation, and consequently, many of those who would now be categorised as having moderate haemophilia were registered as having severe haemophilia. The changes over time have been addressed by classifying people with haemophilia A or B by factor levels rather than the severity classification.

Uncommon or infrequently encountered diagnoses have been grouped in the data extracts into recognised categories such as rare bleeding disorders or acquired bleeding disorders. A small number of individuals without a confirmed bleeding disorder have been recorded on NHD as having a possible bleeding disorder or other coagulation disorders, due to exposure to blood products, including plasma-derived concentrates. This diagnostic group have been listed separately in section 2.6 and excluded from analysis as they are not inherited bleeding disorders, and data submission has not been consistent between the centres.

The categories of bleeding disorder diagnoses that have been used are listed below:

2.1 Congenital factor deficiencies

2.2 Platelet disorders – inherited and acquired

2.3 Rare bleeding disorders

2.4 Acquired factor deficiencies

2.5 Combined and miscellaneous disorders

2.6 Non-bleeding disorders recorded on NHD (excluded from the analysis)

2.1 Congenital factor deficiencies

Haemophilia A* – deficiency of factor VIII
• Severe (<1%, <1 IU/dL or <0.01 IU/mL)
• Moderate (1 to 5%, 1–5 IU/dL or 0.01–0.05 IU/mL)
• Mild (>5% to 40%, >5–40 IU/dL or >0.05–0.40 IU/mL)
• Mild (>40%, >40 IU/dL or >0.40 IU/mL)

*White, G. C., 2nd, F. Rosendaal, L. M. Aledort, J. M. Lusher, C. Rothschild, J. Ingerslev, V. Factor and I. X. S. Factor (2001). "Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardisation committee of the International Society on Thrombosis and Haemostasis." Thromb Haemost 85(3): 560.

Haemophilia B* – deficiency of factor IX
• Severe (<1%, <1 IU/dL or <0.01 IU/mL)
• Moderate (1 to 5%, 1–5 IU/dL or 0.01–0.05 IU/mL)
• Mild (>5% to 40%, >5–40 IU/dL or >0.05–0.40 IU/mL)
• Mild (>40%, >40 IU/dL or >0.40 IU/mL)
Haemophilia A carrier
Females with factor VIII deficiency
Haemophilia B carrier
Females with factor IX deficiency
Factor IX Leyden deficiency
Factor IX Leyden deficiency carrier
Haemophilia A with liver transplant
Haemophilia B with liver transplant
Females with factor VIII deficiency with liver transplant
Factor IX Leyden deficiency with liver transplant
Von Willebrand disease
• Type 1
• Type 2A
• Type 2B
• Type 2M
• Type 2N
• Type 2 not specified
• Type 3
• Low VWF
• Other
• Type not reported
von Willebrand disease with liver transplant
Probable von Willebrand disease
Factor V deficiency
Factor VII deficiency
Factor X deficiency
Factor X deficiency with liver transplant
Factor XI deficiency
Factor XI deficiency with liver transplant

Factor XIII deficiency
Prothrombin (factor II) deficiency
Dysfibrinogenaemia
Hypofibrinogenaemia
Hypodysfibrinogenaemia
Afibrinogenaemia
Fibrinogen deficiency
Unclassified bleeding disorder

2.2 Platelet disorders – inherited and acquired

Glanzmann's thrombasthenia
Bernard-Soulier syndrome
Other severe platelet disorder
Platelet-type pseudo von Willebrand disease
Heritable platelet disorder
Other platelet disorder

2.3 Rare bleeding disorders

Alpha 2-antiplasmin deficiency
Thrombomodulin-associated coagulopathy
Combined factors II, VII, IX and X deficiencies
Combined factors V and VIII deficiencies

2.4 Acquired factor deficiencies

Acquired haemophilia A
Acquired von Willebrand disease
Acquired haemophilia B
Acquired factor V deficiency
Acquired factor XIII deficiency
Acquired prothrombin deficiency
Other acquired factor deficiency

2.5 Combined and miscellaneous disorders

Combined haemophilia A and B
Combined haemophilia A and von Willebrand disease
Combined haemophilia A and factor XII deficiency

Combined von Willebrand disease and haemophilia A carrier
Combined von Willebrand disease and factor V deficiency
Combined von Willebrand disease and factor VII deficiency
Combined von Willebrand disease and factor IX deficiency
Combined von Willebrand disease and factor XI deficiency
Combined von Willebrand disease and factor XII deficiency
Combined von Willebrand disease and lupus anticoagulant
Combined factors V and VII deficiencies
Combined factors V and XIII deficiencies
Combined factors VII and X deficiencies
Combined factors VII and XI deficiencies
Combined factors VII and XII deficiencies
Combined factors IX and XI deficiencies
Combined factors IX and XII deficiencies
Combined factors XI and VIII deficiencies
Combined factors XI and XII deficiencies
Combined factor XI deficiency and dysfibrinogenaemia
Combined factor XI deficiency and platelet disorder
Combined factors XII and VIII deficient haemophilia A carrier
Combined factor XII deficiency and platelet disorder
Multiple diagnoses
Miscellaneous bleeding disorders

2.6 Non-bleeding disorders recorded on NHD (excluded from the analysis)

Factor XII (Hageman) defect
Fletcher Factor
Antithrombin deficiency
Capillary defects
Protein Z deficiency
Temporary coagulation defect, now normal
Partner (Some partners' or spouses' results relating to HIV infection were recorded on the NHD)

3 Clotting factor concentrates and blood products

The clotting factor concentrates (CFCs), and blood products recorded on the NHD are listed in the tables below, categorised by factor type (active ingredient, i.e. clotting factor) and source of the product (recombinant or plasma-derived) as follows:

3.1 FVIII clotting factor concentrates – Recombinant

3.2 FVIII clotting factor concentrates – Plasma-derived including VWF containing concentrates

3.3 FIX clotting factor concentrates – Recombinant

3.4 FIX clotting factor concentrates – Plasma-derived

3.5 Other clotting factor concentrates – Recombinant

3.6 Other clotting factor concentrates – Plasma-derived

3.7 Other blood components recorded on NHD – Potentially used for bleeding disorders

3.8 Other blood components/products recorded on NHD – Not used for bleeding disorders

3.9 Adjunctive treatment – Desmopressin

3.10 Other adjunctive treatments and clinical trials not included in the pivot tables

Each table lists the NHD product name, which may be related to either the generic or trade name. If the NHD product name is not the trade name, attempts have been made to match it to a known trade name and manufacturer. Some products reported in the historical paper returns could not be reconciled to an existing NHD product code, and new codes were created when this data was entered into the database for this report. When an investigational medicinal product in a clinical trial was documented in the NHD, the name of the trial was registered under the NHD product name.

Where available, information has been provided on the active ingredient for recombinant products. If this information is not available, the entry used is 'not stated'. For plasma-derived products, there is no specific nomenclature for the active ingredient. Details of the manufacturer were updated as companies changed ownership and when NHD became aware of the change, but there is no audit trail of these changes on the database. Where the manufacturer's identity is not known, the entry used is 'not recorded'.

3.1 FVIII clotting factor concentrates – Recombinant

NHD - Product Name	Trade name	Active ingredient, Generic name	Manufacturer
Advate	Advate	Octocog alfa	Baxter (Baxalta, Shire, Takeda)
Adynovi	Adynovi	Rurioctocog alfa pegol	Baxalta (Shire, Takeda)
A-Long Trial (rFVIIIFc)	Clinical trial (Elocta)	Efmoroctocog alfa	Biogen/SOBI
ASPIRE	Clinical trial (Elocta)	Efmoroctocog alfa	Biogen/SOBI
BAX826 Trial	Clinical trial	Polysialated octacog alfa	Baxalta

BAX855 PEGylated rFVIII Trial	Clinical trial (Adynovi)	Rurioctocog alfa pegol	Baxalta
Baxter Trial Recombinant FVIII	Clinical trial (Recombinate, formerly Bioclate)	Octocog alfa	Baxter
Bioclate	Bioclate (1993- 2002)	Octocog alfa	Aventis
Cutter FVIII DNA		rFVIII, not stated	Cutter
Cutter VIIIR_DNA		rFVIII, not stated	Cutter
Elocta	Elocta	Efmoroctocog alfa	SOBI
GENA 03, 05, 08. 13. 15 and 21 Trials	Clinical trials (Nuwiq)	Simoctocog alfa	Octapharma
GreenGene	Clinical trial	Beroctocog alfa	Green Cross Corporation
Helixate	Helixate	Octacog alfa	CSL Behring
Helixate Nexgen	Helixate Nexgen	Octacog alfa	CSL Behring
Investigational rFVIII		rFVIII, not stated	Not recorded
Kabi (VIIIr)		rFVIII, not stated	Fresenius Kabi
Kogenate	Kogenate	Octacog alfa	Bayer
Kogenate 2/KSF	Kogenate	Octacog alfa	Bayer
Leopold II Trial	Clinical trial (Kovaltry)	Generic name not recorded	Bayer
N8 (rVFIII) Trial	Clinical trial (NovoEight)	Turoctocog alfa	Novo Nordisk
N8-GP rFVIII	Esperoct	Turoctocog alfa pegol	Novo Nordisk
N8-GP rFVIII, glycopegylatedTrial	Clinical trial (Esperoct)	Turoctocog alfa pegol	Novo Nordisk
NovoEight	NovoEight	Turoctocog alfa	Novo Nordisk
Nuwiq	Nuwiq	Simoctocog alfa	Octapharma
OBIZUR	Obizur	Sustacog alfa	Shire
Other FVIII DNA		rFVIII, not stated	Not recorded
Porcine rVIII Trial (OBI-1)	Clinical trial (Obizur)	Sustacog alfa	Inspiration Biopharmaceuticals
Protect Trial	Clinical trial	rFVIII, not stated	Bayer
Recombinant VIII (Brand Not Specified)		rFVIII, not stated	Not recorded
Recombinate	Recombinate	Octacog alfa	Baxter
Refacto	ReFacto	Moroctocog alfa	Wyeth
ReFacto AF	ReFacto AF	Moroctocog alfa	Pfizer
Refacto AF Trial	Clinical trial (ReFacto AF)	Moroctocog alfa	Wyeth
ReITIrate (SOBI-ITI)	Clinical trial (Elocta)	Efmoroctocog alfa	SOBI
r-VIII SQ	ReFacto	Moroctocog alfa	Wyeth

RVIIIA		rFVIII, not stated	Not recorded
VIII rDNA (Pharmacia)		rFVIII, not stated	Wyeth

3.2 FVIII clotting factor concentrates - Plasma-derived including VWF containing concentrates

NHD - Product Name	Trade Name	Manufacturer
Alphanate	Alphanate	Grifols
American Red Cross VWF concentrate		American Red Cross
Australian FVIII		Manufactured locally and country origin reported in the name
Behring FVIII	Behring FVIII	Aventis
BehringFVIII LoHep	BehringFVIII LoHep	CSL Behring
Beriate P	Beriate P	CSL Behring
Bovine FVIII		The product was manufactured locally, source unknown
Cutter FVIII (Koate)	Koate	Cutter
Cyprus FVIII		Manufactured locally and country origin reported in the name
Factorate	Factorate	Armour
Factorate HP	Factorate HP	Armour
Fanhdi	Fanhdi	Grifols
French FVIII		CRTS
FVIII - Brand Not Specified		The product was manufactured locally, source unknown
BPL FVIII (NHSF8)		Blood Products Laboratory (BPL), Elstree
FVIII (PFC)		Protein Fractionation Centre, Edinburgh
FVIII 8SM (BPL)		Blood Products Laboratory (BPL), Elstree
FVIII 8Y (BPL)	BPL 8Y	Blood Products Laboratory (BPL), Elstree
FVIII 8Y2 (BPL)		Blood Products Laboratory (BPL), Elstree
FVIII HP (PFC)		Protein Fractionation Centre, Edinburgh
FVIII IP (PFC)		Protein Fractionation Centre, Edinburgh
FVIII LoHep (BPL)		Blood Products Laboratory (BPL), Elstree
FVIII Mono (BPL)		Blood Products Laboratory (BPL), Elstree
Haemate P	Haemate P	CSL Behring
Haemoctin	Haemoctin	Biotest
Hemofil-M	Hemofil-M	Baxter
Hemophil (Trial - 1998)	Clinical trial	Baxter
Hoechst FVIII		Hoechst
Humanate	Humanate	Aventis

Immune VIII_G		The product was manufactured locally, source unknown
Innovate	Innovate	CRTS
Kabi FVIII	Kabi FVIII	Kabi
Koate DVI	Koate DVI	Bayer
Koate HP	Koate HP	Bayer
Kryobulin	Kryobulin	Immuno
Liberate	Liberate	Protein Fractionation Centre, Edinburgh
Liberate HT	Liberate HT	Protein Fractionation Centre, Edinburgh
Monarc-M (Trial - 1998)	Clinical trial	American Red Cross
Monoclate	Monoclate	Aventis
Monoclate P	Monoclate P	CSL Behring
NHS 2		The product was manufactured locally, source unknown
NHS FVIII (BPL)		Blood Products Laboratory (BPL), Elstree
Octanate	Octanate	Octapharma
Octapharma FVIII		Octapharma
Optivate	Optivate	Blood Products Laboratory (BPL), Elstree
Oxford DE1		Plasma Fractional Laboratory (PFL), Oxford
Oxford FVIII		Plasma Fractional Laboratory (PFL), Oxford
Plasmapharm FVIII		The product was manufactured locally, source unknown
Porcine FVIII	Hyate C	Speywood
Profilate	Profilate	Alpha
Replenate (BPL)	Replenate (BPL)	Blood Products Laboratory (BPL), Elstree
South African FVIII		Manufactured locally and country origin reported in the name
Travenol/Hyland/Hemofil FVIII	Travenol/Hyland/Hemofil FVIII	Travenol/Hyland/Hemofil
Voncento	Voncento	CSL Behring
Wilate	Wilate	Octapharma

3.3 FIX clotting factor concentrates – Recombinant

NHD - Product Name	Trade name	Active ingredient, Generic name	Manufacturer
Alprolix	ALPROLIX	Efrempmacog alfa	SOBI
BAX326 (rFIX) Trial	Clinical trial (Rixubis)	Nonacog gamma	Baxter
Baxter rFIX 250901 Trial	Clinical trial (Rixubis)	Nonacog gamma	Baxter
BeneFIX	BeneFIX	Nonacog alfa	Pfizer

B-Long Trial (rFIXFc)	Clinical trial (ALPROLIX)	Efrempmacog alfa	SOBI/Biogen
Genetics Institute Trial Factor IX	BeneFIX	Nonacog alfa	Baxter
Idelvion	Idelvion	Albutrepenonacog alfa	CSL Behring
Inspiration IB1001 Trial	Clinical trial (Ixinity)	Trenonacog Alfa	Inspiration Biopharmaceuticals
Investigational rFIX		rFIX, not stated	
Kabi (IXr)		rFIX, not stated	Baxter
N9-GP Trial	Clinical trial (Refixia)	Nonacog beta pegol	Novo Nordisk
Recombinant IX	Rixubis	Nonacog gamma	Baxter
Refixia	Refixia	Nonacog beta pegol	Novo Nordisk
Rixubis	Rixubis	Nonacog gamma	Shire

3.4 FIX clotting factor concentrates – Plasma-derived

NHD - Product Name	Trade name	Manufacturer
Alphanine	Alphanine	Grifols
Armour FIX	Armour FIX	Armour
Australian FIX		Not recorded
Commercial FIX - Brand not specified		Not recorded
Cutter FIX		Cutter
Danish FIX		Not recorded
Faktor IX (Dutch Red Cross)		Dutch Red Cross
FIX (BPL)		Blood Products Laboratory (BPL), Elstree
FIX defix (PFC)		Protein Fractionation Centre, Edinburgh
FIX_9A (BPL)		Blood Products Laboratory (BPL), Elstree
FIX_9MC		Blood Products Laboratory (BPL), Elstree
FIX_Lo_Hep		Blood Products Laboratory (BPL), Elstree
French FIX		CNST
Haemonine	Haemonine	Biotest
HP Factor IX - Brand not specified		Not recorded
Immuno FIX	Immuno FIX	Immuno
Kabi FIX	Kabi FIX	Kabi
Mononine	Mononine	CSL Behring
Nanotiv	Nanotiv	Octapharma
NHS FIX (BPL)	NHS FIX (BPL)	Blood Products Laboratory (BPL), Elstree
Octa FIX	Octa FIX	Octapharma

Oxford Special IX Concentrate		Plasma Fractional Laboratory (PFL), Oxford
PFC FIX_HP		Protein Fractionation Centre, Edinburgh
PFC FIX_IP		Protein Fractionation Centre, Edinburgh
Profilnine	Profilnine	Grifols
Proplex	Proplex	Baxter
Replenine (BPL)	Replenine (BPL)	Blood Products Laboratory (BPL), Elstree
Travenol FIX	Travenol FIX	Baxter

3.5 Other clotting factor concentrates – Recombinant

NHD - Product Name	Trade name	Factor type	Active ingredient, Generic name	Manufacturer
Activated FVIIA	Novoseven	FVIIa	Eptacog alfa	Novo Nordisk
BAX 111 (rVWF 071001) Trial	Clinical trial (Veyvondi)	rVWF	Vonicog alfa	Baxter
FVII - Novo FVIIA	Novoseven	FVIIa	Eptacog alfa	Novo Nordisk
Investigational rFVII	Clinical trial	FVIIa	rFVIIa, not stated	Not recorded
Investigational rFXIII	Clinical trial (Novothirteen)	FXIII	Catridecacog	Novo Nordisk
Investigational rVWF	Clinical trial (Veyvondi)	rVWF	Vonicog alfa	Baxalta
N7-GP (rFVIIa, glycopegylated) Trial	Clinical trial	FVIIa	Eptacog alfa pegol	Novo Nordisk
NovoThirteen	Novothirteen	FXIII	Catridecacog	Novo Nordisk
Recombinant VIIa analogue	Clinical trial	FVIIa	rVIIa analogue	Bayer
rFXIII Trial	Novothirteen	FXIII	Catridecacog	Novo Nordisk
Veyvondi	Veyvondi	rVWF	Vonicog alfa	Takeda

3.6 Other clotting factor concentrates - Plasma-derived

NHD - Product Name	Trade name	Factor type	Manufacturer
Autoplex	Autoplex	Bypass - plasma-derived	Baxter
Beriplex	Beriplex	Prothrombin complex concentrate (PCC)	CSL Behring
BPL FX (Ten02) Trial	Clinical trial (Coagadex)	FX	Blood Products Laboratory (BPL), Elstree
Coagadex	Coagadex	FX	Blood Products Laboratory (BPL), Elstree

FEIBA	FEIBA	Bypass - plasma-derived	Baxter
FibCLOT	FibCLOT	Fibrinogen	LFB Biomedicaments
Fibrogammin P	Fibrogammin P	FXIII	CSL Behring
FVII - Com FVII (Baxter)		FVII	Baxter
FVII - NHS FVII (BPL)		FVII	Blood Products Laboratory (BPL), Elstree
FX (BPL Ten03) Trial	Clinical trial (Coagadex)	FX	Blood Products Laboratory (BPL), Elstree
FX (BPL)	Coagadex	FX	Blood Products Laboratory (BPL), Elstree
FXI (BPL)	Hemoleven	FXI	Blood Products Laboratory (BPL), Elstree
FXIII (CSL)	Fibrogammin P	FXIII	
Haemocomplettan P	Haemocomplettan P	Fibrinogen	CSL Behring
Hemoleven	Hemoleven	FXI	LFB
Hemoleven (LFB XI)		FXI	LFB Biomedicaments
Hoesch FXIII		FXIII	Hoesch
Immuno Fibrinogen		Fibrinogen	Immuno
Immuno FVII		FVII	Immuno
Not recorded		Visitor with own material	
Octaplex	Octaplex	PCC	Octapharma
Oxford XI		FXI	Plasma Fractional Laboratory (PFL), Oxford
Prothromplex	Prothromplex	PCC	Baxter
Prothromplex-T	Prothromplex-T	PCC	Baxter
Riastap	Riastap	Fibrinogen	CSL
THP (French vWF)		VWF	
VII Conc		FVII	Unknown
VW Factor		VWF	CNTS
VWF HP		VWF	
Wilfact	Wilfact	VWF	LFB Biomedicaments
Wilfact /Wilfactin	Wilfact /Wilfactin	VWF	LFB Biomedicaments

3.7 Other blood components recorded on NHD - Potentially used for bleeding disorders

Listed below are products that may have been used to manage a bleeding disorder or other complications unrelated to the inherited bleeding disorders. The clinical indication for the use of the below components has not always been provided by the centres.

NHD - Product Name	Manufacturer
Armour PPF	Armour
Cryoprecipitate	National Blood Transfusion Service
FFP, fresh frozen plasma	National Blood Transfusion Service
Fibrinogen	Not recorded
HPPF	Not recorded
Interhem	Not recorded
Octaplas	Octapharma
Platelets	National Blood Transfusion Service
Whole Blood	National Blood Transfusion Service

3.8 Other blood components/products recorded on NHD – Not used for bleeding disorders

NHD - Product Name	Manufacturer
Albumin	Not recorded, there have been numerous suppliers, including the national Blood Transfusion Service
Antithrombin (Kybernin P)	CSL Behring
Antithrombin, recombinant (Atryn)	LEO Laboratories Ltd
Blood component	Anti D
Immuno G	Not recorded
Immunoglobulin	Not recorded
Packed Cells	National Blood Transfusion Service
Sandoglobulin	Sandoz
Vigam-S	BPL

3.9 Adjunctive treatment - Desmopressin

NHD - Product Name	Manufacturer
DDAVP	Ferring
Desmopressin (4mcg/ml)	Ferring
Desmopressin Nasal Spray	Ferring
Desmopressin Nasal Spray (10mcg/6ml vial)	Ferring
Desmopressin Sub Cut (15mcg/ml)	Ferring
Octostim (Nasal Spray)	Ferring
Octostim (subcutaneous)	Ferring

3.10 Other adjunctive treatments and clinical trial products not included in the pivot tables

Several of the therapies listed below have been reported variably by the haemophilia treatment centres and are not in scope for this report. These include novel drugs used in clinical trials, drugs used for the management of other medical conditions, or for eradication of an inhibitor in patients with an acquired bleeding tendency. It also includes anti-fibrinolytics that stabilise clots, and topical haemostatic treatments, which have not been associated with transfusion transmitted infections.

NHD - Product Name	Product type	Manufacturer
ALN-AT3SC	Non-Factor replacement therapy	Alnylam Pharmaceuticals
Analgesics	Painkillers	
Antibiotics	Anti-infectives	
Azathioprine	Immunosuppressant	
BAY 1093884	Non-Factor replacement therapy	Bayer
BAY 1093884 (anti-TFPI)	Non-Factor replacement therapy	Bayer
Beriplast -fibrin sealant	Topical	CSL Behring
Chlorpheniramine	Anti-allergy medication	Not applicable
CI Esterase Inhibitor	Therapy for an immunological disorder	
Corticosteroids	Immunosuppressant	
Cyclokapron	Antifibrinolytics	
Cyclophosphamide	Immunosuppressant	
Emicizumab / Hemlibra®	Non-Factor replacement therapy	Roche
Engerix B / Hepatitis B Vaccine	Vaccine	
Epsilon-aminocaproic acid (EACA)	Antifibrinolytics	
Explorer4 (Concizumab)	Non-Factor replacement therapy	
Ferrous Sulphate/iron supplements	Iron deficiency treatment	
Hepatitis A vaccine	Vaccine	
Interferon	Immunomodulatory	
Rituximab	Immunosuppressant	IDEC Pharmaceuticals
Steroids - Hydrocortisone prednisolone	Immunosuppressant	
Topical Adrenalin	Topical haemostatic agent	
Topical Thrombin	Topical haemostatic agent	
Tranexamic Acid	Antifibrinolytics	
Warfarin	Anticoagulant	

4 Haemophilia Centres by geographical location

A number of the questions contained within the Rule 9 Request seek data by individual haemophilia centre. The tables below provide a list of the centres and their allocated NHD centre number. Some larger centres achieved designation as 'Haemophilia Comprehensive Care Centres' (CCCs) in 1993 following NHS guidance document HSG93[30]. This stated that a centre could be designated as a CCC if it had a minimum of 40 patients with severe haemophilia A or B. Other centres providing care for patients with PwBD were identified as "Haemophilia Centres" (HC) if the criteria for CCC designation were not fulfilled.

The rationale underpinning the allocation of NHD centre numbers to centres has not been documented. A review suggests that different parts of the country might have been allocated groups of numbers set up discontinuously to account for potential growth. The centres have been grouped by regions in current use and ordered by centre number. The regions used for listing the centres are provided below.

4.1 East Midlands

4.2 East of England

4.3 London

4.4 North East

4.5 North West

4.6 South West

4.7 South East

4.8 West Midlands

4.9 Yorkshire and the Humber

4.10 Northern Ireland

4.11 Scotland

4.12 Wales

In the last 50 years, some centres have closed, new centres have opened, and others have merged due to the merger of host organisations. Further, some centres have formally requested inactivation and been marked as inactive centres on NHD, although they may be providing care in collaboration with a CCC. The 'current designation' column in the tables lists the current status of the centre as known to NHD, with options being CCC, HC, or inactive HC.

The timespan over which each centre submitted annual returns and for which the NHD holds treatment records is also provided below. As the analysis in this report only includes data up to the end of 2020, centres that remain active have been listed with an "End Year" of 2020.

4.1 East Midlands

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year

2	Kettering	HC	1975	2020
3	Northampton	HC-Inactive	1976	2013
42	Derby	HC	1973	2020
43	Leicester	CCC	1976	2020
44	Nottingham	CCC	1974	2020
51	Lincoln	HC	1980	2020

4.2 East of England

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
89	Cambridge	CCC	1969	2020
90	Norwich	HC	1975	2020
91	Stevenage	HC	1987	2020
92	Luton	HC	1987	2020
93	Bedford	HC-Inactive	1975	2012
97	Harlow	HC	1976	2006
98	Colchester	HC	2006	2006
99	Grays (Orsett Hospital)	HC-Inactive	1976	2004
100	Chelmsford	HC-Inactive	1980	2004
101	Southend - Westcliffe on Sea	HC-Inactive	1976	2000
102	Ipswich	HC-Inactive	1971	1998
103	Peterborough	HC-Inactive	1988	1996
104	Kings Lynn	HC-Inactive	1975	1993
105	Bury St. Edmunds	HC-Inactive	1976	1991
134	Great Yarmouth (James Paget)	HC-Inactive	1989	1990

4.3 London

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
79	University College London Hospitals Trust [a]	HC-Inactive	1991	2001
80	Royal Free	CCC	1969	2020
81	Charing Cross	HC-Inactive	1976	1993
82	Hammersmith Hospital	HC	1969	2020
83	University College Hospital [a]	HC-Inactive	1969	1988

84	St. Mary's Hospital	HC-Inactive	1969	1997
85	Westminster Hospital	HC-Inactive	1969	2000
86	Great Ormond Street	CCC	1969	2020
87	The Royal London Hospital	CCC	1969	2020
88	The Middlesex Hospitals [a]	HC-Inactive	1969	1986
94	Edgware	HC-Inactive	1975	1991
95	Hillingdon	HC-Inactive	1976	2002
96	Harrow (Northwick Park Hospital)	HC-Inactive	1976	2002
110	St Thomas' and Guy's Hospital [b,c]	CCC	1969	2020
111	St George's Hospital	HC	1969	2020
112	Guy's Hospital, London [c]	HC-Inactive	1969	1992
113	King's College Hospital	HC-Inactive	1969	2003
114	Lewisham	HC	1969	2020
124	Carshalton	HC-Inactive	1980	2006
128	Kingston on Thames	HC-Inactive	1977	2006
129	Roehampton	HC-Inactive	1978	1997
131	Thornton Heath	HC-Inactive	1978	2007

(a) The Middlesex and University College Hospitals merged in 1989/1990 to become a single organisation. The haemophilia centre at University College London hospital was allocated centre number 79. Treatment records are missing for a few years around the time of the merger.

(b) Centre 110 submitted treatment data from 1969-1994 and from 2007 to date.

(c) In 1993, Guys hospital (112) merged with St. Thomas' hospital (110), and all patients from centre 112 were moved to centre 110, and all treatment was issued from centre 110, although patients could be seen at both sites.

4.4 North East

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
140	Newcastle upon Tyne	CCC	1969	2020
142	Darlington	HC-Inactive	1978	1984
143	Middlesbrough	HC-Inactive	1976	1998
144	Sunderland	HC-Inactive	1979	1979

4.5 North West

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
60	Manchester (Adults)	CCC	1969	2020
61	Manchester Children's	CCC	1972	2020
62	Lancaster	HC	1977	2020
63	Blackburn	HC-Inactive	1978	2010
64	Liverpool (R. I.)	CCC	1977	2020
65	Liverpool Children's	CCC	1975	2020
66	Liverpool (Walton Hospital)	HC-Inactive	1976	1984
68	Booth Hall	HC-Inactive	1972	1972
69	Leighton	HC-Inactive	1977	1998
71	Blackpool	HC-Inactive	1988	1996
141	Carlisle	HC-Inactive	1969	1986
145	Whitehaven	HC-Inactive	1976	1988

4.6 South West

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
6	Bournemouth / Poole	HC	1970	2020
7	Dorchester	HC	1976	2000
9	Salisbury	HC	1975	2020
12	Barnstaple	HC	1977	2020
13	Bristol (Infirmary & Children's)	CCC	1969	2020
14	Exeter	HC	1969	2020
15	Plymouth	HC	1975	2020
16	Taunton / Yeovil	HC	1976	2020
17	Torquay	HC	1977	2020
18	Truro	HC	1977	2020
28	Bath	HC-Inactive	1977	2006
29	Swindon	HC-Inactive	1978	1994
30	Gloucester	HC-Inactive	1980	1995
31	Cheltenham	HC-Inactive	1980	1980

4.7 South East

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
1	Oxford	CCC	1969	2020
4	Slough	HC-Inactive	1977	1997
8	Portsmouth	HC	1969	2020
32	Isle of Wight	HC-Inactive	1982	1983
33	High Wycombe	HC-Inactive	1985	1998
35	Basingstoke and Treloar [(d)]	CCC	1969	2003
36	North Hampshire (Basingstoke)[(d)]	CCC	2004	2020
37	Southampton	CCC	1972	2020
115	Canterbury	CCC	1969	2020
116	Gillingham, Kent (Medway)	HC-Inactive	1977	2013
117	St. Leonard's on Sea	HC-Inactive	1976	2011
118	Brighton	HC	1976	2020
119	Eastbourne	HC-Inactive	1976	2009
120	Maidstone	HC-Inactive	1976	1993
121	Pembury, Tunbridge Wells	HC-Inactive	1977	2002
122	Ashford, Middlesex	HC-Inactive	1976	1992
123	Camberley (Frimley Park)	HC-Inactive	1977	2002
125	Chertsey (St Peter's Hospital)	HC-Inactive	1977	2003
126	Chichester	HC	1977	2020
127	Epsom	HC-Inactive	1977	2001
130	Redhill	HC-Inactive	1977	1993
132	Worthing	HC-Inactive	1977	2006
133	Guildford	HC-Inactive	1980	1992
135	Ashford & St. Peters	HC	2004	2016

(d) North Hampshire from 2004

4.8 West Midlands

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
19	Birmingham (Queen Elizabeth)	CCC	1969	2020
20	Birmingham Children's	CCC	1969	2020
21	Coventry	HC	1974	2020

22	Hereford	HC-Inactive	1975	2004
23	Shrewsbury	HC	1974	2020
24	North Staffordshire (Stoke on Trent)	HC	1975	2020
25	Worcester	HC-Inactive	1975	2011
26	Wolverhampton	HC	1975	2020

4.9 Yorkshire and the Humber

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
40	Sheffield (Royal Hallamshire)	CCC	1969	2020
41	Sheffield (Children's)	CCC	1973	2020
45	Bradford	HC	1969	2020
46	Harrogate	HC-Inactive	1975	2003
47	Huddersfield	HC-Inactive	1972	2009
48	Kingston upon Hull (Hull)	HC	1969	2020
49	Leeds	CCC	1969	2020
50	York	HC-Inactive	1975	2019

4.10 Northern Ireland

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
27	Belfast[(e)]	Split into below CCCs in 2007	1969	2005
72	Belfast - Adult's[(e)]	CCC	2006	2020
73	Belfast - Children's[(e)]	CCC	2006	2020

(e) Belfast Adult's and Children's Hospital became individual centres in 2006; before then, they were a single centre called Belfast, centre number 27.

4.11 Scotland

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
160	Aberdeen	HC	1969	2020
161	Dundee	HC	1969	2020
162	Edinburgh	CCC	1969	2020

163	Glasgow (RI)	CCC	1969	2020
164	Glasgow (RHSC)	CCC	1977	2020
165	Inverness	HC	1969	2020
166	Glasgow - No longer a Centre [f]	HC-Inactive	1980	1984

(f) This centre number recorded products issued by small hospitals in Western Scotland ordered directly from the Scottish National Blood Transfusion Service. The records have been allocated to centres 163 and 164 for this report.

4.12 Wales

Centre Number	Centre Name	Current designation	NHD treatment records	
			Start Year	End Year
67	Bangor	HC	1977	2020
70	Maelor Hospital	HC-Inactive	1980	1989
150	Cardiff	CCC	1969	2020
151	Swansea	HC	1976	2020
152	Abergavenny [g]	HC	2016	2020
153	Newport [g]	HC-Inactive	1977	2015

(g) The Newport Haemophilia Centre was designated centre number 152 from 1977 until 2015. In 2016 the Haemophilia Centre for South-east Wales relocated from Newport to Abergavenny as both hospitals are part of the same health care organisation (Aneurin Bevan University Health Board). Following the transfer of the Centre, despite being the same organisation, Abergavenny has been designated centre 152. To differentiate the two hospitals in this report, centre records from Newport, up to and including 2015, have been reassigned to a newly created centre number labelled as 153.

5 Total annual use of Factor VIII, Factor IX, cryoprecipitate and any other blood product by Haemophilia Centre in England, Wales, Scotland and Northern Ireland from 1976 to 1994, disaggregated by year and centre, including DDAVP usage, showing the different products used to treat different factor deficiencies.

The earliest records in the NHD were from 1969, when the MRC cryoprecipitate working party collected data from a small number of centres. The data collection format frequently changed in the early years, and the pre-1976 submission formats were inconsistent; due to these limitations, the data from pre-1976 has not been included in this report. From around 1977 to around 2005, annual returns included total consumption data for the centre that included all products for all individuals. The consumption figure represents the total number of units of treatment administered in the hospital and/or issued to the person for home treatment. In addition, centres also provided individual level data limited to the product types (but not the quantity of each type) used by individual PwBD for the majority of diagnoses. However, for PwH with inhibitors or people with very rare bleeding disorders, data on product type and consumption in units was reported at an individual level.

5.1 Inclusion criteria

- Data held electronically for treatment issued by centres to PwBD from 1976 to 1994.

5.2 Exclusion criteria

- Non-bleeding disorder diagnosis as described in section 2.6.

5.3 Results

Data for concentrate consumption and the number of PwBD who potentially received treatment is displayed by year, Centre, bleeding disorder diagnosis, type of factor, and product names.

Results are provided electronically as an Excel pivot table attachment "5.3.1_Annual consumption of CFC 1976 to 1994". The explanations for the field labels in the pivot table are detailed below.

5.3.1 Annual consumption of CFC from 1976 to 1994

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Bleeding disorder diagnosis	Bleeding disorder diagnosis consolidated based on the missing factor. Haemophilia A category includes females with FVIII deficiency, haemophilia A carriers, haemophilia A with a liver transplant; Haemophilia B category includes females with FIX deficiency, haemophilia B carriers and haemophilia B with a liver transplant; von Willebrand disease includes von Willebrand with a liver transplant; and FX deficiency includes FX deficiency with liver transplant.

Factor type	Coagulation factor concentrate, i.e. FVIII, FIX etc.
NHD product name	Brand name of the product containing the coagulation factor(s)
Year	1976 to 1994
• **Units**	Consumption of each product in units per calendar year
• **PwBD**	Number of PwBD treated with the product in that year

5.4 Data limitations

- Regular submission of data was resource intensive for haemophilia centres, which were frequently under-resourced, resulting in varying quality of submissions over time. The submission of the returns depended on busy doctors and nurses manually collating data from paper records of multiple PwBD. In particular, the smaller centres struggled to provide data as they often relied on a single consultant to complete the return. This impacted the comprehensiveness of the data collected and the timeliness of submission, and annual reports were often delayed by two to three years. Over the years, the quality of returns improved, aided by computerisation and the subsequent service level agreement with the NHS in 2007 that mandated annual submission.
- Annual consumption data was available at Centre-level in most instances. For some years, if centre level data was unavailable on NHD, individual PwBD level data were aggregated to give a figure for total centre use. However, as the individual PwBD level data was typically not complete, the consumption figures derived in this manner may appear to be disproportionately low compared with consumption in surrounding years for that centre. In the pivot tables, this is evident as a dip in use in some years for some centres.
- Data return on desmopressin use was variable and incomplete across centres and over time. Similarly, data submission on supportive treatments like tranexamic acid fluctuated greatly and is therefore not included in the pivot tables.
- Where the database recorded the number of PwBD but no record of the number of units, or the number of units but not the number of PwBD, the missing value is reported as 'unknown' for that centre. Similarly, where there is a record of the product administered but no description of the number of units issued, the missing value is reported as 'unknown'.
- Some product consumption was reported in volume (bottles, bags, packs, vials or litres) rather than units, and in these instances, the number of units is reported as unknown in the main tab with the information provided in the additional tab.
- 1976 to 1994 was a time of significant change in the source of plasma and manufacturing steps. However, the changes implemented in the manufacturing of products, including measures to decrease the risk of transfusion transmitted infection (e.g., heat treatment), are not fully reflected in the annual returns. This might be because consumption was reported by a generic name (which did not specify whether the product had been heat-treated, for example) rather than the trade name, which might indicate the manufacturing and viral inactivation steps.
- Centres also tended to group products differently for the centre and individual PwBD level submissions. For example, in one year, a centre reported the use of "BPL FVIII LoHep", "BPL FVIII

Mono", and "BPL Replenate (Replenate)" at the centre level but consolidated them under 'BPL FVIII' in the patient-level submission. Therefore, it is impossible to tell which BPL product was used at the individual PwBD level. In addition, suffixes denoting the addition of viral inactivation steps were not always recorded in the submission.

6 Total annual use of recombinant factors by each Haemophilia Centre in England, Wales, Scotland and Northern Ireland from 1995 to 2020, with corresponding data for the total annual use of plasma-derived blood products for the same time frame.

The availability of recombinant clotting factor concentrates (CFC) for managing people with inherited bleeding disorders has increased over the years. Previously, recombinant CFC use was limited to specific disorders. The analysis has been limited to FVIII and FIX deficiency, where both recombinant and plasma-derived (pd) CFCs were available for routine clinical use during the relevant timeframe. The presence of inhibitors necessitated a change in the product used for controlling bleeding.

6.1 Inclusion criteria

- FVIII and FIX deficiency in people with congenital HA and HB, respectively, including women with low levels where both plasma-derived and recombinant CFCs were available for routine clinical use between 1995 and 2020, inclusive.

6.2 Exclusion criteria

- People with acquired haemophilia
- Deficiencies of other coagulation factors, where a licensed recombinant concentrate was not available for routine clinical use in the UK during the relevant timeframe, i.e.:
    - Recombinant factor XIII was used in clinical trials from 2011 and as part of a limited compassionate programme for named individuals from 2014.
    - Recombinant VWF was available for routine clinical use in adults with VWD from the last quarter of 2020.

6.3 Results

Data for consumption of CFC in units, both plasma-derived and recombinant, is displayed by year, centre, bleeding disorder diagnosis, inhibitor status, type of factor concentrate, and the number of PwH.

Results are provided electronically as an Excel pivot table attachment "6.3.1_Annual consumption of CFC from 1995 to 2020". The explanations for the field labels in the pivot table are detailed below.

6.3.1 Annual consumption of CFC from 1995 to 2020

Field label	Field description
Centre number	Number assigned in the database

Centre name	Name of the centre
Year	1995 to 2020 inclusive
Bleeding disorder diagnosis	Inherited FVIII and FIX deficiency, including all severities of haemophilia and females with factor deficiency.
Inhibitor status of PWH	Presence of inhibitors in PwH: yes - inhibitor present; no - inhibitor absent.
Factor type	Coagulation factor concentrate, i.e. FVIII, FIX etc.
Number of PWH	Number of PwH issued treatment in a calendar year at the centre – total and by inhibitor status.
Number of units of pd CFC issued	The total number of units of plasma-derived CFC issued by the centre in a calendar year by diagnostic category. The individual brands included are listed in section 3.
Units of pd CFC issued as % of total units CFC issued	The amount of plasma-derived CFC issued as a percentage of the total CFC units for that diagnostic category in a year
Number of PWH receiving pd CFC	Number of PwH issued with plasma-derived CFC by the centre in a calendar year by diagnostic category.
Number of units of recombinant CFC issued	The total number of units of recombinant CFC issued by the centre in a calendar year by diagnostic category. The individual brands included are listed in section 3.
Units of recombinant CFC issued as % of total units CFC issued	The amount of recombinant CFC issued as a percentage of the total CFC units for that diagnostic category in a year
Number of PWH receiving Recombinant CFC	Number of PwH issued with recombinant CFC by the centre in a calendar year by diagnostic category.
Total units CFC issued	Consolidated CFC consumption of either plasma-derived or recombinant CFC issued by diagnostic category per year.

6.4 Data limitations

- The data demonstrate increased consumption of clotting factors over time. The increase is due to increasing numbers of PwBD and changes in clinical practice, with an increasing number of severe PwH adopting prophylaxis. Occasionally, changes in use represent changes to the NHD data submission process across the country or at a centre level; for example, centre 110 submitted records in 2005 for the preceding ten years, which would not have been reflected in the annual statistical reports but are included in the current pivot table.
- The severity of haemophilia has a dominant influence on annual consumption, and persons with severe haemophilia require more CFC than those with moderate or mild disease. On average, people with severe haemophilia account for more than two-thirds of CFC consumption in a centre. It is important to note that the average consumption per person, where the denominator includes PwBD of all severities, cannot be used to compare clinical practice between centres as the percentage of PwBDs with different severities is variable across the centres.

- The presence of an inhibitor also influences the type and amount of product used. As FVIII or FIX are ineffective, they require treatment with either recombinant activated factor seven (rFVIIa) or plasma-derived bypassing agents. The number of units of plasma-derived bypassing agents needed for treatment is higher because of potency labelling and contribute substantially to the total units of plasma-derived CFCs consumed. Further, PwH with a previous inhibitor when using CFC may report higher consumption as the CFC may be cleared rapidly from the body.
- Consumption of recombinant factor IX is higher when compared to plasma-derived factor IX due to minor differences in the sugar structure between the two products. These differences affect the pharmacokinetic properties of the recombinant FIX, i.e., how the body handles the drug.
- Some results in this pivot table have a negative value for consumption of both plasma-derived and recombinant factors due to submission errors. Centres routinely reported consumption data separately for PwH with inhibitors and all PwH. The report presents data separately for inhibitor PwH and non-inhibitor PwH by subtracting the inhibitor PwH usage from the total usage. On occasions in error, centres appear to have submitted data for non-inhibitor PwH rather than all PwH, and in these instances, subtracting can result in negative values. For example, in 1996, centre 1 reported 450,360 units of plasma-derived bypass agent (FEIBA) issued for PwH with inhibitors and, presumably in error, submitted a total usage of 429,000 units for all PwH, resulting in a negative figure (-21,360 units) for the PwH without inhibitors. Such errors in submission by centres are apparent where a negative number is noted but may not always be easily identifiable; however, the proportion of such errors is probably less than 1% due to data checks undertaken during the publication of annual reports. Where such errors in submission have been noticed, they have been checked against the source data where available.
- Consumption data presented in the attached pivot table is the amount of product reported by centres as having been issued to PwH. In a small number of PwH, CFC may have been returned to the centre by the PwH. This tends to be common in people with mild bleeding disorders, where a product might have been issued as a safety net for travel or emergencies but not used. In such cases, the figure for the product issued does not equate to the product used by the PwH. However, the figure for products issued by the centre and used by PwBD is similar in the majority of cases.

7 The number of patients registered at each Haemophilia Centre in England, Wales, Scotland and Northern Ireland in one year intervals from 1969 to 2020, disaggregated to show the disorder (not limited to Haemophilia A, B, females with VIII and IX deficiencies and VWD) and the severity or type of the disorder.

Individuals are registered with a haemophilia centre following a diagnosis of an inherited bleeding disorder. Although five-year intervals were suggested by the Inquiry in their Rule 9 request, after discussions, it was agreed that data are presented for each centre by year. Annual statistics reflect real-time changes related to the transfer of PwBD between centres, new registrations due to births and immigration, de-registrations due to any cause, including death and emigration, and finally, centre closures or mergers.

The bleeding disorders presented in this analysis are described in section 2. HA and HB in congenital factor deficiency are categorised by factor levels, rather than as mild, moderate, and severe, to account for changes in classification over time. Reporting of the sub-type of VWD similarly has changed over the years and has been included where available. Amongst the acquired bleeding disorders (section 2.4), the more common acquired haemophilia A and acquired von Willebrand disease are presented as discrete categories, and the others are combined into 'Acquired factor deficiency (other)'. PwBD in the miscellaneous factor and platelet disorders category (section 2.5) are presented as a consolidated miscellaneous group because of small numbers.

7.1 Inclusion criteria

- PwBD registered with the NHD by 31st December 2020.
- Annual registrations include PwBD who were alive for some or all of that year.

7.2 Exclusion criteria

- Deceased PwBDs are excluded from a centre's results from the year after their death.

7.3 Results

Data on the number of registered PwBD per year is displayed by centre and bleeding disorder diagnosis.

Results are provided electronically as an Excel pivot table attachment "7.3.1_Bleeding disorder registrations from 1969 to 2020". The explanations for the field labels in the pivot table are detailed below.

7.3.1 Bleeding disorder registrations from 1969 to 2020

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Bleeding disorder diagnosis	Type of bleeding disorder
Severity or type	The severity of haemophilia, with regards to baseline FVIII or FIX level (IU/dl) or type of VWD
Year	The number of registrations per diagnosis from 1969 to 2020, and an additional column for registrations where the year(s) are not known

- The initial registration date is available for most PwBD, and submission of this data improved over time. A PwBD was considered registered at a centre in the years between a centre specific registration date and a de-registration date or a date of death.
- In total, 51,885 PwBD contributed to 68,985 registrations in the NHD. Shared care between centres is common where one of the centres is a comprehensive care centre and the other a

local haemophilia centre. In these instances of shared care, PwBD were allocated to all the centres associated with their care resulting in more registrations than the number of PwBD.

- Of the total PwBD, 40,906 were registered at a single centre, and 10,979 PwBD received care across more than one centre, with the latter contributing to 28,079 registrations. Therefore, the total number of registrations (68,985) is made up of 40,906 single Centre registrations and 28,079 multi-centre registrations. However, the total number of PwBD remains the same at 51,885.
- The allocation to a centre of PwBDs without a centre-specific registration date was challenging and required assumptions. PwBD were allocated to the centre for which NHD held treatment records for treated years and any in-between years. If one of the centres was paediatric, this was assumed to be the first registration centre.
- In 235 registrations involving 234 PwBD, the years of registration are missing
- Where PwBDs' registration history had no identifiable dates using the above methodology, they are reported in the 'Year not known' column.

7.4 Data limitations

- Data on the number of severely affected PwBD registered at any centre are more robust than for less severely affected PwBD as they require regular treatment, ensuring yearly contact.
- People with mild disorders tend to have less frequent contact, as their hospital attendance is often precipitated by the need for treatment for surgery or trauma.
- On occasions, people with mild bleeding disorders may have been de-registered from a centre if there is no documented contact over extended periods. The practice of active de-registration and notification to the NHD varies between centres.
- PwBDs may have been deregistered if their disorder improved with time. This phenomenon is reported in persons with mild haemophilia or mild von Willebrand disease, where the factor levels improve and normalise with age. In some instances, deregistration may result from improved diagnostic techniques, including advances in molecular techniques.
- PwBD allocated to "Dr Craske's surveillance project" on the NHD were reallocated to the centre where the person had most of their treatment except in six of the 759 PwBD. These six people have been included in the "Missing" category for people who could not be allocated to a specific centre.

8 The number of HIV positive and negative persons with bleeding disorders at each Haemophilia Centre in the UK broken down by year.

The NHD actively recorded information about the presence of HIV infection from 1985 onwards. It recorded in most instances, the date of the first positive result in a field labelled 'date first pos'. Data fields were also available to record negative results and sample date. The date of the first positive result was used to confirm seroconversion. During this analysis, the dates were also checked for plausibility to account for reporting errors.

8.1 Inclusion criteria

- PwBD with documented results for an HIV test in NHD.
- Five PwBD who had AIDS as the underlying cause of death recorded on either NHD or NHS digital.

8.2 Exclusion criteria

- Partners of PwBD.
- PwBD whose records were labelled as 'not yet tested'.

8.3 Results

Two sets of data are presented. Table 8.3.1 displays the total number of HIV positive PwBD by diagnosis, gender and whether they were normally resident abroad. NHD has records for 1338 HIV positive PwBD (1324 males, 14 females) and HIV test results (positive and negative) for 5565 PwBD. There were five PwBD with no HIV test results but were presumed to be HIV positive as HIV/AIDS was reported on the death certificate.

8.3.1 HIV positive PwBD

PwBD not resident abroad according to NHD records	Total	No. of Male PwBD	No. of Female PwBD
Severe haemophilia A	**941**	**940**	**1**
Severe haemophilia B	**18**	**18**	**0**
Non-severe haemophilia A or B	**305**	**304**	**1**
Females with factor VIII deficiency	**3**	**-**	**3**
Haemophilia A with liver transplant	**11**	**11**	**0**
Other bleeding disorders	**17**	**8**	**9**
Total	***1295***	***1281***	***14***
Resident abroad, according to NHD records			
Severe haemophilia A	**33**	**33**	**0**
Severe haemophilia B	**1**	**1**	**0**
Non-severe haemophilia A or B	**9**	**9**	**0**
Females with factor VIII deficiency	**0**	**0**	**0**
Haemophilia A with liver transplant	**0**	**0**	**0**
Other bleeding disorders	**0**	**0**	**0**
Total	***43***	***43***	***0***
All HIV + PwBD	*1338*	*1324*	*14*

8.3.2 HIV results from 1979 to 2000

- Data are also presented on the number of PwBD affected with HIV by the centre. The pivot table includes the number of people with a first positive HIV result and the cumulative number of people with positive and negative results.
- Multiple tests in a year were common, but a PwBD was included only once per year in one of the categories. PwBD with a positive result for the first time were included in the newly positive column and the cumulative positive column in subsequent years.
- Results are provided electronically as an Excel pivot table attachment "8.3.2_HIV results from 1979 to 2000". The explanations for the field labels in the pivot table are detailed below.

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Year	1979 to 2000
Total number of PwBD tested for HIV	The total number of PwBD tested for HIV by year of sample.
Number of HIV negative PwBD	The total number of PwBD who tested HIV negative by year of sample. If a PwBD had two or more negative results from the same year, the PwBD was counted once for that year and not included if one of the results was positive.
Number of new HIV positive PwBD	The total number of PwBD who tested HIV positive for the first time by year of sample. A positive result takes precedence over a negative result for a year.
Cumulative number of HIV positive PwBD	Cumulative number of PwBD who tested positive for HIV by year of sample.

8.4 Data limitations

- The date of the first positive HIV test reflects information reported to NHD and has been identified from data in either of two fields, "date of sample" or "date of first positive". The date documented in the NHD is not necessarily the date of the first positive result (if that was not reported to the NHD), and as such, results as late as the early 1990s are observed in the data. Furthermore, the date of the first positive test in the database provides no guide to the date the person was infected as centres may not have had access to stored samples when the HIV antibody test became widely available in 1985.
- When a newly immigrated PwBD with HIV infection was registered on the database, the NHD did not record the country where the infection was potentially acquired. Details of HIV tests and the country where it was acquired are only available in the individual's clinical record held by the centre.

- A test year was not available for eight positive and 268 negative results in either of the "date of sample" or "date of first positive" fields. The reporting of positive results was generally more robust than negative results.
- In two PwBD, potential transcription errors by centres have resulted in a sample date which does not correlate to the known epidemiology of HIV infection in the UK or other results from that centre. The sample dates reported were 1967 and 1975, both reported as negative. In the former case, the PwBD had another negative test reported in 1989, and in the second case, the second test year is missing.
- Five PwBD are included as being HIV positive because they had HIV or AIDS reported as the cause of death. For two PwBD, the centres reported to the NHD that AIDS was the cause of death. A third patient who acquired the infection abroad was noted to have died due to HIV infection, with a note that he did not suffer from AIDS-defining illness. Two PwBD were identified through death certificate information provided by NHS Digital, one of whom had a platelet dysfunction and another had non-severe haemophilia.
- A limited dataset for partners and spouses of PwBD is available but excluded in the current pivot table.

9 The number of people with bleeding disorders at each Haemophilia Centre in the UK showing positive and negative HCV antibody and PCR test results, disaggregated to show the disorder (not limited to Haemophilia A, B, females with VIII and IX deficiencies and VWD) and the severity or type of the disorder.

From 1969 onwards, intermittent collection of data about hepatitis infection was undertaken using prospective or retrospective centre surveys and national look-back exercises. In the years before 1990, surveys were used to collect data (individual and aggregate data at centre level) about hepatitis and jaundice. A limited number of centres provided data, with most of these surveys being coordinated by Dr Craske. During this period, testing was possible for hepatitis B, and hepatitis C was a diagnosis of exclusion and termed non-A, non-B hepatitis. The Hepatitis C virus was formally identified in 1989.

In 2010, following the Archer Inquiry recommendations, the Department of Health (DH) requested UKHCDO/NHD to undertake a national HCV look-back exercise to scope the extent of HCV infection in PwBD. The exercise aimed to generate data to inform healthcare planning and potential financial implications for the Skipton Fund, established in 2004. It was recognised that the NHD did not have a comprehensive dataset of blood product treatments that could have potentially transmitted HCV, as in the early years of the NHD, not all PwBD were registered at Haemophilia Centres, and submission of treatment records was not complete. Furthermore, treatments administered at small centres or hospitals which did not routinely care for PwBD were unlikely to be reported to NHD.

To mitigate for incomplete records, for the DH look-back exercise the NHD assumed that all people registered with a bleeding disorder before the advent of universal HCV testing of blood donations in September 1991 were potentially at-risk. This exercise identified approximately 29,500 at-risk PwBD, for whom data was requested from the centres. About 16% of this cohort was reported as deceased. The

centres struggled to provide a comprehensive dataset to NHD due to inadequate local resources. Subsequent discussions with the DH resulted in centres providing data on a randomly selected sample representing 10% of the PwBD cohort assumed to be at-risk by NHD. This information was reported as part of annual returns to NHD between 2011 and 2014.

In 2018, the UKHCDO's Data Management Working Party initiated another HCV look-back exercise to support haemophilia centres in identifying any PwBDs who might have missed screening for HCV infection despite exposure to products associated with HCV transmission. A PwBD was considered potentially 'at-risk of HCV infection' if there was documentation in NHD of exposure to a pooled plasma-derived CFC manufactured before 1988 or a blood component before 1992. These cut-off dates relate to the introduction of viral inactivation of plasma-derived CFCs in the mid-'80s and universal blood donor screening in September 1991.

The exercise was limited to PwBDs believed to be alive at the time of the exercise. Each centre was provided with a list of PwBD considered at-risk of HCV and any relevant data known to NHD. In PwBD who were HCV antibody positive, information was also sought about the use of anti-viral treatment and treatment outcomes, evidence of chronic liver disease and follow-up arrangements if appropriate. Information about liver transplants and hepatocellular carcinomas was also requested. It was recognised at the time that this information would be of value to the Infected Blood Inquiry. Where a PwBD was registered at more than one centre, all the centres were approached for information. If a PwBD was not actively registered with a centre in 2018, details were sent to the centre that first treated the individual with an at-risk blood product. Centres were encouraged to liaise, and NHD facilitated this process.

Further updates on the current HCV PCR status were sought in mid-2020, in the context of the rapid roll-out of anti-HCV therapies and the look-back exercise is still active.

9.1 HCV data analysis

Three analyses have been provided in this section.

1. The first analysis profiled the HCV status of all people considered potentially at-risk of HCV infection (section 9.2 below).
2. The second analysis reviews the timelines of testing for HCV infection (section 9.3 below).
3. The third analysis is related to the eradication of HCV infection (section 9.4 below).

In these analyses, a positive HCV antibody test confirms exposure to HCV and a positive HCV polymerase chain reaction (PCR) confirms the presence of viral RNA in blood, indicating active infection. A PwBD is considered to have cleared HCV infection when they have a positive HCV antibody test confirming exposure and a negative PCR test, confirming the lack of viral RNA in the bloodstream.

9.2 HCV status of PwBD considered at-risk of HCV infection

In this analysis, all PwBDs (alive and deceased) considered at-risk of HCV infection or known to have HCV infection were identified from NHD and allocated to the six groups described below. All data from the

2018 look-back exercise and the 2020 update are included. Additional at-risk people were identified when the archived paper records were transcribed into NHD for the purposes of responding to the Inquiry's Rule 9 request. All at-risk and potentially at-risk people have been included.

9.2.1 Inclusion criteria

- PwBDs considered potentially at-risk of HCV infection
    - People with documentation in NHD of exposure to a pooled plasma-derived CFC manufactured before 1988 or a blood component before 1992.
    - PwBD with a HCV antibody result born before 1992 or unknown date of birth.
    - PwBD reported deceased with liver failure and/ or hepatocellular carcinoma (HCC) born before 1992 or unknown date of birth.
    - Overseas PwBD with a positive antibody result.

9.2.2 Exclusion criteria

- Partners of PwBD

9.2.3 Categorisation of HCV status

Seven mutually exclusive categories of PwBDs at-risk of HCV have been defined based on documentation of infection with HIV and HCV and records of exposure to at-risk products on NHD. PwBDs allocated to each group sequentially.

(1) **HIV positive**: The analysis assumed this group was inevitably co-infected with hepatitis C although many PwBD who were HIV positive died before HCV testing was available. This group includes PwBD with positive HIV antibody results reported to the NHD or who had AIDS documented as their underlying cause of death on their death certificate.

(2) **HCV positive**: This group includes PwBD with a positive HCV antibody result reported to NHD or HCV documented on the death certificate. This group includes a small number of PwBD who might have acquired the infection abroad.

(3) **HCV presumed positive**: This group includes PwBD born before 1992 with liver disease or hepatocellular carcinoma reported as the underlying cause of death or documented as significant co-morbidity in the absence of any HCV antibody result.

(4) **HCV antibody-negative**: PwBD with a negative HCV antibody result on NHD.

(5) **HCV status unknown, exposed to an at-risk pooled plasma product**: This group includes PwBDs, without HCV antibody results known to NHD, who had a record of exposure to at-risk pooled plasma concentrates. Some of these PwBD would have also been exposed to at-risk blood components, as known to NHD. This group is potentially at high risk for infection.

(6) **HCV status unknown, exposed at-risk to blood component**: This group includes PwBD without HCV antibody results but with evidence of exposure to at-risk blood components only.

(7) **Not known to be at-risk:** This group includes PwBD with no records of exposure to at-risk pooled concentrates or blood components on NHD. It is inevitable that some of these people will have been exposed to an at-risk blood product without NHD being informed.

9.2.4 Number of PwBDs at-risk by HIV and HCV status

In total, 8752 PwBD were considered at-risk of HCV using the above criteria and grouped into six categories. This includes patients alive and known to have died by December 2020.

	HIV+ve	HCV+ve	HCV presumed +ve	HCV-ve	HCV unknown, exposed to at-risk pooled PP	HCV unknown, exposed to an at-risk BC
Number of PwBD by category	1338	2178	117	2741	1469	909
HIV + blood result	1333	Negative/ Unknown	Negative/ Unknown	Negative/ Unknown	Negative/ Unknown	Negative/ Unknown
AIDS on DC*	5					
HCV + blood result	Positive, negative/ Unknown	2007	Negative/ Unknown	Negative	Unknown	Unknown
HCV on DC *		171				
Liver failure or HCC on DC* as UCOD** or significant event			117			
NHD data on exposure to at-risk products present (n)	1310	2008	74	1672	1469	909
NHD data on exposure to at-risk products absent (n)	28	170	43	1069		
Born in or before 1992 (n)	1338	2175	117	2741	1387	831
DOB unknown (n)		2			82	78
Born after 1992 (n)¥		1				

*DC death certificate; **UCO underlying cause of death; ¥ Overseas patient

9.2.5 Results

A PwBD is only included once in the analysis, and the results also include those who have died. Some PwBD have multiple test results, and they are considered HCV positive if they ever had a positive result and negative if they never had a positive result.

Data are displayed by centre, diagnosis and severity of the bleeding disorder for the six HCV categories.

Results are provided electronically as an Excel pivot table attachment "9.2.5.1_HCV status of PwBD at-risk of HCV infection". The explanations for the field labels in the pivot table are detailed below.

9.2.5.1 HCV status of PwBD at-risk of HCV infection

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Bleeding disorder diagnosis	Bleeding disorder diagnostic categories
Severity / type	All severities/types of HA, HB and VWD
PwBD status	Alive or deceased as of December 2020
No. of HIV positive (co-infected) PwBD	The number of at-risk PwBDs who are HIV positive and therefore inevitably co-infected with HCV (alive and deceased)
No. of HCV positive PwBD	The number of PwBD with positive HCV antibody result reported to NHD or HCV documented on the death certificate (alive and deceased)
No. of HCV presumed positive PwBD	The number of at-risk PwBD born before 1992 with liver disease or Hepatocellular carcinoma reported as the underlying cause of death or documented as significant co-morbidity in the absence of any HCV antibody result
No. of HCV negative PwBD	The number of at-risk PwBD who have tested negative for HCV antibody (alive or deceased)
No. of HCV unknown PwBD, exposed to pooled plasma products.	The number of at-risk PwBD due to exposure to pooled plasma products for whom the NHD does not have HCV antibody results (alive or deceased)
No. of HCV unknown PwBD, exposed to blood component	The number of at-risk PwBD due to exposure to blood components only for whom the NHD does not have HCV antibody results (alive or deceased)
Total	Total number of people who were at risk of HCV

Centre allocation has been challenging as many PwBD received care at more than one centre, but each PwBD was allocated to one centre only for this analysis as follows:

- Of the total 8752 PwBD considered at-risk, the NHD holds positive HIV results for 1333 PwBD. They were allocated to the centre that first reported the positive HIV result. Five PwBD reported to be deceased due to AIDS but with no positive test (see 8.3 above) were allocated to the centre that they were registered with at the time of death.

- PwBD with negative HIV result and positive HCV antibody result or documentation of HCV on death certificate (2178 PwBD) were allocated to the centre that first reported the positive HCV result or where they were registered at the time of death.
- In 2741 PwBD, the HCV antibody test was negative, and they were allocated to the centre that reported the first negative result. Three PwBD had equivocal results on more than one occasion with negative PCR and were considered HCV negative and assigned to the centre submitting that result.
- HCV antibody results were not available on the NHD for 2495 PwBD. Amongst this group, 2407 had records of exposure to at-risk products in the NHD from an identifiable centre, of whom 2390 PwBD were assigned to the centre where they had the most records of at-risk treatment in the year they were first exposed to at-risk products. The remainder were allocated to the CCC or the largest centre where they had the most records of exposure in the year they were first exposed to at-risk products. A further three PwBD had at-risk treatment records with no identifiable centre. No exposure to at-risk products was identifiable for 85 PwBD in NHD, of whom the majority were assigned to the centre where they had the most treatment records in the year they were first issued with any product. The remainder with no treatment records in the NHD were assigned to the centre (CCC by default) where they were first registered.

9.3 HCV positive antibody results by year

Two exercises have been undertaken previously in 2010 and 2018, to collect information about the HCV testing of the cohort considered at-risk of HCV infection. The reporting of the first positive HCV antibody result year was reviewed.

9.3.1 Inclusion criteria

- PwBD with a positive HCV antibody result.

9.3.2 Exclusion criteria

- PwBD with no HCV antibody results or negative HCV antibody results.

9.3.3 Results

Data are displayed for HCV positive antibody results by centre and year if known. For many PwBD, the test year is not available on the NHD, and these are grouped under an unknown year.

Results are provided electronically as an Excel pivot table attachment "9.3.3.1_HCV antibody positive results by year". The explanations for the field labels in the pivot table are detailed below.

9.3.3.1 HCV antibody positive results by year

Field label	Field description
Centre number	Number assigned in the database

Centre name	Name of the centre
Range of years	Earliest to December 2020
HIV and HCV status of PwBD	Co-infected or HCV positive only
No. of positive HCV antibody results by year	Year of the first positive antibody result as submitted to NHD if known

9.4 HCV PCR status by centre

HCV PCR status reflects the number of PwBD who have an active infection. NHD did not regularly collect this information, and centres do not report this unless asked as part of a look back exercise.

9.4.1 Inclusion criteria

- PwBD with a positive HCV antibody result who are alive as of December 2020

9.4.2 Exclusion criteria

- PwBD with no HCV antibody results or negative HCV antibody results.
- Deceased PwBD

9.4.3 Results

Data for the most recent PCR result (positive or negative) are displayed by the centre, age group, and presence of HIV co-infection. This extract only includes PwBD known to be HCV antibody positive.

Results are provided electronically as an Excel pivot table attachment "9.4.3.1_Last HCV PCR status by centre." The explanations for the field labels in the pivot table are detailed below.

9.4.3.1 Last HCV PCR status by centre

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Age Group	Age group (as of 31/12/2020). • < 11 years • 11 - 30 years • 31 - 50 years • 51 - 70 years • 70 + years
HIV and HCV status of PwBD	Co-infected or HCV positive only
HCV PCR results	Last reported HCV PCR result. Categorised as positive, negative or unknown.

9.5 Data limitations

- This analysis includes all NHD data as of the end of December 2020. Centres continue to update the records on PwBD with active infection or severe liver disease complications. HCV PCR status is likely to change as people receive anti-viral therapy, and therefore the information in this report is only accurate as of December 2020.
- A significant limitation is the intermittent nature of data collection about hepatitis infection, as explained above.
- Many PwBDs exposed to a blood product during the at-risk time had died before HCV tests became available. In these cases, the HCV result is reported as unknown. On the balance of probabilities, many of these PwBD would have been HCV positive; therefore, this report is likely to underestimate the number of infected people.
- Centres have struggled to access historical records for some PwBD or trace individuals to offer them a test so that there is no test result for some at-risk PwBD. This category includes deceased PwBD and visitors from abroad. In many cases, before the introduction of NHS numbers, PwBD registered in the '70s and '80s may not have had unique identifiers for tracing.
- Some PwBDs exposed to at-risk products might not have been reported to NHD or may have been treated at centres or hospitals which did not submit data to NHD. Thus the at-risk dataset is likely to be incomplete.
- Three people had HCV antibody tests that were equivocal on more than one occasion, and all three were negative by PCR, suggesting the absence of active infection.
- The year of the result was often not requested or reported. Further, the date of the first positive HCV antibody result documented in the NHD may not be the date of the PwBD's first positive result for various reasons. Centres might have repeated blood tests if old documentation was missing before submitting a result to the NHD; further, the reporting Haemophilia Centre may not have carried out the first positive test.
- In some instances, the HCV result represents the testing of stored sample results. In this situation, the result may be dated before the HCV test was available for routine testing as the sample year was recorded in preference to the test year.
- For new registrations where a PwBD has acquired HCV infection overseas, NHD does not record the year and country where the infection was acquired.
- The allocation of PwBD to the centre reporting the first positive HCV test when treated at multiple centres, rather than the centre responsible for prescribing the treatment that led to the HCV infection, makes epidemiological investigations challenging.

10 The number of people with bleeding disorders determined to be "at-risk" of vCJD at each Haemophilia Centre in the UK, the number of "at-risk" haemophilia patients who have been exposed to an implicated batch (including the name of the product if available and the number known by the NHD to have been notified of that exposure) and the number not exposed to an implicated batch, or whether not known, and the methodology used to categorise.

A blood donor having developed variant Creutzfeldt–Jakob disease (vCJD) was reported for the first time in 1997, with additional cases reported in 1999 and 2000. In 2000, an independent expert advisory committee, the CJD Incidents Panel (CJDIP), was established on behalf of the UK Chief Medical Officers to advise organisations responsible for providing and delivering health care about the management of incidents involving the potential transmission of vCJD between people.

The batches of concentrates manufactured from plasma donated by these donors were identified and categorised as "implicated" batches. Subsequently, in December 2003, a case of transfusion-associated vCJD was described, raising concerns about vCJD's potential transmission through blood and blood products. In July 2004, a second probable case was reported. Although the risk of vCJD transmission through blood products was uncertain, it was considered likely that additional batches of UK-sourced plasma products would become implicated as future vCJD cases arose. Therefore, public health measures were implemented to minimise the potential risk of human to human transmission of vCJD. These included measures for protecting the blood supply, improvements in decontamination standards for surgical instruments, and implementing special infection control precautions when operating on people with or 'at-risk' of vCJD.

As part of these measures, in 2004, all PwBDs in the UK who were alive and had received UK pooled plasma products between 1980 and 2001 were identified as "at-risk of vCJD for public health purposes". In September 2004, the Health Protection Agency (HPA) recommended that all haemophilia centres forward a letter of notification (dated 20th September 2004) to all living PwBD providing information on the new public health policy concerning vCJD. The PwBD who received the notification, and had been treated with pooled UK plasma products between 1980 and 2001, were required to inform their medical team of their 'at-risk for public health purposes' status so that extra infection control precautions could be taken should they need a procedure.

The HPA led the notification in England, Wales, and Northern Ireland, with the Scottish Centre for Infection and Environmental Health (SCIEH) leading notification in Scotland. The chronology of events preceding the notification exercise led by the HPA in 2004 are detailed in Millar et al. 2010. †

As part of the notification exercise haemophilia centres had to assess all living PwBD for their exposure to coagulation factor concentrates manufactured from UK pooled plasma between 1980 and 2001 and

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† MILLAR, C.M., CONNOR, N., DOLAN, G., LEE, C.A., MAKRIS, M., WILDE, J., WINTER, M., IRONSIDE, J.W., GILL, N. and HILL, F.G.H. (2010), Risk reduction strategies for variant Creutzfeldt–Jakob disease transmission by UK plasma products and their impact on patients with inherited bleeding disorders. Haemophilia, 16: 305-315. https://doi.org/10.1111/j.1365-2516.2010.02220.x

specific implicated batches. BPL provided NHD with a list of implicated batches of concentrate, and NHD forwarded this information to haemophilia centres. The exposure assessment for each individual required a review of treatment records held locally by centres or within the transfusion department of the hospital. NHD provided an exposure assessment form to facilitate this assessment. The submission of assessment forms to NHD occurred over years following local evaluations. Another exercise was undertaken in 2006 when two additional batches were identified and categorised as implicated.

The exposure assessment exercise was designed to ascertain information to facilitate risk stratification. The three items of information required were as follows:

a. Whether the person was in the at-risk group for public health purposes as described above
b. Whether the person had received an implicated batch (as listed on the form)
c. In the event of receipt of an implicated batch, the number and amount of FVIII or FIX units issued to the PwBD

The outcome of this risk assessment identified the following groups of people:

a. PwBD with no documented evidence of exposure to UK pooled blood products between 1980 and 2001. These people were designated as not at-risk of vCJD for public health purposes.
b. PwBD with evidence of exposure to UK pooled blood products between 1980 and 2001. These people were designated as being at-risk of vCJD for public health purposes. This group was further risk assessed to determine whether they had been exposed to an implicated batch of UK pooled blood products.

The notification letter was sent to all living PwBD and not only those at-risk for public health purposes. Therefore, the notification letter did not explicitly inform individuals whether they were at-risk unless they had pre-existing knowledge of exposure to the at-risk products or had been informed of this by their centre. A reply slip was included with the notification letter enabling PwBD to respond with their preferences about the amount of information they would like to receive concerning receipt of implicated batches. Some centres chose to send additional letters to PwBD to confirm whether they had been exposed to at-risk products, and other centres provided this information in person.

The notification exercise was conducted differently across the centres. Some centres considered all PwBD to be at-risk and, following an exposure assessment, re-categorised them as 'at-risk' or 'not at-risk'. Other centres only included PwBD with evidence of exposure to UK pooled plasma products between 1980 and 2001 in the at-risk group, with exposure assessments limited to this group.

The NHD does not hold data about when or how PwBD were informed about their at-risk status, nor was the submission of this information ever requested, but it would be expected that this would be recorded within clinical records. The assessment form requested submission of the date of the discussion concerning exposure to an implicated batch. Information is available for a minimal number of PwBD (125), with the majority of these (83) documented to have had their discussions in 2004.

10.1 Inclusion criteria

- PwBD exposed to UK pooled plasma-derived concentrate manufactured between 1980-2001 as evidenced by records in NHD or local records based on the 2004 and 2006 HPA exercises.

10.2 Exclusion criteria

- PwBD who were reported as deceased before 7th September 2004.
- PwBD identified as not at-risk following local assessment, particularly mild PwBD who were issued with factor product but never required its use.

10.3 Results

Data on the number of at-risk PwBD are displayed by centre and diagnosis. The post-notification exposure assessment (exposed to an implicated batch, exposed to non-implicated batch, batches not known) of PwBD is also provided. Based on NHD records and local assessment, a total of 5147 PwBD are included as 'at-risk of vCJD for public health purposes' in the pivot table.

Results are provided electronically as an Excel pivot table attachment "10.3.1_PwBD at-risk of vCJD and post-notification exposure assessment". The explanations for the field labels in the pivot table are detailed below.

10.3.1 PwBD at-risk of vCJD and post-notification exposure assessment

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Bleeding disorder diagnosis	Type of bleeding disorder
Severity or type	The severity of haemophilia, with regards to baseline FVIII or FIX level (IU/dl) or type of VWD
No. of PwBD identified as potentially at risk of vCJD for public health purposes	No. of PwBD with evidence on NHD records and/ or local centre records of potential exposure to UK pooled blood products (1980-2001)
Post-notification exposure assessment	
• **No. of PwBD at-risk, exposed to implicated batch**	Number of PwBD at-risk of vCJD for public health purposes exposed to an implicated batch
• **No. of PwBD at-risk, exposed to non-implicated batch**	Number of PwBD at-risk of vCJD for public health purposes not exposed to an implicated batch
• **No. of PwBD at-risk, exposure assessment incomplete**	Number of PwBD at-risk of vCJD for public health purposes for whom limited exposure information is available

- A total of 5147 PwBD are included in this analysis. Initially, NHD records identified 5175 PwBD as potentially at-risk, of whom 270 PwBD were excluded following local assessment leaving 4905.

An additional 242 PwBD (making 5147 in total) were identified to have received treatment with the at-risk products from local records.

- Of the total 5147, the at-risk status was confirmed through local exposure assessment for 3769 PwBD. The allocation of these PwBD to centres was based on the number of centres returning the exposure assessment forms. For 3294 PwBD, only one centre submitted the assessment forms. When assessment forms were submitted by more than one centre, 135 PwBD were allocated to the centre that reported the receipt of an implicated batch, 140 PwBD to a CCC in preference to smaller centres, and the remaining 200 to centres with the most number exposure assessments.
- The at-risk status was not confirmed by local exposure assessment for 1378 PwBD. For these PwBD, centre allocation was based on the issue of at-risk products. In total, 1144 PwBD were issued an at-risk product by one centre, 209 PwBD were allocated to the largest centre at which they were registered in 2004 (size of centre defined in terms of the total number of PwBD registered by a centre in 2004). The remainder were allocated to CCC, the largest HC or the centre that issued the highest number of at-risk products.

10.3.2 PwBD exposure to implicated batches

Data on the number of PwBD exposed to an implicated batch is displayed by centre and diagnosis, and the number of PwBD exposed to each implicated batch and multiple implicated batches is shown. Of the 5147 PwBD at-risk, 785 received an implicated batch.

Results are provided electronically as an Excel pivot table attachment "10.3.2_PwBD exposure to implicated batches". The explanations for the field labels in the pivot table are detailed below

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Bleeding disorder diagnosis	Type of bleeding disorder
Severity or type	The severity of haemophilia, with regards to baseline FVIII or FIX level (IU/dl) or type of VWD
No. of PwBD exposed to an implicated batch	Number of PwBD exposed to an implicated batch as confirmed in the exposure assessment form
No. of PwBD exposed to different implicated products	Implicated batches of the following products are presented: 8Y, 9A, HT Defix, High purity F8, Replenate, Replenine, and Z8. A PwBD can be exposed to more than one product

10.4 Data limitations

- Although NHD provided a list of implicated products and batches, centres undertook the exposure assessment exercise based on their local records. These records may have been incomplete or inaccurate where Centres closed or PwBDs moved between Centres. Similar issues

have affected the assessment of PwBDs who have de-registered, moved abroad or were from overseas.

- The NHD holds information about treatment issued to PwBD rather than the use of the product. In most cases, the amount of product issued and used is the same or similar, but this may not be the case for people with mild haemophilia where a PwH might have been issued with a single dose of treatment for travel or emergency use, which might have expired before use. Centres hold information in PwBD records about the actual use, and indeed, 270 PwBD were categorised as not at-risk following local exposure assessments.
- The submission of the exposure assessment forms by Centres was variable. Some forms were not submitted, and most were submitted months after the exercise.
- Tracking the use of implicated batches was challenging as BPL could not provide a complete list of centres supplied with the implicated batches. Some products had been supplied directly to haemophilia centres, but others had been distributed through Transfusion Centres. All centres had to review their records to establish receipt and use of implicated batches, with variable success for each batch, with only around half of some batches tracked to affected PwBD.
- The results presented in the pivot tables are based on data collected as part of the 2004 and 2006 HPA exercises. The submission of assessment forms was more complete for the 2004 exercise.
- In 2010, a denotification exercise was undertaken to identify PwBD mistakenly notified as at-risk in 2004. This primarily involved people with factor XI deficiency and some people with von Willebrand disease because the plasma source used to manufacture these concentrates was from donors in the USA rather than the UK. These PwBD have **not** been excluded from the pivot table.
- In 2013, another denotification exercise was conducted when the risk period was changed from 1980-2001 to 1990 -2001 by Public Health England and the CJD Incidents Panel. The pivot table is based on the initial assessment of the risk period (1980-2001).

11 The number of alive and deceased patients with bleeding disorders at all Haemophilia Centres in England, Wales, Scotland and Northern Ireland, from 1969 to 2020, disaggregated to show the disorder (not limited to Haemophilia A, B, females with VIII and IX deficiencies and VWD) and the severity or type of the disorder.

Death and causes of death were only collected for PwBD registered with the NHD with specific diagnoses, the number of which increased over time. The NHD started data collection on deceased people with haemophilia A and B from 1971, backdated to 1969. Between 1993 and 2013, the reports from centres were supported with additional information from death certificates provided by the Office for National Statistics (ONS) and its successor organisations (currently NHS Digital). UKHCDO's contract with ONS for death certification data was initiated in partnership with the Cancer Research Council Epidemiology Unit in Oxford as a part of an epidemiological investigation into life expectancy and causes of death in PwBD. Although this helped ascertain the date and cause of death in many cases, the lack

of an NHS number or other unique identifier hindered this linkage analysis. After a few renewals, the contract lapsed in 2013, and since then, NHD has been dependent on information provided by centres for the date and cause of death. In 2020, the Inquiry provided NHD with death certificate information for PwBD in England, Wales, Scotland and Ireland, for whom the cause of death information had not been available to NHD.

11.1 Inclusion criteria

- PwBD registered as deceased with the NHD by 31st December 2020.

11.2 Exclusion criteria

- PwBD registered after 31st December 2020.
- People with no evidence of inherited bleeding disorder.

11.3 Results

Data on the number of deceased PwBD and the number of registrations per year are displayed by centre and bleeding disorder diagnosis.

Results are provided electronically as an Excel pivot table attachment "11.3.1_Annual mortality from 1969 to 2020". The explanations for the field labels in the pivot table are detailed below.

11.3.1 Annual mortality from 1969 to 2020

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Bleeding disorder diagnosis	Type of bleeding disorder
Severity or type	The severity of haemophilia, with regards to baseline FVIII or FIX level (IU/dl) or type of VWD
Year	1969 to 2020, including a column for the year not known
• Deaths (n)	Number of PwBD reported deceased, allocated to a unique centre
• PwBD registered (n)	Number of registrations in each centre, including multiple registrations for PwBD with shared care

- All deceased PwBD (7249) were allocated to a single centre for the purposes of this report, although many had received care at more than one centre over their lifetime.
- PwBD who have died have been excluded from a centre's results from the year after their death.
- Of the total deceased PwBD, 6750 were registered with at least one centre in their year of death. 491 were not registered with a centre in their year of death, and for eight PwBD, no centre registration at any time could be determined.

- Of the 6750 deceased PwBD registered with at least one centre in their year of death, 5550 PwBD were registered at only one centre in their year of death and were allocated to this centre. The remaining 1200 PwBD registered at more than one centre in their year of death were allocated sequentially according to the following criteria. If a PwBD was treated at both a paediatric centre and a non-paediatric centre in their year of death, they were allocated to a paediatric centre if they were aged under 18 years (n=21) and to a non-paediatric centre if they were aged over 18 years (n=25). They were then allocated to the centre where they were registered longest (n=169), followed by CCCs (n=567) and larger centres (n=418).

11.4 Data limitation

- The registration data includes PwBDs registered with multiple centres so that the total number of registrations is higher than the total number of PwBD, as some PwBDs were registered with more than one centre. However, for this section of the report, deceased PwBD were only allocated to one centre, even if they had been treated at more than one centre, which might not reflect their entire treatment history.

12 Mortality data and HIV and HCV infection in people exposed to plasma-derived products.

Data relating to deceased PwBD has been categorised using multiple criteria to help analyse the excess mortality from transfusion transmitted infections across the UK. Data have been consolidated to address the issue of small numbers. The categorisations and consolidations are described below.

1. The number of deceased PwBD have been consolidated in five-year intervals.
2. Diagnoses have been consolidated and categorised based on the disease phenotype. All diagnoses have been categorised into one of four phenotypic groups: severe inherited, non-severe inherited, acquired, and platelet disorders.
    a. Severe inherited: this group includes persons with severe and moderate haemophilia A and B and type 3 von Willebrand disease. PwBD with these diagnoses have excess mortality at a young age if untreated, and the majority start to receive treatment in the first five years of life but no later than the first decade.
    b. Non-severe inherited disorders: this group includes persons with other factor deficiencies who may be exposed to their first treatment anytime between birth and adulthood.
    c. Acquired disorders: this group includes persons who have presented with new onset bleeding, i.e. acquired in the fourth or fifth decade of life and often have multiple comorbidities.
    d. Platelet disorders: this group includes platelet disorders of all severity and who may require blood products in the form of platelet transfusions from an early age in severe disease.
3. PwBD were further stratified by age at death into five groups.
    a. < 11 years
    b. 11 - 30 years

c. 31 - 50 years
d. 51 - 70 years
e. 70 + years

4. PwBD were considered at-risk of acquiring HCV if they had received a pooled plasma-derived CFC manufactured before 1988 or were treated with a blood component before 1992. The at-risk categories described in section 9.2.3 based on the exposure assessment to pooled plasma-derived blood products and blood components are included in this stratified analysis.

12.1 Inclusion criteria

- PwBD registered as deceased with the NHD by 31st December 2020, including those for whom a registration date is unknown.

12.2 Exclusion criteria

- People with no evidence of inherited bleeding disorder.

12.3 Results

The mortality figures for deceased PwBD (7242) have been summarised by five-year intervals, disease phenotype category, age at death group, and exposure to at-risk products (as categorised in section 9.2.3 above: HIV or HCV positive, presumed HCV positive, HCV negative, HCV status unknown and HCV not at-risk).

Results are provided electronically as an Excel pivot table attachment "12.3.1_Mortality trends in PwBD over time". The explanations for the field labels in the pivot table are detailed below.

12.3.1 Mortality trends in PwBD over time

Field label	Field description
Range of years	Five year time intervals (1969 to 2020)
Categorisation of bleeding disorder by disease phenotype	Four disease phenotypes have been described for this analysis A. Severe Inherited B. Non-severe inherited C. Acquired disorders D. Platelet disorders
Age at death	PwBD were stratified by age at death as below a. < 11 years b. 11 - 30 years c. 31 - 50 years d. 51 - 70 years e. 70 + years

HCV and HIV status based on exposure to at-risk products for HCV infection	1. HIV positive 2. HCV positive 3. HCV presumed positive 4. HCV negative 5. HCV unknown, exposed to at-risk pooled plasma products 6. HCV unknown, exposed to at-risk blood component 7. Not known to be at-risk of HCV

12.4 Data limitations

- These broad-based categorisations can provide mortality trends but cannot wholly quantify the burden of transfusion transmitted infections.

13 Overview of the underlying causes of death (where available) for all deceased PwBD, focusing on hepatitis C infection and the annualised deaths from liver disease, including hepatocellular carcinoma, from the earliest available records to date.

The cause of death data collected by NHD in the annual returns from centres was limited to pre-selected lists of causes of death of interest that changed over time. In contrast, data on the cause of death from death certificates are comprehensive. For this report, all deceased PwBD data (as provided to the NHD by Centres and death certificate data from the ONS/NHS Digital) were reviewed and coded to a limited number of simplified underlying causes of death relevant to PwBD, as detailed below.

13.1 Inclusion criteria

- PwBD registered as deceased with the NHD by 31st December 2020.

13.2 Exclusion criteria

- PwBD registered after 31st December 2020.
- People with no evidence of inherited bleeding disorder.

13.3 Method of allocation to the simplified underlying cause of death

Data available in the NHD and death certificate information provided by NHS Digital (via the Inquiry) were reviewed to categorise the underlying cause of death. There was a particular focus on whether the underlying cause of death could be related to HIV or HCV or a bleeding complication caused or exacerbated by the bleeding disorder. The World Health Organization (WHO) guidance was used when defining the underlying cause of death. The WHO defines this as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury."

In the initial review, the data on the cause of death (the event leading to death) and underlying cause of death were reviewed by one consultant, which led to the development of a simplified categorisation of the underlying causes of death pertinent to the Inquiry. This included causes related to bleeding, transfusion transmitted infections and other significant causes of death. When no information was available on the death certificate, NHD cause of death was used where available; the latter typically included the underlying cause of death.

The underlying cause of death was coded independently by three consultants in total for all PwBD known to be positive for HIV and HCV, according to NHD. Similarly, PwBD who had HCV or AIDS documented on their death certificate or had liver failure as the underlying cause of death or had hepatocellular carcinoma (or equivalent terminology for liver cancer) anywhere on the death certificate, irrespective of viral status, were also reviewed by three consultants in the majority of cases. Where there was disagreement, a consensus was achieved in a virtual meeting with a fourth additional consultant. Two consultants coded the remainder of the PwBD, and discrepancies were reviewed in a meeting with a third additional consultant. In total, four consultants took part in the process of categorising the underlying causes of death.

The categorisation of the simplified underlying COD was iterative, with the underlying cause of death categories evolving through the discussions. The categorisations were only applied to people with inherited bleeding disorders, with acquired bleeding disorders as a separate category (see below).

13.4 Simplified underlying causes of death

- Accidental death (this excluded trauma, suicide and overdose)
- Acquired bleeding disorder
- Bleeding - abdomen
- Bleeding - chest and lung
- Bleeding - gastrointestinal (excludes variceal bleed due to liver disease, which is included in one of the liver failure categories)
- Bleeding - intracranial (includes intracerebral haemorrhage and other intracranial bleeding such as subdural and subarachnoid haemorrhage.
- Bleeding - other
- Cancer - diagnosis unknown (it is unknown whether the person had HCC or another cancer)
- Cancer - other (the person had a type of cancer that was not HCC)
- COVID- 19
- Creutzfeldt-Jakob Disease (there were no deaths caused by vCJD)
- Details unknown (on both death certificate and NHD records)
- Frailty/ dementia
- Heart disease
- Hepatocellular carcinoma (HCC, Hepatoma)
- HIV/AIDS
- HIV related lymphoma

- Infection
- Liver failure – unspecified (where no underlying aetiology has been provided)
- Liver failure – HCV (includes liver failure as the underlying cause of death in a person with documented HCV infection either via NHD or on the death certificate)
- Liver failure – other diagnoses (if another cause of liver failure is stated explicitly)
- Other medical disorders (including the majority of conditions related to renal, lung, bowel, neurological and immunological disorders)
- Overdose (includes the ingestion of combinations of various medications where the intention is unclear. If the intention to self-harm was documented, they were included under suicide).
- Post-operative complication (includes infections and bleeding post-surgery)
- Ruptured aneurysm (includes both intraabdominal and other non-intracranial aneurysms)
- Stroke – thrombotic (all deaths described as "cerebrovascular accidents" were assumed to be thrombotic unless haemorrhage was documented)
- Suicide
- Trauma (includes falls and road traffic accidents)
- Venous thromboembolism

13.5 Specific categories

13.5.1 Acquired bleeding disorders

All acquired bleeding disorders were coded as such for the underlying cause of death. This is a complex group with multiple comorbidities, and their disease is unlikely to have been impacted significantly by HIV and HCV infection.

13.5.2 HIV positive PwBD

The underlying cause of death was reviewed for all PwBD recorded as HIV positive on NHD. Any additional cases of AIDS/HIV identified through the death certificates, where HIV status was unknown to NHD, were also included. Many of the HIV related deaths were reported to NHD in the '80s on a proforma with pre-selected causes of death.

Where the NHD recorded HIV/AIDS as the underlying cause of death, this was categorised as "HIV/AIDS" for this report unless the death certificate data stated one of the causes below, to which they were then allocated in preference to HIV/AIDS.

- Liver failure - this was presumed to be related to HCV
- Hepatocellular carcinoma
- Cancer other than HCC
- Bleeding - intracranial
- HIV related lymphoma
- Bleeds that are typical of haemophilia were allocated to the appropriate bleed category

Where infection was the recorded cause of death, unless the death certificate stated one of the above causes, HIV/AIDS was chosen as the underlying cause of death. Similarly, if a PwBD presented with bleeding from a pathology linked to AIDS, they were also allocated to the HIV/AIDS category. If a PwBD was identified as having AIDS/HIV for the first time from the death certificate, this was investigated where possible with the centre that had registered the person. These PwBD were included in the HIV+ve group, and the above rules were implemented for the categorisation of their underlying cause of death.

13.5.3 Liver failure – HCV

A search was done for any mention of HCV across all fields of the death certificate and the NHD cause of death in order to attribute liver disease to HCV where appropriate. HCV related liver failure was considered the underlying cause of death in the following circumstances:

- Liver failure in the context of HIV infection
- Gastrointestinal bleeding related to oesophageal varices (a complication of liver disease), or gastrointestinal bleeding unspecified, as the cause of death with HCV related liver disease.
- Infection or multiorgan failure as a cause of death with HCV related liver disease.
- Non-A and non-B hepatitis, when identified on the death certificate, was treated as HCV positive for this exercise.

13.5.4 Hepatocellular carcinoma

- Data for hepatocellular carcinoma was reviewed across all sections of the death certificate. Where this was identified in the absence of HCV infection known to the NHD, PwBD were allocated to the presumed HCV+ve category if born before 1992.
- In PwBD with HCV infection, the decision to categorise the underlying cause of death as hepatocellular carcinoma or liver failure was determined by information provided in the death certificate. The NHD information was used where no data was available on death certificates. Where the cause of death was unrelated to liver disease, the underlying cause of death was not attributed to HCC.

13.5.5 "HCV presumed + ve"

- PwBD who had hepatocellular carcinoma recorded anywhere on the death certificate, with no information about HCV infection and born before 1992 were categorised as "HCV presumed +ve" irrespective of the exposure history known to NHD.
- Similarly, liver failure with no apparent aetiology in people with a history of exposure to an at-risk treatment but no confirmed evidence of HCV either on the death certificate or NHD records were categorised as "HCV presumed positive".

13.5.6 Cancers

Cancers were categorised as hepatocellular carcinoma if this was recorded or if primary liver cancer or hepatoma was recorded. "Cancer - other" refers to all other types of cancers. "Cancer - unknown" refers

to cases where the only record is of "cancer". In these cases, the person may or may not have had hepatocellular carcinoma.

13.5.7 Bleeding

Where bleeding has been reported as the immediate cause of death, cases have been categorised by bleed location. In the event of a neurological event such as stroke being the cause of death, both NHD data and death certificate data were reviewed to establish whether a bleed or thrombosis was the underlying cause. If this was not clear, the case was considered secondary to thrombosis.

13.5.8 Other causes

Surgical causes and trauma were reported separately, as were deaths due to other organ failures.

13.6 Results

The causes of death are aggregated in five-year intervals and displayed by their HIV and HCV status (as per section 9.2.3). Data has been presented at the national level without disaggregation by centre or diagnosis to aid trend analysis.

Results are provided electronically as an Excel pivot table attachment "13.6.1_ Simplified underlying causes of death in PwBD – Stratified by exposure". The explanations for the field labels in the pivot table are detailed below.

13.6.1 Simplified causes of death in PwBD – Stratified by exposure

Field label	Field description
Simplified underlying cause of death	As described above in paragraph 13.4
Year range	1969 to 2020 in five-year intervals
HIV and HCV status	1. HIV positive 2. HCV positive 3. HCV presumed positive 4. HCV negative 5. HCV unknown, exposed to at-risk pooled plasma products 6. HCV unknown, exposed to at-risk blood components 7. Not known to be at-risk

13.7 Data limitations

- Deaths may not have been reported to the NHD when the management of PwBD's final illness did not involve their haemophilia centre.
- Reporting of the cause of death to the NHD by the submitting clinician was subject to interpretation and from a pre-selected list. Clinicians reported either the immediate cause of

death or the underlying cause of death. For many years, centres reported a single cause of death, and, for most people, that remains the case. For example, in a person with an HIV infection, the cause of death could be recorded as pneumonia as the immediate cause of death with HIV either mentioned in other causes or potentially omitted.

- The collection of death data has generally been subject to the limitations described in earlier sections and the incompleteness of registration, especially in the early years of the NHD.

14 The number of patients with bleeding disorders registered at each Haemophilia Centre in England, Wales, Scotland and Northern Ireland who have undergone a liver transplant, disaggregated to show the disorder (not limited to Haemophilia A, B, females with VIII and IX deficiencies and VWD) and the severity or type of the disorder, showing whether these patients are alive or deceased, and if deceased the cause of death.

Liver transplant is a treatment modality for liver failure secondary to hepatitis C infection. The submission of liver transplant data to the NHD has been variable over the years. The NHD has never requested this information from haemophilia centres, and centres have only submitted data as information of potential interest. Therefore, there is minimal data in the NHD about PwBD who have had liver transplants. Additional PwBD with liver transplantation have been identified from mortality data.

The UK liver transplant registry (LTR) hosted by NHSBT has a complete list of all people who have undergone a liver transplant in the UK. Haemophilia or other bleeding disorders is not a field on the current LTR registration form. However, a comprehensive list of people with a bleeding disorder who have undergone a liver transplant in the UK could be generated through a data match between the two databases (NHD and the UK LTR) supported by a data transfer agreement.

14.1 Inclusion criteria

- People with bleeding disorders where the NHD has information on a liver transplant
- Alive and deceased

14.2 Exclusion criteria

- No evidence of liver transplant on NHD

14.3 Results

Data are presented for liver transplants by diagnosis and by Centre. If PwBDs have been reported as deceased post-liver transplant, the underlying cause of death has also been categorised as per section 13.4.

Results are provided electronically as an Excel pivot table attachment "14.3.1_Liver transplant prevalence and outcomes". The explanations for the field labels in the pivot table are detailed below.

14.3.1 Liver transplant prevalence and outcomes

Field label	Field description
Centre number	Number assigned in the database
Centre name	Name of the centre
Bleeding disorder diagnosis	Type of bleeding disorder
Severity or type	The severity of haemophilia, categorised as severe or non-severe with regards to baseline FVIII or FIX level (IU/dl), or type of VWD
No. of PwBD with liver transplant	Number of PwBD with liver transplant as identified in NHD records
• **Alive**	Number of PwBD alive at the end of December 2020, post-liver transplant
• **Deceased**	Number of PwBD deceased at the end of December 2020, post-liver transplant
Cause of death in deceased post-liver transplant PwBD	The simplified underlying cause of death

14.4 Data limitations

- The issues about the comprehensiveness of the data have been mentioned in the introduction.

15 Data about people with bleeding disorders and Hepatitis B virus infection.

HBV test results have not been collected from centres since vaccination was introduced early in 1980. Jaundice surveys were carried out intermittently over the years, either at the centre level or individual PwBD level, but with no consistency and were not submitted to the NHD. The consolidated results were typically presented at UKHCDO meetings and are part of the minutes, and no electronic record is available. Paper copies of those consolidated results and/or meeting minutes have been submitted to the Inquiry where available.