UKHCDO

UNITED KINGDOM HAEMOPHILIA CENTRES DOCTORS' ORGANISATION

UKHCDO ANNUAL REPORT 2022 & Bleeding Disorder Statistics for the Financial Year 2021/22

A report from the UKHCDO and NHD

UKHCDO

UNITED KINGDOM HAEMOPHILIA CENTRES DOCTORS' ORGANISATION

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1.0 Chairperson's Report

Welcome to the 23rd Annual general body meeting and to our first in-person meeting since the COVID pandemic. Since the handover from Ri, time has passed swiftly, with some significant milestones.

I am pleased to report that the final version of 'Bleeding Disorders Statistics for The Infected Blood Inquiry 2022' on behalf of NHD and UKHCDO was submitted in September 2022 following the receipt of Rule 9 to the NHD in Feb 2020. Indeed, there were several final versions, and the version control was probably a reflection of my wishful thinking. The generation of the report took three times the expected time, and the UKHCDO executive is immensely grateful to the NHD team for facilitating this work. A big thank you to Ben, Hua, Lynne, and Rachel for the months dedicated to data cleaning, updating from paper archives, and generating iterative reports. The incisive comments from Peter, Ri, Charlie, and Kate made the information presented insightful, robust, and comprehensive. The data submitted underpins some of the analysis submitted by the statistical expert group appointed by IBI.

The working parties continue to be productive. Of note, the Paediatric working party has set up a national MDT, facilitating shared learning amongst the small group of treaters. The Lab working party has been prolific with their publications, and the involvement of the biomedical scientists has been greatly appreciated. The Peer Review working party was reformed in October 2022, with Rachel Rayment appointed the group's Chair. A five-year cycle was agreed upon at the last round of peer review in 2018/19, and we are behind by a few months. Reviews are expected to start in 2024, acknowledging the impact of COVID on all our services. The NHD will coordinate all the activities starting the second quarter of next year. A significant task for the group will be to evaluate the impact of the new audit cycle interval length on the services. The clinical reference group was finally reformed and congratulations to Susie Shapiro for being appointed as the National Speciality Advisor (NSA).

The Infected Blood Inquiry published an interim report on 29 July 2022 in response to the study by Sir Robert Francis KC into a framework for compensation for victims of infected blood. The interim report endorsed Sir Robert's recommendation that the Government should immediately consider offering "substantial interim payments" not less than £100,000. On 17 August 2022, the Government announced interim payments of £100,000 for infected beneficiaries and bereaved partner beneficiaries currently registered with the Infected Blood Support Schemes and was welcomed by all stakeholders.

The infected blood inquiry is slowly drawing to end of its evidence gathering, with all written submissions completed by the end of this year. We continue to have regular meetings with our legal team, and the UKHCDO IBI group includes Kate, Rachel, Charlie, Ri, Peter and me. The IBI is expected to pronounce its judgement in 2023, and it will be a time of reflection on any criticisms against UKHCDO. The organisation has learned and evolved over the decades with the primary purpose of promoting the care of patients with bleeding disorders, and I am confident we will continue to do so in the future.

The next few years will also see a further increase in the choice of therapeutic products, and it appears that we might be in the golden period of haemophilia care. Increasing choice brings challenges, and for the first time, our discussions inform and facilitate shared decision making. As haemophilia is better controlled, we are left with the challenges the average person faces, a focus of certain working parties.

An important endeavour for the next few years is the development of NHD2, a total redevelopment of the National Haemophilia Database that will provide significant benefits for all stakeholders. NHD2 will improve our future capacity, capability, and efficiency in analysing data and enable new developments and services that will meet our aims and objectives up to 2030 and beyond.

There have been some staffing changes at NHD. The database has struggled with long term sickness of staff members. In better news, we welcome our new analyst Ridita Ali, who joined us in March, and our two new administrators, Alex Godsall and Hasina Ngyou, who joined us in the summer to support the team across our general and data administration services.

Of note, the average age of our organisation has steeply dropped in the last year, and peer support over the following years will be crucial if we are not to build on the learning of our predecessors. All this work would not have been possible without the support of my fellow executive members, Kate, Susie and Rachel, and I look forward to working with all of you for the next two years.

Prof Pratima Chowdary,
UKHCDO Chair
7 November 2022

Bleeding Disorder Statistics for

April 2021 to March 2022

A report from the UK National Haemophilia Database

October 2022

Appendix 1 Glossary

AE	Adverse Event
AGM	Annual General Meeting
ASH	American Society of Hematology
BCSH	British Committee for Standards in Haematology
BMI	Body mass index
BMS	Biomedical Scientists
BSH	British Society for Haematology
CCC	Comprehensive Care Centre
CEO	Chief executive officer
CMWP	Co-morbidities Working Party
COVID-19	Corona Virus Disease
CPD	Continuing Professional Development
CQUIN	Commissioning for Quality and Innovation
CRG	Clinical Reference Group
DAG	Data Analysis Group
DMWP	Data Management Working Party
EAHAD	European Association for Haemophilia and Allied Disorders
EHL	Enhanced Half-life
EU	European Union
EUHASS	European Haemophilia Safety Surveillance
FEIBA	Factor eight inhibitor bypass agent
FIX	Factor nine
FVII	Factor seven
FVIII	Factor eight
GCP	Good clinical practice
GLH	Genomics Laboratory Hub
GLN	Genetic Laboratory Network
GOSH	Great Ormond Street Hospital
GWP	Genetics Working Party
HC	Haemophilia Centre
HCC	Hepatocellular carcinoma

HCIS	Haemophilia Clinical Information System
HCPA	Haemophilia Chartered Physiotherapists' Association
HCV	Hepatitis C virus
HEE	Health Education England
HJHS	Haemophilia Joint Health Score
HNA	Haemophilia Nursing Association
ICS	Integrated Clinical Academic
IPSG	International Prophylaxis Study Group
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
ITI	Immune tolerance induction
IU	International units
IU/dl	International units per decilitre
IU/kg	International units per kilogram
IWP	Inhibitor Working Party
kg	Kilogram
MAHA	Microangiopathic hemolytic anemia
MDSAS	Medical Data Solutions and Services
MDT	Multidisciplinary meeting
MTP	Minimally treated patients
NEQAS	National External Quality Assessment Service
NHD	National Haemophilia Database
NHF	National Hemophilia Foundation
NHS	National Health Service
NIBSC	National Institute for Biological Standards and Control
NIHR	National Institute for Health Research
PC	Personal computer
PDF	Portable Document Format
pd-FIX	Plasma derived factor nine
PPIE	Patient and Public Involvement and Engagement
PUP	Previously untreated patient
PwHA	People with haemophilia A
PwHB	People with haemophilia B
PWP	Paediatric Working Party
PwSHA	People with severe haemophilia A

RCEM	Royal College of Emergency Medicine
RCPCH	Royal College of Paediatrics and Child Health
RfPB	NIHR Research for Patient Benefit
rFIX	Recombinant factor IX
rFVIII	Recombinant factor VIII
SAE	Serious Adverse Event
SHA	Severe Haemophilia A
SHL	Standard Half-life
SOP	Standard operating procedure
TF	Task Force
THS	The Haemophilia Society
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centre Doctors' Organisation
UKNEQAS	United Kingdom National External Quality Assessment Service
vCJD	Variant Creutzfeldt-Jakob disease
VWD	Von Willebrand disease
VWF	Von Willebrand factor
WAPPS-Hemo	Web-Accessible Population Pharmacokinetic Service—Hemophilia
WFH	World Federation of Hemophilia
WP	Working party

Appendix 2 Participating Centres

Centre Name	
Aberdeen	Leicester
Abergavenny	Lewisham
Bangor	Lincoln
Barnstaple	Liverpool (R. I.)
Belfast - Adult's	Liverpool Children's
Belfast - Children's	Manchester (Adults)
Birmingham (Queen Elizabeth)	Manchester Children's
Birmingham Children's	Newcastle upon Tyne
Bournemouth / Poole	North Hampshire (Basingstoke)
Bradford	North Staffordshire (Stoke on Trent)
Brighton	Norwich
Bristol (Infirmary & Children's)	Nottingham
Cambridge	Oxford
Canterbury	Peterborough
Cardiff	Plymouth
Chichester	Portsmouth
Coventry	Royal Free
Derby	Salisbury
Dundee	Sheffield (Children's)
Eastbourne	Sheffield (Royal Hallamshire)
Edinburgh	Shrewsbury
Exeter	Southampton
Glasgow (R.H.S.C.)	St George's Hospital, London
Glasgow (R.I.)	St Thomas' and Guy's Hospital
Great Ormond Street	Swansea
Hammersmith Hospital, London	Taunton / Yeovil
Inverness	The Royal London Hospital
Ipswich	Torquay
Kettering	Truro
Kingston upon Hull (Hull)	Wolverhampton
Leeds	York

2.0 Comments on the Bleeding Disorder Statistics for 2021 / 2022

The statistics for the financial year 2021/2022 follow. Most of the commentary is to be found with the tables and charts temselves.

This is an interim report since there are some data issues that remain unresolved with a single large centre, such that their data has been omitted from some charts for the time being. A final version will appear in about two weeks.

The main continuing treatment trends are a continued transfer of patients with severe haemophilia A to emicizumab and gradual transfer of patients with haemoophilia B to extended half-life products. In both cases there is a degree of variation in uptake from centre to centre probably reflecting differences in clinical opinion. In the case of emicizumab patients who do well with factor VIII prophylaxis or who have a very low bleeding rate or who have a past history of inhibitors are overall less likely to be switched. The uptake of extended half-life IX has been relatively slow though the majority of severe haemophilia B patients now use these products. Why uptake has been slow and variable from centre to centre is unclear, but in my experience, patients often say they are happy with their existing products and do not want to switch.

These treatment changes make some of the charts more difficult to interpret. The interpretation of the box and whisker plots showing factor VIII or IX usage per patient per year by centre, is distorted by the uptake of EHL products, since there is no unit equivalence with standard half-life products. Unit usage of factor IX appears to be declining as EHL-products are substituted for standard half-life products and patients require fewer units/kg because of the extended half-life of the products that they switch to. For Haemophilia A, the distortion is more marked because emicizumab was prescribed first to people with the highest annualised bleed rate and the highest factor VIII use so conversion to Hemlibra decreases the number of units of factor VIII prescribed and will also appear to reduce the average factor VIII usage per patient. This effect is most marked for those centres who have switched more than 80% of their patients with severe Haemophilia A to emicizumab since those centres may have switched all their severe haemophilia A patients except those that seldom bleed and treat themselves on-demand. Effectively, mean or median factor IX/VIII use per patient can no longer be used to compare one centre with another.

The data also chart an increasingly aging population and increasing numbers of deaths attributed to old age or dementia. There are also increasing reports of the normal degenerative diseases of old-age, the management of which may be complicated by an underlying bleeding disorder. The data presented include causes of death from death certification provided by NHS digital so far fewer causes of death are listed as “unknown”. The adverse event working group are also working on a method to present cause of death going beyond a single principal cause of death so that the effect of contributory causes is not minimised. This suggestion has arisen because death certificates frequently report the mode of death as the principal cause rather than the underlying condition that has led to that mode of death. I have tried to take this into account when interpreting the death certification data from NHD digital.

Adverse events reports, assessed monthly by the Adverse Event Panel show the usual range of adverse events. All-drug-related adverse events are reported back to the manufacturer.

Although a number of thrombotic events were reported in the year, these occurred most commonly in patients with fibrinogen disorders and von Willebrand's disease and none were attributed to emicizumab. In fact, side effects that were attributed to emicizumab (mostly local reactions and headache) occurred mostly in the first few weeks of use and the drug was generally well tolerated. Adverse event reports also show that, of the almost 100 ex-inhibitor patients switching to emicizumab, only 5% had recurrent or resurgent inhibitor activity. This should put this risk into context and inform discussion with the patients when considering such a switch of products.

There were several reports of loss of efficacy with Esperoct necessitating a change back to their previous product. This is a well-recognised but relatively uncommon adverse event.

I would like to take this opportunity to thank the staff of the Haemophilia centres for collating and sending in all the data and helping us with data cleaning. Without this effort, we would have no report at all. The database and several modulkes used at a centre lkevel are currently being redeveloped. This development is sumarised by the Rob Hollingsworth's MDSAS report elsewhere in the Annual report. When this redevelopment si complete we should be able to collect the data more easily and it will be more readily available and visible for the reporting centres.

The report does not include usage figures for Birmingham Children's Hospital. Unfortunately, data transmission to the database from the hospital was badly affected by a software issue that proved difficult to identify and then to resolve. Although we delayed issuing a final report in the hope that we could resolve this and bring the centre's data up to date, this has not proved possible. This will have a knock-on effect on a number of tables, especially those reporting emicizumab usage.

We hope that you find the statistics useful and of interest and if you have any suggestions for future issues, please let us know. We hold a report review meeting usually in January, attended by a group of stakeholders including commissioners, and working party chairs.

Professor Charles RM Hay,
Lynne Dewhurst,
Ben Palmer, Dr Hua Xiang & Dr Ridita Ali
On behalf of the UK National Haemophilia Database
Manchester, November 2022

Important Note: Throughout this report, haemophilia A includes carriers who have haemophilia A and females with FVIII deficiency.

Haemophilia B includes carriers of haemophilia B, females with FIX deficiency, FIX Leyden and FIX Leyden carriers.

Time Periods: The tables and figures presented in this report relate to the period April 2021 – March 2022 inclusive unless stated otherwise.

Age is calculated at the midpoint of the financial year, i.e., 30th September 2021

2.1 Haemophilia A

Table 1 People with congenital haemophilia A (including carriers) registered and treated, 2021/22

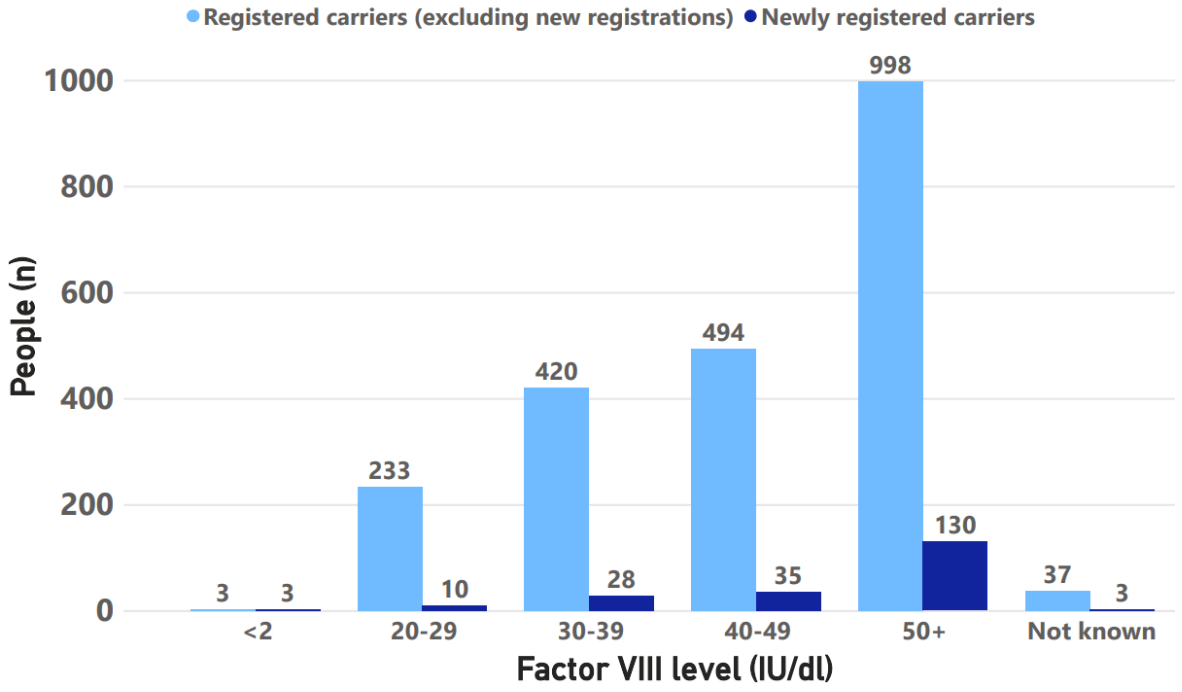
Haemophilia A	Age Range	Number of people by factor VIII level (IU/dl)																	
		< 1			1 - 5			>5 & <40			≥ 40			Unknown severity			Total		
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Total registered	<18 years	724	1-2	**724**	204	4	**208**	653	113	**766**	29	164	**193**	-	1-2	-	1,610	281	**1,891**
	≥18 years	1,450	4	**1,454**	623	5	**628**	2,619	663	**3,282**	174	1,491	**1,665**	-	39	**39**	4,866	2,202	**7,068**
	Total*	**2,174**	**4**	**2,178**	**827**	**9**	**836**	**3,272**	**776**	**4,048**	**203**	**1,655**	**1,858**	**-**	**39**	**39**	**6,476**	**2,483**	**8,959**
New registrations**	<18 years	37	1-2	**37**	12	-	**12**	57	16	**73**	5	26	**31**	-	1-2	-	111	42	**153**
	≥18 years	7	1-2	**7**	7	-	**7**	26	26	**52**	4	139	**143**	-	1-2	-	44	165	**209**
	Total*	**44**	**-**	**44**	**19**	**-**	**19**	**83**	**42**	**125**	**9**	**165**	**174**	**-**	**-**	**-**	**155**	**207**	**362**
Treated with concentrate FVIII/Emicizumab in year***	<18 years	695	-	**695**	142	3	**145**	156	1-2	**156**	1-2	1-2	-	-	-	-	993	3	**996**
	≥18 years	1,389	1-2	**1,389**	396	1-2	**396**	472	31	**503**	16	12	**28**	-	-	-	2,273	43	**2,316**
	Total*	**2,084**	**-**	**2,084**	**538**	**3**	**541**	**628**	**31**	**659**	**16**	**12**	**28**	**-**	**-**	**-**	**3,266**	**46**	**3,312**

** This is the total excluding numbers which have been suppressed*
*** New registrations are a subset of the 'In Register' numbers*
**** Excluding people only treated with DDAVP and tranexamic acid*

Table 1: This shows the total number of people with haemophilia A (including low factor VIII level carriers and factor VIII deficient females) registered and/or treated with concentrate in the UK during 2021/22 and broken down by age and disease severity.

There were over 90 people registered with severe haemophilia A who had no recorded treatment with concentrate within the year.

Figure 1 Carriers of haemophilia A currently registered and newly registered, broken down by baseline FVIII level, 2021/22



N.B: Includes carriers of haemophilia A and females with FVIII deficiency

Diagnosis	Number of people by factor VIII level (IU/dl)								
	<2	2-9	10-19	20-29	30-39	40-49	50+	Not known	Grand total
Registered carriers (excluding new registrations)	3	17	72	233	420	494	996	38	2,273
Newly registered carriers	3	-	4	10	28	35	130	3	213
Total	**6**	**17**	**76**	**243**	**448**	**529**	**1126**	**41**	**2486**

Figure 1: This shows the number of carriers of haemophilia A currently registered with the NHD by baseline FVIII level. This includes females registered by their centre as having FVIII deficiency or haemophilia A. New registrations of carriers with normal FVIII levels continues but is incomplete.

Table 2 New registrations of congenital haemophilia A (including carriers), by age at mid-year, gender and severity, 2021/22

Haemophilia A Age (years)	Number of people by factor VIII level (IU/dl)																	
	< 1			1 - 5			> 5 & < 40			≥ 40			Unknown			Total*		
	Male	Female	Total*	Male	Female	Total*	Male	Female	Total*	Male	Female	Total*	Male	Female	Total*	Male	Female	Total*
0 - < 2	26	1-2	26	6	-	6	29	6	35	4	6	10	-	-	-	65	12	77
2 - 4	4	-	4	3	-	3	8	3	11	-	1-2	-	-	1-2	-	15	3	18
5 - 9	3	-	3	1-2	-	-	10	3	13	-	4	4	-	-	-	13	7	20
10 - 19	4	-	4	1-2	-	-	13	5	18	1-2	21	21	-	-	-	17	26	43
20 - 29	3	-	3	1-2	-	-	5	6	11	-	31	31	-	1-2	-	8	37	45
30 - 39	1-2	1-2	-	1-2	-	-	5	5	10	-	42	42	-	-	-	5	47	52
40 - 49	1-2	1-2	-	1-2	-	-	7	7	14	-	21	21	-	1-2	-	7	28	35
50 - 59	-	-	-	1-2	-	-	4	3	7	1-2	15	15	-	-	-	4	18	22
60 - 69	-	-	-	-	-	-	1-2	4	4	-	16	16	-	-	-	-	20	20
70 and over	-	-	-	-	-	-	1-2	-	-	3	7	10	-	-	-	3	7	10
Total*	**40**	**-**	**40**	**9**	**-**	**9**	**81**	**42**	**123**	**7**	**163**	**170**	**-**	**-**	**-**	**137**	**205**	**342**

**This is the total excluding numbers which have been suppressed*

Table 2: This shows the number of new registrations of haemophilia A broken down by reported severity and age at mid-year (30/09/2021).

The underlying birth rate of people with severe haemophilia A born in the UK usually runs at 40-45 per year. The proportion of new registration of severe haemophilia A aged two years or above (without suppression of small numbers) in 2021/22 was 43%. It is presumed that most of those with severe haemophilia registered at aged two years or above have migrated or are visitors to the UK.

Table 3 New registrations of people with severe haemophilia A aged 2 years and over, and subsequent treatment by year

Haemophilia A	Registration year										Total
	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20	2020/21	2021/22	2012/2022
New registrations / year	10	19	17	17	21	19	17	14	16	19	169
Treated in each year											
2012/13	10										10
2013/14	10	19									29
2014/15	10	18	17								45
2015/16	9	19	16	16							60
2016/17	9	19	17	17	21						83
2017/18	10	19	17	17	21	17					101
2018/19	10	19	17	16	20	18	14				114
2019/20	10	18	17	15	20	17	17	13			127
2020/21	10	17	16	15	19	16	14	12	15		134
2021/22	9	17	16	16	19	14	11	13	14	18	147

Table 3: This shows the number of people with severe haemophilia A over two years of age when newly registered (and therefore thought potentially to be migrants) each year from 2012/13. It also shows the number treated in each year subsequent to their registration. This shows that up to 169 people with severe haemophilia A may have migrated to the UK since 2012/13. This is may be an underestimate, since children under two years old are not included in this table. 147 were treated in 2021/22, suggesting that most remain and continue to require regular treatment.

Figure 2 Trend in the number of people with haemophilia A by severity aged 60 years and above, 2002 - 2021

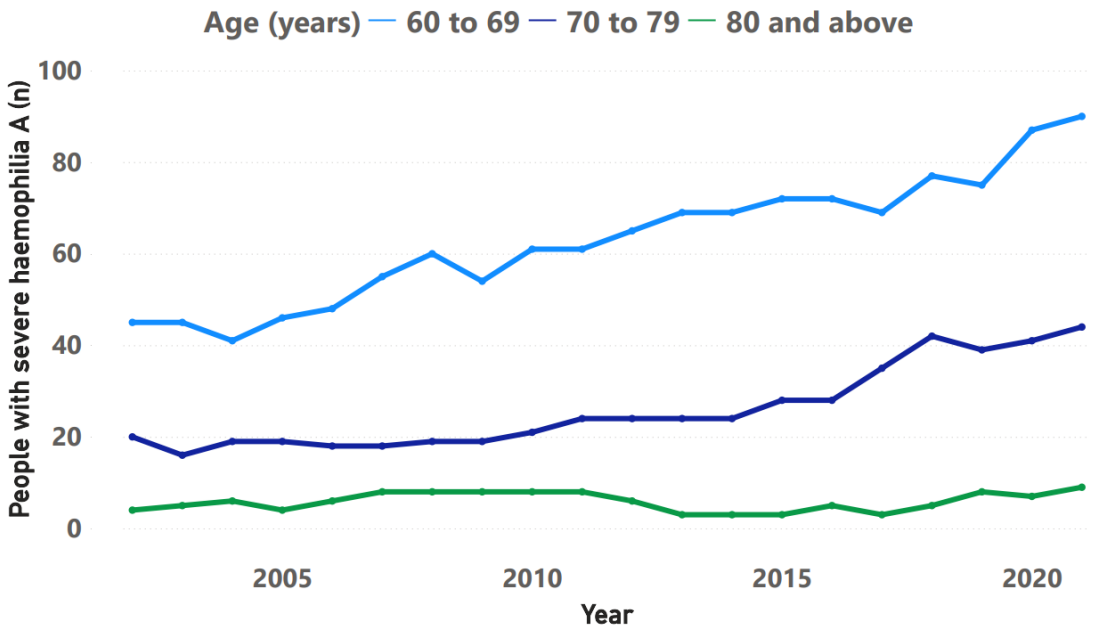


Figure 2 (severe): This shows the number of people with severe haemophilia A (PwSHA) in the register aged 60-69, 70-79 and 80 and above from 2002. This shows that although we have few registered PwSHA aged 80 and over throughout this period, the number aged 60-79 years is increasing steeply as life expectancy increases. There is clearly an aging population of PwSHA, and the management of associated comorbidities is expected to increase commensurately.

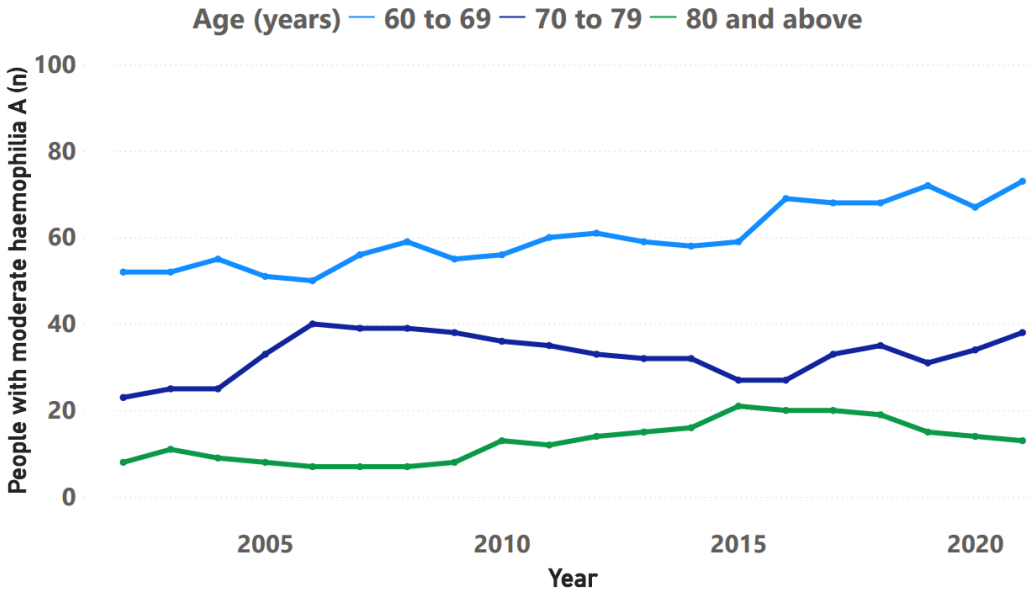


Figure 2 (moderate): This shows the age trends since 2002 for people with moderate haemophilia A aged 60 years and above. There has been an overall increase in the number of people in the two younger age groups, although the number of people with moderate haemophilia is relatively small rendering interpretation of this data difficult.

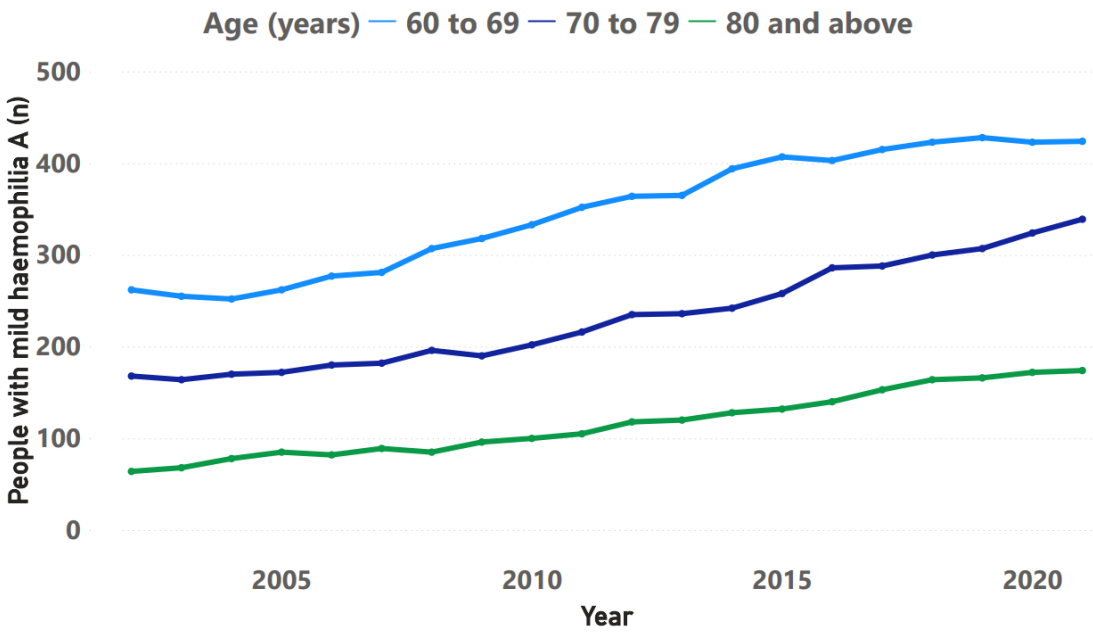


Figure 2 (mild): This shows the age trends since 2002 for people with mild haemophilia A aged 60 years and above. This appears to show an increasing number of registrations for all age groups during this period. This is attributable to an increase in life expectancy for the general population and increased recognition, diagnosis and registration of people with mild haemophilia. The literature suggests that this group had near-normal life expectancy throughout this period.

N.B. Carriers are included in Figure 2

Figure 3 Factor VIII units issued by UK haemophilia centres to treat severe haemophilia A, 2012/13 – 2021/22

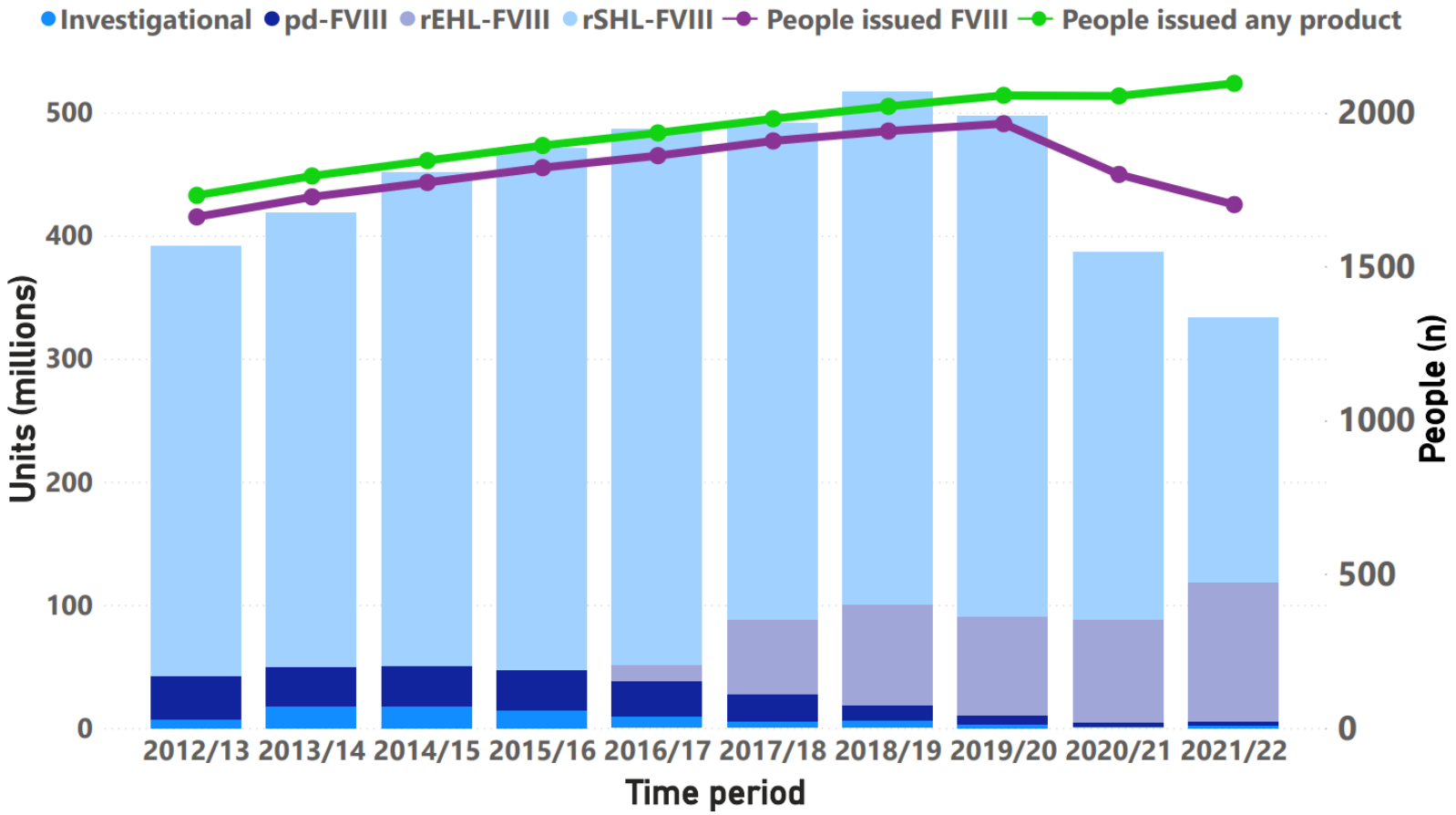


Figure 3: This shows FVIII units issued to treat PwSHA between 2012/13 to 2021/22, including people with FVIII inhibitors. The number of people reported to have been treated with FVIII (standard and extended half-life) is shown by the purple line using a secondary axis, and the total number of people treated with any product (including emicizimab and novoseven) is shown by the green line. This chart shows the beginning of a significant fall off in FVIII issues from 2020/21, which is attributable to the introduction of emicizumab prophylaxis from September of 2019. There has also been a dramatic fall-off in the use of plasma-derived products over the past five years.

Figure 4 Factor VIII units issued by UK haemophilia centres to treat non-severe haemophilia A, 2012/13 - 2021/22

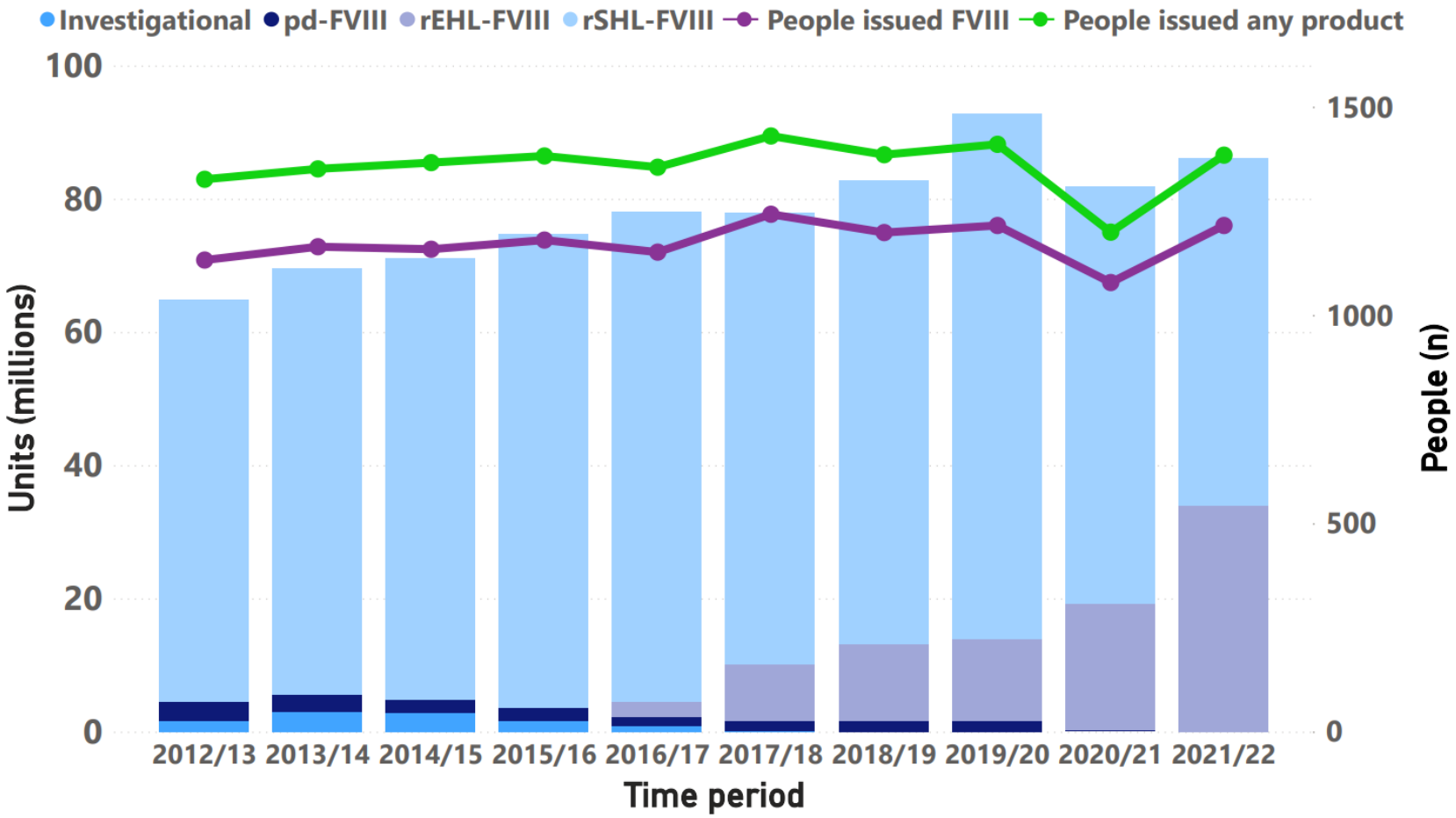


Figure 4: This shows FVIII units issued to treat people with non-severe haemophilia A in the UK from 2012/13 to 2021/22, including people with FVIII inhibitors. The number of people reported to have been treated with FVIII is shown by the purple line using a secondary axis, and the total number of patients treated with any product is shown by the green line. Emicizumab is currently not licensed for use in this group.

Data table for Figure 3: Factor VIII units issued by UK haemophilia centres to treat severe haemophilia A, 2012/13 - 2021/22

Year	pd-FVIII		Standard half-life FVIII (excluding investigational)		Investigational rFVIII		Enhanced half-life rFVIII		Total		People issued FVIII		People issued any product	
	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2016/17	IU (millions)	% difference since 2012/13	n	% difference since 2012/13	n	% difference since 2012/13
2012/13	34.6	-	349.7	-	7.5	-	-	-	391.7	-	1661	-	1731	-
2013/14	31.3	-9.6	369.1	5.6	18.2	143.4	-	-	418.5	6.8	1726	3.9	1794	3.6
2014/15	33.4	-3.4	400.7	14.6	17.3	131.4	-	-	451.4	15.2	1773	6.7	1844	6.5
2015/16	32.6	-5.8	424.3	21.3	14.4	93.2	-	-	471.6	20.4	1821	9.6	1893	9.4
2016/17	28.6	-17.3	435.4	24.5	9.7	30.5	12.9	-	486.8	24.3	1860	12	1934	11.7
2017/18	21.8	-36.9	403.7	15.5	5.7	-23.4	60.9	370.7	492.2	25.6	1908	14.9	1980	14.4
2018/19	11.8	-66	416.3	19.1	6.5	-13	81.9	532.7	516.5	31.8	1940	16.8	2020	16.7
2019/20	7	-81	406.8	16.3	3.3	-55.6	80.2	519.9	497.0	26.9	1964	18.2	2056	18.8
2020/21	3	-90	298.2	-14.7	1.5	-79.8	83.7	546.5	386.8	-1.3	1799	8.3	2054	18.7
2021/22	3.8	-88.9	215.4	-38.4	0.1	-98.8	112.5	769.7	333.4	-14.9	1701	2.4	2095	21

Data table for Figure 4: Factor VIII units issued by UK haemophilia centres to treat non-severe haemophilia A, 2012/13 - 2021/22

Year	pd-FVIII		Standard half-life FVIII (excluding investigational)		Investigational rFVIII		Enhanced half-life rFVIII		Total		People issued FVIII		People issued any product	
	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	n	% difference since 2012/13	n	% difference since 2012/13
2012/13	2.8	-	60.3	-	1.7	-	-	-	64.8	-	1133	-	1327	-
2013/14	2.5	-11.4	64.0	6.2	3.0	74.7	-	-	69.5	7.2	1165	2.8	1352	1.9
2014/15	1.9	-33.2	66.2	9.8	2.9	68.1	-	-	71.0	9.5	1159	2.3	1367	3.0
2015/16	1.9	-31.4	71.1	18.0	1.7	0.8	-	-	74.7	15.4	1181	4.2	1383	4.2
2016/17	1.3	-51.7	73.5	21.8	0.9	-48.5	2.3	-	78.0	20.4	1152	1.7	1356	2.2
2017/18	1.5	-47.6	67.7	12.3	0.1	-94.7	8.6	269.1	77.9	20.1	1243	9.7	1431	7.8
2018/19	1.6	-42.3	69.6	15.4	-	-100.0	11.6	402.2	82.8	27.8	1199	5.8	1386	4.4
2019/20	1.6	-41.1	78.9	30.9	-	-100.0	12.3	432.5	92.8	43.4	1216	7.3	1411	6.3
2020/21	0.3	-89.9	62.6	3.9	-	-99.2	19.0	721.9	81.9	26.5	1079	-4.8	1200	-9.6
2021/22	-	-99.4	52.2	-13.4	-	-99.4	33.9	1364.4	86.1	33.0	1216	7.3	1385	4.4

Figure 5 Number of people with haemophilia A issued product, 2012/13 - 2021/22

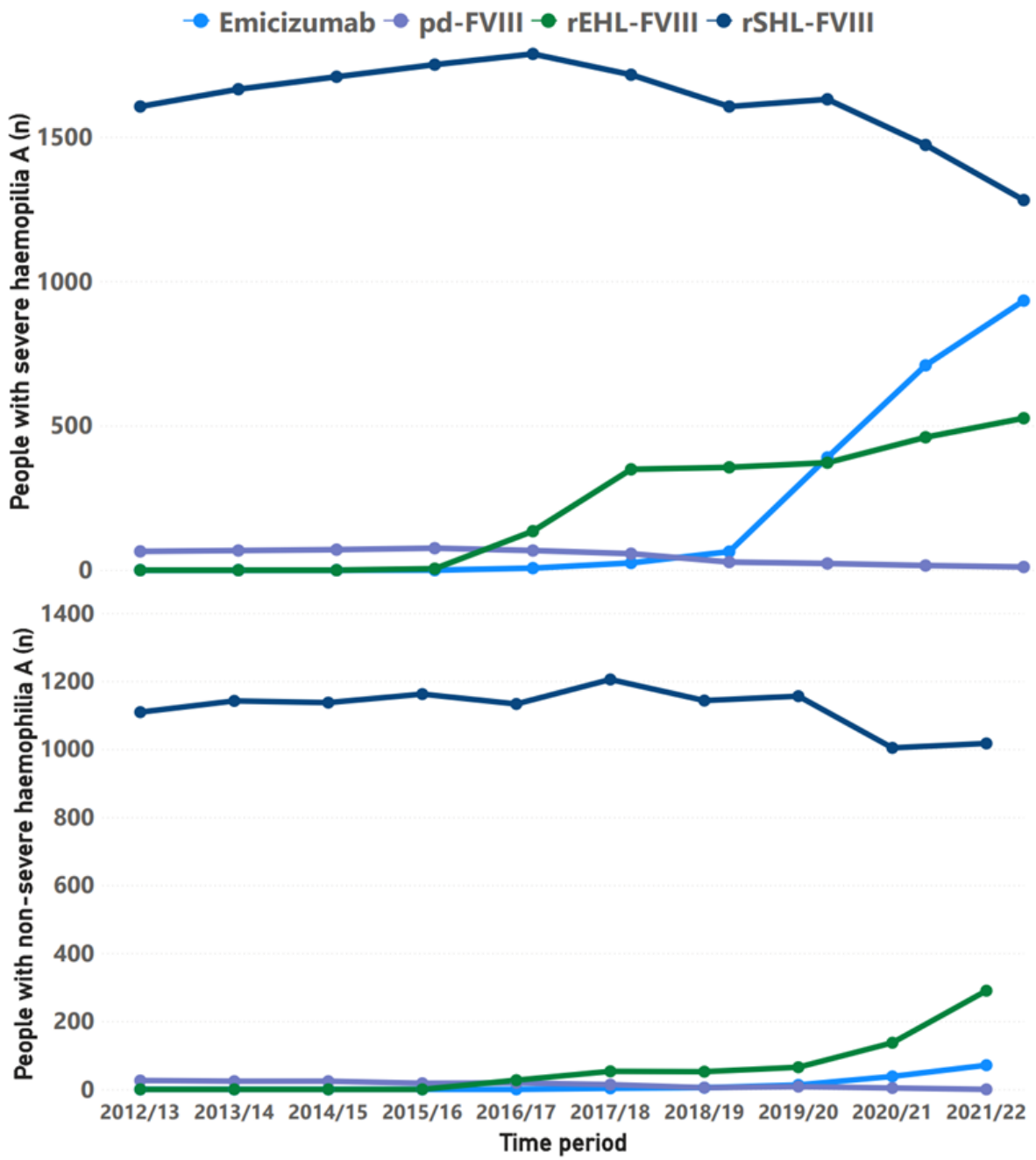


Figure 5: This shows the number of people with haemophilia A (with and without FVIII inhibitors) using different product types, by severity. This shows a gradual introduction of enhanced half-life (EHL) FVIII from 2016. It also shows an overall reduction in the number of people with severe haemophilia A treated with standard half-life (SHL) FVIII as emicizumab was introduced for people with inhibitors in 2018 and for people with severe haemophilia A without inhibitors in 2019. As people may be issued with more than one product type in any given year, there is some double counting in this chart.

Table 4 Factor VIII mean issues by region for people with severe haemophilia A (including treatment for inhibitors and EHL-FVIII), 2012/13 - 2021/22

Country	Region	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20	2020/21	2021/22
England	North East & Yorkshire	256,205	261,159	260,229	291,180	303,210	294,241	318,902	305,292	240,702	176,529
	North West	186,871	193,969	208,457	221,597	225,490	226,437	219,660	200,114	117,461	81,775
	Midlands	168,460	180,867	190,491	186,807	190,872	193,914	204,921	206,132	152,458	125,917
	East of England	232,472	262,953	265,370	274,063	291,560	287,620	239,310	210,763	196,372	145,691
	London	300,593	310,200	329,785	328,718	318,407	302,795	311,835	279,968	263,517	261,469
	South East	208,923	210,616	227,170	240,291	241,616	244,979	249,471	250,808	213,519	201,612
	South West	184,240	200,516	211,955	216,503	230,091	227,525	257,147	234,983	192,391	167,925
Wales	Wales	182,446	201,678	209,704	217,153	237,842	241,798	256,926	273,408	222,801	221,561
Scotland	East of Scotland	328,837	286,671	261,230	265,055	282,548	286,010	286,277	265,185	255,993	212,022
	West of Scotland	207,812	210,545	234,063	267,379	314,008	281,273	288,282	257,828	230,527	202,240
Northern Ireland	Northern Ireland	239,654	250,527	229,004	212,593	204,045	204,496	226,913	227,093	242,039	243,540

Table 4: This shows mean FVIII issues by region. Units are assigned to region by haemophilia centre rather than home postcode, as requested by the Lead Commissioner. Treatment trends appear to differ from region to region. Whilst usage of factor VIII appears relatively stable in Northern Ireland London and the South East, a marked reduction in the use of factor VIII has been reported for the North West, the Midlands, North East and Yorkshire, which is attributable to significant numbers of people switching to emicizumab prohylaxis.

Table 5 People with haemophilia A issued with FVIII by severity, 2012/13 - 2021/22

Haemophilia A	Number of people by factor VIII level (IU/dl)											
	<1			1 - 5			>5 & <40			≥ 40		
Treatment year	Registered	Treated	% change year on year	Registered	Treated	% change year on year	Registered	Treated	% change year on year	Registered	Treated	% change year on year
	n	n (%)		n	n (%)		n	n (%)		n	n (%)	
2012/13	1787	1661 (92.9)	-	779	477 (61.2)	-	3212	630 (19.6)	-	684	24 (3.5)	-
2013/14	1843	1726 (93.7)	3.9	778	499 (64.1)	4.6	3274	642 (19.6)	1.9	804	23 (2.9)	-4.2
2014/15	1893	1773 (93.7)	6.7	779	500 (64.2)	4.8	3417	639 (18.7)	1.4	1010	19 (1.9)	-20.8
2015/16	1952	1821 (93.3)	9.6	781	499 (63.9)	4.6	3555	654 (18.4)	3.8	1132	25 (2.2)	4.2
2016/17	1991	1860 (93.4)	12.0	779	486 (62.4)	1.9	3611	638 (17.7)	1.3	1257	25 (2.0)	4.2
2017/18	2040	1908 (93.5)	14.9	789	502 (63.6)	5.2	3714	708 (19.1)	12.4	1373	31 (2.3)	29.2
2018/19	2076	1940 (93.4)	16.8	797	486 (61.0)	1.9	3827	683 (17.8)	8.4	1503	27 (1.8)	12.5
2019/20	2113	1964 (92.9)	18.2	807	508 (62.9)	6.5	3907	683 (17.5)	8.4	1608	23 (1.4)	-4.2
2020/21	2141	1799 (84.0)	8.3	820	495 (60.4)	3.8	3966	567 (14.3)	-10.0	1669	17 (1.0)	-29.2
2021/22	2179	1701 (78.1)	2.4	836	524 (62.7)	9.9	4048	658 (16.3)	4.4	1822	31 (1.7)	29.2

Table 6a Treatment intensity of people with severe haemophilia A without inhibitors issued with standard half-life FVIII, 2012/13 - 2021/22

Treatment period	FVIII Units		People (n)		Treatment intensity (units/person/year)		Change in treatment intensity year on year (%)	
	<18 Years	≥18 years	<18 Years	≥18 years	<18 Years	≥18 years	<18 Years	≥18 years
2012/13	92,294,635	227,896,739	504	919	183,124	247,983	-	-
2013/14	98,380,097	252,207,754	523	974	188,107	258,940	2.7	4.4
2014/15	103,713,972	275,236,275	523	1,017	198,306	270,635	5.4	4.5
2015/16	101,954,740	288,712,170	516	1,032	197,587	279,760	-0.4	3.4
2016/17	91,826,048	289,600,211	457	1,034	200,932	280,078	1.7	0.1
2017/18	83,290,418	259,195,470	399	952	208,748	272,264	3.9	-2.8
2018/19	86,543,617	289,906,198	416	972	208,038	298,257	-0.3	9.5
2019/20	72,933,643	253,672,676	341	861	213,882	294,626	2.8	-1.2
2020/21	53,791,806	175,826,381	241	639	223,203	275,159	4.4	-6.6
2021/22	41,290,450	122,208,658	184	457	224,405	267,415	0.5	-2.8

***Table 6a*:** This shows that SHL-FVIII treatment intensity (units/person/year) for people with severe haemophilia A appears to fluctuate.

NOTE - exclusions from this analysis:

People issued with emicizumab, people issued with both EHL- and SHL-FVIII, people using gene therapy, people resident overseas, people not registered for full treatment period, people for whom inhibitors are reported within the treatment period

Table 6b Treatment intensity of people with severe haemophilia A without inhibitors treated with enhanced half-life FVIII, 2016/17-2021/22

Treatment period	Enhanced half-life FVIII units		People (n)		Treatment intensity (units/person/year)		Change in treatment intensity year on year (%)	
	<18 Years	≥18 years	<18 Years	≥18 years	<18 Years	≥18 years	<18 Years	≥18 years
2016/17	857,566	682,500	6	3	142,928	227,500	-	-
2017/18	13,336,000	17,809,810	70	62	190,514	287,255	33.3	26.3
2018/19	20,386,258	45,911,020	115	166	177,272	276,572	-7.0	-3.7
2019/20	20,329,710	34,876,480	112	131	181,515	266,233	2.4	-3.7
2020/21	14,865,325	34,516,000	86	131	172,853	263,481	-4.8	-1.0
2021/22	18,109,295	66,257,900	89	214	203,475	309,616	17.7	17.5

Table 6b: This shows the introduction of EHL-FVIII for the treatment of severe haemophilia A from April 2016 to March 2022. There is an apparent increase in treatment intensity from 2020/21 to 2021/22.

NOTE - exclusions from this analysis:

People issued with emicizumab, people issued with both EHL- and SHL-FVIII, people using gene therapy, people resident overseas, people not registered for full treatment period, people for whom inhibitors are reported within the treatment period

Table 7a Treatment intensity of people with moderate haemophilia A (0.01 - 0.03 IU/ml) treated with standard half-life FVIII, with no inhibitor, 2012/13 - 2021/22

Treatment period	FVIII units		People (n)		Treatment intensity (units/person/year)		Change in treatment intensity year on year (%)	
	<18 Years	≥18 years	<18 Years	≥18 years	<18 Years	≥18 years	<18 Years	≥18 years
2012/13	89,203,042	214,127,539	515	944	173,210	226,830	-	-
2013/14	94,276,892	236,616,193	526	991	179,234	238,765	3.5	5.3
2014/15	98,830,172	259,282,071	533	1,031	185,422	251,486	3.5	5.3
2015/16	99,759,740	271,968,153	535	1,048	186,467	259,512	0.6	3.2
2016/17	90,387,048	268,634,832	479	1,036	188,699	259,300	1.2	-0.1
2017/18	81,393,602	236,619,179	430	948	189,287	249,598	0.3	-3.7
2018/19	85,340,917	261,864,772	431	962	198,007	272,209	4.6	9.1
2019/20	74,657,393	231,670,942	362	872	206,236	265,678	4.2	-2.4
2020/21	51,857,055	162,412,845	250	657	207,428	247,204	0.6	-7.0
2021/22	39,879,700	110,646,126	195	473	204,511	233,924	-1.4	-5.4

Table 7a: This table shows the trend in treatment intensity in people with haemophilia A and factor level between 0.01 - 0.03 IU/ml over the last ten years. Only people treated during this time are included. However, the range of baseline FVIII levels and bleeding phenotypes included in this data ranges from those on regular prophylaxis to those requiring only occasional treatment. This renders the data more difficult to interpret and impossible to compare directly with the relatively more homogeneous group of people with severe haemophilia A. Emicizumab is not currently licensed for this group. This shows, in general, a modest increase in treatment intensity since 2012, reflecting the re-evaluation of bleeding severity in this group over this time.

NOTE - exclusions from this analysis:

People issued with emicizumab, people issued with both EHL- and SHL-FVIII, people using gene therapy, people resident overseas, people not registered for full treatment period, people for whom inhibitors are reported within the treatment period

Table 7b Treatment intensity of people with haemophilia A (0.01 - 0.03 IU/ml) treated with enhanced half-life FVIII, with no inhibitor, 2016/17 - 2021/22

Treatment period	Enhanced half-life FVIII units		People (n)		Treatment intensity (units/person/year)		Change in treatment intensity year on year (%)	
	<18 Years	≥18 years	<18 Years	≥18 years	<18 Years	≥18 years	<18 Years	≥18 years
2016/17	992,566	682,500	7	3	141,795	227,500	-	-
2017/18	11,175,464	18,733,810	61	63	183,204	297,362	29.2	30.7
2018/19	18,947,808	47,835,020	106	169	178,753	283,047	-2.4	-4.8
2019/20	19,286,460	37,173,730	104	141	185,447	263,643	3.7	-6.9
2020/21	13,972,575	36,770,250	80	138	174,657	266,451	-5.8	1.1
2021/22	18,213,645	70,611,150	96	230	189,725	307,005	8.6	15.2

Table 7b: This illustrates the introduction of EHL-FVIII to a relatively small group of people with haemophilia A and a factor level between 0.01 - 0.03 IU/ml between April 2016 and March 2022.

NOTE - exclusions from this analysis:

People issued with emicizumab, people issued with both EHL- and SHL-FVIII, people using gene therapy, people resident overseas, people not registered for full treatment period, people for whom inhibitors are reported within the treatment period

Figure 6a Treatment intensity (IU/person/year) of people *aged under 18 years* with haemophilia A treated with standard half-life FVIII, with no inhibitor by severity, 2021/22

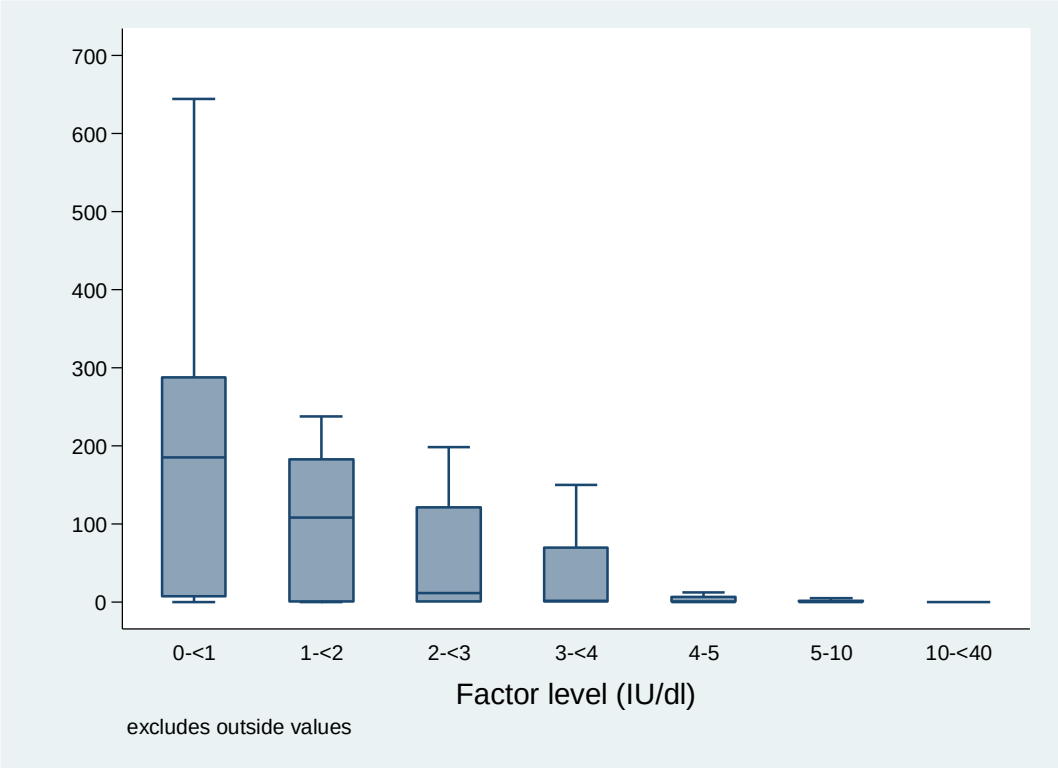


Figure 6a: This box and whisker plot shows the median, IQR and range of SHL-FVIII (IU/person/year) broken down by baseline FVIII level in people under 18 years old with haemophilia A. This shows that young people with a FVIII baseline level of 1 - <2 IU/dl have greater factor VIII requirements than those with 2 - <3 IU/dl, and the factor VIII requirement falls off rapidly at higher factor VIII baseline levels.

Summary statistics for figure 6a

Annual FVIII units (thousands)	People (n)	Annual FVIII units (thousands) (median (IQR))
<1	208	185.5 (7.3; 288.3)
1 - <2	24	108.8 (0.4; 183.0)
2 - <3	27	12.0 (0.0; 121.5)
3 - <4	31	2.0 (0.0; 70.0)
4 - 5	60	0.0 (0.0; 7.0)
5 - 10	126	0.0 (0.0; 2.0)
10 - 40	531	0.0 (0.0; 0.0)
Total	**1,007**	0.0 (0.0; 4.5)

Exclusions from this analysis:
Issued Hemlibra or EHL 2021/22
Registered for only part of the year 2021/22
Inhibitor 2021/22

Figure 6b Treatment intensity (IU/Person/year) of people *aged 18 years and above* with haemophilia A treated with standard half-life FVIII, with no inhibitor by severity, 2021/22

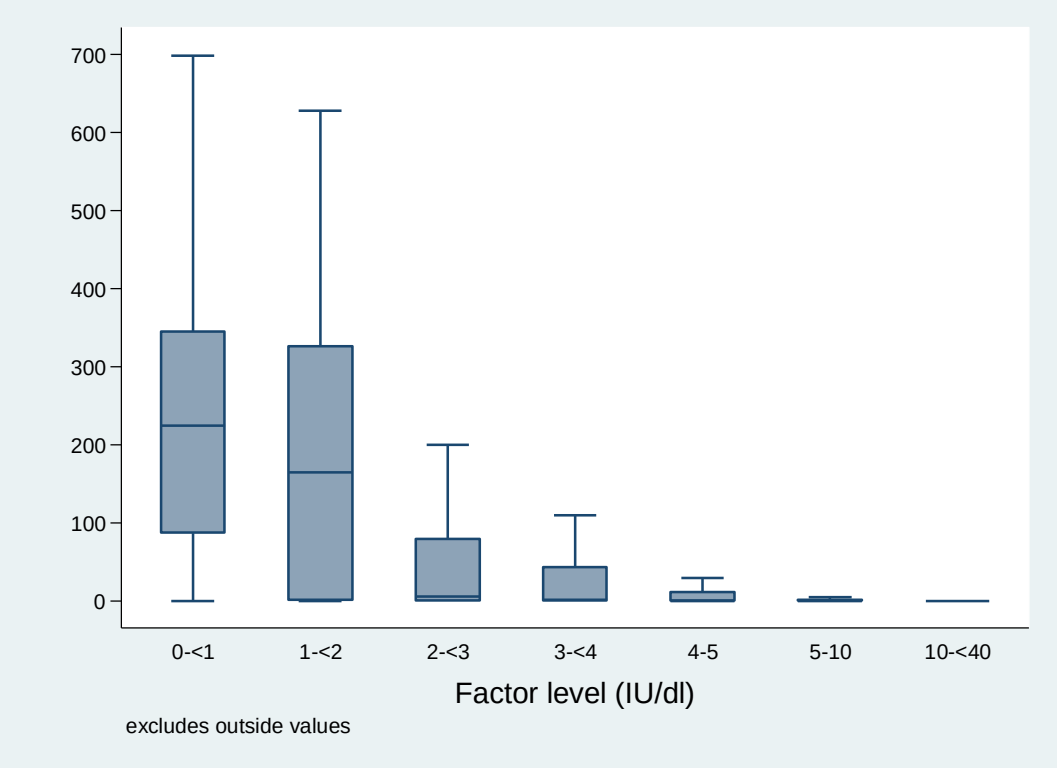


Figure 6b: This box and whisker plot shows the median, IQR and range of SHL-FVIII (IU/person/year) broken down by baseline FVIII level in people aged 18 years and above with haemophilia A. This shows that adults with a FVIII baseline of <1 and 1 - <2 IU/dl have substantial factor VIII requirements, the factor VIII requirement falls off dramatically at higher levels of baseline factor VIII.

Summary statistics for figure 6b

Annual FVIII units (thousands)	People (n)	Annual FVIII units (thousands) (median (IQR))(median (IQR))
<1	499	225.0 (87.5; 345.0)
1 - <2	45	165.0 (1.5; 326.0)
2 - <3	83	6.0 (0.0; 80.0)
3 - <4	90	2.0 (0.0; 44.0)
4 - 5	219	0.0 (0.0; 12.0)
5 - 10	454	0.0 (0.0; 2.0)
10 - 40	2,576	0.0 (0.0; 0.0)
Total	**3,966**	0.0 (0.0; 2.0)

Exclusions from this analysis:
Issued Hemlibra or EHL 2021/22
Registered for only part of the year 2021/22
Inhibitor 2021/22
Resident overseas
Gene therapy
Issued trial product 2021/22
Issued plasma 2021/22`

Figure 7a Annual FVIII issues (IU/kg/person) in people with severe haemophilia A aged under 18 years with no current inhibitor, by centre, ranked by median issues

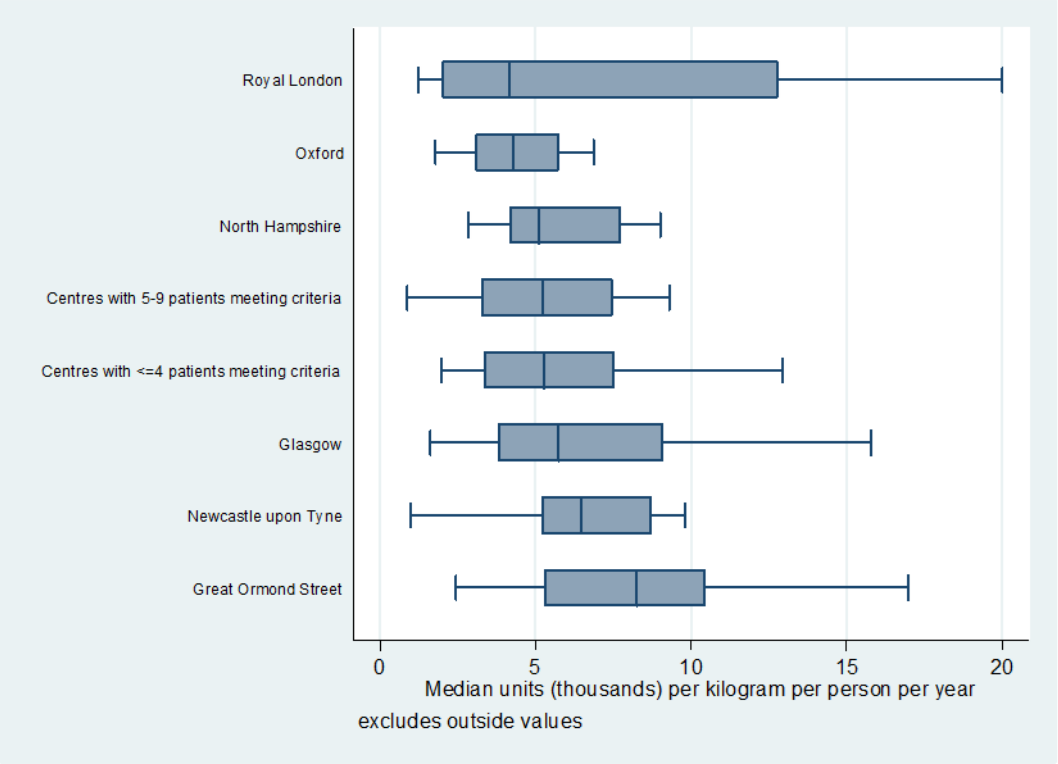


***Figure 7a*:** This shows FVIII issues per kilogram per person by haemophilia centre, ranked by median issues, in people with severe haemophilia A aged under 18 years old with no reported current inhibitor and a body weight reported in 2021/22. Please note that issues from Birmingham Children's Hospital have been omitted due to technical data collection issues which we are investigating but have not completely resolved at this time. Centres with fewer than three people with weight reported are excluded. This figure should be interpreted with extreme caution since the median factor VIII usage is likely to be significantly distorted by the very variable uptake of emicizumab from centre to centre and also by variations in prescribing policy for this drug. In general, when new treatments are introduced, heavy users of factor VIII and those with the most severe bleeding phenotype tend to be switched first. If this policy is adopted for emicizumab that would result in a reduction in the median factor VIII consumption

This shows an almost twofold range in median treatment intensity between centres. This is a much lower range than in the past, suggesting greater uniformity in prophylaxis and possibly switching of high users and outliers to emicizumab. Most centres have broadly similar treatment intensity, as one would expect, given that prophylaxis is the standard of care.

Centres such as Great Ormond Street, which conduct a far greater number of immune tolerance induction procedures than other paediatric centres, will be expected to have high median issues but the difference is not dramatic. Although this chart excludes people with a reported current inhibitor, they may have a higher proportion of people with unreported low-level inhibitors following immune tolerance induction. It is now well recognised that some people who fulfil the internationally recognised criteria for tolerance (half-life greater than seven hours), and who have traditionally been thought to be inhibitor-free, continue to have low level inhibitor activity, which is too low to detect in

the Bethesda assay but high enough to impair FVIII pharmacokinetics and increase FVIII consumption.

Summary statistics for this chart are presented in the data table below.

Data table for Figures 7a & b

Haemophilia centre	People (n)	People with weight reported	Total units	Median units	Median units/kg
Belfast	16	0	2,667,250	145,000	-
Glasgow	13	13	2,875,000	193,250	5,734
Great Ormond Street	56	19	16,481,500	270,500	8,250
Leeds	14	2	2,115,545	117,500	-
Newcastle upon Tyne	10	10	3,443,000	320,250	6,447
North Hampshire	11	10	3,057,000	279,000	5,098
Oxford	29	28	5,580,500	182,000	4,267
Royal London	15	4	2,462,250	126,000	4,169
St George's	11	0	4,232,000	283,500	-
St Thomas'	18	1	3,718,750	194,750	-
Centres with <=4 people meeting criteria	30	23	6,663,750	188,500	5,265
Centres with 5-9 people meeting criteria	45	34	9,679,000	187,500	5,222

**Median units/kg is not presented for centres with fewer than three people with weight reported*

Exclusions from this analysis:
Issued Hemlibra 2021/22
Registered for only part of the year 2021/22
Inhibitor 2021/22
Resident overseas
Gene therapy
Issued trial product 2021/22

Figure 7b Annual FVIII issues (IU/person) in people with severe haemophilia A aged under 18 years with no current inhibitor, by centre, ranked by median issues per person

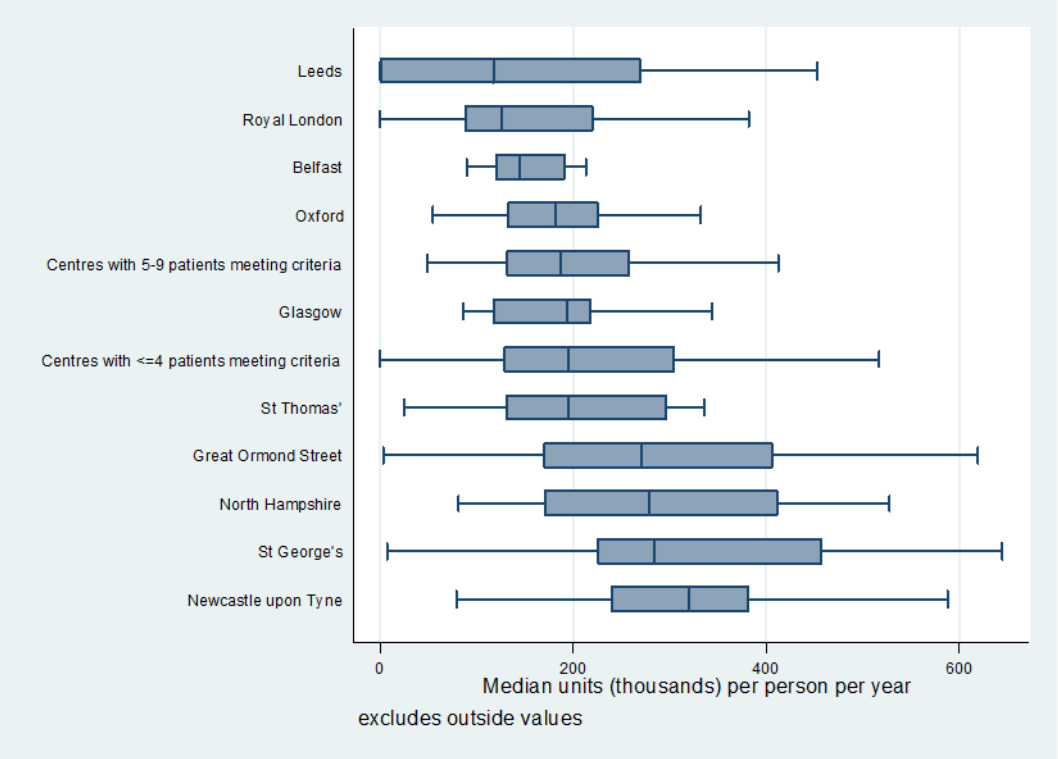


Figure 7b: This shows issues per person with severe haemophilia A, aged under 18 years by centre with no reported current inhibitor, as in the previous figure, but not corrected for body weight. Please note that issues from Birmingham Children's Hospital have been omitted due to technical data collection issues which we are investigating but have not completely resolved at this time. It shows a more than twofold range in median units used per person between centres. The interpretation is similar to the previous figure. The sample size is larger since the table includes people with and without known body weight.

The ranking of centres differs depending on whether it is expressed in IU/kg/person/year or IU/person/year.

Figure 8a Annual FVIII issues (IU/kg/person) in people with severe haemophilia A aged 18 years or more with no current inhibitor, by centre, ranked by median issues

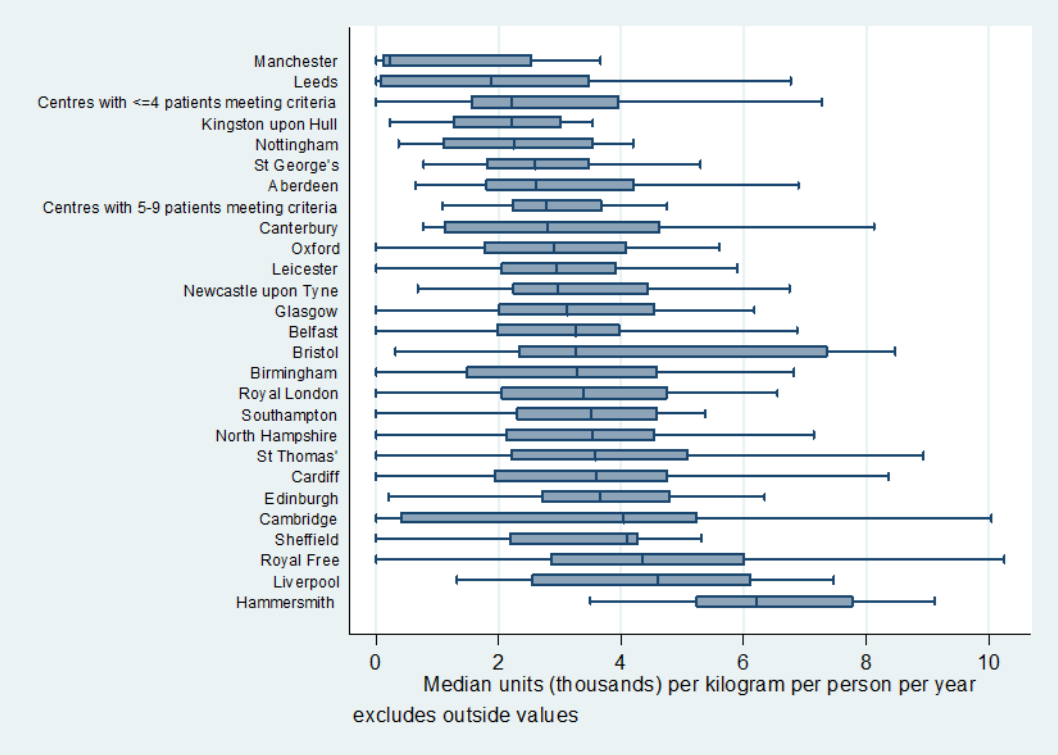


Figure 8a: This shows FVIII issues per kilogram per person by haemophilia centre, ranked by median issues, in people with severe haemophilia A aged 18 years or more with no reported current inhibitor, and an updated body weight reported. As weight reporting has been impacted by the COVID-19 pandemic, weight measurements from up to three years prior to 2021/22 have been used where no later weight measurement is available, where the person was aged 18 years or more at the time the weight measurement was reported.

Although it appears, superficially, that there is a wide range in factor VIII treatment intensity from centre to centre, these figures are now grossly distorted by the variable uptake of Hemlibra from centre to centre. Manchester, for example, has switched about 85% of its people with severe Haemophilia A to emicizumab and those that continue to use factor VIII as their primary treatment are mostly those with a mild bleeding phenotype and/or treating themselves on-demand. Consequently, median factor VIII issues per kilogram (based on only 11 people) appears to have reduced dramatically from year to year for that centre.

Exclusions from this analysis:
Issued Hemlibra 2021/22
Registered for only part of the year 2021/22
Inhibitor 2021/22
Resident overseas
Gene therapy
Issued trial product 2021/22

Data table for Figure 8a & b

Haemophilia centre	People (n)	People with weight reported	Total units	Median units	Median units / Kg
Aberdeen	14	14	3,910,250	267,000	2622
Belfast	50	41	12,986,500	244,500	3257
Birmingham	41	39	10,376,500	288,000	3291
Bristol	15	13	4,531,250	251,500	3266
Cambridge	14	14	4,311,750	319,500	4038
Canterbury	14	14	4,176,000	199,500	2807
Cardiff	25	23	7,938,900	327,000	3588
Edinburgh	14	14	5,206,500	269,500	3650
Glasgow	24	24	6,775,000	260,000	3122
Hammersmith	10	10	4,772,000	473,500	6207
Kingston upon Hull	11	11	2,253,500	208,000	2222
Leeds	34	27	5,785,000	85,750	1883
Leicester	12	12	2,989,000	274,000	2955
Liverpool	14	8	4,176,000	279,000	4606
Manchester	14	11	1,620,500	29,750	224
Newcastle upon Tyne	22	21	6,241,000	275,000	2970
North Hampshire	34	31	9,276,250	308,000	3538
Nottingham	14	14	2,520,650	145,000	2253
Oxford	66	66	16,171,500	253,750	2895
Royal Free	100	99	34,765,000	355,000	4355
Royal London	45	36	11,128,500	231,000	3380
Sheffield	15	13	3,352,000	287,000	4100
Southampton	13	12	3,708,500	254,000	3512
St George's	35	30	6,943,250	201,000	2593
St Thomas'	66	42	20,589,500	306,500	3581
Centres with <=4 people meeting	35	26	7,119,500	206,000	2222
Centres with 5-9 people meeting	14	14	3,059,500	209,500	2772

Figure 8b Annual FVIII issues (IU/person) in people with severe haemophilia A aged 18 years or more with no current inhibitor, by centre, ranked by median issues

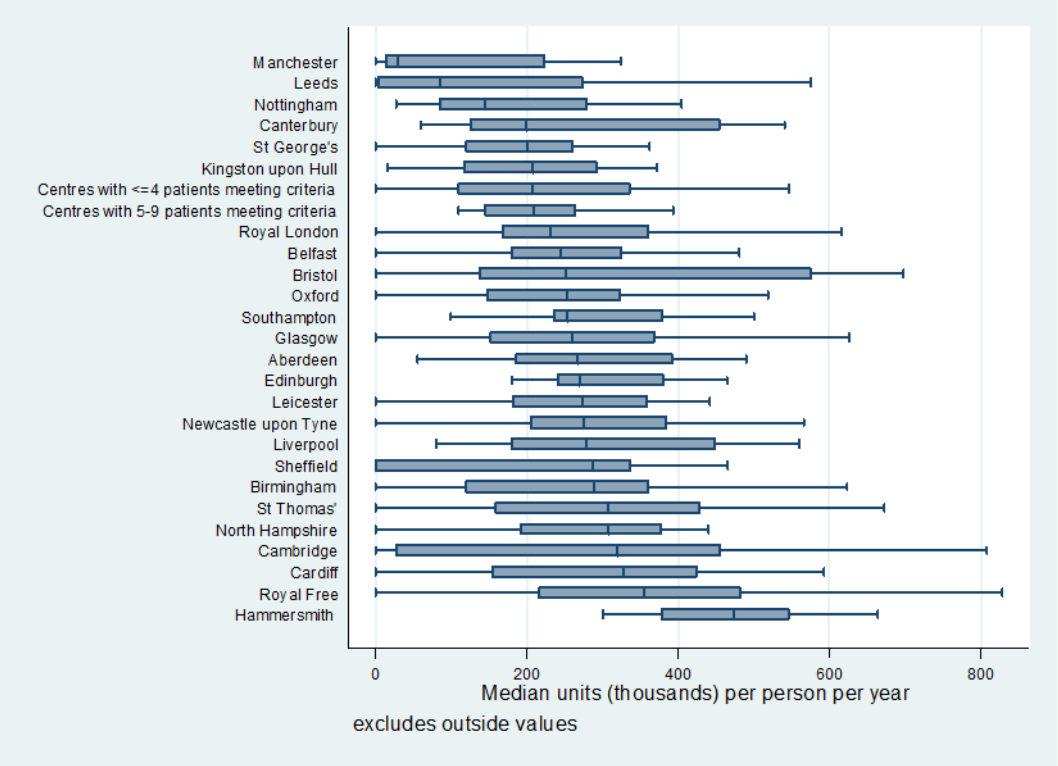


Figure 8b: This shows issues per person aged 18 years or more by centre, for people with severe haemophilia A with no reported current inhibitor not corrected for bodyweight. It shows a wide range in treatment intensity and interpretation is similar to the previous figure, though the sample size is larger since it includes people with and without a known bodyweight.

Figure 9 Median FVIII units issued per kilogram body weight per year in people with severe haemophilia A without inhibitors, by age

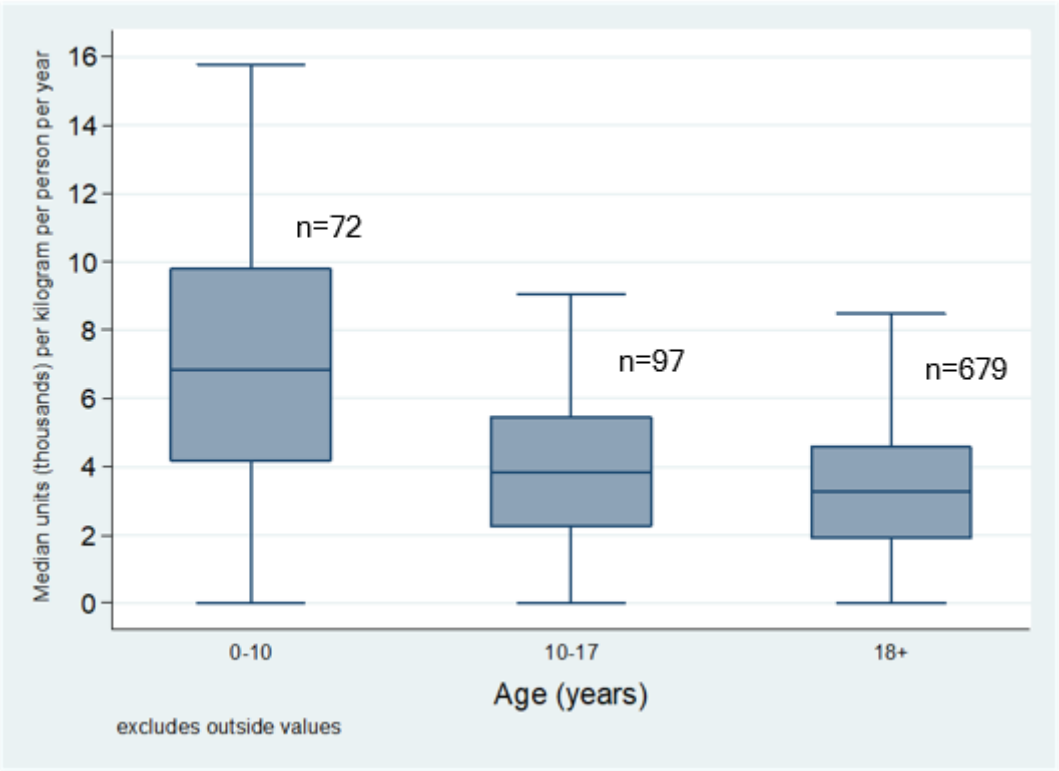
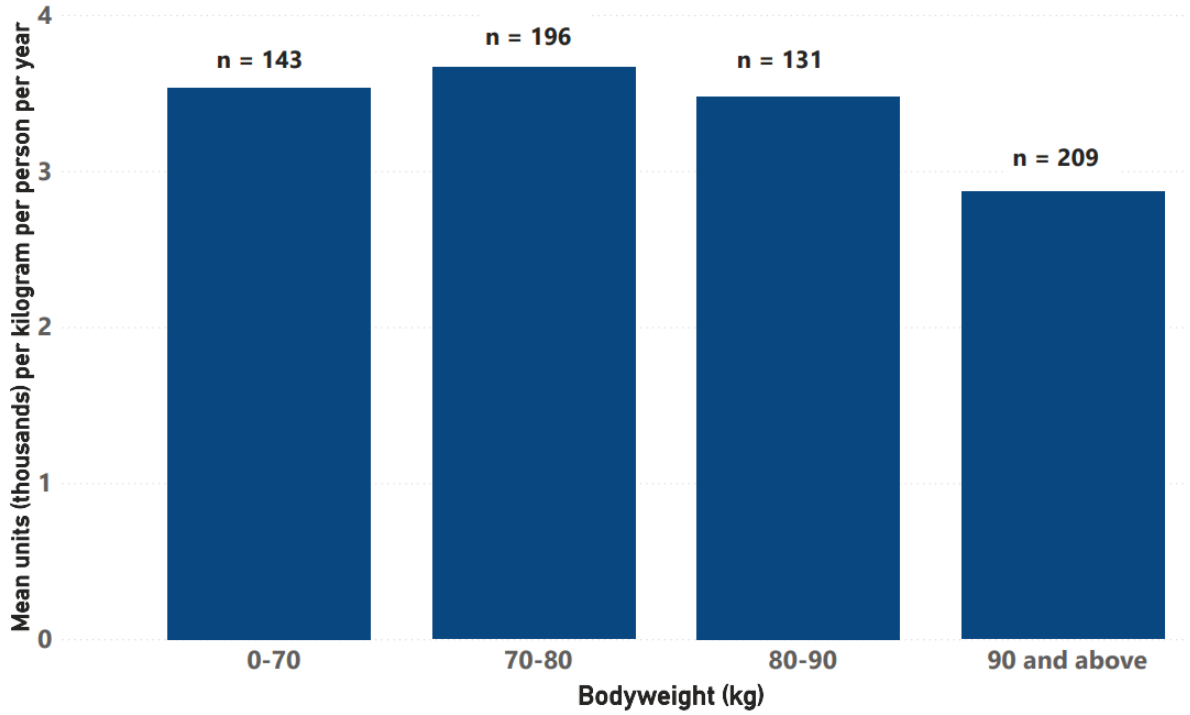


Figure 9: This shows the median FVIII issues per kilogram body weight per year in people with severe haemophilia A without inhibitors, broken down by age.

The most intensive general issues appears to be in children, as would be expected. Vial size is also an issue for small children. Doses will often be rounded up because the range of available vial sizes does not make it possible to make small dose adjustments in very small individuals.

Exclusions from this analysis:
Issued Hemlibra 2021/22
Registered for only part of the year 2021/22
Inhibitor 2021/22
Resident overseas
Gene therapy
Issued trial product 2021/22

Figure 10 Mean annual FVIII units issued per kilogram body weight in people with severe haemophilia A without inhibitors aged 18 and over



Weight data are missing for n= 86/866

Spearman's rank correlation coefficient: p<0.005

Figure 10: This shows mean units per kilogram per person issued to people with severe haemophilia A aged 18 and over without inhibitors, broken down by body weight. The total number of people in each group is indicated by the number over each box. Since FVIII recovery increases progressively as Body Mass Index (BMI) increases, one would expect FVIII consumption per kilogram body weight to decline as body weight increases. This appears to be the case generally.

It is presumed that the '>= 90 kg' group will all be overweight, but the NHD does not record height, and therefore BMI cannot be calculated.

Exclusions from this analysis:
Issued Hemlibra 2021/22
Registered for only part of the year 2021/22
Inhibitor 2021/22
Resident overseas
Gene therapy

Table 8 Products issued to treat haemophilia A (including inhibitors), 2020/21 and 2021/22

Product Type	Manufacturer	Description	2020/21		2021/22	
			Units (IU)	People (n)	Units (IU)	People (n)
Non-factor	IDEC Pharmaceuticals	Rituximab	-	-	3	1-2
	Roche	Hemlibra (mg)	2,565,909	747	3,795,498	1,004
	Various manufacturers	Tranexamic Acid	247,100	11	158,114	10
		Desmopressin	5,204	112	6,557	145
Recombinant	CSL Behring	Helixate Nexgen	6,000	1-2	-	-
	Novo Nordisk	Esperoct	27,835,500	181	70,007,900	376
		NovoEight	85,493,000	445	52,868,150	329
		NovoSeven (mg)	6,817	92	11,909	118
	Octapharma	Nuwiq	11,224,500	81	10,606,500	88
	Pfizer	ReFacto AF	117,940,125	849	84,137,970	774
	SOBI/Biogen	Elocta	74,261,611	428	72,419,145	434
	Takeda	Advate	146,201,436	1,157	119,977,100	1,144
		ADYNOVI	609,000	6	4,042,000	16
		OBIZUR	-	-	14,000	1-2
	Withheld	Investigational FVIII	Withheld	Withheld	Withheld	Withheld
Plasma-derived	BPL	BPL FVIII 8Y	163,800	1-2	444,525	1-2
		Optivate	392,640	1-2	-	-
	Biotest	Haemoctin	328,000	1-2	384,000	1-2
	CSL Behring	Voncento	-	-	17,800	6
		Fibrogammin P	-	-	10,000	1-2
		Riastap	-	-	3	1-2
	Grifols	Fanhdi	1,330,000	11	1,478,000	5
	Octapharma	Octanate	1,485,500	6	1,525,000	4
	Takeda	FEIBA	535,500	16	1,110,000	22
Blood component	National blood transfusion service	Platelets	3	1-2	-	-
Other	Withheld	Investigational other	Withheld	Withheld	Withheld	Withheld

Units in IU unless otherwise stated
Products which include VWF and FVIII are reported in FVIII units

Table 8: This shows a breakdown of product volumes, listed by supplier, issued to treat people with haemophilia A during 2020/21 and 2021/22, including those with inhibitors but excluding acquired haemophilia. People may be issued multiple products. This shows a reduction in the use of all brands of factor VIII as Hemlibra is introduced to treat people with severe haemophilia A with and without inhibitors.

These figures have been cross-checked against sales figures supplied by the manufacturers for the same period. Whilst one would not expect a perfect match between NHD figures based on issues and the manufacturers' sales figures, there is a high level of correlation for all but the low usage rFVIII products, as well as Hemlibra. These sales figures are not reported, by agreement with suppliers, for reasons of commercial sensitivity.

By and large, the plasma-derived products listed were used for immune tolerance induction. The exception, Fanhdi, is also used for a rapidly diminishing group of people without inhibitors attending two centres in the South of England. In general, there is a very steep decline in the use of plasma-derived factor VIII.

We have deliberately aggregated and anonymised investigational products to avoid any breach of confidentiality agreements and to take account of commercial sensitivities.

Figure 11 Number of people with haemophilia A treated in the UK 2021/22 broken down by product used

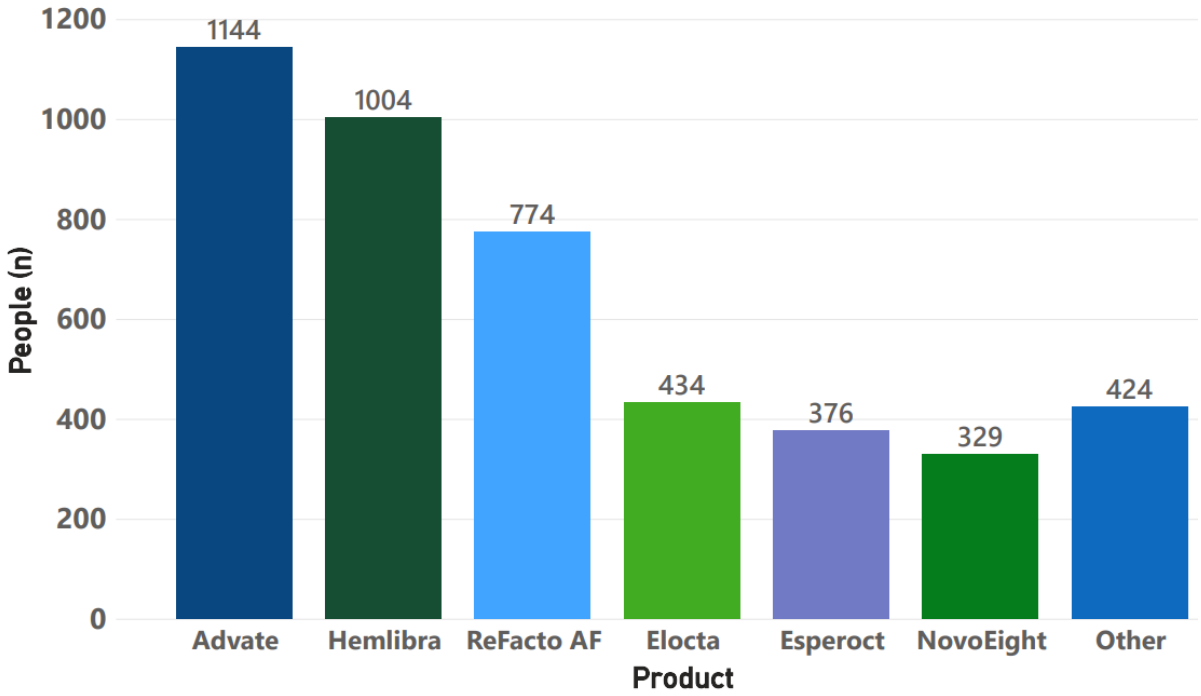


Figure 11: This shows the number of people with haemophilia A treated with each product during the course of the year, including those issued to people with an inhibitor. The data that informs this graph can be found in Table 8. People issued multiple products in the year are included in the numbers for each product. There were 3,478 individual people with haemophilia A treated during the year.

Table 9 Factor VIII and Hemlibra treatment issued by UK haemophilia centres, by diagnosis 2021/22

Diagnosis	FVIII (IU)						Non-factor concentrate (mg)		Total
	People (n)	pd-FVIII	Standard half-life recombinant	Enhanced half-life recombinant	Investigational**	Total	People (n)	Hemlibra	People (n)
Haemophilia A	2,917	3,849,325	267,603,720	146,469,045	Withheld	417,922,090	1,004	3,795,498	3,321
von Willebrand disease	766	28,484,650	164,750	908,000	-	29,557,400	1-2	840	766
Combined V + VIII deficiency	5	-	29,500	-	-	29,500	-	-	5
Other combined diagnoses	16	53,100	822,000	621,500	-	1,496,600	3	7,140	17
Acquired haemophilia A	35	5,000	1,445,500	-	-	1,450,500	1-2	1,680	35
Acquired von Willebrand disease	38	1,371,800	28,000	-	-	1,399,800	-	-	38
Probable von Willebrand disease	1-2	2,000	-	-	-	2,000	-	-	1-2
Other platelet defects	1-2	3,000	-	-	-	3,000	-	-	1-2
Miscellaneous	4	123,820	-	-	-	123,820	-	-	4
Unclassified	3	13,000	1,000	-	-	14,000	-	-	3
Total*	3,784	33,905,695	270,094,470	147,998,545	Withheld	451,998,710	1,007	3,805,158	4,189

** Excludes suppressed numbers*

*** Due to commercial sensitivities, units have been withheld*

Products containing VWF as well as FVIII are reported in FVIII units

Table 9: This table shows factor VIII and Hemlibra treatment use broken down according to diagnosis, including any apparently anomalous use reported to the NHD. Products used to treat von Willebrand disease which include VWF and FVIII are included and are reported in FVIII units. More detail on the use of these products to treat VWD is given in table 17. Please note people issued with both FVIII and Hemlibra are counted only once in the final column.

Potentially anomalous use of FVIII in Table 9 is accounted for as follows:

Miscellaneous bleeding disorders: thrombotic thrombocytopenia purpura.

Figure 12 The proportion of people with severe haemophilia A and no inhibitor issued treatment by product type 2019 Q2 - 2022 Q2

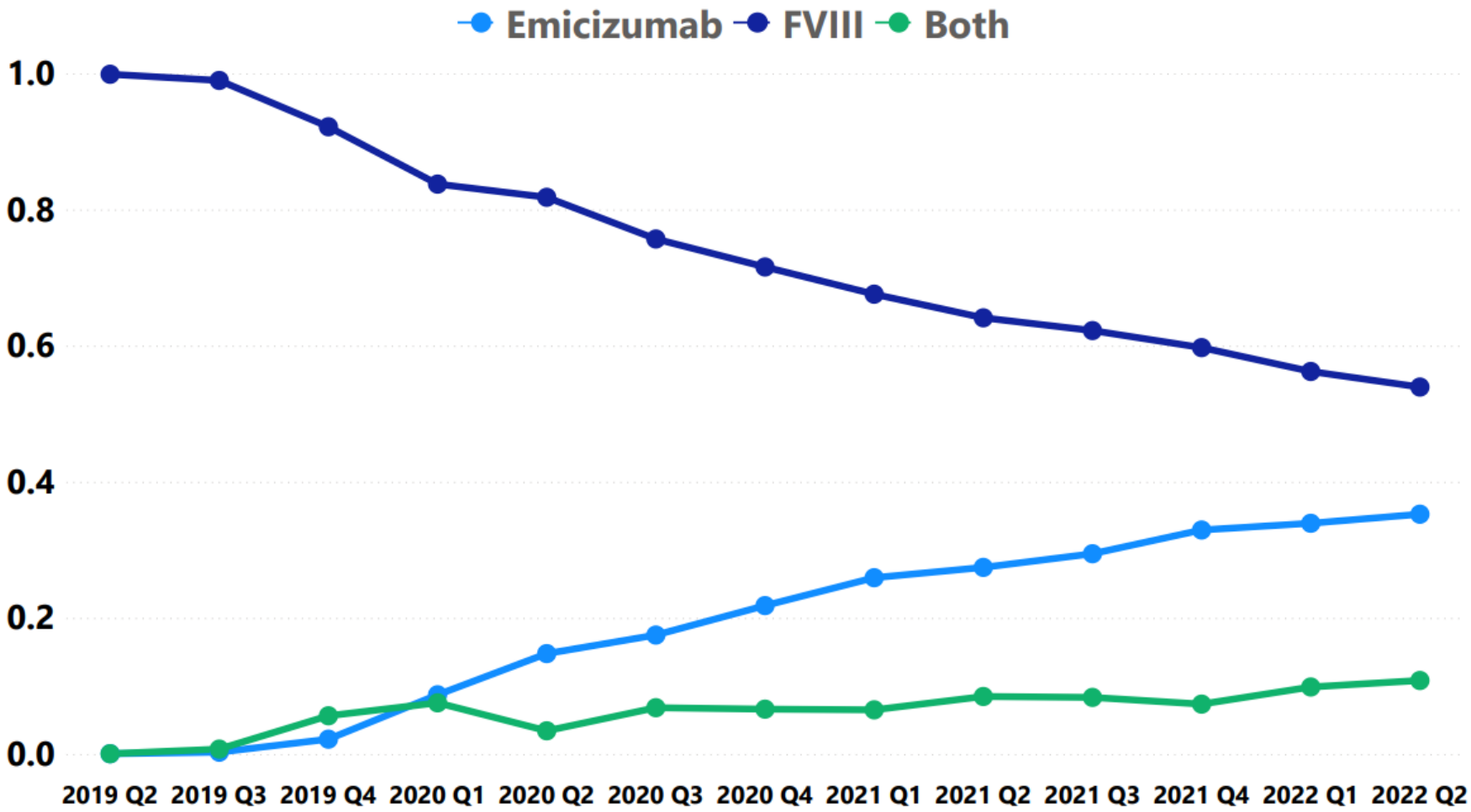


Figure 12: This shows a reduction in the proportion of people with severe haemophilia A, without inhibitors, who require factor VIII since emicizumab was introduced to this group in 2019 Q2.

Figure 13 The proportion of people with severe haemophilia A, without inhibitors treated with Emicizumab by centre

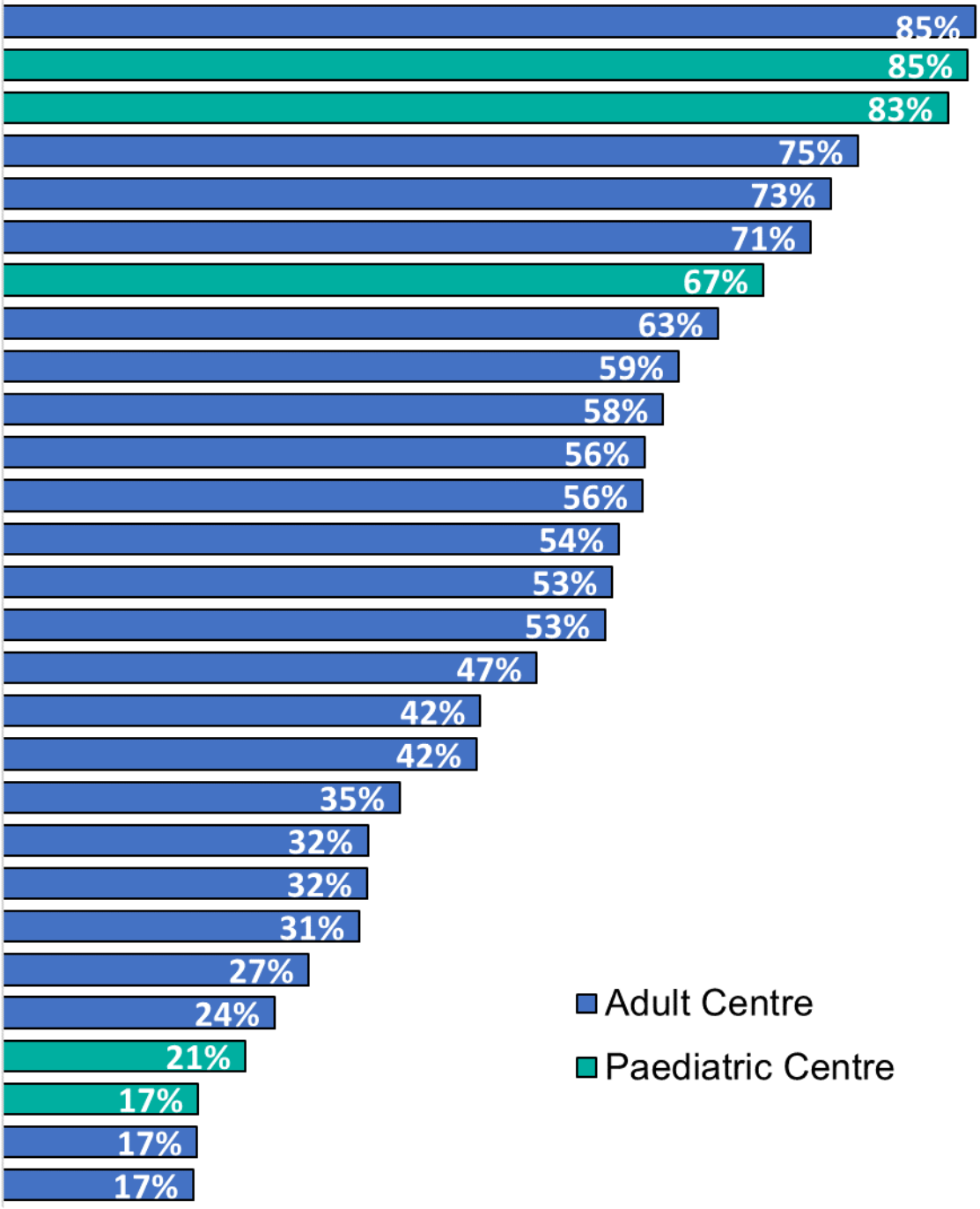


Figure 13: This shows the ranked proportion of people with severe haemophilia A without an inhibitor who were issued Hemlibra, by centre, in 2021/22. This shows considerable centre-to-centre variation (median 53%, IQR 32-64%). The centres identified as "paediatric centres" only manage children, whereas some of the other centres may manage both children and adults.

2.2 Haemophilia B

Table 10 People with congenital haemophilia B (including carriers) registered and treated, 2021/22

Haemophilia B	Age range	Number of people by factor IX level (IU/dl)																	
		< 1			1 - 5			>5 & <40			≥ 40			Unknown			Total		
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Total in register	<18 years	130	-	130	79	-	79	102	84	186	5	45	50	-	1-2	-	316	129	445
	≥18 years	242	1-2	242	265	6	271	437	250	687	38	307	345	-	3	3	982	566	1,548
	Total*	372	-	372	344	6	350	539	334	873	43	352	395	-	3	3	1,298	695	1,993
New registrations **	<18 years	7	-	7	5	-	5	4	8	12	1-2	5	5	-	1-2	-	16	13	29
	≥18 years	-	-	-	3	-	3	7	7	14	1-2	20	20	-	1-2	-	10	27	37
	Total*	7	-	7	8	-	8	11	15	26	-	25	25	-	-	-	26	40	66
Treated with concentrate FIX in year***	<18 years	123	-	123	39	-	39	29	6	35	-	-	-	-	-	-	191	6	197
	≥18 years	211	1-2	211	154	3	157	106	23	129	1-2	8	8	-	1-2	-	471	34	505
	Total*	334	-	334	193	3	196	135	29	164	-	8	8	-	-	-	662	40	702

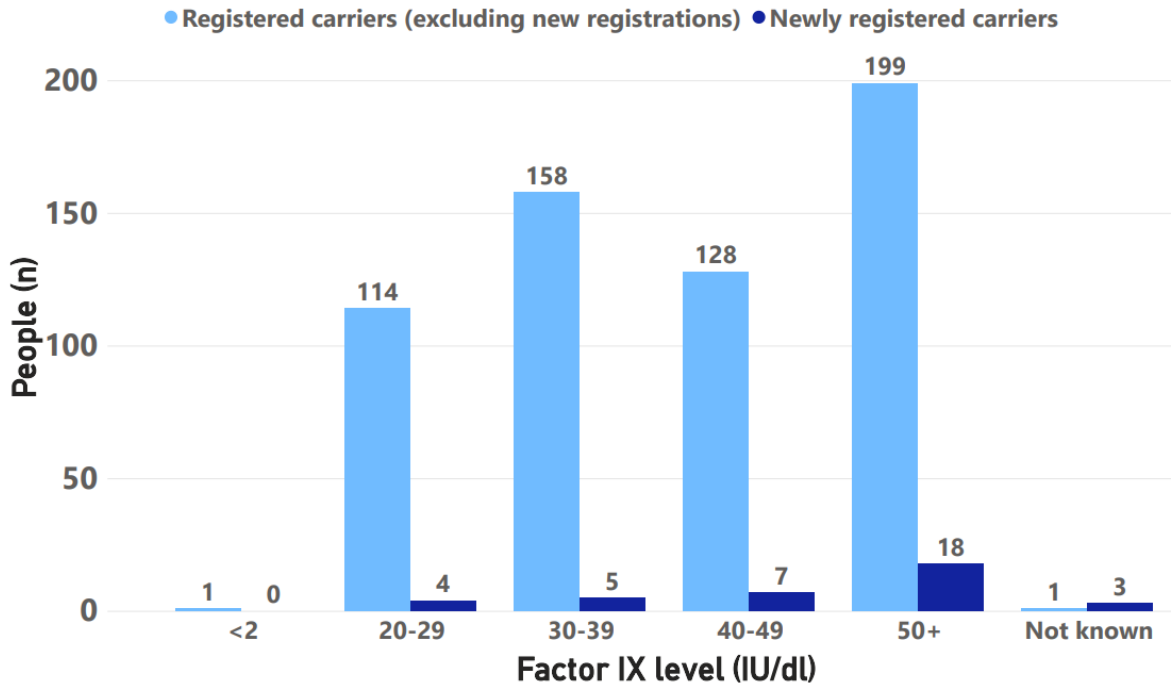
** This is the total excluding numbers which have been suppressed*

*** New registrations are a subset of the 'In Register' numbers*

**** Excluding people only treated with DDAVP and tranexamic acid*

Table 10: This shows the number of people with haemophilia B (including FIX Leyden, carriers and females with factor IX deficiency), broken down by severity, gender and age. The number of new registrations is also shown, as are the numbers treated with concentrate.

Figure 14 Carriers of haemophilia B currently registered and newly registered, by baseline FIX level, 2021/22



N.B: Includes carrier of haemophilia B and females with FIX deficiency

Diagnosis	Number of people by factor IX level (IU/dl)								
	<2	2-9	10-19	20-29	30-39	40-49	50+	Not known	Grand total
Registered carriers (excluding new registrations)	1-2	14	39	114	158	128	199	1-2	652
Newly registered carriers	0	0	6	4	5	7	18	3	43
Total	**0***	**14***	**45***	**118***	**163***	**135***	**217***	**3***	**695***

** This is the total excluding numbers which have been suppressed*

Figure 14: This shows the distribution of reported FIX levels amongst registered carriers of haemophilia B in the UK. All carriers should be registered.

It is interesting that there is a relatively large number of very low-level carriers. These mostly have an extreme degree of lyonisation, but some are homozygous daughters from consanguineous unions.

Table 11 New registrations of haemophilia B (including carriers), by age at mid-year, gender and severity, 2021/22

Haemophilia B	Number of people by factor IX level (IU/dl)																	
Age (years)	< 1			1 - 5			> 5 & < 40			≥ 40			Unknown			Total*		
	Male	Female	Total*	Male	Female	Total*	Male	Female	Total*	Male	Female	Total*	Male	Female	Total*	Male	Female	Total*
0 - < 2	5	-	5	4	-	4	1-2	1-2	-	-	1-2	-	-	-	-	9	-	9
2 - 19	1-2	-	-	1-2	-	-	3	7	10	1-2	4	4	-	1-2	-	3	11	14
20 and over	-	-	-	1-2	-	-	6	6	12	-	20	20	-	1-2	-	6	26	32
Total*	**5**	**-**	**5**	**4**	**-**	**4**	**9**	**13**	**22**	**-**	**24**	**24**	**-**	**-**	**-**	**18**	**37**	**55**

**This is the total excluding numbers which have been suppressed*

Table 11: This shows new registrations of haemophilia B broken down by reported severity and age at mid-year. Less severe disease will often present at a later age and the proportion of that group not native to the UK has not been investigated. The people with severe disease registered after the age of two years were born overseas.

Figure 15 Trend in the number of people with haemophilia B by severity aged 60 years and above, 2002 - 2021

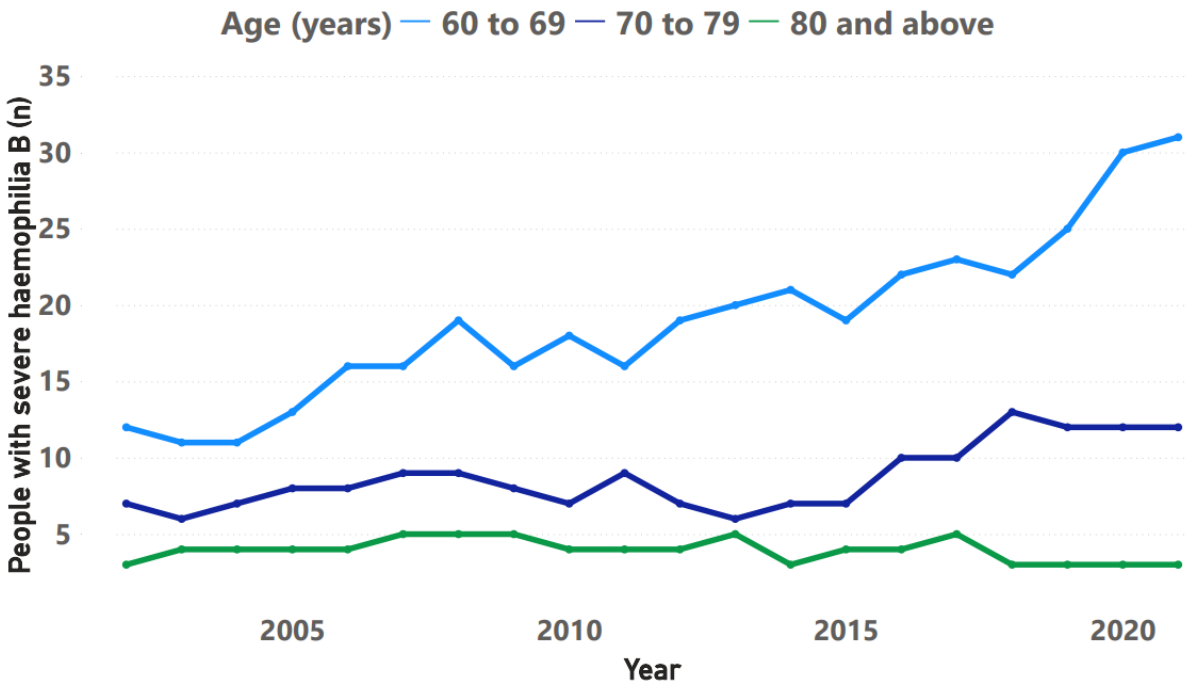
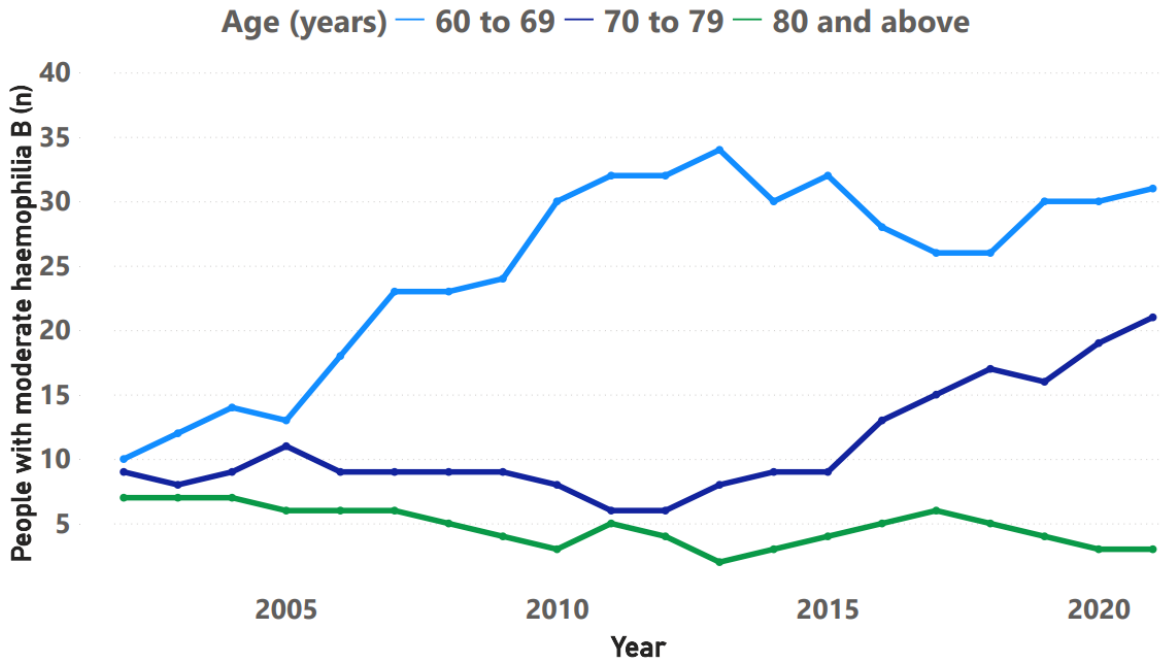


Figure 15 (severe): This chart shows the number of registrants with severe haemophilia B aged 60 years or more since 2002. This shows similar demographic changes to the chart for haemophilia A. It shows an aging population who will, increasingly, present us with management issues associated with the comorbidities of old age.



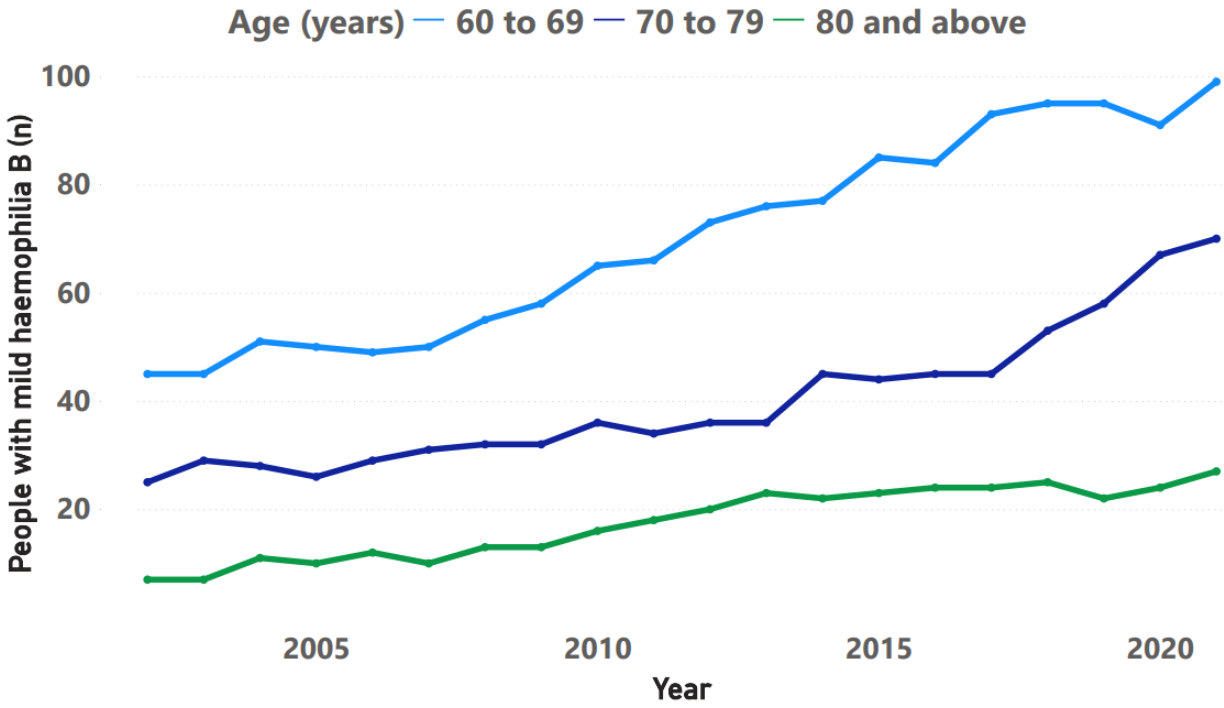


***Figure 15 (moderate) and 15 (mild)*:**

These charts show the number of registrants aged 60 years or more with moderate and mild haemophilia B respectively, since 2002. They show an aging population, though the pattern of change is uneven, which is to be expected given the relatively small number of people. The increasing number of older people with mild haemophilia B in the registry may also reflect increasing diagnosis and registration of this group.

N.B. Carriers are included in Figure 15

Figure 16 Factor IX units issued by UK haemophilia centres to treat severe haemophilia B, 2012/13 – 2021/ 22

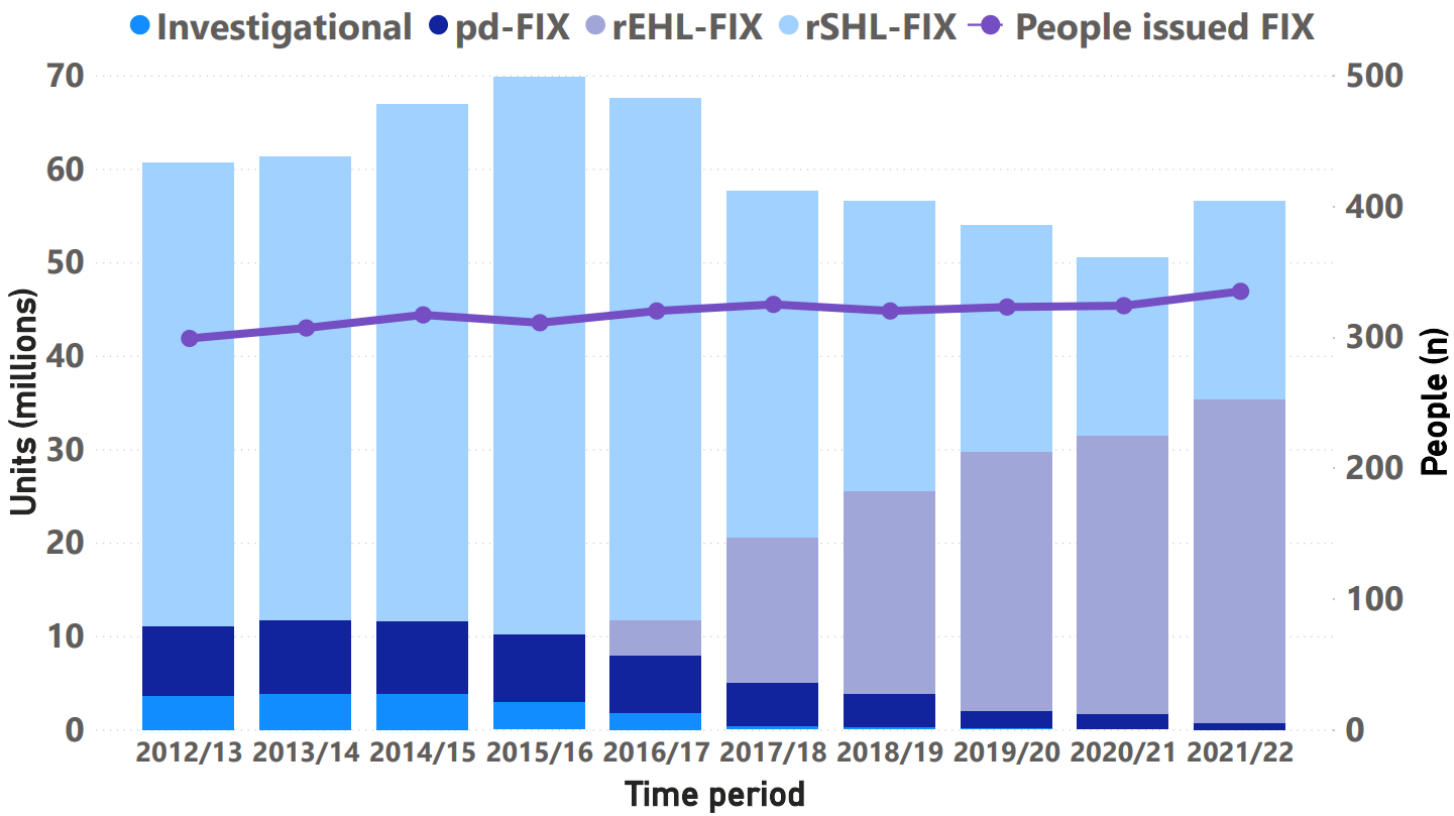


Figure 16: This shows FIX issues for severe haemophilia B 2012/13 to 2021/22. The number of people reported to have been treated is shown by the purple line using a secondary axis and shows a gradual increase. Generally, FIX units issued have declined as a direct consequence of the switch to EHL-FIX products, which are generally prescribed in lower doses than standard products due to their longer half-life. There may also have been a temporary decline in issues associated with the general reduction in surgical interventions attributable to COVID-19 restrictions. This shows that people continue to switch from standard half-life to extended half-life products and plasma-derived factor IX concentrate is now used by very few. Gene therapy is also reducing the numbers requiring FIX to some degree.

Figure 17 Factor IX units issued by UK haemophilia centres to treat non-severe haemophilia B, 2012/13 – 2021/ 22

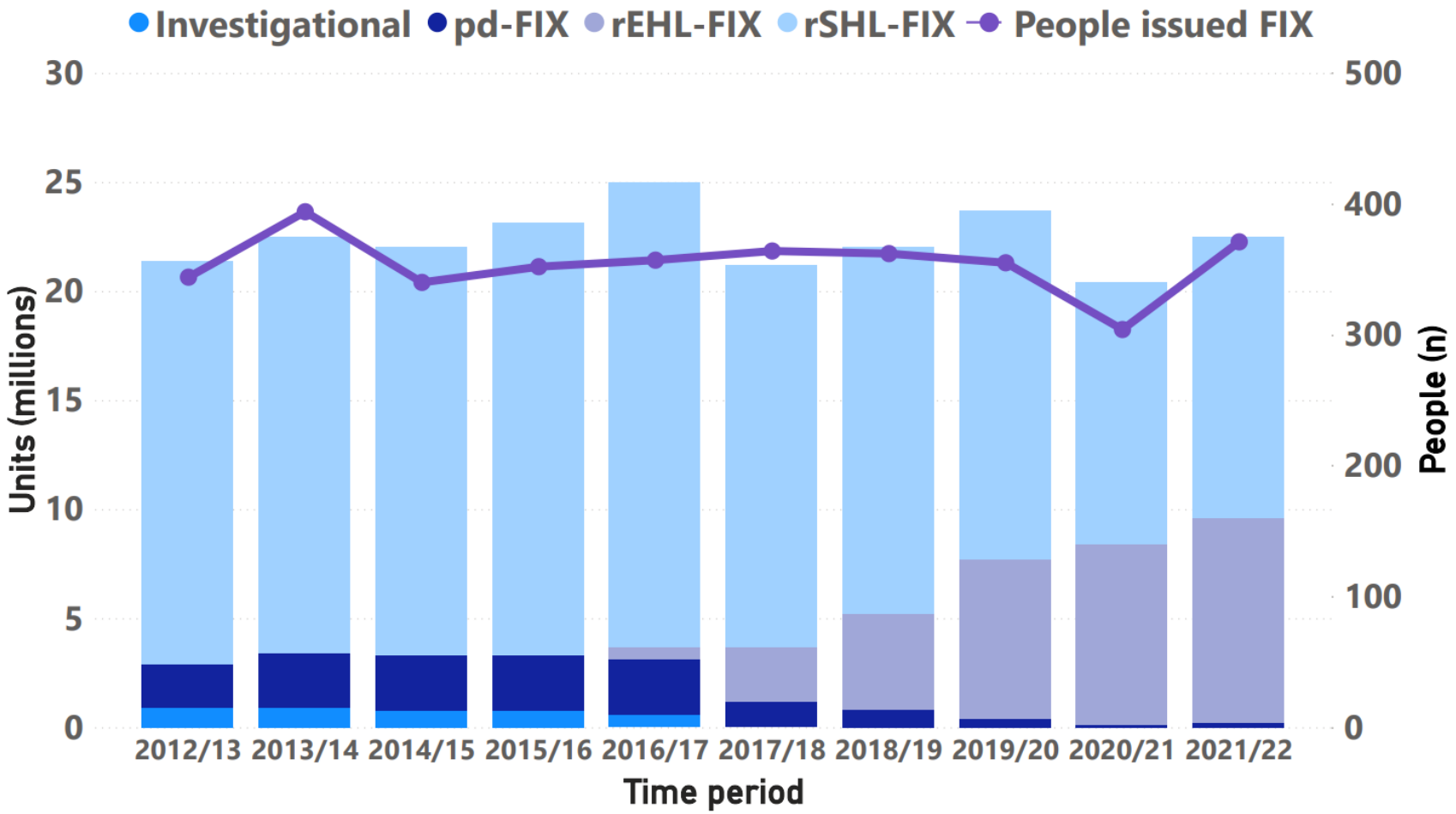


Figure 17: This shows FIX issues for non-severe haemophilia B 2012/13 to 2021/22. The number of people reported to have been treated is shown by the purple line using a secondary axis.

Data table for Figure 16: Factor IX units issued by UK haemophilia centres to treat severe haemophilia B, 2012/13 - 2021/22

Year	pd-FIX		Standard half-life rFIX (excluding investigational)		Investigational rFIX		Enhanced half-life rFIX		Total		People issued FIX	
	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2016/17	IU (millions)	% difference since 2012/13	n	% difference since 2012/13
2012/13	7.5	-	49.6	-	3.6	-	-	-	60.7	-	299	-
2013/14	7.8	4.2	49.6	0.2	3.9	8.8	-	-	61.3	1.2	307	2.7
2014/15	7.8	4.1	55.3	11.6	3.8	3.8	-	-	66.9	10.2	317	6.0
2015/16	7.2	-4.4	59.6	20.3	3.0	-18.1	-	-	69.8	15.0	311	4.0
2016/17	6.2	-17.2	55.9	12.8	1.8	-50.3	3.7	-	67.6	11.4	320	7.0
2017/18	4.6	-38.6	37.1	-25.1	0.4	-90.0	15.6	318.4	57.7	-5.0	325	8.7
2018/19	3.6	-51.7	31.0	-37.5	0.3	-92.9	21.7	482.4	56.6	-6.9	320	7.0
2019/20	1.8	-75.4	24.2	-51.1	0.2	-95.0	27.8	646.6	54.0	-11.0	323	8.0
2020/21	1.6	-78.2	19.0	-61.6	0.1	-98.0	29.8	700.9	50.5	-16.8	324	8.4
2021/22	0.7	-90.2	21.2	-57.3	-	-99.9	34.7	833.9	56.6	-6.7	335	12.0

Data table for Figure 17: Factor IX units issued by UK haemophilia centres to treat non-severe haemophilia B, 2012/13 - 2021/22

Year	pd-FIX		Standard half-life rFIX (excluding investigational)		Investigational rFIX		Enhanced half-life rFIX		Total		People issued FIX	
	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2012/13	IU (millions)	% difference since 2016/17	IU (millions)	% difference since 2012/13	n	% difference since 2012/13
2012/13	2.0	-	18.5	-	0.9	-	-	-	21.4	-	344	-
2013/14	2.5	20.8	19.1	3.3	0.9	9.6	-	-	22.5	-	394	14.5
2014/15	2.5	23.5	18.7	0.9	0.8	-9.0	-	-	22.0	-	340	-1.2
2015/16	2.5	19.8	19.8	6.6	0.8	-4.3	-	-	23.1	-	352	2.3
2016/17	2.5	22.7	21.3	15.1	0.6	-28.6	0.6	-	25.0	-	357	3.8
2017/18	1.2	-43.4	17.5	-5.5	-	-	2.5	327.8	21.2	-	364	5.8
2018/19	0.8	-58.8	16.8	-9.2	-	-	4.4	652.2	22.0	-	362	5.2
2019/20	0.4	-78.1	16.0	-13.5	-	-	7.3	1134.4	23.7	-	355	3.2
2020/21	0.1	-92.9	12.0	-35.5	-	-	8.3	1313.3	20.4	-	304	-11.6
2021/22	0.2	-91.0	12.9	-30.4	-	-	9.4	1500.8	22.5	-	371	7.8

Figure 18 Number of people with haemophilia B issued product, 2012/13 - 2021/22

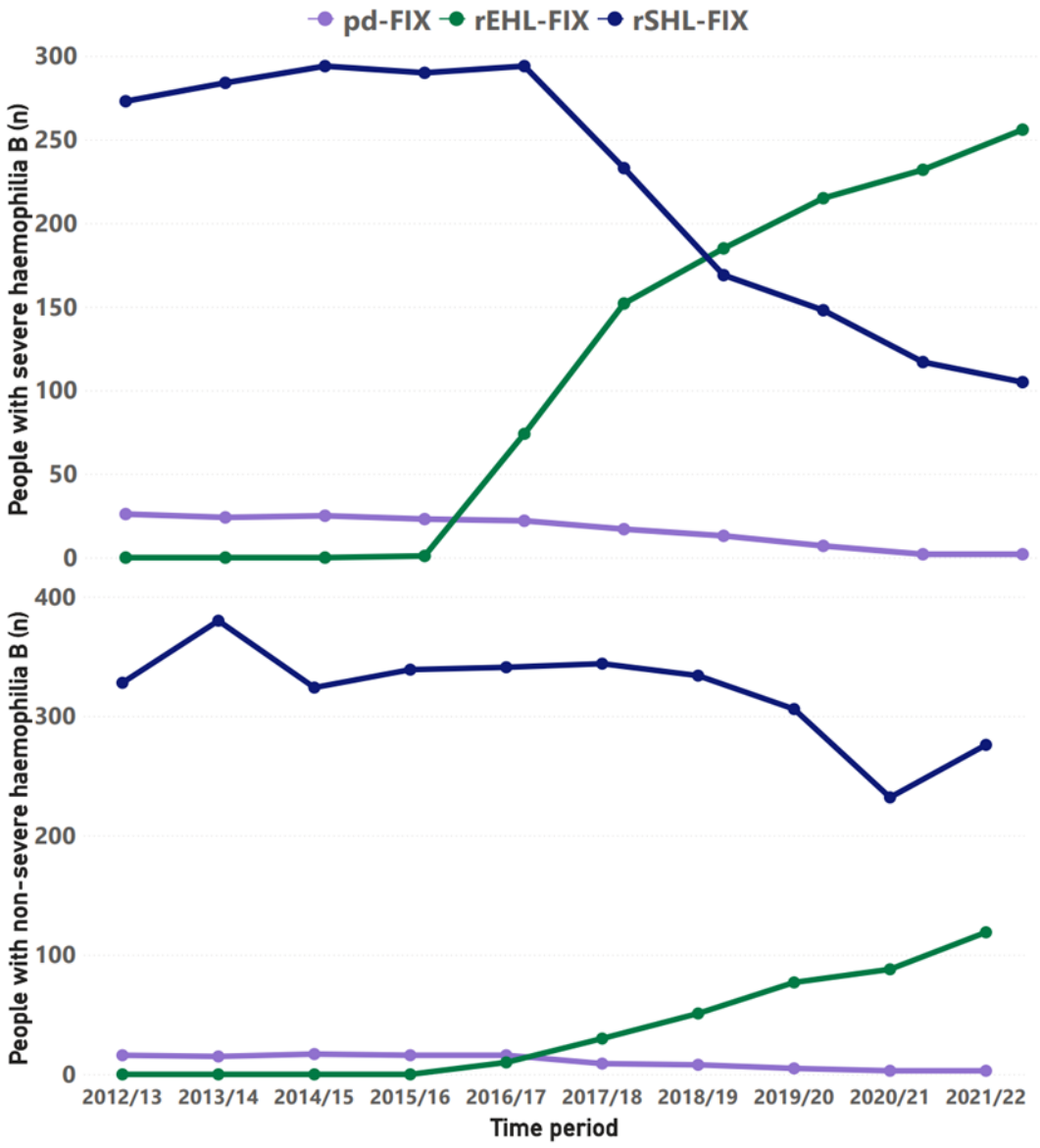


Figure 18: This shows a decline in the number of people with severe haemophilia B issued SHL-FIX, probably caused by the increasing use of EHL-FIX. Plasma-derived IX issues have also declined to a very low level.

Table 12 Factor IX mean issues by region for people with severe haemophilia B (including treatment for inhibitors and EHL-FIX), 2021/22

Country	Region	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20	2020/21	2021/22
England	North East & Yorkshire	196,715	204,306	221,689	237,003	215,799	181,754	173,930	158,606	146,679	143,694
	North West	229,958	215,299	205,344	242,343	233,596	211,423	181,310	175,390	155,125	151,927
	Midlands	191,356	190,277	197,930	221,639	189,776	154,264	139,026	135,500	100,533	124,879
	East of England	161,774	191,613	201,908	186,524	184,000	176,784	204,648	196,648	189,477	189,807
	London	234,231	227,257	250,677	254,066	223,327	200,205	212,171	182,997	178,216	196,544
	South East	175,037	168,590	185,200	193,711	209,040	154,866	158,845	146,055	145,341	168,000
	South West	230,407	183,140	229,958	189,964	231,909	249,000	237,591	277,037	342,492	228,864
Wales	Wales	156,473	152,501	166,419	146,046	156,337	136,909	147,727	146,854	122,792	209,308
Scotland	East of Scotland	240,659	237,554	205,222	278,000	196,278	86,477	78,250	100,227	81,917	79,139
	West of Scotland	185,500	167,333	158,288	178,717	164,450	146,500	140,567	155,567	153,875	152,054
Northern Ireland	Northern Ireland	220,031	241,188	261,643	278,888	258,438	245,417	158,531	215,906	191,531	194,833

Table 12: This shows mean FIX issues by region. This shows similar variation in treatment intensity to that observed with haemophilia A, although the number of people with this diagnosis is very much smaller and so between-region comparisons of treatment intensity cannot really be made. Also, there is greater interpersonal variation in clinical phenotype for this condition than for haemophilia A. Overall issues, in terms of units per person per year, have declined overall, reflecting the switch to EHL products.

Table 13 Products issued to treat haemophilia B (including inhibitors), 2020/21 - 2021/22

Product type	Manufacturer	Description	2020/21		2021/22	
			Units (IU)	People (n)	Units (IU)	People (n)
Non-factor	Various manufacturers	Tranexamic Acid	100,506	4	40,030	1-2
		Desmopressin	-	-	30	1-2
Recombinant	CSL Behring	IDELVION	8,358,000	92	8,793,750	98
	Novo Nordisk	Refixia	4,123,000	50	6,696,000	62
		NovoSeven (mg)	5,412	11	8,350	11
	Pfizer	Benefix	30,294,760	340	32,968,300	375
	SOBI/Biogen	ALPROLIX	25,617,000	186	28,657,400	224
		Elocta	12,000	1-2	-	-
	Takeda	RIXUBIS	700,000	5	1,107,000	4
	Withheld	Investigational FIX	Withheld	Withheld	Withheld	Withheld
Plasma-derived	BPL	BPL Replenine	1,785,605	5	920,360	5
	Takeda	FEIBA	414,000	4	689,000	3
Other	Withheld	Investigational other	Withheld	Withheld	Withheld	Withheld

Units in IU unless otherwise stated
** Due to commercial sensitivities, units have been withheld*

Table 13: This gives a breakdown of the products issued to treat haemophilia B in the UK in 2020/21 and 2021/22, presented by supplier. These figures have been cross-checked with sales figures provided by the suppliers. Whilst a perfect match between manufacturers sales figures and NHD issue figures would not be expected, there is a high level of correlation for the rFIX products. Sales figures are not reported here for reasons of confidentiality. The use of EHL-FIX continues to increase.

The use of investigational FIX has largely ceased due to clinical trials coming to an end. *It is advised that data on trial products be reported to the NHD, anonymising the product, and at a local level with commissioners so that they have a realistic estimate of future product consumption and avoid any inadvertent reduction in future budget.*

Potentially anomalous use is accounted for as follows:
Elocta was delivered and used in error.

Table 14 Factor IX units issued by UK haemophilia centres, by diagnosis, 2021/22

Diagnosis	People (n)	FIX (IU)				
		Plasma-derived	Standard half-life FIX	Enhanced half-life FIX	Investigational rFIX**	Total
Haemophilia B	706	920,360	34,075,300	44,147,150	Withheld	79,142,810
Factor XI deficiency	1-2	2,000	-	-	-	2,000
Other combined diagnoses	1-2	-	-	36,000	-	36,000
Total*	**706***	**922,360**	**34,075,300**	**44,183,150**	**Withheld**	**79,180,810**

** Excludes suppressed numbers*

*** Due to commercial sensitivities, units have been withheld*

Table 14: This shows FIX issued in 2021/22, broken down by product type and diagnosis.

Figure 19a Number of people with haemophilia B treated in the UK 2021/22 broken down by product used

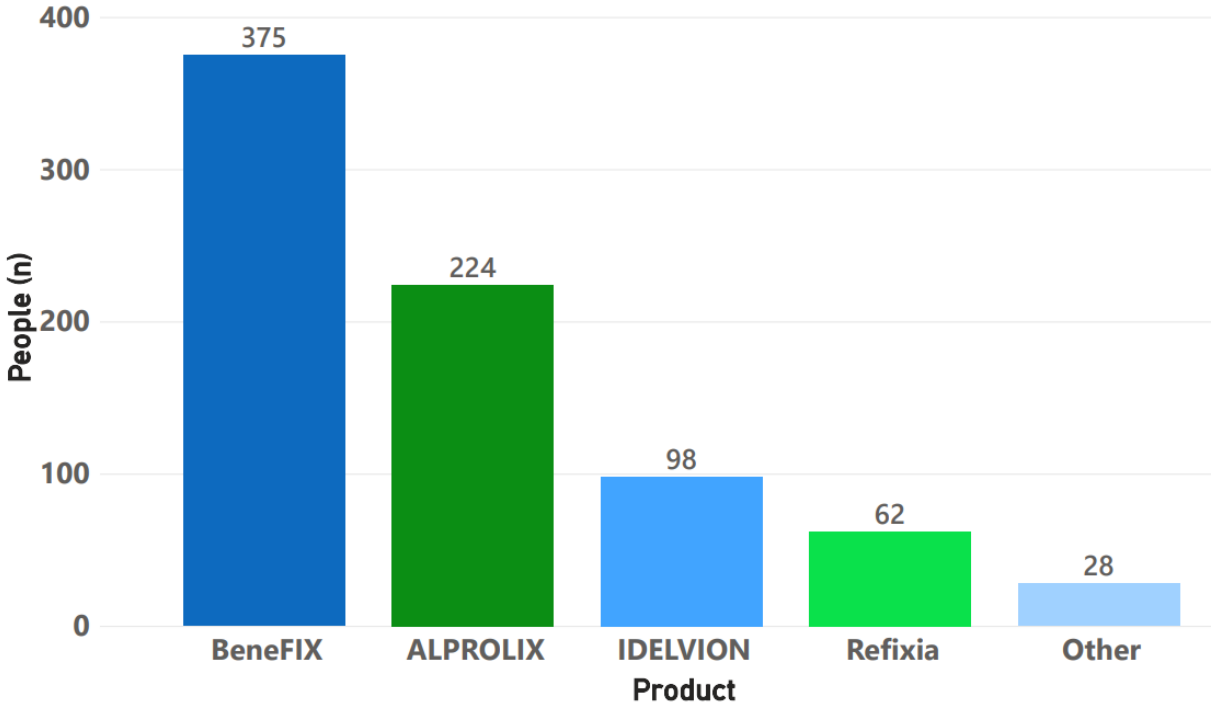


Figure 19a: This shows the number of people with haemophilia B treated by product, including those issued to people with an inhibitor.

The data that informs this graph can be found in table 13.

People issued multiple products in the year are included in the numbers for each product, resulting in some double counting. There were 719 individual people with haemophilia B treated during the year.

Figure 19b The proportion of people with severe haemophilia B, without inhibitors treated with EHL products by centre

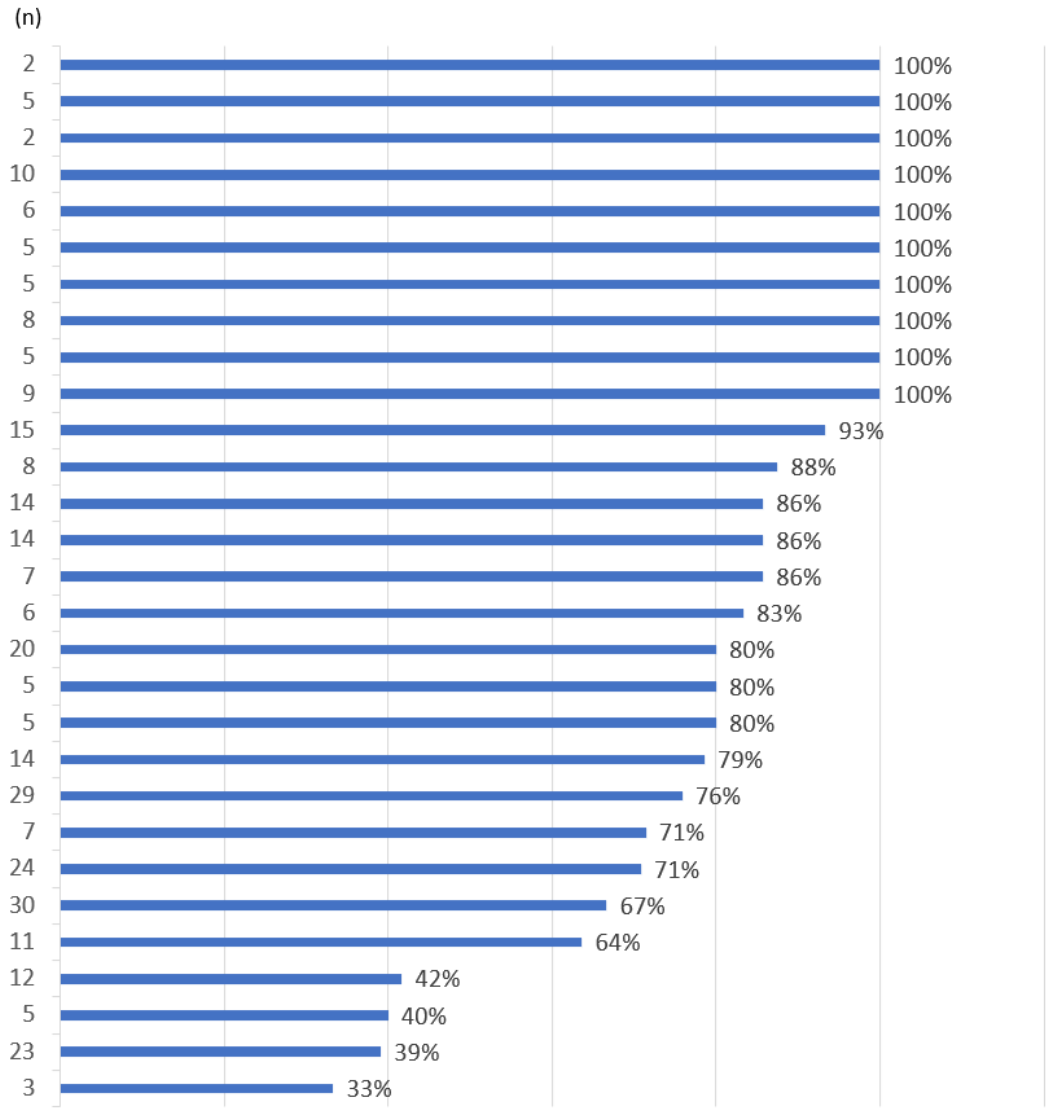


Figure 19b: This shows the ranked proportion of people with severe haemophilia B without an inhibitor who were issued EHL products, by centre, in 2021/22. The centres are not identified. The number of patients per centre is, in many cases small but proportional uptake of EHL-IX concentrates does appear to vary considerably amongst centres.

2.3 Von Willebrand's Disease

Table 15 People with von Willebrand disease registered and treated 2021/22

von Willebrand disease	VWD activity IU/dl										Total*	Treated with Concentrate	Treated with Desmopressin
	<10	10 - <30	≥30	N/K	Sub total*	<10	10 - <30	≥30	N/K	Sub total*			
	<18 years					≥18 years							
Males													
Type 1	20	216	244	6	**486**	105	435	673	87	**1,300**	**1,786**	**95**	**14**
Type 2A	47	43	11	-	**101**	111	105	38	1-2	**254**	**355**	**74**	**4**
Type 2B	10	11	5	-	**26**	16	41	20	-	**77**	**103**	**20**	**-**
Type 2M	18	12	4	-	**34**	48	45	12	1-2	**105**	**139**	**25**	**3**
Type 2N	1-2	1-2	3	-	**3**	3	4	30	1-2	**37**	**40**	**7**	**-**
Type 2 unspecified	17	15	1-2	-	**32**	30	24	12	1-2	**66**	**98**	**15**	**4**
Type 3	21	1-2	-	-	**21**	61	15	1-2	1-2	**76**	**97**	**80**	**-**
Low VWF	1-2	7	76	-	**83**	1-2	6	130	-	**136**	**219**	**-**	**3**
Other	-	-	1-2	-	**-**	-	1-2	1-2	-	**-**	**-**	**-**	**-**
Type unreported	46	106	161	1-2	**313**	140	281	515	37	**973**	**1,286**	**86**	**26**
										Sub total males*	**4,123**	**402**	**54**
Females													
Type 1	28	160	168	1-2	**356**	148	797	1,721	147	**2,813**	**3,169**	**106**	**70**
Type 2A	43	37	9	-	**89**	148	146	69	3	**366**	**455**	**92**	**6**
Type 2B	10	14	7	-	**31**	19	45	38	3	**105**	**136**	**26**	**-**
Type 2M	14	24	1-2	-	**38**	70	88	33	3	**194**	**232**	**37**	**5**
Type 2N	1-2	3	7	1-2	**10**	9	10	70	5	**94**	**104**	**12**	**-**
Type 2 unspecified	12	12	1-2	-	**24**	31	37	21	-	**89**	**113**	**13**	**1-2**
Type 3	25	1-2	1-2	-	**25**	50	9	-	-	**59**	**84**	**67**	**-**
Low VWF	1-2	3	66	-	**69**	1-2	14	341	1-2	**355**	**424**	**3**	**15**
Other	-	-	-	-	**-**	-	-	1-2	1-2	**-**	**-**	**-**	**-**
Type unreported	46	108	109	3	**266**	179	559	1,328	116	**2,182**	**2,448**	**130**	**31**
										Sub total females*	**7,165**	**486**	**127**
										Grand total - males and females*	**11,288**	**888**	**181**

** Please note that totals and subtotals exclude suppressed numbers*

Table 15 (previous page): This shows the number of people with von Willebrand disease registered and/or treated broken down by age, activity level, subtype, gender and treatment. Whilst there is no generally agreed severity classification for VWD, the data are reported by the subdivisions <10, 10-<30 and ≥30% VW activity to give some indication of the distribution of severity amongst the UK cohort.

A VW subtype is reported for approximately 67% of registrations. Efforts are ongoing to tidy up this part of the database, but challenges include changing classification over time, archaic data, and changing opinion in relation to the diagnosis of mild type 1 VWD, which may have been over-diagnosed in the past. The diagnostic process for VWD is frequently in two stages (basic diagnosis and then subtyping) and the registration may be submitted to the NHD part-way through this process. The registration should be updated when the subtype becomes known. Type 1 defects should be reported at the time of original registration. The new database will send automatic reminders to complete registration of subtypes after initial incomplete registration. Changes in diagnosis should also be registered with the database.

There remains a relative excess of adult females especially for type 1 VWD, reflecting referral bias of women with menorrhagia and possible over-diagnosis of mild type 1 VWD in the past. Some people have been de-registered or their diagnosis changed when they are re-investigated or when their VW activity level normalises with increasing age.

Table 16 (overleaf)**:** This shows that at least 371 people with von Willebrand disease were newly registered in the past year, of whom 12% were registered without a reported subtype.

This table supports previous reports of an apparent relative excess of female registrants after menarche, which reflects referral bias. New registrations of von Willebrand disease are more equally distributed between genders in people under 18 years of age.

Table 16 New registrations of von Willebrand disease between 2021/22, by age at mid-year, severity and gender

von Willebrand disease	VWD activity IU/dl								Total*
	<30	≥30	N/K	Sub total*	<30	≥30	N/K	Sub total*	
	<18 years				≥18 years				
Males									
Type 1	19	18	-	**37**	13	11	1-2	**24**	**61**
Type 2A	5	3	-	**8**	3	-	-	**3**	**11**
Type 2B	1-2	1-2	-	**-**	1-2	1-2	-	**-**	**-**
Type 2M	3	-	-	**3**	3	1-2	-	**3**	**6**
Type 2N	-	1-2	-	**-**	-	1-2	-	**-**	**-**
Type 2 unspecified	10	-	-	**10**	5	-	-	**5**	**15**
Type 3	1-2	-	-	**-**	1-2	-	-	**-**	**-**
Low VWF	5	14	-	**19**	-	3	-	**3**	**22**
Type unreported	4	5	-	**9**	6	6	1-2	**12**	**21**
								Sub total males*	**136**
Females									
Type 1	23	24	-	**47**	27	35	-	**62**	**109**
Type 2A	4	-	-	**4**	7	1-2	-	**7**	**11**
Type 2B	3	-	-	**3**	1-2	-	-	**-**	**3**
Type 2M	1-2	1-2	-	**-**	6	1-2	-	**6**	**6**
Type 2N	1-2	3	1-2	**3**	-	4	-	**4**	**7**
Type 2 unspecified	3	-	-	**3**	3	1-2	-	**3**	**6**
Type 3	5	-	-	**5**	-	-	-	**-**	**5**
Low VWF	3	19	-	**22**	3	38	-	**41**	**63**
Type unreported	3	4	-	**7**	7	11	1-2	**18**	**25**
								Sub total females*	**235**
								Grand total - males and females*	**371**

** Please note that totals and subtotals exclude suppressed numbers*

Figure 20 Trend in the number of people with von Willebrand disease aged 60 years and above, 2002 - 2021

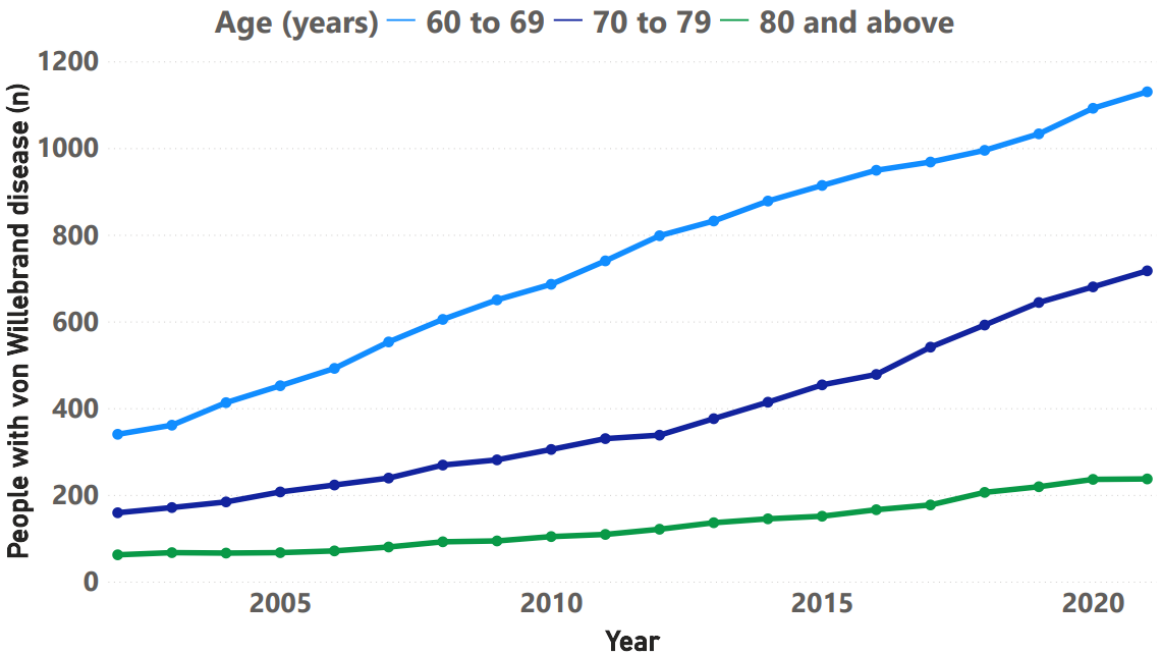


Figure 20: This shows age trends for people registered with VWD aged 60 years or more since 2002. This shows a steady increase in the number of older people with VWD. This is a reflection not just of increasing life expectancy but of increased diagnosis and registration of VWD overall.

Figure 21 Units of von Willebrand Factor issued by UK haemophilia centres to treat von Willebrand disease 2012/13 – 2021/22

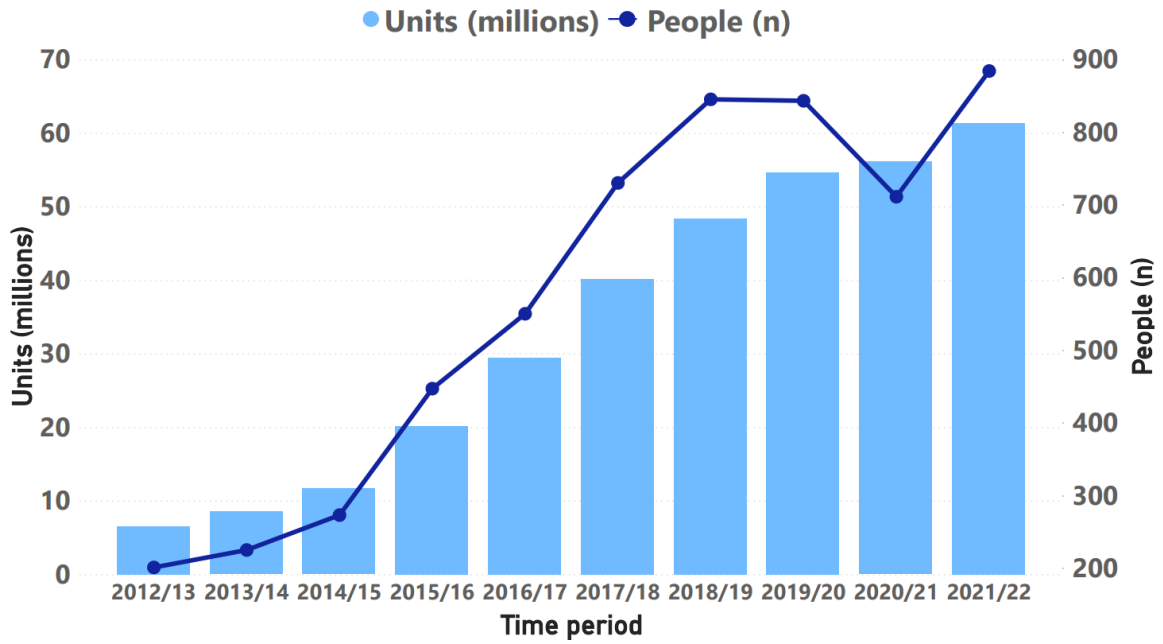


Figure 21: This shows von Willebrand factor units issued to treat von Willebrand disease from 2012/13 to 2021/22. This shows a steady and marked increase in the use of von Willebrand factor concentrate over this time period, probably attributable to increased surgical need and the greater use of prophylaxis in patients with type 2 and type 3 VWD. The apparent fall in the number of people treated in 2020/21 is probably attributable to deferral of surgery and other procedures during the COVID-19 pandemic.

Table 17 Products issued to treat von Willebrand disease (including inhibitors), 2020/21 and 2021/22

Product type	Manufacturer	Description	2020/21		2021/22	
			Units (IU)	People (n)	Units (IU)	People (n)
Non-factor	IDEC Pharmaceuticals	Rituximab	2,000	1-2	-	-
	Roche	Hemlibra (mg)	-	-	840	1-2
	Various manufacturers	Desmopressin	11,527	138	6,541	182
Recombinant	Novo Nordisk	NovoEight	-	-	5,500	1-2
		NovoSeven (mg)	449	5	2,601	6
	Pfizer	ReFacto AF	-	-	82,500	7
	SOBI/Biogen	Elocta	472,500	1-2	908,000	4
	Takeda	Veyvondi	202,800	29	3,012,150	181
		Advate	17,000	6	76,750	26
Plasma-derived	CSL Behring	Voncento (FVIII units) (VWF units)	19,563,736 46,952,966	518	20,441,650 49,059,960	552
		Beriplex	2,000	1-2	-	-
	Grifols	Fanhdi	3,000	1-2	8,000	1-2
		Alphanate (FVIII units) (VWF units)	2,000 2,400	1-2	- -	-
	LFB Biomedicaments	Willfact	1,055,500	20	1,232,000	19
	Octapharma	Wilate (FVIII units) (VWF units)	7,901,500 7,901,500	177	8,035,000 8,035,000	206
Blood component	National blood transfusion service	Platelets	4	1-2	-	-

Products containing VWF and FVIII are reported separately in VWF and FVIII units

Table 17: This shows a breakdown of concentrates products issued to treat von Willebrand disease in the UK by supplier. These are generally listed by and priced by their labelled FVIII content, with the exception of Willfact (LFB) and Veyvondi (Takeda), which are labelled and priced only by VWF content. Veyvondi is currently licensed for surgery and on-demand use only, which may have limited market penetration following its recent launch in the UK. Where factor VIII and VW units are shown for Voncento, Alphanate and Willate, the VW units have been derived by converting the factor VIII units issued, using the published FVIII:VWF ratio.

Potentially anomalous product use in Table 17 is accounted for as follows:

Advate: Used pre-procedure for twenty-six people in 2021/22,and reported to have been used in conjunction with Veyvondi for two people.

Elocta: Used for four people in 2021/22.

2.4 Congenital and Acquired factor VIII, IX and VW Inhibitors

Table 18 Inhibitors by disease severity – congenital haemophilia A, haemophilia B & von Willebrand disease

Diagnosis	Severity (IU/dl) / subtype	In register **	Inhibitors n (%)			
			Newly Reported	Ongoing	Historical	Total*
Haemophilia A	< 1	2,179	12 (0.6)	172 (7.9)	329 (15.1)	513 (23.5)
	1 - 5	836	6 (0.7)	31 (3.7)	52 (6.2)	89 (10.6)
	> 5	5,947	4 (0.1)	14 (0.2)	43 (0.7)	61 (1.0)
	Total*	**8,962**	**22 (0.2)**	**217 (2.4)**	**424 (4.7)**	**663 (7.4)**
Haemophilia B	< 1	373	1-2 (-)	13 (3.5)	6 (1.6)	19 (5.1)
von Willebrand disease	Type 3	188	1-2 (-)	5 (2.7)	3 (1.6)	8 (4.3)

** Please note that totals and subtotals exclude suppressed numbers*

*** Including those not regularly treated*

New: Reported this year and not in previous years
Ongoing: Reported this year and in previous years
Historical: Reported in previous years and not in this year

Table 18 (previous page): This table shows the incidence of new inhibitors in the past year, the history of inhibitors ever registered and the prevalence of those still considered active for haemophilia A, B and von Willebrand disease, broken down by disease severity.

Those labelled "new" were reported for the first time in the year 2021/22. Those labelled "ongoing" are reported in previous years and have not been eradicated and remain clinically significant in 2021/22. Those reported as "historical" were reported in previous years and not reported to be ongoing in 2021/22 and are therefore assumed to have been tolerised.

An inhibitor is designated as historical if it is no longer reported in the quarterly returns within 2021/22. There is necessarily some lack of precision surrounding this categorisation, as inhibitors thought to have been eradicated may persist at a variable low level, below the level of detection of the Bethesda assay although high enough to shorten the FVIII half-life. These inhibitors may re-emerge as have up to 25% of inhibitors after tolerisation (International ITI registry data) or after FVIII prophylaxis is replaced with Emicizumab. We have received a number of reports of recurring inhibitors after switching to Emicizumab. Some of these were clearly ongoing. To add to the "softness" of the "historical inhibitor" designation, it is clear anecdotally that there may be inconsistency in reporting that an inhibitor has been eliminated when, in some cases, the factor VIII half-life remains very short.

The table shows that a history of inhibitor is over twice as prevalent in severe as in moderate haemophilia A and twenty times more prevalent than in mild haemophilia A. The proportion of people with non-severe haemophilia A thought to have eliminated their inhibitor cannot be known with certainty, however, since some may have an undetectable inhibitor which may reappear as soon as they have FVIII replacement. Similarly, many "ex-inhibitor" people with severe haemophilia probably continue to have some low-level inhibitor activity, below the level of detection of the Bethesda assay.

Inhibitors in haemophilia B are far less common, with a prevalence of 0.7% of people registered. These arise early in the person's treatment and usually only in people with severe haemophilia B caused by FIX gene deletions. Inhibitors in von Willebrand disease appear in our cohort almost exclusively in type 3 VWD. The relatively low numbers of inhibitors in haemophilia B and von Willebrand disease marked as "historical" suggest these inhibitors are difficult to eradicate.

Table 19 (overleaf): This shows products reported to have been issued to people with a current inhibitor during 2020/21 and 2021/22, broken down by diagnosis, supplier and product.

Table 19 Products issued to people with congenital bleeding disorders reported to have a positive inhibitor during 2021/22

Product type	Manufacturer	Product	2020/21		2021/22	
			People (n)	Units (IU)	People (n)	Units (IU)
Haemophilia A						
Non-factor	IDEC Pharmaceuticals	Rituximab	-	-	1-2	3
	Roche	Hemlibra (mg)	132	495,313	143	530,354
	Various manufacturers	Desmopressin	1-2	30	1-2	105
Recombinant	Novo Nordisk	NovoEight	5	2,097,500	7	1,895,500
		Esperoct	1-2	10,000	5	1,086,000
		NovoSeven (mg)	83	5,824	101	10,308
	Octapharma	Nuwiq	7	1,759,000	7	1,994,250
	Pfizer	ReFacto AF	17	2,816,354	16	2,153,750
	SOBI/Biogen	Elocta	25	5,085,286	30	5,250,750
	Takeda	Advate	33	5,613,250	27	3,953,300
		OBIZUR	-	-	1-2	14,000
Plasma-derived	BPL	BPL FVIII 8Y	1-2	163,800	1-2	444,525
	Grifols	Fanhdi	1-2	241,000	1-2	306,000
	Octapharma	Octanate	4	1,215,500	3	1,200,000
	Takeda	FEIBA	13	445,000	18	1,016,000
Other	Withheld	Investigational other	Withheld	Withheld	-	-
Haemophilia B						
Recombinant	Novo Nordisk	NovoSeven (mg)	11	5,412	11	8,350
	Pfizer	Benefix	1-2	489,500	3	1,355,800
	SOBI/Biogen	ALPROLIX	1-2	3,500	1-2	2,000
Plasma-derived	Takeda	FEIBA	4	414,000	3	689,000
Other	Withheld	Investigational other	Withheld	Withheld	Withheld	Withheld
von Willebrand Disease						
Non-factor	Roche	Hemlibra	-	-	1-2	840
Recombinant	Novo Nordisk	NovoSeven (mg)	3	436	4	2,590
	SOBI/Biogen	Elocta	1-2	472,500	1-2	619,500
	Takeda	Veyvondi	-	-	1-2	26,000
		Advate	1-2	5,000	1-2	6,750
Plasma-derived	CSL Behring	Voncento	4	482,000	3	228,500
	Octapharma	Wilate	1-2	6,000	-	-
Factor VII deficiency						
Recombinant	Novo Nordisk	NovoSeven (mg)	1-2	2,307	1-2	1,828
Factor XI deficiency						
Recombinant	Novo Nordisk	NovoSeven (mg)	1-2	3	-	-
Co-inherited diagnoses						
Non-factor	Roche	Hemlibra	1-2	4,680	1-2	4,320
Recombinant	Novo Nordisk	NovoSeven (mg)	-	-	1-2	3
Plasma-derived	Takeda	FEIBA	1-2	145,000	1-2	155,000

Units in IU unless otherwise stated

Table 20 Products issued to people with acquired disorders 2021/22

Product type	Manufacturer	Product	2020/21		2021/22	
			People (n)	Units (IU)	People (n)	Units (IU)
Acquired haemophilia A						
Non-factor	IDEC Pharmaceuticals	Rituximab	5	9,865	7	4,318
	Roche	Hemlibra (mg)	-	-	1-2	1,680
	Various manufacturers	Tranexamic Acid	1-2	174,000	1-2	99,000
Recombinant	Novo Nordisk	NovoSeven (mg)	16	2,767	19	2,053
	Takeda	OBIZUR	28	1,257,500	29	1,315,000
	Takeda	Advate	1-2	136,500	6	130,500
Plasma-derived	Octapharma	Wilate	-	-	1-2	5,000
	Takeda	FEIBA	82	7,391,500	94	9,185,000
Acquired von Willebrand disease						
Non-factor	Various manufacturers	Tranexamic Acid	3	54,080	1-2	60,000
	Various manufacturers	Desmopressin	-	-	1-2	39
Recombinant	Pfizer	ReFacto AF	-	-	1-2	22,000
	Takeda	Veyvondi	-	-	11	104,650
	Takeda	Advate	1-2	4,000	1-2	6,000
Plasma-derived	CSL Behring	Voncento	28	983,700	24	1,106,800
	LFB Biomedicaments	Willfact /Wilfactin	3	179,000	1-2	424,000
	Octapharma	Wilate	13	475,500	13	265,000
Acquired factor XIII deficiency						
Recombinant	Novo Nordisk	NovoSeven (mg)	1-2	15	-	-
Plasma-derived	CSL Behring	Fibrogammin P	3	37,250	3	27,750
	Octapharma	Fibryga	1-2	84	-	-
	Various manufacturers	Fibrinogen	1-2	147	-	-
Other acquired factor deficiency						
Non-factor	Various manufacturers	Desmopressin	1-2	90	-	-
Plasma-derived	BPL	COAGADEX	1-2	20,000	1-2	161,250
Unknown	Unknown	Unknown	1-2	85	-	-

Units in IU unless otherwise stated

Table 20: This shows products issued for people with an acquired inhibitors in 2021/22, broken down by diagnosis and supplier.

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Table 21 FEIBA® issues: breakdown by diagnosis 2019/20 - 2021/22

Diagnosis	2019/20		2020/21		2021/22	
	Units (IU)	People (n)	Units (IU)	People (n)	Units (IU)	People (n)
Haemophilia A	2,896,000	22	535,500	16	1,110,000	22
Haemophilia B	873,000	3	414,000	4	689,000	3
Glanzmann's thrombasthenia	-	-	104,000	1-2	-	-
Acquired haemophilia A	9,015,150	97	7,391,500	82	9,185,000	94
Acquired von Willebrand disease	15,000	1-2	-	-	-	-
Combined and miscellaneous disorders	157,500	1-2	145,000	1-2	155,000	1-2
Total*	**12,956,650**	**122**	**8,590,000**	**102**	**11,139,000**	**119**

** This is the total excluding numbers which have been suppressed.*

Table 22 NovoSeven® issues: breakdown by diagnosis 2019/22 - 2021/22

Diagnosis	2019/20		2020/21		2021/22	
	Units (mg)	People (n)	Units (mg)	People (n)	Units (mg)	People (n)
Haemophilia A	6,262	98	6,773	90	11,835	112
Haemophilia B	7,541	9	5,412	11	8,350	11
von Willebrand disease	801	4	449	5	2,601	6
Factor V deficiency	-	-	-	-	48	1-2
Factor VII deficiency	4,195	62	4,396	64	5,067	81
Factor XI deficiency	42	1-2	15	3	-	-
Hypodysfibrinogenemia	1	1-2	-	-	-	-
Unclassified bleeding disorder	69	6	9	1-2	42	5
Glanzmann's thrombasthenia	8,855	49	16,110	41	6,525	53
Bernard-Soulier syndrome	223	8	112	9	1,093	15
Heritable platelet disorder	-	-	-	-	59	1-2
Other platelet disorder	26	4	9	1-2	22	3
Acquired haemophilia A	3,650	14	2,767	16	2,053	19
Other acquired factor deficiency	-	-	15	1-2	-	-
Combined and miscellaneous disorders	213	5	13	4	7	3
Total*	**31,878**	**259**	**36,080**	**243**	**37,702**	**308**

** This is the total excluding numbers which have been suppressed.*

Tables 21, 22 (previous page) ***& 23*** show in greater detail how much FEIBA, NovoSeven and Hemlibra were issued for each diagnosis in 2019/21. People with any hereditary or acquired bleeding disorder, either with or without inhibitors, are included. There is no estimate given for off-label usage or usage for reversal of over-anticoagulation as this occurs outside haemophilia centres and is consequently not systematically collected. FEIBA issued for congenital haemophilia A with inhibitors declined markedly between 2019/20 and 2020/21, as people started using Hemlibra, and then increased in 2021/22. NovoSeven issues for congenital haemophilia A have increased, probably because it is now used in preference to FEIBA for surgery in people with FVIII inhibitors who are co-prescribed Hemlibra.

Table 23 Hemlibra® issues: breakdown by diagnosis 2019/20 – 2021/22

Diagnosis	2019/20		2020/21		2021/22	
	Units (mg)	People (n)	Units (mg)	People (n)	Units (mg)	People (n)
Haemophilia A	912,153	403	2,565,729	746	3,785,640	981
von Willebrand disease	-	-	-	-	840	1-2
Acquired haemophilia A	-	-	-	-	1,680	1-2
Combined and miscellaneous disorders	6,300	1-2	5,760	1-2	7,140	3
Total*	**918,453**	**403**	**2,571,489**	**746**	**3,795,300**	**984**

** This is the total excluding numbers which have been suppressed.*

Table 23: This includes Hemlibra issues for people with and without inhibitors, and off-license issues to isolated patients with von Willebrand disease and acquired haemophilia.

Figure 22 The proportion of people with haemophilia A and an inhibitor broken down by treatment product issued

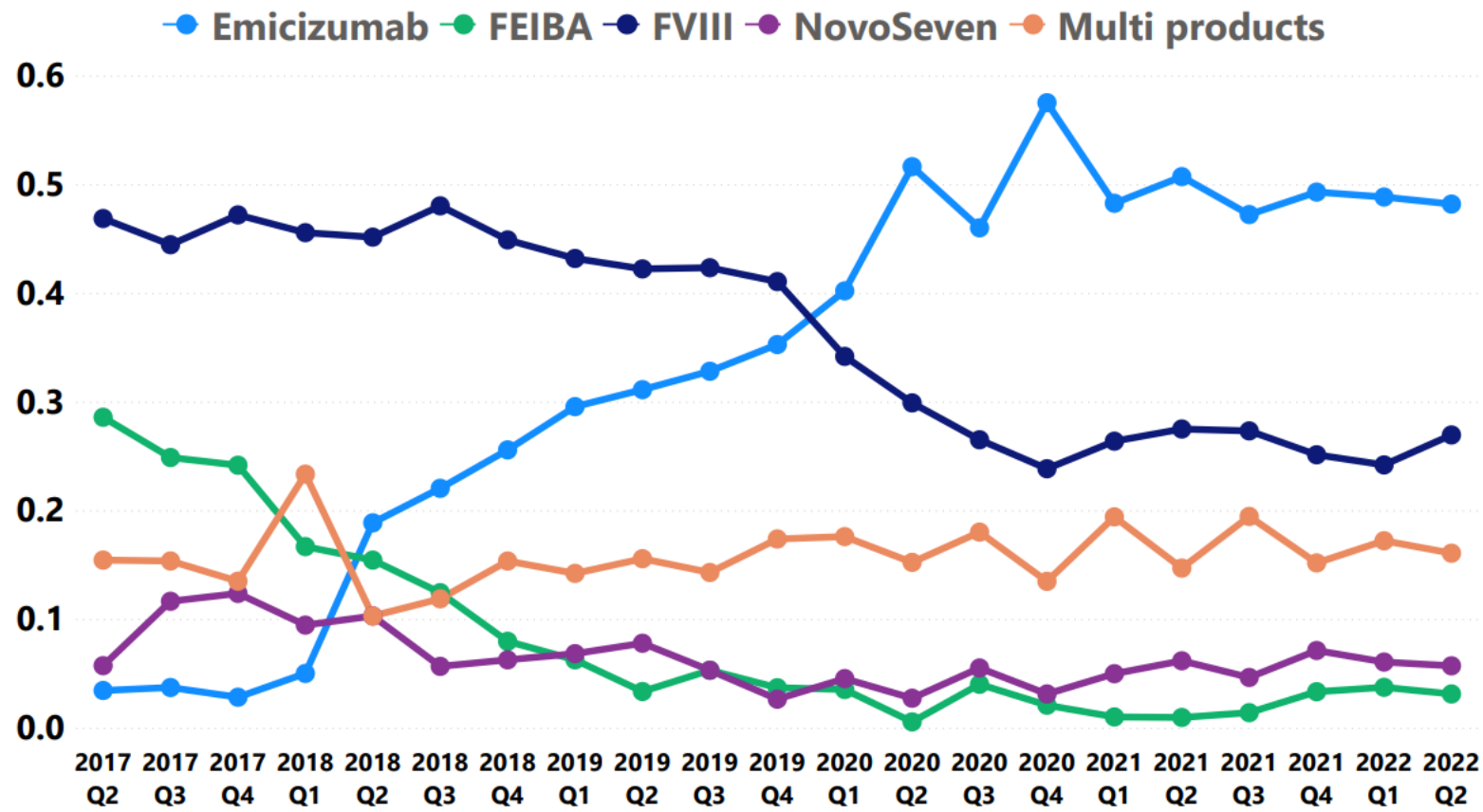

Figure 22: This shows the change in the proportion of PwHA and an inhibitor issued with FEIBA, NovoSeven, FVIII and Emicizumab since Emicizumab was licensed for use in this group. People may be issued with more than one product during a given quarter. Novoseven, in particular, is often used in patients treated also with other products. The introduction of Emicizumab has led to a marked reduction in the use of FVIII and FEIBA in this group, although not in the use of NovoSeven, which may be used for surgery and intercurrent bleeding in preference to FEIBA in people prescribed Emicizumab. The proportion of PwHA with inhibitors issued Hemlibra appears to have stabilised.

Figure 23 The proportion of people with severe haemophilia A and an inhibitor treated with Emicizumab by centre 2021/22

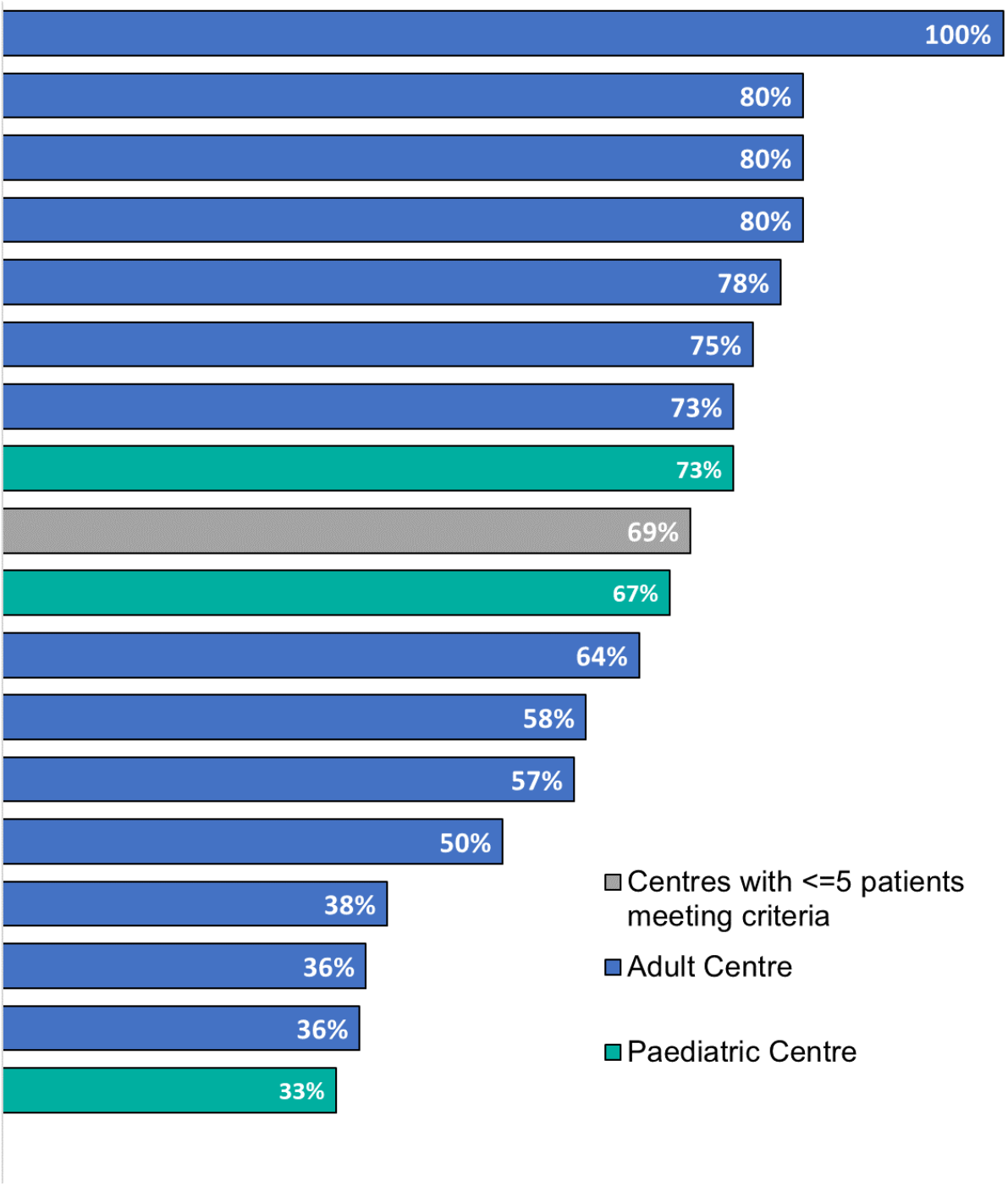

Figure 23: This bar diagram shows the proportion of people with severe haemophilia A and inhibitors issued with Emicizumab, broken down by centre. Centres labelled paediatric centres manage only children, whereas some adult centres also manage some children. Centres with ≤ 5 patients are aggregated and shown as the grey bar. This shows considerable centre to centre variation in clinical practice (median 67%, IQR 44-76%).

2.5 Other Bleeding Disorders

Table 24 People with other bleeding disorders registered and treated 2021/22

Diagnosis	People in register		Treated with		
	Males	Females	Any product	Concentrate	Desmopressin
Haemophilia A with liver transplant	11	-	-	-	-
Haemophilia B with liver transplant	1-2	-	-	-	-
von Willebrand disease with liver transplant	1-2	-	-	-	-
Probable von Willebrand disease		185	4	1-2	3
Factor V deficiency	96	181	11	4	1-2
Factor VII deficiency	954	1,117	88	86	1-2
Factor X deficiency	140	198	35	35	-
Factor XI deficiency	1,615	2,359	67	56	1-2
Factor XIII deficiency	48	37	64	64	-
Prothrombin (factor II) deficiency	7	10	5	5	-
Dysfibrinogenemia	282	455	21	21	-
Hypofibrinogenemia	98	137	8	8	-
Hypodysfibrinogenemia	18	22	3	3	-
Afibrinogenemia	11	6	14	14	-
Fibrinogen deficiency	-	-	1-2	1-2	-
Unclassified bleeding disorder	159	979	52	9	41
Glanzmann's thrombasthenia	63	83	55	54	-
Bernard-Soulier syndrome	50	50	17	15	1-2
Other severe platelet disorder	61	142	5	-	5
Platelet-type pseudo von Willebrand disease	16	25	1-2	1-2	-
Heritable platelet disorder	82	124	7	1-2	5
Other platelet disorder	924	2093	68	4	58
Other disorders	17	22	6	5	1-2
Acquired haemophilia A	320	310	124	52	-
Acquired von Willebrand disease	105	80	44	43	1-2
Other acquired factor deficiency	23	21	4	4	-
Combined and miscellaneous disorders	230	483	35	25	8
Total*	**5,395**	**9,119**	**737**	**507**	**120**

** This is the total excluding numbers which have been suppressed.*

Table 24: This shows the number of people registered with other disorders and the proportion treated during the year. It is suspected that liver transplantation is under-reported.

Table 25 a, b People with selected other bleeding disorders registered and treated 2021/22, by disease severity

Diagnosis	Number of people by factor level (IU/dl)							
	<5		≥5		Not known		Total	
	In reg	Treated	In reg	Treated	In reg	Treated	In reg	Treated
Factor V deficiency	58	9	219	1-2	-	-	277	9
Factor VII deficiency	170	38	1901	50	-	-	2071	88
Factor X deficiency	42	30	296	5	-	-	338	35
Factor XI deficiency	302	32	3669	35	3	-	3974	67
Total*	**572**	**109**	**6,085**	**90**	**3**	**-**	**6,660**	**199**

** Small numbers have been suppressed.*

Table 25a: It is acknowledged that these other disorders have no recognised classification of disease severity. However, the table above gives an idea of the range of registered levels.

Diagnosis	Number of people by factor level (IU/dl)											
	<2		2-<10		10-<15		>=15		Not known		Total	
	In reg	Treated	In reg	Treated	In reg	Treated	In reg	Treated	In reg	Treated	In reg	Treated
Factor XIII deficiency	38	36	27	24	4	1-2	15	1-2	1-2	1-2	84	60

** Small numbers have been suppressed.*

Table 25b: The table above gives an idea of the range of registered levels for factor XIII deficiency.

Table 26 New registrations of other bleeding disorders 2021/22, by coagulation defect and gender

Diagnosis	Male	Female	Total
Probable von Willebrand disease	6	8	14
Factor V deficiency	5	10	15
Factor VII deficiency	68	107	175
Factor X deficiency	7	14	21
Factor XI deficiency	99	145	244
Factor XIII deficiency	3	1-2	3
Prothrombin (factor II) deficiency	1-2	1-2	-
Dysfibrinogenemia	24	49	73
Hypofibrinogenemia	8	15	23
Hypodysfibrinogenemia	1-2	1-2	-
Afibrinogenemia	1-2	-	-
Unclassified bleeding disorder	25	120	145
Glanzmann's thrombasthenia	-	1-2	-
Other severe platelet disorder	1-2	-	-
Heritable platelet disorder	60	103	163
Other platelet disorder	28	68	96
Other disorders	1-2	1-2	-
Acquired haemophilia A	83	48	131
Acquired von Willebrand disease	10	14	24
Other acquired factor deficiency	3	3	6
Combined and miscellaneous disorders	12	44	56
Total*	**441**	**748**	**1,189**

** This is the total excluding numbers which have been suppressed.*

Table 26: This table shows new registrations of other bleeding disorders during the year. This shows a large number of newly registered females for all autosomal disorders, presumably reflecting referral and diagnostic bias of women with menorrhagia.

Table 27 Concentrates used to treat selected other bleeding disorders between 2021/22

Product type	Manufacturer	Product	F.V deficiency		F.VII deficiency		F.X deficiency		F.XI deficiency		F.XIII deficiency	
			People (n)	Units	People (n)	Units	People (n)	Units	People (n)	Units	People (n)	Units
Non-factor	Various manufacturers	Desmopressin	1-2	90	1-2	90	-	-	1-2	45	-	-
		Tranexamic Acid	-	-	1-2	90,000	-	-	5	82,071	-	-
Recombinant	Novo Nordisk	NovoSeven (mg)	3	58	82	5,068	-	-	-	-	-	-
		NovoThirteen	-	-	-	-	-	-	-	-	1-2	65,000
Plasma-derived	BPL	BPL FIX	-	-	-	-	-	-	1-2	2,000	-	-
		BPL FXI	-	-	-	-	-	-	34	63,925	-	-
		COAGADEX	-	-	-	-	25	2,108,500	-	-	-	-
	Baxter	Com FVII	-	-	3	914,400	-	-	-	-	-	-
	CSL Behring	Beriplex	-	-	-	-	9	679,500	-	-	-	-
		FXIII	-	-	-	-	-	-	-	-	1-2	26,000
		Fibrogammin P	-	-	-	-	-	-	-	-	61	1,112,000
		Riastap	-	-	1-2	7	-	-	1-2	1-2	-	-
	LFB Biomedicaments	Hemoleven (LFB XI)	-	-	-	-	-	-	22	45,000	-	-
	Octapharma	Octaplas (bags)	6	41	-	-	1-2	40,000	6	30	-	-
		Octaplex	-	-	-	-	4	321,000	-	-	-	-
Blood component	-	Platelets	1-2	1	-	-	-	-	-	-	-	-

Units in IU unless otherwise stated.
Small numbers have been suppressed.

Table 27: This gives a breakdown of products issued during 2021/22 for people with other bleeding disorders, broken down by diagnosis and supplier.

2.6 Adverse Events

2.6.1 Introduction and Adverse Event Assessment Panel

Pharmacovigilance has become an increasingly important function of the database. Treatments are monitored for safety signals and drug-related adverse events are reported to the manufacturer and, through them, to the regulators. Consequently, the conduct of post-license safety and efficacy studies has become a routine for the database. This function has assumed even greater prominence as we enter a new therapeutic era, using drugs with novel modes of action with side effect profiles very different from the products we are used to and which they may replace.

In response to this increasing need and the need for an objective, independent and robust evaluation of adverse events and working closely with the Co-Morbidities Working Party (CMWP), an SOP was developed for managing and investigating adverse events in 2019 and 2021. Adverse Events (AEs) and Serious Adverse Events (SAEs) were defined as for GCP clinical trials. Where required, adverse event reports are further investigated by the CMWP.

The CMWP met once a month by video conference to adjudicate on repeated AEs and all SAEs. scoring their severity (1-5) and the potential relationship to drug therapy (unrelated; possibly related; probably related or definitely related), again using the same framework that would apply for AE and SAE reporting in GCP-standard clinical trials. Serious Adverse events may be evaluated more urgently by e-mail and ad-hoc meetings, if necessary. The CMWP considered principally adverse events of special interest. It was considered that all adverse events should be reviewed, however, a larger task, which was felt to potentially detract from the other functions of the group. For that reason, a new pharmacovigilance and adverse event group was proposed.

In May 2022, assessment of adverse events was adopted by a newly formed NHD Adverse Event Assessment Panel. The membership of this panel is as follows:

Prof Charles RM Hay Co-Chair, Representing NHD
Prof Pratima Chowdary, Co-Chair representing NHD
Simon Fletcher, representing the HNA
Prof Mike Makris representing EUHASS
Dr Sarah Mangles
Dr Mary Mathias, Representing the Paediatric Working Party
Dr Charles Percy, Representing the Inhibitor Working Party
Dr Kate Talks, representing the Data Management Working Party

The group meets once a month by video conference and the meetings are recorded to facilitate production of accurate minutes. The group may meet or communicate between meetings as required.

All adverse events reported to the database are considered by the group. Where further enquiries or follow up are required to resolve issues in relation to reported events, these are delegated to panel members to follow up and events are not “closed” until data queries have been resolved or exhausted.

Where adverse events are considered possibly or definitely drug-related, the event is reported on to the manufacturer and through them to the regulator.

An important task of the early meetings was to expand and refine the SOP for the operation of the group and processing of adverse events, which has now been agreed.

Most adverse events are reported to the database spontaneously soon after they occur, using the electronic reporting system. Many adverse events are unresolved at the time of reporting and require follow up from the database and CMWP before the report can be concluded.

Reports on the following events are actively solicited with monthly reminder "orange email*". (*successor to the orange reminder postcard!):

Acute or Allergic reactions
Deaths
Infections
Intracranial Haemorrhage (paediatric and adult)
Thrombotic events (including MAHA)
Other events
COVID-19 infection
Malignancy
Inhibitors
Neurological Events
Unexpected poor efficacy

Adverse events are summarised overleaf, and serious adverse events described in more detail. Personal details have been supressed to minimise the risk of a breach of confidentiality.

All adverse events reported by centres who participate in the European Haemophilia Safety Surveillance (EUHASS) program are anonymised and automatically forwarded via the NHD website to avoid the need for double reporting.

Table 28 Summary of Adverse Events reported between April 2021 & March 2022

Adverse events	People (n)	Number of events
Allergy event	6	6
COVID-19 event	68	72
Death event	128	128
ICH event	13	13
Infection event	0	0
Inhibitor event	12	12
Malignancy event	33	34
Neurological event	3	4
Other event	6	6
Poor efficacy event	4	5
Thrombotic event	9	10
Total	**282**	**290**

Table 28 summarises the number and category of adverse events reported to the database during 2021/22. These events are reported in greater detail in the tables that follow.

In future, events of special interest should probably not merely be broken down by bleeding diagnosis, treatment, and treatment-relationship, if any, but also expressed in events per period of risk so that it is possible to compare the incidence of such events in different treatment risk-groups.

Further details of these events are as follows.

Table 29 Allergic / Other Reactions

Diagnosis	Event	Material	Relationship to material	Outcome
Haemophilia A	Rash	Nuwiq	Definite	Resolved
Haemophilia A	Shortness of breath, wretching / redness to face	Esperoct	Definite	Resolved
Haemophilia A	Headache	Hemlibra	Possible	Resolved
von Willebrand disease	Rash, allergy symptoms	Veyvondi	Definite	Resolved
von Willebrand disease	Rash, allergy symptoms	Advate	Definite	Resolved
von Willebrand disease	Rash, dry cough	Voncento	Definite	Resolved
von Willebrand disease	Rash, dry cough	Wilate	Definite	Resolved

In each case the events were evaluated by the Adverse Events Assessment Panel and are reported on to the manufacturer. Hemlibra-related allergy events appear to occur almost exclusively in the first few weeks of treatment.

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Table 30 Intracranial Haemorrhage (all ages)

Diagnosis	Severity	Age (years)	Trauma present	Material	Maintenance therapy	Outcome
Acquired haemophilia A	Mild	78	Minor head bump	FEIBA	On demand	Unknown
Acquired von Willebrand disease	Unknown	73	Unknown	Voncento	On demand	Unknown
F.V deficiency	Unknown	0	Unknown	FVII - Novo FVIIA	Prophylaxis	Unknown
Glanzmanns thrombasthenia	Unknown	21	Unknown	FVII - Novo FVIIA	On demand	Unknown
Haemophilia A	Mild	77	Unknown	FVIII (BPL)	On demand	Unknown
Haemophilia A	Moderate	60	Major trauma	FFP	On demand	Died
Haemophilia A	Severe	74	Unknown	FVIII (BPL)	Prophylaxis	Mlld expressive dysphasia
Haemophilia A	Severe	63	Unknown	Cutter FVIII (Koate)	Prophylaxis	Unknown
Haemophilia A	Moderate	0	Unknown	Advate	Prophylaxis	Unknown
Haemophilia A	Severe	27	Major trauma	Voncento	On demand	Unknown
Haemophilia B	Severe	75	Unknown	FIX (BPL)	Prophylaxis	Unknown
Haemophilia B	Severe	0	Unknown	IDELVION	Prophylaxis	Unknown
von Willebrand disease	Mild	74	Unknown	Wilate	On demand	Died

Table 31 Factor VIII Inhibitors

Bleeding disorder	Age at time of inhibitor development (years)	Product(s) in use at time of inhibitor development	Exposure days	Maximum inhibitor titre
Severe haemophilia A	16	Emicizumab	>50	Unknown
Severe haemophilia A	0	Advate	<=50	2
Severe haemophilia A	0	ReFacto AF	<=50	5
Severe haemophilia A	1	Advate	<=50	89
Severe haemophilia A	0	Elocta	<=50	30
Severe haemophilia A	0	Nuwiq	<=50	14
Non-severe haemophilia A	5	Advate	Unknown	3
Non-severe haemophilia A	64	NovoEight	Unknown	4
Non-severe haemophilia A	63	ReFacto AF	Unknown	8
Non-severe haemophilia A	59	ReFacto AF	Unknown	31
Non-severe haemophilia A	40	Advate	Unknown	4
Non-severe haemophilia A	7	Advate	Unknown	1

Table 31: Fifteen factor VIII inhibitors and no FIX or VW inhibitors were reported between April 2021 and March 2022. Outline data for those where a full report was submitted is summarised in the table above.

* One of these was a pre-existing inhibitor in a person with severe haemophilia A who had recently migrated to this country. He developed an inhibitor to an unknown product after 36 exposure-days.

Inhibitors appearing or re-appearing after switching to Emicizumab are probably recurrences of inhibitors that were already present at a relatively low level below the level of detection of the Bethesda assay at the time of switching. In some of these cases there may be direct evidence that this is the case in the form of an abnormally short FVIII half-life.

There was also a single report of a Emicizumab anti-drug antibody. This reduced circulating Emicizumab levels but so far has not led to any loss of efficacy. It was picked up by routine surveillance.

See table 18 for breakdown of inhibitors by disease severity.

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Table 32 Malignancy Events

Malignancy	Diagnosis	People
Adenocarcinoma of breast	von Willebrand disease	1
Basal cell carcinoma	Haemophilia A	1
Breast cancer	Bernard Soulier	1
Carcinoma of the tounge	Haemophilia B	1
Clear cell carcinoma	Platelet defects (misc)	1
Gliomatosis cerebri	Acquired haemophilia A	1
Grade 3 invasive urothelial carcinoma of the bladder	Haemophilia A	1
Hepatocellular carcinoma	Haemophilia A	2
	von Willebrand disease	1
Left lingular cavitating lesion	F.XI deficiency	1
Lymphoma	Unclassified	1
Lymphoplasmacytic lymphoma	Haemophilia A	1
Metastatic adenocarcinoma (lung)	von Willebrand disease	1
Metastatic colon cancer	Platelet defects (misc)	1
Metastatic disease	Haemophilia B	1
Metastatic prostate cencer	Haemophilia B	1
Metastatic spindle cell cancer	Acquired Haemophilia A	1
Oesophageal cancer	Dysfibrinogenemia	1
Pancreatic cancer	Haemophilia A	1
	Platelet defects (misc)	2
Pleomorphic salivary adenoma	F.VII deficiency	1
Primary lung & brain mets	von Willebrand disease	1
Prostate cancer	Haemophilia A	1
	Haemophilia B	2
Recurrent metastatic hepatocellular carcinoma	Haemophilia A with liver transplant	1
Squamous cell carcinoma	Haemophilia A	1
Throat cancer	von Willebrand disease	1
Underwent laparoscopic biopsy	Haemophilia A	1
Vulval cancer	Females with VIII deficiency	1
Well differentiated neuroendocrine tumour	Haemophilia B	1

Table 32: The bleeding diagnosis has not been shown since the malignancies reflect both the types and frequencies seen in the general population as a broad generalisation and are found in all groups of people with bleeding disorders with no specific associations. The exception to this is hepatocellular carcinoma, which was found exclusively in haemophilia A and B and which presumably relates to previous infection with hepatitis C or B in most cases.

Table 33 Neurological Events

Diagnosis	Event	Prophylaxis	Material	Outcome
Haemophilia A	Intracranial haemorrhage – bleed into thalamus	No	Advate	Right thalamic bleed
Haemophilia A	Stroke	Unknown	Unknown	Stroke
Haemophilia A	Intracranial haemorrhage	Yes	Advate	Related to high blood pressure

Table 34 Other Events

Diagnosis	Event	Material	Relationship to material	Outcome
Haemophilia A	Increased bleed frequency	Esperoct	Related	No bleeds were reported so far
Haemophilia A	Left elbow bleed, fatigue, pain in both knees and ankles	Hemlibra	Probably related	Unresolved
Haemophilia A	Headache	Emicizumab	Probably related	Unresolved
Haemophilia A with liver	Metastatis hepatocellular carcinoma	Unknown	Probably related	Unresolved
von Willebrand disease	Feeling unwell, vomitting	Veyvondi	Probably unrelated	Unresolved
von Willebrand disease	Pre-operative recovery	Voncento	Probably related	Unresolved

These events were adjudicated by the membership of the Co-Morbidities Working Party.

Table 35 Thrombotic Events

Diagnosis	Event	Material	Relationship to material	Outcome
Acquired haemophilia A	Deep vein thrombosis (DVT)	None	Unrelated	Unknown
	Thrombotic stroke	None	Probably related	Unknown
	Pulmonary embolism (PE)	None	Unrelated	Died
F.VII deficiency	Pulmonary embolism (PE)	FVII - Novo FVIIA	Unrelated	Unknown
F.XI deficiency	Thrombotic stroke	None	Unrelated	Unknown
Haemophilia A	Bilateral renal infarcts	Hemlibra	Probably contributing factor	Unknown
von Willebrand disease	Transient ischemic attack (TIA)	None	Related	Unknown
	Pulmonary embolism (PE)	Voncento	Unrelated	Mobility reduced
	Thrombotic stroke	None	Unrelated	Unknown

2.6.2 COVID-19 Report

The National Haemophilia Database has been collecting reports of COVID-19 infection since March 2020 and it is our current intention to continue to collect such reports until the summer of 2022. This Data is also shared with EUHASS.

We acknowledge that the data reported to us is inevitably incomplete. In the early days many COVID-19 diagnoses were missed or uncertain because of a lack of a test. More recently, mild infections may not be notified to the centre and therefore not notified to the database. There may be reporting bias such that deaths are relatively more likely to be reported. Nevertheless, we would encourage centres to continue to report.

Despite these limitations, several trends can be discerned. The table below shows the 161 reports received since March 2020 broken down by the main diagnoses. It is quite striking that despite its relative rarity, 16/37 deaths were reported in people with acquired haemophilia. This relative excess probably reflects a number of factors, including the comparatively high underlying mortality from all causes associated with the condition, immunosuppression and the very high median age at which the condition presents. 73% of COVID-19 cases reported in this group died compared to 21 of 180 cases reported in all other bleeding disorders.

Diagnosis	Alive	Dead	Total
Haemophilia A	71	0	71
Haemophilia B	19	0	19
von Willebrand disease	32	2	34
Acquired haemophilia A	6	16	22
Other disorder	37	19	56
Total	**165**	**37**	**202**

Figure 24 COVID-19 cases by month – March 2020 - February 2022

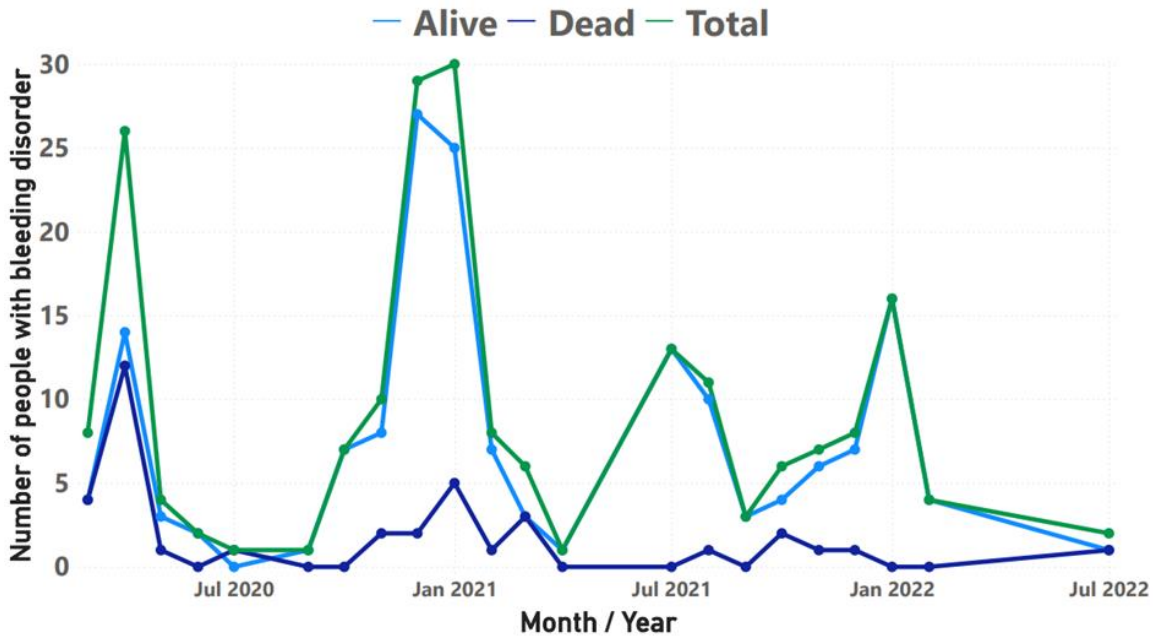


Figure 24: This shows the cases reported broken down by month of infection. During the first peak, in early Spring 2021, 50% of the cases reported died, suggesting strong reporting bias towards reporting death. In the earlier part of the pandemic only hospitalised cases had a confirmed infection, which may have further biased reporting and, since face to face consultations were abandoned for six months or more, many milder cases may have gone unreported at that time.

The second wave in winter 2020/21 shows fewer deaths and a much lower proportion of reported cases dying. By this stage COVID-19 testing was widely available and far more confirmed cases were coming to light. Towards the end of this period most people in vulnerable groups were fully or partly vaccinated and this may also have contributed to the relatively low death rate. Even so, the approximate 20% death rate may reflect continued reporting bias towards reporting the most serious cases, since it is higher than the mortality rate reported for the general population.

The third wave was interesting because it is not as high as previous waves and very few deaths have been reported. This is similar to the pattern observed in the general population, reflecting the efficacy of vaccination in the more vulnerable groups.

Figure 25 COVID-19 cases by age range - March 2020 - February 2022

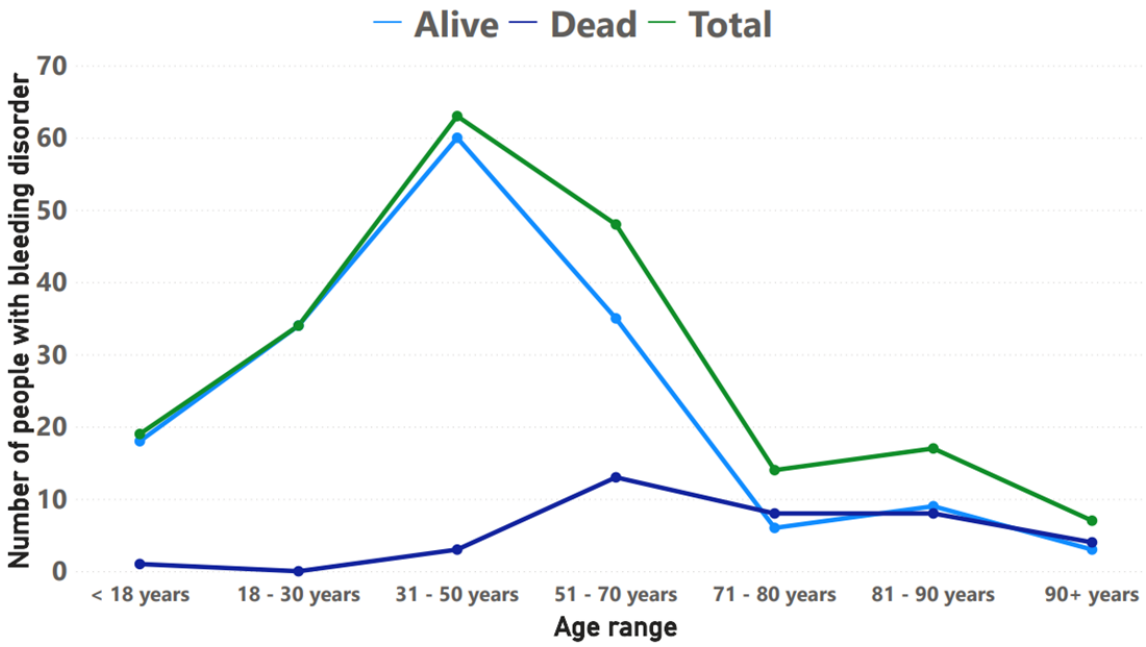


Figure 25: shows the distribution of cases and deaths broken down by age bands. This shows reports of cases in all age bands, but especially the young. This apparent imbalance may reflect the age distribution of people with bleeding disorders in the registry. There are relatively few elderly patients in the register especially past the age of 70. It may also reflect early diagnostic/reporting difficulties, the age-prioritization of the vaccine program and greater adherence to COVID-19 avoidance strategies, such as lockdown, amongst more vulnerable groups.

Deaths, on the other hand, were almost completely confined to those over the age of 50.

The data provide no evidence that patients with a bleeding disorder are unusually susceptible to COVID-19 infection or more likely to die from it. The exception to this generality is acquired haemophilia. As a broad generalisation these patients have several risk factors for an adverse COVID-19 outcome. They are generally elderly, usually have co-morbidities and will be immunosuppressed.

2.7 Mortality

Table 36 Causes of death in people with haemophilia A and B between April 2021 & March 2022

Cause of death	Haemophilia A				Haemophilia B		
	Severe	Non-severe	Not known	Total	Severe	Non-severe	Total
Acute respiratory distress syndrome	-	-	-	-	-	1	1
Chronic obstructive airways disease	-	1	-	1	-	-	-
Cancer	3	7	-	10	-	4	4
Hepatocellular carcinoma	-	3	-	3	-	-	-
Cerebral haemorrhage	2	3	-	5	1	-	1
Venous thromboembolism	-	1	-	1	-	-	-
Infection (bacterial)	1	4	-	5	-	1	1
Ischaemic heart disease	-	5	-	5	-	-	-
Dementia/Alzheimer's disease	-	2	-	2	-	1	1
Stroke	-	3	-	3	-	-	-
Renal failure	1	-	-	1	-	-	-
Not known	2	13	1	16	-	-	-
Total	**9**	**42**	**1**	**52**	**1**	**7**	**8**

Tables 36 & 37 (overleaf): These show the causes of death amongst people with haemophilia A and B (including carriers), broken down by severity (table 36) and for other bleeding disorders (table 37) during 2021/22. At present, it can be ascertained who has died from the NHS spine although the only source of cause of death data is haemophilia centres themselves. All causes of death should be reported to the database, where known. An application to NHS digital to renew the contract to receive death certification data has been agreed.

Table 37 Causes of death in other coagulation defects between April 2021 & March 2022

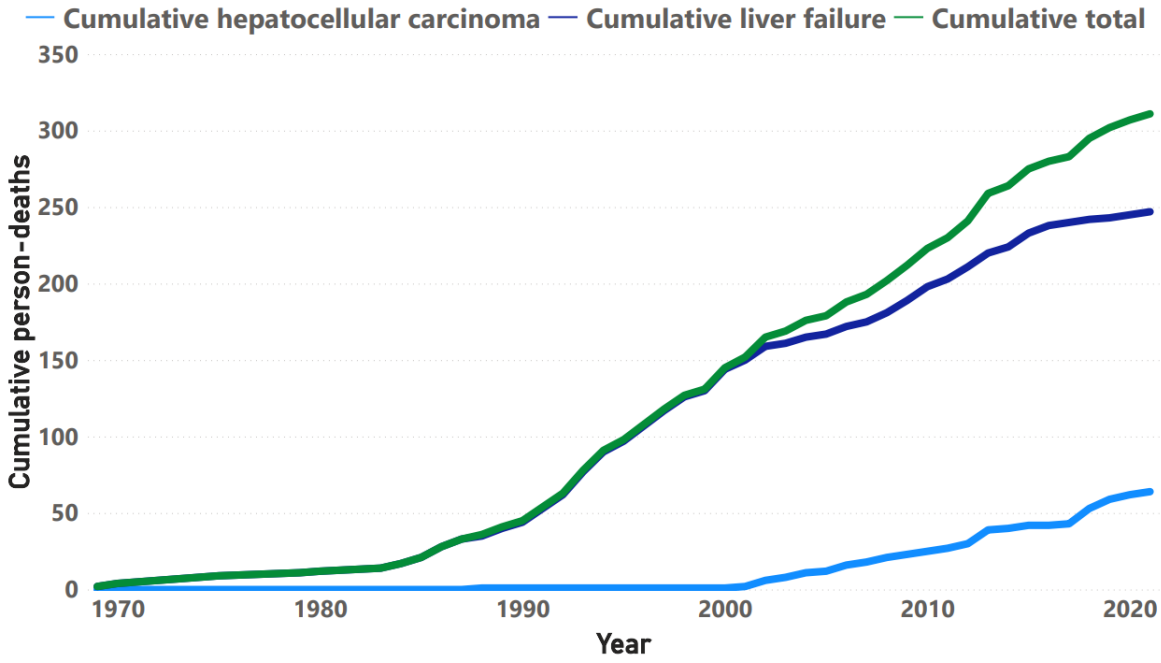
Diagnosis	Cause of death	Total
Haemophilia A with liver transplant	Not known	1
von Willebrand disease	Cancer	8
	Lymphoproliferative malignancy	1
	Cerebral haemorrhage	1
	Venous thromboembolism	1
	Infection (bacterial)	10
	Ischaemic heart disease	8
	Dementia/Alzheimer's disease	4
	Stroke	4
	Dissecting aortic aneurysm	1
	Liver failure	1
	Spontaneous perforation of sigmoid colon	1
	Not known	23
Probable von Willebrand disease	Infection (bacterial)	1
	Not known	1
Factor V deficiency	Infection (bacterial)	1
	Not known	2
Factor VII deficiency	Cancer	2
	Haemorrhage	1
	Infection (bacterial)	2
	Ischaemic heart disease	3
	Goucher's Disease	1
	Not known	3
Factor XI deficiency	Acute respiratory distress syndrome	1
	Chronic obstructive airways disease	1
	Cancer	9
	Infection (bacterial)	2
	Ischaemic heart disease	5
	Liver failure	2
	Not known	23
Factor XIII deficiency	Ischaemic heart disease	1
Prothrombin (factor II) deficiency	Not known	1
Dysfibrinogenemia	Haemorrhage	1
	Dementia/Alzheimer's disease	1
	Stroke	1
Hypofibrinogenemia	Cancer	1
	Not known	2
Unclassified bleeding disorder	Chronic obstructive airways disease	1
	COVID-19	1
	Haemorrhage	1
	Infection (bacterial)	2
	Dementia/Alzheimer's disease	1
	Dissection of the aorta	1
	Not known	1

Continued overleaf

Causes of death in other coagulation defects between April 2021 & March 2022 continued

Diagnosis	Cause of death	Total
Other severe platelet disorder	Not known	3
Other platelet disorder	COVID-19	1
	Cancer	3
	Lymphoproliferative malignancy	1
	Infection (bacterial)	1
	Ischaemic heart disease	2
	Intestinal failure	1
	Suicide	1
	Not known	9
Acquired haemophilia A	Acute respiratory distress syndrome	1
	Chronic obstructive airways disease	2
	COVID-19	6
	Cancer	7
	Hepatocellular carcinoma	1
	Lymphoproliferative malignancy	1
	Haemorrhage	6
	Venous thromboembolism	2
	Infection (bacterial)	16
	Ischaemic heart disease	7
	Dementia/Alzheimer's disease	3
	Stroke	1
	Stroke (thrombotic)	1
	Liver failure	2
	Renal failure	1
	Intestinal obstruction	1
	Not known	33
Acquired von Willebrand disease	Chronic obstructive airways disease	1
	Cancer	2
	Lymphoproliferative malignancy	2
	Infection (bacterial)	2
	Dementia/Alzheimer's disease	2
	Not known	1
Other acquired factor deficiency	Infection (bacterial)	2
	Ischaemic heart disease	1
	Not known	1
Combined and miscellaneous disorders	COVID-19	1
	Haemorrhage	1
	Stroke	1
	Stroke (thrombotic)	1
	Not known	2
Factor XII (Hageman) defect	Not known	1
	Total	**274**

Figure 26 Cumulative incidence chart of deaths from hepatocellular carcinoma or liver failure in people with bleeding disorders in the UK 1969 - 2021



Year	Hepatocellular carcinoma	Liver failure	Total
1969	0	2	2
1970	0	2	2
1972	0	2	2
1973	0	1	1
1974	0	1	1
1975	0	1	1
1979	0	2	2
1980	0	1	1
1983	0	2	2
1984	0	3	3
1985	0	4	4
1986	0	7	7
1987	0	5	5
1988	1	2	3
1989	0	5	5
1990	0	4	4
1991	0	9	9
1992	0	9	9
1993	0	15	15
1994	0	13	13
1995	0	7	7
1996	0	10	10
1997	0	10	10
1998	0	9	9

Year	Hepatocellular carcinoma	Liver failure	Total
1999	0	4	4
2000	0	14	14
2001	1	6	7
2002	4	9	13
2003	2	2	4
2004	3	4	7
2005	1	2	3
2006	4	5	9
2007	2	3	5
2008	3	6	9
2009	2	8	10
2010	2	9	11
2011	2	5	7
2012	3	8	11
2013	9	9	18
2014	1	4	5
2015	2	9	11
2016	0	5	5
2017	1	2	3
2018	10	2	12
2019	6	1	7
2020	3	2	5
2021	2	2	4
Total	**64**	**247**	**311**

Figure 26 (previous page): This shows deaths directly attributable to liver disease.

The table documents the number whose death certificate listed liver disease as the principal cause of death or who were reported to the NHD by their centre as having died from complications of HCV. Liver disease may have been a subsidiary contributory factor in other deaths although not listed as the primary cause. Please note these results may vary from those produced for the NHD & UKHCDO report "Bleeding disorder statistics for the Infected Blood Inquiry 2020" because the extensive bespoke data collection and cleaning for the latter has yet to be incorporated into the National Haemophilia Database.

This table may underestimate deaths from liver disease since people who have died outside a hospital with a haemophilia centre and whose death has not been reported to a haemophilia centre may not be reported to us. In the past we have closed that information-gap by obtaining death certification data from the Office for National statistics and its successor organisation NHS Digital. This contract expired in 2013. After an extremely difficult and protracted process, this contract has been re-established and so our data should be more complete in future. It should be born in mind, however that even severe liver disease may not be documented on the death certificate if the person died from some other, unrelated, cause.

This appears to show some levelling-off of deaths from hepatocellular failure. This may be a reporting artefact, as the NHD has not received death certification data from NHS Digital for six years, although reports of death are collected directly from the haemophilia centres. However, as HCV has now been eradicated from almost all surviving patients, one would expect a reduction in the incidence of hepatocellular carcinoma (HCC), which declines after viral eradication, even in the presence of ongoing cirrhosis. It is sobering, however, that five new cases of hepatocellular carcinoma were reported in the last two years. A reduction in this complication of hepatitis C may take some time to become evident. There may also be a delay before a further reduction in deaths from hepatocellular failure is seen, as some people have advanced cirrhosis with hepatocellular failure and not all are suitable for transplantation or have a donor. However, successful viral eradication will result in complete recovery of early cirrhosis or less advanced liver disease, and they should not go on to develop advanced cirrhosis and will have a greatly reduced risk of HCC, which usually complicates cirrhosis.

Table 38 Summary of people 'at risk' of vCJD for public health purposes who received UK sourced plasma products as reported by centres

Summary table of 'at risk' people with bleeding disorders who received UK sourced		Implicated batches	Non-implicated batches	Batches not known	Combined
Current status of 'at risk' people	Alive	642	285	1835	2762
	Dead	165	104	606	875
	Total	807	389	2441	3637
Sex	Male	766	307	2020	3093
	Female	41	82	421	544
	Total	807	389	2441	3637
Current age band of living 'at risk' people	0-19	0	0	0	0
	20-39	229	88	497	814
	40-59	295	123	734	1152
	60-79	110	64	514	688
	80+	8	10	90	108
	Not known	0	0	0	0
	Total	642	285	1835	2762

These data were last updated on 31/12/2021

Table 38: This summary of vCJD surveillance is sent to the UK Health Security Agency regularly. It lists the number of people exposed to UK-sourced blood products or components, according to NHD treatment records, during the period of risk (1990-2001) broken down by those who were known to have received an implicated batch and those not known to have been exposed to an implicated batch. Implicated batches of factor concentrates were those batches which included a donation of plasma from a donor known to have subsequently developed vCJD. In some cases, red-cell donations from those donors are known to have caused vCJD transmission to recipients. So far, there is no evidence of any transmission of vCJD through clotting factor concentrates and no people with bleeding disorders have developed the disease. Given the known incubation period for this condition, it seems increasingly unlikely that people exposed to UK-sourced blood products or components will be affected by vCJD, but the population will continue to be monitored for this.

Batches not known comprises:

1. Patients presumed as at risk 1990-2001 because they were classified as at risk via the 1980-2001 risk assessment exercise although they have no 1980-2001 NHD treatment records.
2. Patients identified as at risk 1990-2001 via 1990-2001 NHD treatment records but not via risk assessment exercise.

Figure 27 Total number of people with haemophilia A, haemophilia B or von Willebrand disease issued product by UK haemophilia centres

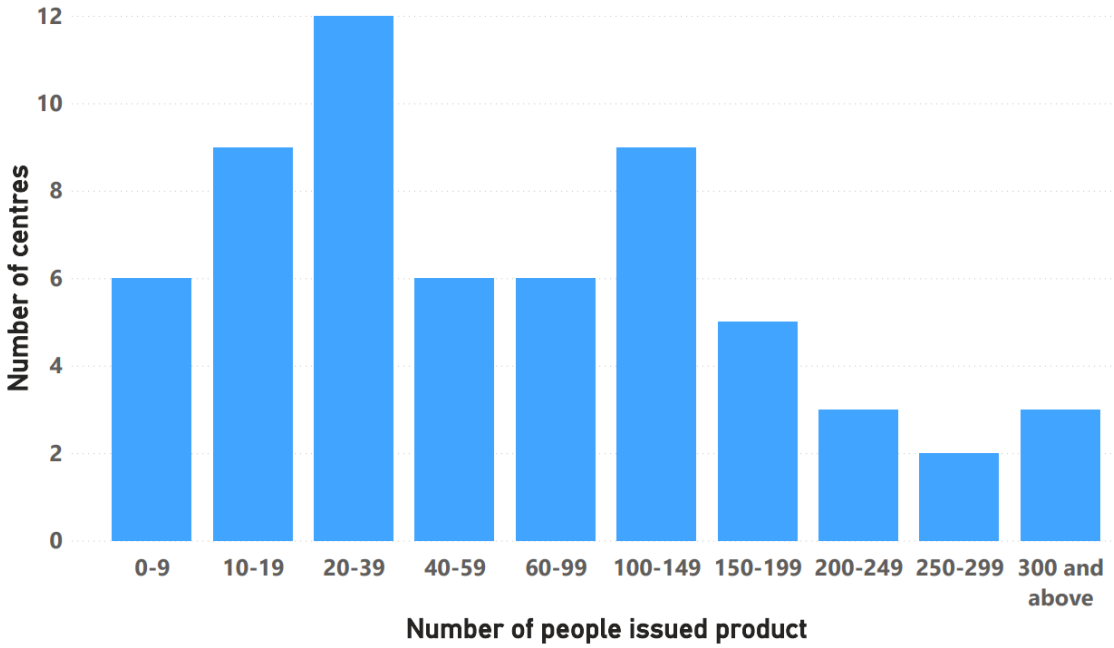
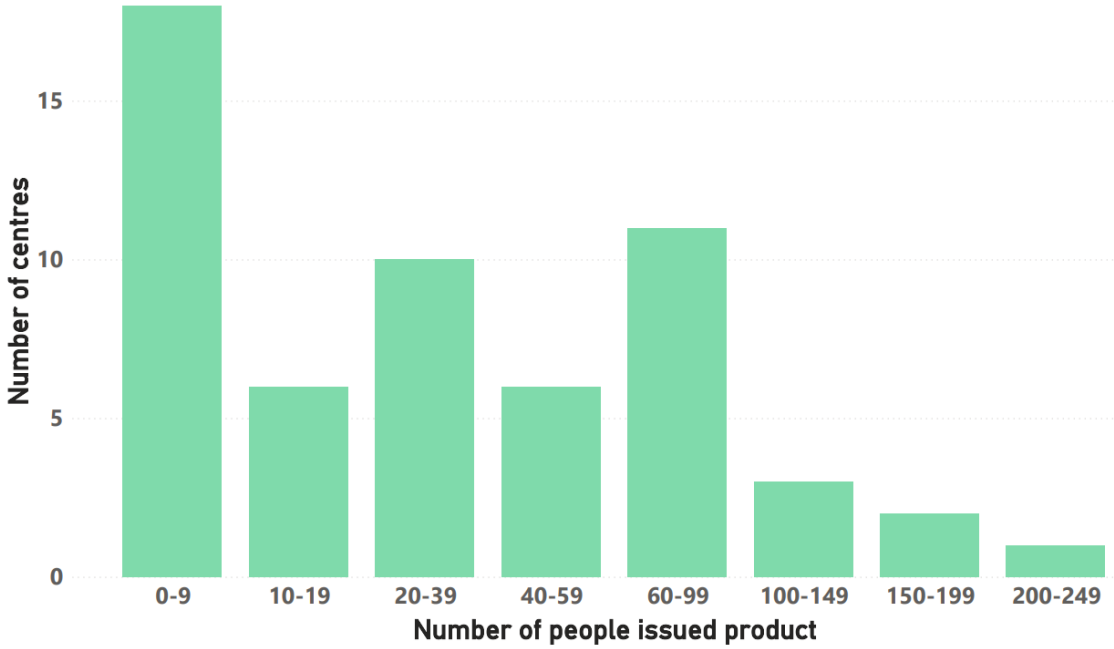


Figure 28 Total number of people with severe haemophilia A and haemophilia B issued product by UK haemophilia centres



NB: Haemophilia A includes carriers of haemophilia A and females with FVIII deficiency
Haemophilia B includes carriers of haemophilia B, females with FIX deficiency, FIX Leyden and FIX Leyden carriers.

3. Haemtrack Annual Report for the calendar year 2021

Introduction

This report is reported by calendar year rather than by financial year since 10% of the data is reported on paper, incurring a significant delay.

Haemtrack is used by patients to report home therapy to their haemophilia centre and so its use is not limited to haemophilia A or B but includes other, rarer, bleeding disorders for which patients also use home therapy. Both haemophilia centres and patients vary in their reporting compliance with Haemtrack and so the quality of individual patient self-reported data varies and the proportion of patients using the system also varies from centre to centre. In general, data quality is improving and the proportion of patients using the system is increasing.

Broadly speaking, reporting compliance is best for severe haemophilia A and B and less good for von Willebrand's disease and rarer conditions. This data is extremely valuable however and we would urge centres to press their patients to report in all their home therapy so that we are in a better position to assess relative efficacy of different products and regimens.

Our aim is that Haemtrack should become a routine part of home-therapy management and a valuable tool for the review and optimisation of home-therapy and for patient education. For that to happen, compliance will have to improve and be reinforced by Health Care Professionals (HCP's) reviewing Haemtrack records with patients in clinic and checking the data for accuracy before downloading into HCIS, where it should be checked by HCPs prior to uploading into the National Haemophilia Database.

Haemtrack should also be used in multidisciplinary team meetings (MDTs). Many haemophilia centres already do this and in those centres recruitment and data quality are steadily improving. This requires a consistent investment in time by the centre staff which results in improving compliance with both home therapy and record keeping.

Some haemophilia centres appear not to have realised the full clinical utility of this reporting system and consequently return sub-optimal data, which may reflect some degree of non-engagement by both HCPs and their patients. It is important to demonstrate to the patient, by referring to Haemtrack data on screen in clinics, that collecting and reporting treatment data is useful for their clinical management, and that its collection is not just an empty bureaucratic exercise.

NHS funding is always under extreme pressure and NHS England, desiring responsible use of drugs and accountability, have made it clear that compliant use of Haemtrack will be a prerequisite for access to new treatments such as Hemlibra® and EHL-FIX and Veyvondi®. NHS England require evidence that new drugs are cost effective and lead to better clinical outcomes in normal use. Haemtrack provides such evidence.

Haemtrack Update

Haemtrack continues to be a fundamentally important component of the UKHCDO Haemophilia IT Strategy. It integrates with the Haemophilia Clinical Information System (HCIS) and the National Haemophilia Database (NHD) providing patient entered data on treatments and bleeds that is unavailable from any other source. The data from Haemtrack is invaluable to support centres in the management of patient therapy and optimising treatment regimens, whilst also providing its data nationally to support research and introduction of new treatments and regimens.

Haemtrack now has over 2 million patient recorded entries, with over 100 thousand bleeds recorded. On average between 15 and 20 thousand entries a month are being added by patients. The majority of patients using the system are severe as would be expected, though some mild and moderate severity patients also use the system. The main diagnosis of patients using the system are Haemophilia A, Haemophilia B, von Willebrand disease, Factor VII deficiency and Factor X deficiency. A patient video explaining its use is available on-line (https://youtu.be/MVQbhJe7Rmk).

Haemtrack currently has a number of different platforms for patients to enter their data, phone apps, website and paper. The majority of entries are made by patients using the Haemtrack apps. Patients using the Haemtrack app enter their data nearest to the point of treatment with nearly 80% entered within 7 days, comparatively paper records can take up to 3 months to reach a similar level of completeness.

Haemtrack continues to evolve and a new version of Haemtrack is in development (Haemtrack 3) which will use the very latest technologies (progressive web apps) and introduce new functionality for patients, including an electronic version of the patient bleeding card. The new Haemtrack will simplify use of the system for patients and clinicians whilst also facilitating simpler and faster updates to the system. Launch of the new version of Haemtrack will be done in conjunction with an eventual withdrawal of the current patient apps resulting in a streamlined single Haemtrack platform used by clinicians and patients usable on any mobile device.

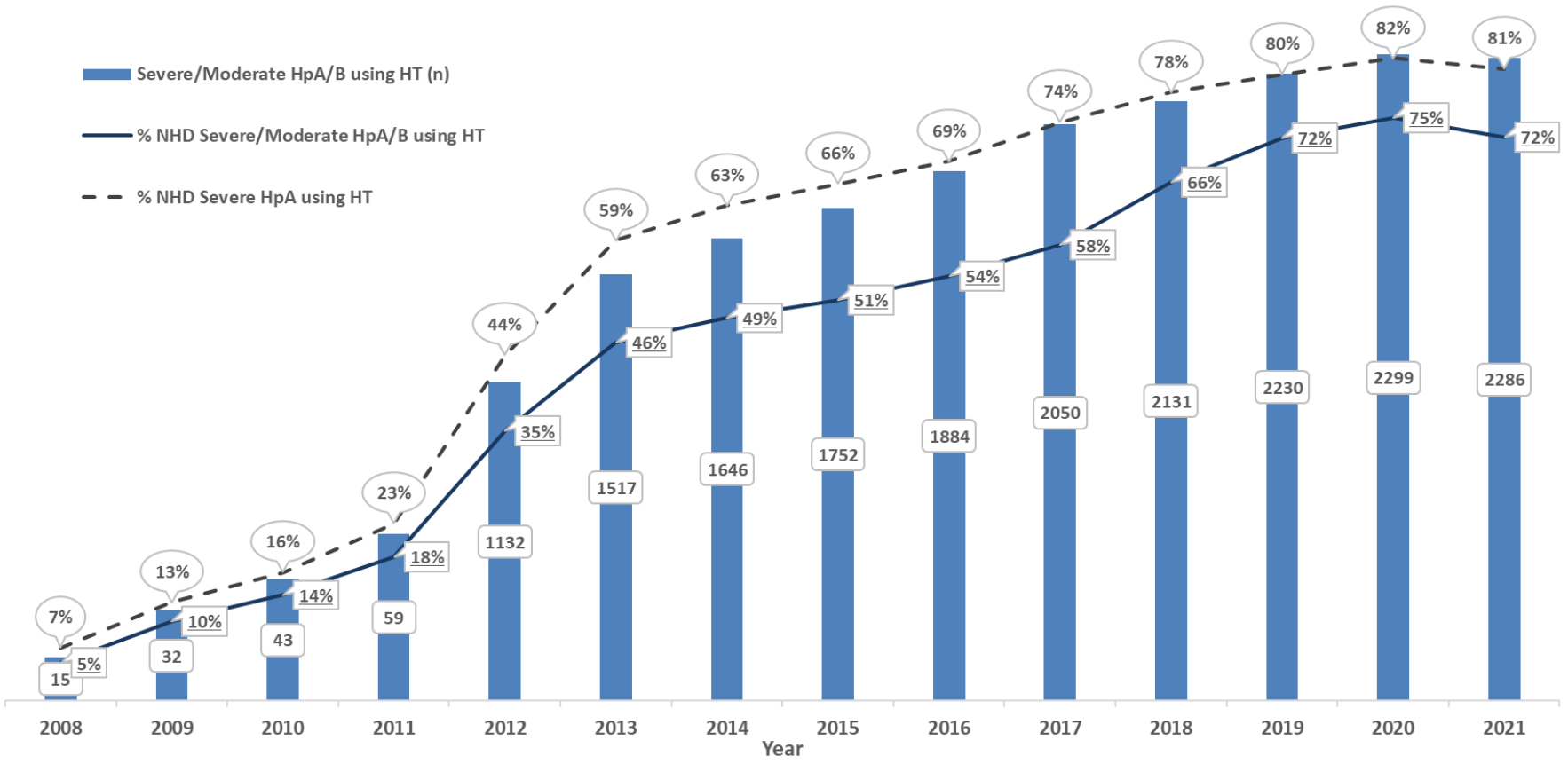
We have extended the use of Haemtrack to inpatient use (data entered by centre staff) so that it will provide a complete treatment record. Some centres are using this routinely and others not. We would encourage the universal adoption of inpatient use of Haemtrack so that the treatment record becomes complete.

3.1 Patients' Haemtrack Usage Analysis

3.1.1 Overall

Figure 1 (overleaf) presents an overview of severe and moderate patients with haemophilia A or haemophilia B using Haemtrack from 2008 to 2021. The blue columns give the numbers of patients that use Haemtrack, and the lines show the proportion of NHD patients who use Haemtrack. This illustrates rapid growth in 2012, when recruitment was the subject of a CQUIN and increased growth from 2017 when Haemtrack became a condition for access to new treatments. Figure 1 also reveals that there has been a gradual rise in the rate of recruitment, especially in severe haemophilia A cohort.

Figure 1 Number of patients using Haemtrack and recruitment rate, 2008-2021



3.1.2 Haemtrack usage analysis at centre level - patients with severe Haemophilia

Use of Haemtrack has increased at a rapid rate in recent years and most Comprehensive Care Centres (CCCs) use Haemtrack to some degree, though far fewer Haemophilia Centres (HCs). This may relate to staffing issues and perhaps a lower degree of engagement in HCs who may only have a few patients suitable for the system.

Figures 2 and 3 display the proportion of patients with severe haemophilia A/B using Haemtrack in each CCC (Figure 2) and HC (Figure 3). Recruitment is a little better in CCCs than in HCs.

Figure 2 Comparison of recruitment to Haemtrack by centre for patients with severe haemophilia A/B: Comprehensive Care Centres (CCCs) in 2021

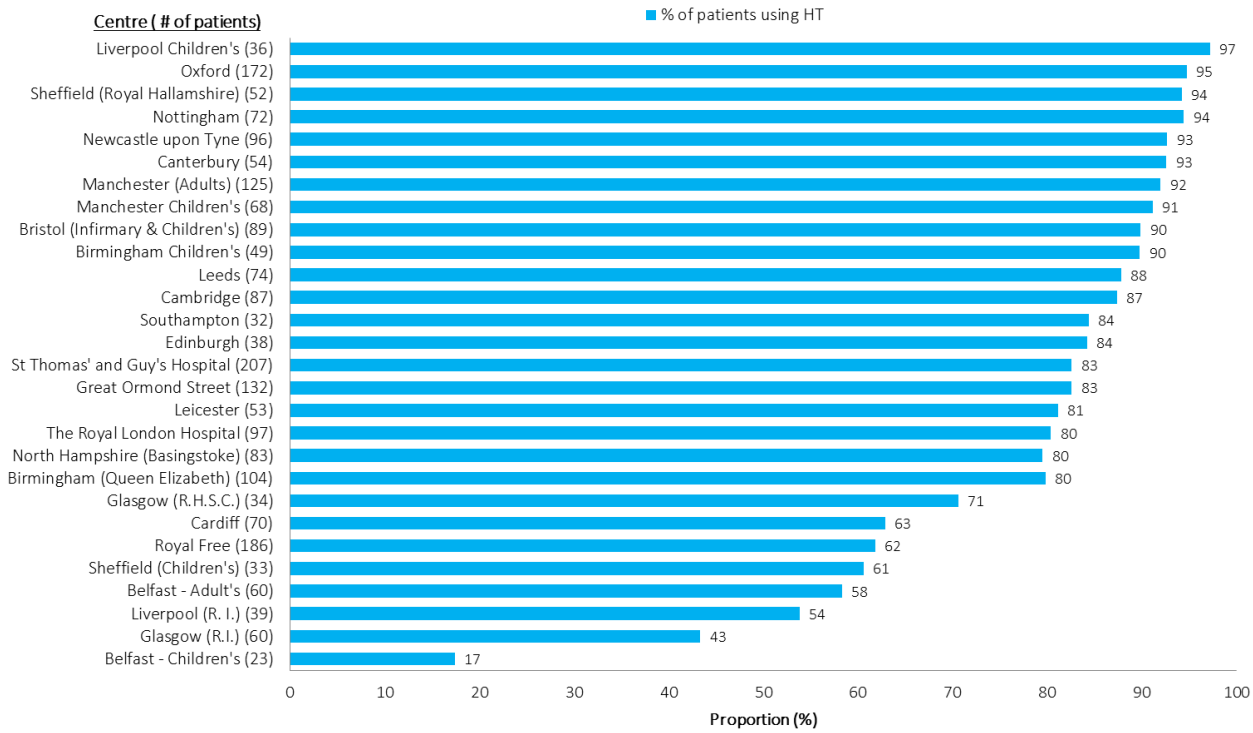
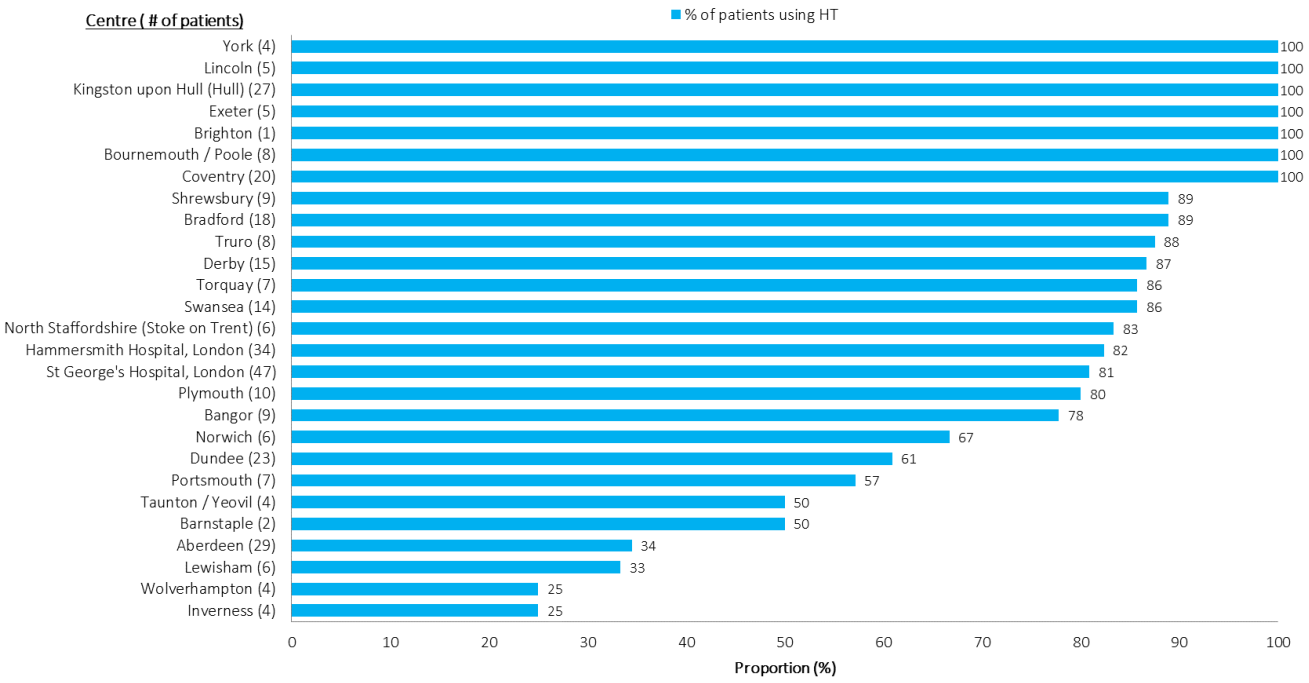


Figure 3 Comparison of recruitment to Haemtrack by centre for patients with severe haemophilia A/B: Haemophilia Centres (HCs) in 2021



Compliance with record keeping amongst patients using Haemtrack also varied considerably. For the purposes of this report, compliance refers to the patient's annual product usage reported through Haemtrack as a proportion of the factor issued to the patient, as reported quarterly to the NHD. Good compliance has been arbitrarily defined as Haemtrack reporting of use of >75%.

Figures 4 and 5 (overleaf) exhibit the overall compliance by severe haemophilia A patients for CCCs and HCs respectively. The compliance value closer to 100 indicates better usage compliance. The figures show the mean (diamond), median (vertical line), interquartile range (bar) and range (whiskers) compliance.

Compliance has improved considerably in recent years, both in CCCs and HCs, and is generally quite good.

Figure 4 Overall compliance in patients with severe haemophilia A, by Comprehensive Care Centre

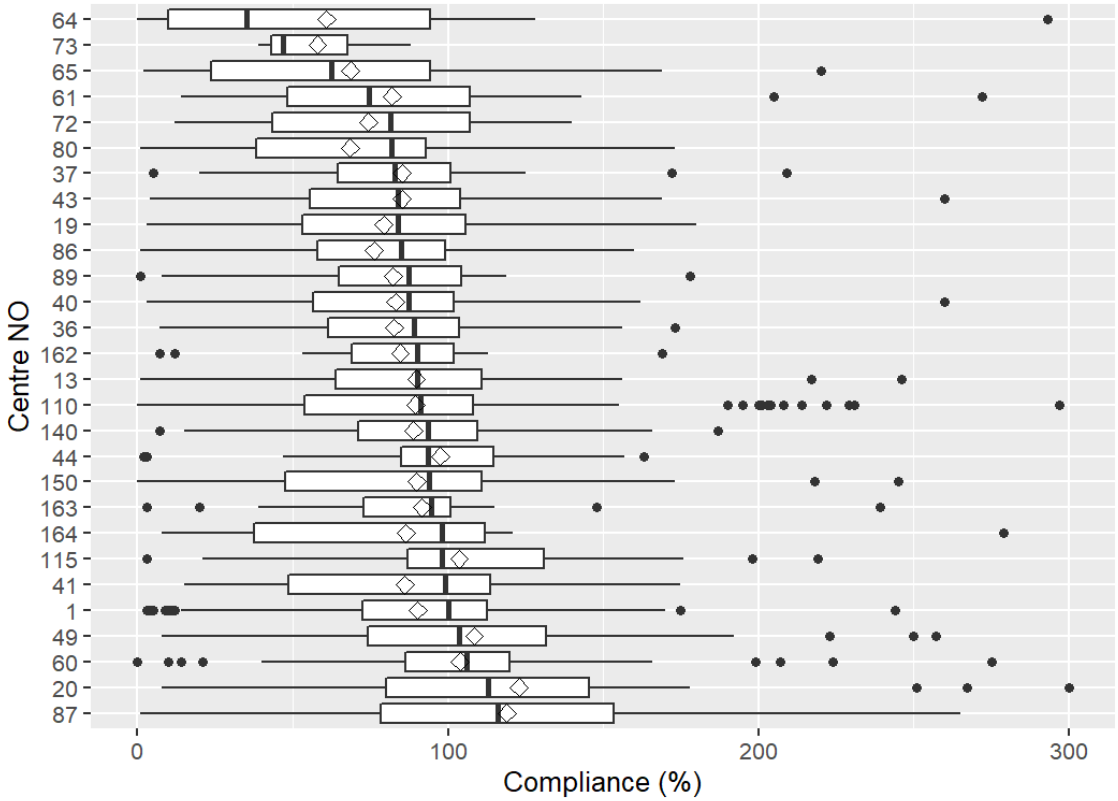
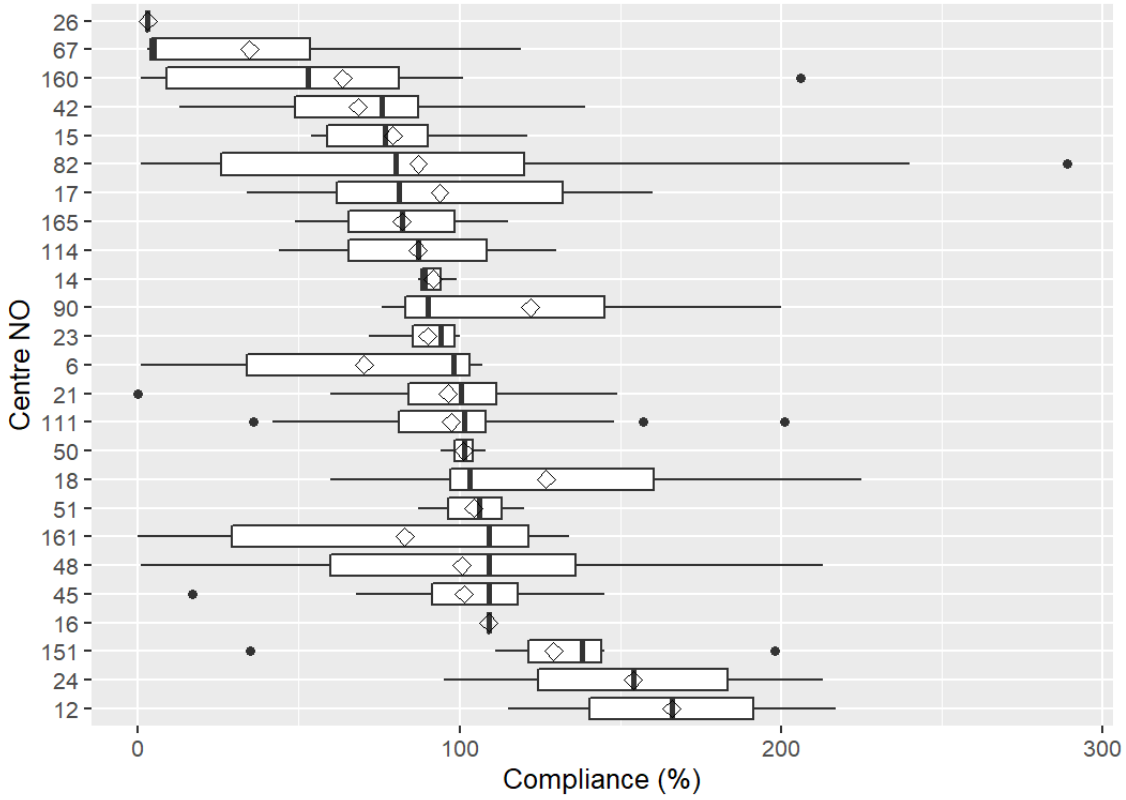


Figure 5 Overall compliance in patients with severe haemophilia A, by Haemophilia Centre

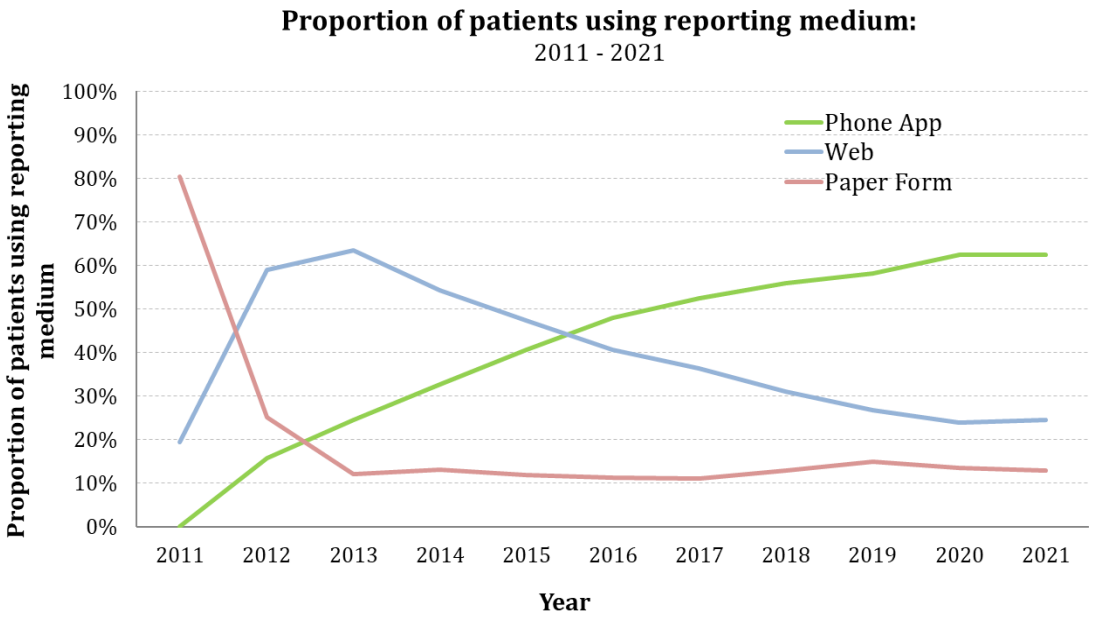


3.2 Patients' Reporting Analysis

3.2.1 Patients' Reporting Medium

Figure 6 shows the proportion of Haemtrack users using different reporting methods between 2011 and 2021. This shows an initial rapid uptake of the use of the web application at the expense of paper reporting. Subsequently, when the iPhone and then the Android app were introduced, they rapidly gained popularity at the expense of the web application. Oddly, the use of paper has remained stable over the past several years. This is curious given that electronic data can be very quickly quality-checked and rapidly imported into the haemophilia Centre Information System (HCIS) whereas paper records need to be laboriously keyed in by centre personnel. Most centres have a small proportion of patients using paper, but some centres still have most of their patients reporting on paper even though this creates more work for centre staff. The number of patients who are statistical outliers for compliance and use a paper reporting system suggests that some of these records had been manually entered by centres without checking or reconciliation. More recently, there seems to be a considerable increased in checking at centre level since there are far fewer obvious errors.

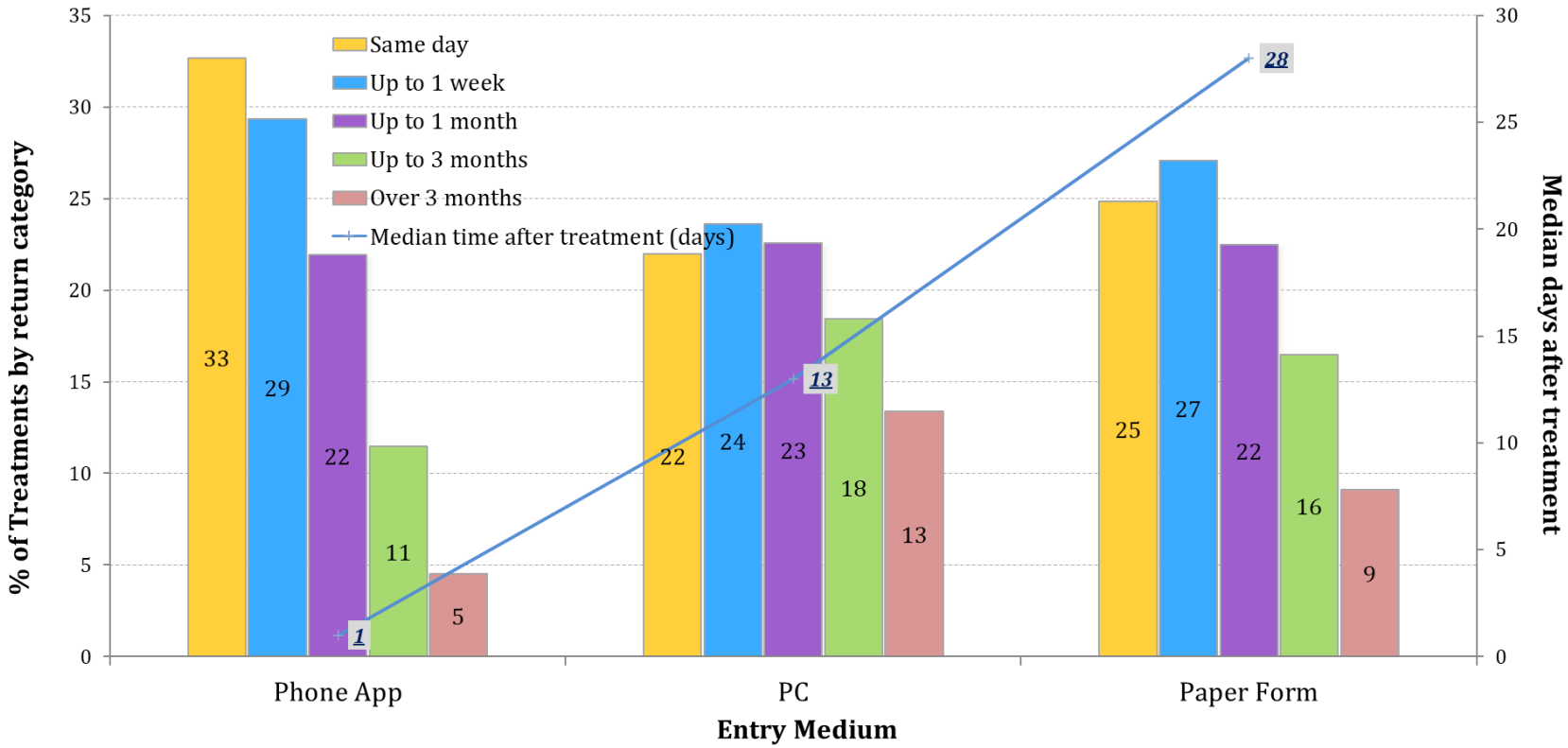
Figure 6 Change in the use of different Haemtrack Reporting Media: 2011- 2021



This is further analysed in Figure 7 (overleaf), which breaks down the interval between treatment and reporting by the reporting method used (smartphone apps, web and paper). Use of phone apps is associated with the most rapid reporting, with 33% of data being recorded on the day of treatment and a further 29% within a week. In contrast, only 22% of treatments were reported the same day and a further 24% within a week using web. Most data submitted on paper was reported after an interval of up to one month, either by post or at the next review clinic. Data reported by phone app was returned after a median of only 1 day, whereas paper-recorded data was reported after a median of 28 days with the web being intermediate. There is difference in the median age of patients using phone app, web, and paper form. The median age being 24, 33 and 31 years for phone app, web and paper reporters, respectively.

We are actively promoting the use of the phone apps in preference to other methods of reporting because we believe that the data are not only available to centres more quickly but are likely to be more accurate.

Figure 7 Haemtrack Reporting Delay by Reporting Medium 2021



4. Data Management Working Party

Membership

Chair:	Dr Kate Talks
Commissioner representative:	Will Horsley
Co-Director of the National Haemophilia Database:	Professor Charles Hay
Co-Director of the National Haemophilia Database:	Prof Pratima Chowdary
Data Manager Forum representative:	Lynne Dewhurst
Haemophilia Nurses Association representative:	Emma Franklin
Haemophilia Physiotherapists Group representative:	Dr David Stephensen
Haemophilia Society representative:	Kate Burt
MDSAS representative:	Dr Rob Hollingsworth
Patient representatives:	William McKeown
	Paul Sartain

Representatives of Northern Ireland, Scotland and Wales:

Northern Ireland	Dr Gary Benson
Scotland	Dr Ryan Rodgers
Wales	Professor Peter Collins

UKHCDO Working Party Chairs:

Co-morbidities Working Party	Dr Susie Shapiro
Genetics Working Party	Dr Keith Gomez
Inhibitor Working Party	Dr Charles Percy
Musculoskeletal Working Party	Prof Pratima Chowdary
Paediatric Working Party	Dr Mary Mathias
Von Willebrand Working Party	Prof Mike Laffan (for Dr C Millar)
Laboratory Working party	Dr Vince Jenkins & Will Lester
Unclassified Bleeding Disorder Working Party	Drs William Thomas & Mike Desborough

UKHCDO Executive Committee:

Chair	Prof Pratima Chowdary
Secretary	Dr Susie Shapiro
Treasurer	Dr Rachel Rayment

Members of the NHD as nominated by the Director(s) of the National Haemophilia Database:

NHD Manager	Andrew McNally
Working Party Secretary	Lynne Dewhurst
Data Analyst	Ben Palmer
	Dr Hua Xiang
	Dr Ridita Ali

Meetings

Since the last report the UKHCDO Data Management Working Party (DMWP) has met on 26th April 2022 (virtual) and 3rd October 2022 (virtual). The terms of reference for the Working Party were reviewed and are available on the UKHCDO website; in the course of the year there have been a number of changes in roles and new members welcomed; the list provided reflects the current membership.

The DMWP oversees data collection and analysis of patients with inherited bleeding disorders undertaken by the National Haemophilia Database (NHD). The DMWP and NHD are jointly responsible for the accuracy and completeness of the data collected. The DMWP has delegated most of the responsibility for assessing and overseeing requests for analysis of NHD data to the Data Analysis Group (DAG), which is a subcommittee of the DMWP.

The DMWP reviews the information that is collected on patients and revises this as necessary. Any member of UKHCDO can suggest changes to the data that are collected which will be considered by the DMWP. The Database governance arrangements and information governance compliance are reviewed at each meeting and the database remains compliant with all the relevant information governance regulations, Caldicott principles and NHS legislation, guidance and best practice. Over the last year quarterly mortality data from England, Wales and Scotland has been received and an agreement for sharing mortality data with Northern Ireland is being developed. New patient information leaflets have been developed to reflect these changes. Discussions are ongoing to clarify with the Health Research Agency (HRA) and the Confidentiality Advisory Group (CAG) how consent can be taken for research proposals without putting the section 251 application required for mortality data to be released at risk.

An Adverse Events Panel supports the consistent and timely assessment of all Adverse Events (AE) reported electronically to the NHD. The panel meets monthly and is co-chaired by an NHD director and the DMWP chair with additional UKHCDO members providing representation from EUHASS and the paediatric and inhibitor working parties. Data collection on COVID infection stopped 31/03/2022. Summary reports are provided to the DMWP and included in the annual NHD report.

Examples of Current UKHCDO projects supported by NHD include:

Real world experience of Emicizumab for people with and without inhibitors
Immune Tolerance Induction registry
The previously untreated patient (PUP) registry

The DMWP and NHD have made all data held by the NHD available to the Infected Blood Inquiry. In April 2020 the NHD/UKHCDO received a Rule 9 request asking for detailed statistical analyses of the data held. Work on the report continued through 2022 with the final report submitted in early September 2022.

Haemtrack

Commissioners for England and the devolved countries of the UK continue to encourage the use of Haemtrack as a means of capturing individual patient events and treatment. This has allowed important information about the impact of enhanced half-life factor VIII and IX and Emicizumab to be collated.

A Haemtrack user group was established in early 2021 to review the current version of Haemtrack and recommend updates in functionality. Work on a new version, Haemtrack 3 is still ongoing and will increase connectivity between the other NHD systems, HCIS2 and NHD2.

Pharmacokinetic analyses through NHD

A system has been developed whereby individual pharmacokinetic data can be entered through NHD into the WAPPs-Hemo system. This supports tailoring and personalisation of prophlyaxis for individual patients. The system functions for all licensed brand of factor VIII and factor IX.

The UKHCDO would like to thank the many individuals involved in the work of the NHD including Professor Charles Hay and Professor Pratima Chowdary, the Co-directors of NHD working on behalf of UKHCDO.

The following people have worked for the National Haemophilia Database in the last year and have been invaluable in their commitment to collecting and analysing the data on our behalf. Their role in supporting the aims of the Infected Blood Inquiry has been especially important.

Radita Ali
Katie Allen
Liz Ardern
Lynne Dewhurst
Mike Grove
Rachel Lockwood
Andrew McNally
Ben Palmer
Hua Xiang

We also thank Rob Hollingsworth and MDSAS for their continued support and maintenance of our national information systems.

We also wish to acknowledge all the important work done at the Centre level and for the support of all the patients for supporting this important work.

Dr Kate Talks,
Chair UKHCDO Data Management Working Party

November 2022

5. Data Analysis Group

Membership

Co-Chair (ex Chair of Data Management Working Party)	Professor Peter Collins
Co-Chair (Director of NHD)	Professor Charles Hay
User representatives:	Dr Ryan Cheal Paul Sartain Dr Richard Gorman
UKHCDO members:	Dr Charles Percy Prof Pratima Chowdary Dr Susie Shapiro Dr Mary Mathias Dr Kate Talks Dr Rachel Rayment
Haemophilia Nurses and physiotherapy representatives:	Dr David Stephenson
National Haemophilia Database:	Ben Palmer Dr Martin Scott Dr Ridita Ali Dr Hua Xiang

Meetings

The Data Analysis Group (DAG) is a subgroup of the Data Management Working Party. Its role is to assess and prioritise applications to analyse data held by NHD, including Haemtrack and joint score data. Applications are assessed based on data governance considerations, scientific merit and available resources. The group meets once a month by videoconference which last on average 60-90 mins. The terms of reference of the DAG are available on the UKHCDO website.

Requests for analyses are submitted on a standardised form. This form is available from NHD.

The DAG reviews and discusses all applications. It provides feedback to the applicant and works with them to refine the proposal, if necessary. The contributions from the user representatives have been particularly useful in assessing the applications and interpreting results.

The data analyses that are generated from the requests are reviewed and commented on by the group and may be further revised, if necessary, before release. Reports often contain caveats about data limitations that impact on the interpretation of reports.

All reports are made available to UKHCDO members through the UKHCDO website.

The DAG leads an investigator-led proposal to Roche/Chugai to analyse data held on the NHD relating to the introduction of Emicizumab and a paper about people with haemophilia and inhibitors has been submitted. This project is likely to be extended to cover people with moderate haemophilia A.

Requests for data analyses have been submitted by individual members of UKHCDO, UKHCDO working parties, NHS England and pharmaceutical companies. A number of requests have been made to support applications to NICE.

All members of UKHCDO and UKHCDO working parties are encouraged to suggest analyses and are invited to collaborate with the DAG on these projects. The DAG is open to new members from UKHCDO and anyone interested should contact Charlie Hay and Peter Collins.

Prof Peter Collins,
Chair UKHCDO Data Management Working Party

Prof Charles RM Hay,
Director NHD

October 2022

6. Co-Morbidities Working Party

Membership

Chair	Dr Susie Shapiro, Oxford
UKHCDO representatives:	Dr Gary Benson, Belfast Dr Gillian Evans, Canterbury Dr Sarah Mangles, Basingstoke Dr Rhona Maclean, Sheffield (member until Feb 2022) Prof Mike Makris, EUHASS (member until Feb 2022)
Haemophilia Nurses Association Representative:	Cathy Harrison, Sheffield

Remit

To consider comorbidity issues in patients with bleeding disorders within the UK and review any unmet need with respect to data collection, guidelines and patient related information / material.

To develop a Work Plan for the CMWP.

To advise the DMWP as to what data the NHD should collect regarding comorbidities in patients with haemophilia and bleeding disorders.

Any publications arising from the CMWP should be approved by the UKHCDO Executive in line with the UKHCDO publication policy.

Meetings

We held 5 online video meetings April 2021 – April 2022 to support Work Plan.

Activities

1. The group previously agreed that the initial focus of the Work Plan would be on cardiovascular disease and bleeding disorders.
2. The group previously agreed to write an up-to-date review on cardiovascular disease in patients with haemophilia (prevalence and management) in order to highlight areas of unmet need/lack of data and potential areas for future data collection/research/service improvement. The review was published in the British Journal of Haematology Feb 2022: "Cardiovascular disease in hereditary haemophilia: The challenges of longevity," doi.org/10.1111/bjh.18085
3. Following this review, the group have agreed that a key area of need is to improve data and further understanding for PWH with AF (prevalence, use of anti-thrombotics, risk of bleeding and stroke). This is also a James Lind Alliance top 10 research priority 2019. The group would like to initiate a national registry for PWH with AF to prospectively record AF management including antithrombotics, bleeds, strokes. The group have approached UKHCDO and NHD with regards to the possibility of support of data collection through NHD.

Dr Susie Shapiro,
Chair, Co-Morbidities Working Party
October 2022

7. Genetics Working Party

Membership

Keith Gomez	Chair
Vicky Cloke	Representing Genetics Laboratory Network
Nicola Curry	
Claire Forrester	
Mike Laffan	
Jayashree Motwani	
Suthesh Sivapalaratnam	
Megan Sutherland	Representing Genetics Laboratory Network
Kate Talks	

Remit

1. Provide oversight of issues related to genetics in haemophilia
2. Review guidance on genomic testing and update as required
3. Support genetic analysis of all patients with heritable haemostatic disorders and facilitate recording of data on NHD

Meetings and main work streams

The working party last met by web conference in May 2022.

Provision of Genetic Services

Testing is available for all NHS patients with heritable bleeidng or thrombotic disorders. The genes that can be tested are listed in the following panels:

- Bleeding and platelet disorders (R90) https://panelapp.genomicsengland.co.uk/panels/545/
- Thrombophilia (R97) https://panelapp.genomicsengland.co.uk/panels/516/

The NHS service is provided through Genomic Laboratory Hubs in England and Regional Centres in Scotland, Wales and Northern Ireland.

The Code on Genetic testing and Insurance stipulates that individuals do not have to disclose the results of predictive genetic testing using the above panels when applying for life insurance. All insurers in the UK have signed up to the code.

https://www.abi.org.uk/data-and-resources/tools-and-resources/genetics/code-on-genetic-testing-and-insurance/.

Laboratory Genetics Network

All NHS providers of genetic testing for heritable bleeding are members of the laboratory genetics network which continues to meet regularly.

Quality Assurance

The main provider of EQA in the UK is NEQAS Blood Coagulation. Two members of the working party sit on the Specialist Advisory Group for genetics which sends out EQA surveys covering the main heritable factor deficiencies.

Consent

The British Society of Genetic Medicine has updated its 2010 guidance on the consent process for children. Members of the working party have reviewed and commented on the final draft which contains case studies of worked examples. The final version is due to be published in November 2022.

Heritable Platelet Disorders category on NHD

A new category of Heritable Platelet Disorders was added to the NHD in September 2020. The main issue remains that the portal is only accessible if a patient is registered through NHD and not via HCIS. The plan from MDSAS is to include this category when HCIS is updated but it is not clear yet when that will be.

A form has been developed to enable offline completion of the dataset and is being trialled by the Data Managers Forum. The working party is currently considering how best to deal with registrations under the discontinued categories.

Capture of genetic diagnosis in the NHD

There has been little change in capture in the last few years. This is because BMS working in genetics lab have difficulty in finding the time to enter data. MDSAS are working on a solution using optical character recognition to extract the data directly from genetic reports submitted in PDF format. As all reports in the UK are independently verified by two scientists, the requirement for verification on the capture portal will be relaxed.

Dr Keith Gomez,
Chair, Genetics Working Party
November 2022

8. Genetic Laboratory Network (UKHCDO-GLN)

Background

The UKHCDO GLN was formed in 2002, arising out of the UKHCDO Genetic Working Party (UKHCDO GWP), with the aim of improving collaboration between laboratories and of ensuring quality and equity of service across the U.K. The network currently comprises 8 laboratories, 7 across the UK plus Dublin, involved in the molecular genetic analysis of haemophilia and other inherited bleeding and thrombotic disorders (many of the laboratories are also involved in other areas as well).

Representatives of the Network attend meetings of the UKHCDO Genetics Working Party.

Meetings

The UKHCDO GLN holds bi-annual meetings. The GLN met virtually on 09 December 2021 and on 26 May 2022. The next meeting is scheduled to be another virtual meeting in December 2022.

Chair & Secretary

Megan Sutherland and Catriona Keenan continue in their roles as Chair and Secretary, respectively.

Current activities

1. NHS England genetic laboratory re-designation exercise: The new structure of service provision in England went live in February 2021. The NHS England genomic test directory now specifies which disorders and gene targets will be investigated under this new service model and by which methodologies they should be performed (https://www.england.nhs.uk/publication/national-genomic-test-directories/). The 'Non-malignant Haematology' service, including the investigation of bleeding and thrombotic disorders, is provided by four Genomic Laboratory Hubs.

2. Laboratory Audit – ISO 15189: Laboratories in the Network are accredited by the United Kingdom Accreditation Service (UKAS). Laboratories are required to adhere to ISO 15189 quality standards. The GLN continues to share examples of good practice, practical advice and knowledge as the inspection process is applied to member laboratories. The Network continues to provide an informal sample exchange scheme between its members for disorders and methodologies that are not provided for by UK NEQAS. All laboratories continue to participate in the UKAS inspection process cycle.

3. National Haemophilia Database (NHD) Genetics Portal: The NHD Genetics Portal allows members of the GLN to upload genetic variant data for patients they have investigated into the patient's record on the NHD. The Genetics Portal is used by members of the GLN to see if a variant they have found has been reported by other centres, thereby providing evidence for pathogenicity calculations of genetic variation. During these searches the patient details are not shown. Members are also able to search for patients to confirm which centre they are registered at, and if a genetic variant

has been reported, prior to contact for release of relevant details if appropriate (no further information regarding the variant is made available at this time). Due to the reconfiguration of services it has been recognised that there is a severe constraint on time and resources to complete the data entry process using the current method, therefore a large number of genotypes have not been entered into the NHD. A solution to this problem is currently undergoing investigation.

4. **Bleeding Disorder Genetic Analysis Best Practice Guidelines:** The UK Best Practice Guidelines (BPG) for genetic analysis of Haemophilia A, Haemophilia B and VWD are in the process of being reviewed and updated in accordance with the NHS England genomic test directory and associated changes in service re-designation (see item 1). The classification of genetic variation will also be considered and addressed in the guidelines. Working groups have been assigned to each of the guidelines to be produced – those for VWD, and a combined BPG for haemophilia A and B. In addition, a working group has been established to produce a BPG for the genetic investigation of rare bleeding disorders. Due to the recent reconfiguration of genetic services in England and the ongoing effects of the pandemic, the updates to these guidelines have stalled, however we anticipate that progress will be made in the coming year.

5. **UK NEQAS Genetics of Heritable Bleeding and Thrombotic Disorders scheme:** The UK NEQAS Genetics of Heritable Bleeding and Thrombotic Disorders EQA scheme provides four EQA exercises per year, two of these are the traditional 'wet' exercises which always include analysis of one of *F8*, *F9* or *VWF*. The two new additional 'paper' exercises provide a clinical scenario and genetic variant for a patient which are to be interpreted by the participants and a report produced. The paper exercises aim to expand the scope of gene targets for interpretation to include rare bleeding and thrombotic disorders. The UK NEQAS paper exercises also include analysis of MLPA data and to provide an interpretative report for the clinical scenario. The results for each round of the scheme are reviewed and discussed at the following GLN meeting and any relevant comments fed back to the steering group.

6. **Participation in other groups:** Representatives of the Network input to the UKHCDO GWP. A representative of the Network is a member of the World Federation of Hemophilia Laboratory Science committee.

7. **General:** At each of the GLN meetings there is an open forum to discuss scientific and technical issues. We also aim to include an educational session at least once a year to focus on difficult areas for interpretation. Our main focus continues to be on the classification of rare or novel variants with reference to the current ACMG variant classification guidelines, and the sharing of this information throughout the network. It is recognised within the group that the sharing of knowledge and expertise is an essential mechanism for the interpretation of previously uncharacterised genetic variants.

Megan Sutherland,
Chair, UKHCDO Genetic Laboratory Network
November 2022

9. Inhibitor Working Party

Membership

Dr Charles Percy Chair
Dr John Grainger
Dr Dan Hart (stood down June 2022)
Prof Mike Makris
Dr Mary Mathias
Ben Palmer
Dr Anne Riddell
Dr Kate Talks
Dr Georgina Hall (stood down Oct 2022)

Meetings

The inhibitor working party (IWP) has met three times online since December 2021. It continues to benefit from membership from various disciplines and a number of related working parties. Activities have encompassed the following areas:

1. In conjunction with the paediatric working party (PWP) and the National Haemophilia Database (NHD), reports of new or recurrent factor VIII inhibitors in patients receiving prophylaxis with emicizumab continue to be reviewed.

2. In conjunction with representatives of the haemostasis and thrombosis task force of the British Society for Haematology (BSH), work has begun to update the guideline on acquired coagulation factor inhibitors. This will be a joint BSH and UKHCDO guideline.

3. The guidance on treating bleeds using recombinant factor VIIa (rFVIIa) in patients with haemophilia severe A who are receiving emicizumab has been reviewed. Data provided by the NHD for 27 patients was analysed. The median first dose was 59µg/kg with an interquartile range of 52 to 90µg/kg. There was no correlation between the initial dose of rFVIIa used and the need for additional follow up doses (i.e. using a lower initial dose did not increase the likelihood of needing additional doses to control the episode of bleeding). Irrespective of the dose used, thus far there have been no reports to the NHD of thrombosis in this group of patients.

4. Meetings have been held with the NHD to move forward with analysis of data from acquired haemophilia A project.

5. Participation in other meetings: Data Management Working Party, NHD Adverse Events Review Panel.

Dr Charles Percy
Chair, Inhibitor Working Party
October 2022

10. Laboratory Working Party

Membership

Dr Will Lester	Co-Chair

The group membership has been revised and expanded.

Laboratory

Anne Riddell	Royal Free Hospital, London
Annette Bowyer	Royal Hallamshire Hospital, Sheffield
Caroline Lawrence	Glasgow Royal Infirmary, Glasgow
Paul Murphy (retired)	Royal Victoria Infirmary, Newcastle
Sean Platton	Royal London Hospital, London
Vince Jenkins (stepped down)	University Hospital of Wales, Cardiff

Clinical

Dr Mohammed Khan	Aberdeen Royal Infirmary, Aberdeen
Dr Will Lester (Co-chair)	Birmingham Women's and Children's Hospital
Dr Andrew Page	Edinburgh Royal Infirmary

Invited representation

UKNEQAS Blood Coagulation	Anna Lowe (on leave, covered by Chris Reilly-Stitt)
NIBSC	Elaine Gray (retired) and Stella Williams invited to take this role

Activities

The main activity of the working group has been an update of the VWD laboratory guidelines which is a joint UKHCDO/BSH guideline which is separated from the clinical guidelines. This should be completed and submitted early 2023.

The group held two online meetings over the past 12 months 19/11/21 and 29/9/22, although there has been e-mail correspondence between group members.

The group membership has been revised with the retirement of Elaine Gray, Paul Murphy and Vince Jenkins retiring from the NHS. Applications for a replacement scientist and co-chair have been advertised.

Items in progress

To develop an educational networking program for laboratory scientists with an interest in haemostasis.

Dr Will Lester

Co-Chair, Laboratory Working Party
October 2022

11. Musculoskeletal Working Party

Membership

1Prof Pratima Chowdary	Chair Royal Free Hospital, London
1Dr Gary Benson	Belfast - Adult's
1Melanie Bladen	Great Ormond Street, Hospital
Peter Briggs	Royal Victoria Infirmary, Newcastle
1Dr Elizabeth Chalmers	Glasgow Children's
1Mr Stephen Classey	St Thomas' Hospital, London
1Dr Desmond Creagh	Royal Cornwall Hospital
1Dr Gerry Dolan	St Thomas' Hospital, London
Prof Simon Frostick	Royal Liverpool University Hospital
Dr Joanna Farrant	Royal Free Hospital, London
1Nicholas Goddard	Royal Free Hospital, London
1Dr John Hanley	Royal Victoria Infirmary, Newcastle
Dr Angela McKernan	Royal Derby Hospital
1Paul McLaughlin	Royal Free Hospital, London
1Dr David Stephensen	Kent & Canterbury
1Emily Symington	Addenbrooke's Hospital, Cambridge
Angela Westoby	St James' University Hospital, Leeds
1Anna Wells	North Hampshire Hospital, Basingstoke

The MDT MSK working party has been partially reformed with the inclusion of Gary Benson and Emily Symington. Several of our orthopaedic colleagues have retired, and we now lack adequate representation from orthopaedic surgeons. Further across the country, there is a shift towards joint sub-specialisation posing challenges for the delivery of comprehensive care. The guideline development is in progress for submission in the first quarter of 2023 following the completion of a Delphi consensus. The working party is due to be reformed under the new chair. Key messages from the consensus are related to outcome monitoring for haemostatic efficacy and joint health, including pain and activity limitation. There was a particular focus on the need for health and activity promotion and implementing solutions for gathering data on long-term outcomes post-surgical intervention.

Prof Pratima Chowdary
Chair, Musculoskeletal Working Party
November 2022

12. Paediatric Working Party

Membership

Dr Mary Mathias	Chair, London (GOSH)
Dr Jeanette Payne	Secretary, Sheffield
Jayanthi Alamelu	London (Evelina)
Neha Bhatnagar	Oxford
Tina Biss	Newcastle
Jayashree Motwani	Birmingham
John Grainger	Manchester
Simone Greene	Hull
Simone Stockley	Nottingham
Anne Kelly	Addenbrookes

Meetings

Since the last AGM the PWP has held 3 teleconference meetings in January, April and September

Summary of activities

1. *Data collection on children under 18yrs with severe FVII deficiency*

National data was collected for children under 18 yrs with severe FVII deficiency (< 5 IU/dL) and presented by Tina Biss at ISTH 2022. There were 24 patients of whom 38% required prophylaxis and 17% had intracerebral bleeding (all early in life). There was insufficient data to link genotype and bleeding phenotype. The aim is to publish this data.

2. *PUP registry on the NHD*

Although this has been available since last year there have been on-going teething problems with the data entry within the NHD, the resolution of which has been delayed by personnel changes at MDSAS. PWP Chair and MDSAS team now meeting until smooth data entry and follow-up form performance has been established.

3. *Access to Veyvondi for children*

A letter from the PWP Chair on behalf of the members was sent to Miranda Matthews in January 2022 outlining the concerns of the PWP about non-availability of Veyvondi to children. It expressed a hope that at least adolescents would be able to have access as per adult commissioning in line with the Medicines for Children document. This has been agreed, with a Blueteq step being put in place. Veyvondi use for pre-adolescent children will not be commissioned/refunded until a paediatric license is achieved, which is unlikely to be before 2025.

4. *The national advisory group/MDT*

Continues to run smoothly with 3 monthly teleconferences with terms of reference for discussion and recording of outcome. Calls for cases to discuss are sent out to paediatric treating centres prior to the dates with a data pro forma. The feedback continues to be positive in terms of support for centres and allows for ad hoc emailing of complex cases in between meetings if there is a clinical necessity with follow up and minuting at the next meeting.

5. *PWP membership at other UKHCDO meetings*

Inhibitor WP, DMWP, DAG and Adverse events panel. The PWP continue to review any new cases of children switched to emicizumab from FVIII prophylaxis, or who are emicizumab PUPS, who develop or recrudesce an inhibitor. Attendance at IWP and Adverse event panel meetings help with communication.

Dr Mary Mathias
Chair, Paediatric Working Party
October 2022

13. Von Willebrand Working Party

Membership

Dr Carolyn Millar Chair

Cathy Farrelly
Vince Jenkins
Mike Laffan
Will Lester
Shapiro Susie
Thynn Thynn Yee

Meetings

The VWD working party has met formally since the last AGM.

Summary of activities

The VWD working party has met formally since the last AGM, primarily to discuss the revision and update of the BCSH/UKHCDO 2014 guidelines. It has been agreed with the BSH taskforce that the guideline will be divided into two separate documents: a clinical diagnosis and management guideline and a laboratory testing guideline. The UKHCDO laboratory working party, together with the BSH taskforce, has set up a joint writing group chaired by Sean Platton for the laboratory guideline. In parallel, the VWD working party are revising and updating the clinical guideline, which includes consideration of the 2021 ASH/ISTH/NHF/WFH guidelines on the Diagnosis and Management of VWD.

Lists of patients whose entries require review by the registering centre with a view to updating, reclassifying or removing have been compiled by NHD. Discussion has previously taken place with NHD about compiling these lists and how to revise the registrations. Some centres have large numbers and to avoid overwhelming centres, a stepwise plan was previously proposed for NHD to send a limited number to centres every 2 months with a request for them to review the cases and update or delete them. Discussions regarding the most suitable approach are ongoing.

Dr Carolyn Millar,
Chair, Von Willebrand Working Party
November 2022

14. Unclassified Bleeding Disorders Working Party

Membership

Mike Desborough	Co-chair
Will Thomas	Co-chair
Samya Obaji	Secretary
Gillian Evans	
Gill Lowe	
Gillian Gidley	
Stephen MacDonald	
James O'Donnell	
Kate Downes	
Fernando Pinto	

Remit

1. To examine UK registration trends and practice in this area; this has led to a publication (listed below).
2. To consider whether guidance in this area should be produced.
3. To produce data on pregnancy outcomes in this patient group.

Meetings and main work streams

The main work stream this year has been to produce data on pregnancy and UBD, which has led to the recent publication in the Journal of Thrombosis and Haemostasis regarding management of pregnancy which was from Guy's & St Thomas' Hospital, Cardiff, Birmingham and Cambridge.

Further discussions are actively occurring about whether a guidance document or pathway for these patients can be created.

Notably, there were sessions at the ISTH Congress in London about UBD and consensus at ISTH was to call this *Bleeding Disorder of Unknown Cause*.

Publications

1. Thomas W, Downes K, Evans G, Gidley G, Lowe G, MacDonald S, Obaji S, O'Donnell JS, Palmer B, Pinto F, Desborough M. Current practice and registration patterns among United Kingdom Haemophilia Centre Doctors' Organisation centers for patients with unclassified bleeding disorders. J Thromb Haemost. 2021 Nov;19(11):2738-2743.

2. Castle D, Desborough MJR, Kemp M, Lowe G, Thomas W, Obaji S. Outcomes and management of pregnancy in women with bleeding disorder of unknown cause. J Thromb Haemost. 2022 Nov;20(11):2519-2525.

Dr Will Thomas & Dr Mike Desborough
Co-Chairs, Unclassified Bleeding Disorders Working Party
November 2022

15. Dental Task Force

Membership

Dr Julia Anderson Chair

Dr Sara Boyce (Consultant Haematologist)
Mr Andrew Brewer (Associate Specialist, Special Care Dentistry and Oral Surgery)
Dr Janet Davies (British Paediatric Dental Association representative)
C/N Jayne Keaney (Haemophilia Nurses Association)
Dr Bella Madan (Consultant Haematologist)
Dr Lochana Nanayakkara (Consultant in Restorative Dentistry)
Dr Emily Symington (Consultant Haematologist)
Dr Alice Taylor (Consultant Paediatric Haematologist)
Dr Albert Yeung (Public Health Dentist)

Remit

Dr Anderson chairs the Dental Task Force. The Task Force met on 1 February 2022, 17 May 2022, 16 August 2022 and 1 November 2022 on MS-TEAMS.

Group membership consists of adult and paediatric haemophilia consultants, adult and paediatric dental and oral surgeons, and nurse representatives.

The group has a focus on the update of the previous 2013 guideline and will be adding sections on gene therapy, extended half life products and emicizumab. The guidance is intended primarily for dental practitioners, with a separate publication aimed at haemophilia treaters.

The task force has conducted a literature review, and sections of the guide are now allocated to group members with the aim of a first draft by Spring 2023.

Thereafter the aim is to focus on audits of access to dental services across the UK, and an update of leaflets.

Dr Julia A M Anderson
Chair, Dental Task Force
November 2022

16. Emergency Care Guideline Task Force

Membership

Lishel Horn	Chair
Kate Forsyth	
Richard Gooding	
Richard Gorman	
Deepan Gosrani	
Jason Mainwaring	
Vicky McDonald	
Charles Percy	

Emergency Medicine Representatives (recruitment underway via RCEM and RCPCH)

Remit and Aims

Progress has been delayed this year due to several logistic issues. Since the report in 2021, a literature search is now in progress via the University of Leeds Library service in order to provide published evidence on which to base the rewriting of the guideline. An emergency medicine specialist has now been identified to join the group. A pilot patient survey on emergency care has been carried out in North West Yorkshire. Preliminary analysis of responses indicates suboptimal patient experience and a need for both staff and patient education regarding emergency pathways. This concurs with other data recently collected on behalf of Haemnet. A broad structure has been agreed for the updated guideline and work is in progress designing a triage tool amongst other resources. A meeting of the group is planned before the end of 2022 and dates have been proposed for further meetings in 2023 with a view to having the updated guideline ready for submission by the end of July 2023.

Dr Lishel Horn
Chair, Emergency Care Re-Write Task Force
Lead Clinician for the NW Yorkshire Haemophilia Network
November 2022

17. Gene Therapy Guideline Task Force

Membership

Prof Pratima Chowdary Chair

Dr John Hanley
Dr Gavin Ling
Dr Gillian Lowe
Dr Jayshree Motwani
Debra Pollard
April Jones
David Hopper
Stephen Classey
Bea Duran
Anne Black
Sara Boyce
Dr Susie Shapiro

Following its initial establishment, the task force has somewhat struggled through COVID. It has met three times with input from experienced pharmacists in Advanced therapy medicinal products. Several themes have been identified for inclusion in the specification document. The first area is related to the development of patient information and education, along with a pre-consent counselling checklist in conjunction with the Haemophilia society. The second aspect concerns the network arrangements for infusion and monitoring post-infusion, the 'hub' and 'spoke' model for care delivery. The third relates to patient selection, assessments and support during gene therapy. Finally, the development of registry fields in the national haemophilia database. The group aims to meet on a couple more occasions and draft a final specification document for submission in the second quarter of 2023.

Prof Pratima Chowdary
Chair, Gene Therapy Guideline Task Force
November 2022

18. Gynaecology Guideline Task Force

Membership

Dr Nikki Curry	Consultant Haematologist, Oxford
Dr Rezan Abdul-Kadir	Consultant Obstetrician and Gynaecologist, Royal Free
Dr Louise Bowles	Consultant Haematologist, Royal London
Professor Justin Clark	Consultant Obstetrician and Gynaecologist, Birmingham
Dr Gill Lowe	Consultant Haematologist, Birmingham
Dr Jason Mainwaring	Consultant Haematologist, Bournemouth
Dr Sarah Mangles	Consultant Haematologist, Basingstoke
Dr Bethan Myers	Consultant Haematologist, Leicester

The gynaecology working party was tasked with writing a UKHCDO Guideline on the management of gynaecological issues relating to women and girls with inherited bleeding conditions. The guideline was published online in the journal of Haemophilia this year: DOI: 10.1111/hae.14643. The guideline is split into two sections: the first focuses on heavy menstrual bleeding (HMB) and offers guidance both about how to manage HMB but also about how to think about diagnosing a patient who presents with HMB, with an inherited bleeding condition. The second part of the guideline focuses on the management of other gynaecological conditions and gynaecological surgery and offers guidance on practical issues, for example, such as the use of surgical proformas to guide haemostatic treatments peri-operatively, and 'menstruation plans'/education for girls with known bleeding conditions, as a means by which the girl and her family can prepare for menses with their haemophilia team.

An editorial on the guideline (titled: 'Inherited bleeding disorders in heavy menstrual bleeding: the case for joint haematological and gynaecological care') has also very recently been accepted for publication. The editorial was written with the aim of increasing the reach of the guideline to gynaecologists and also to highlight the need for haematology and gynaecology teams to work together with a joint goal of improving management for this patient group.

Importantly, the guideline and editorial offered suggestions for future work. In particular the Gynae Working Party consider that prospective national data collection for women and girls with inherited bleeding conditions is an important starting point, fostering the development of an understanding of national clinical practices as well as helping to inform future research projects.

Dr Nikki Curry
Chair, Gynaecology Task Force writing committee
October 2022

19. Haemtrack Upgrade Task Force

Membership

Dr Martin Scott	Chair - Manchester
Dr Charles Percy	Birmingham
Dr Rhona Maclean	Sheffield
Dr Jessica Sandham	Liverpool Children's
Pam Green	Birmingham
Sharon Thind	Liverpool Children's
Simon Fletcher	Oxford
Mike Grove	UKHCDO
Enis Muminovic	MDSAS
Karen Dean	Taunton
Anne-Marie Ley	Manchester Children's
Ray McKeown	Belfast
Anette Quirk	Liverpool Children's
Janice Ward	Birmingham
James Harrison	Parent Representative
William McKeown	Patient Representative
Paul Sartain	Patient Representative

This Task Force will report next year.

Dr Martin Scott
Chair, Haemtrack Users Group
October 2022

20. Haemophilia Nurses' Association

Membership

Julia Spires	Chair
Sharon Thind	Vice-Chair
Molly Musarara	Secretary
Marie Eales	Treasurer
Helen Hupston	
Siwan Owen	
Debra Pollard	

The Haemophilia Nurses Association (HNA) continues to represent specialist nurses who care for people with bleeding disorders in the UK. The HNA-UK has held meetings online giving the group an opportunity to meet and chat, bringing positive interaction and support for its members nationally.

We are making plans to run our highly successful Annual Conference January 2023, which will be a fantastic opportunity to meet old colleagues and welcome those new to the speciality who have commenced their foray into haemophilia and bleeding disorders during the past 3 years!

The committee have been busy setting up as an independent charity (charitable status pending). The focus of the charity will be professional development and mental wellbeing; the annual conference; AGM; and Nurse Education including introduction to bleeding disorders; the Contemporary Care Course (CCC) and the ASPIRE leadership programme. We are taking over the running of the courses following the closure of The Haemnet Foundation Charity. The CCC has been exceptionally well attended and has maintained its accreditation through Middlesex University, providing this with the academic validation it deserves. It is truly a practical, hands-on course developed and run by nurses and physios from four key haemophilia centres supplemented by external invited speakers, covering all aspects of multi-disciplinary care in bleeding disorders.

Over the year, we have lost members of our community to retirement, changes in service and brighter futures and to say these individuals and their expertise will be a loss to our community is an understatement. However, we do wish them all the best in their chosen pathways.

2023 brings with it opportunities for education and networking through international meetings, such as EAHAD and ISTH. As always, we ask the centre directors for their support for their nursing colleagues in being able to access the opportunities these meetings afford.

As well as being active on the steering committees of EAHAD and WFH committees, our members are active on other initiatives within the UK haemophilia treaters community, including the CRG for Specialised Blood Disorders, and various UKHCDO working parties. I thank all those who have participated in these groups and those who respond to questions to ensure that the national voice of haemophilia nursing is represented at these events.

Julia Spires
Chair, Haemophilia Nurses' Association
October 2022

21. Haemophilia Chartered Physiotherapists' Association

The HCPA consists of specialist physiotherapists working in haemophilia and allied bleeding disorders services across the UK and Ireland. We aim to define, promote and encourage best practice for physiotherapy within haemophilia care, providing professional leadership and directing national physiotherapy policy.

Executive Committee

David Hopper	Chair
Stephen Classey/Paula Loughnane	Vice-Chair
David Stephensen	Research Lead
Hannah Harbidge	Secretary
Steph Taylor	Treasurer

The committee was re-elected at the 2021 AGM in March and the positions will be held for a two-year period before another election at the 2023 AGM.

Peer Review

The peer review process 2019/20 highlighted inadequate levels of physiotherapy provision in 60% of the haemophilia services reviewed across the UK. HCPA members have been able to use the reports to raise the profile of this problem to local senior managers and commissioners. To date, of the 22 centres where provision was assessed as inadequate, 9% have achieved a significant improvement, 59% are in progress with on-going meetings and business cases being put in place, and 32% remain with significant barriers.

Work with the HCPA working closely with the CRG and the Haemophilia Society to raise the profile of the importance of physiotherapy within haemophilia care has been completed. Raising the profile will hopefully help address the disparity in care across the UK. A Checklist for centres to audit their physiotherapy service against current UKHCDO guidelines and a comprehensive information sheet with documenting the importance and benefits of adequate physiotherapy provision for all CCC was signed off by the CRG and ratified by the UKHCDO earlier this year.

Work has also been ongoing with individual centres helping them prepare business cases to present to their centre directors to help increase physiotherapy provision nationwide.

This accumulated with the work being presented in a roundtable event at the house of commons in June 2022 (David Hopper).

Research

The HCPA is proud to support and facilitate a thriving research environment. Members have successfully received NIHR and commercial grant funding. Current NIHR funded research includes:

- Haemarthrosis of the ankle in haemophilia A and B: prevalence, impact and intervention.
  NIHR Academy HEE/NIHR ICA Clinical Doctoral Academic Fellowship, ICA-CDRF-2015-01-012

  Richard Wilkins

- Developing a rehabilitation intervention for the management of chronic arthritic joint pain in people with haemophilia.
  NIHR Academy HEE/NIHR ICA Clinical Doctoral Academic Fellowship, ICA-CDRF-2017-03-050

  Paul McLaughlin

- Development of a haemophilia physiotherapy intervention for optimum musculoskeletal health in children (DOLPHIN-II) - a randomised controlled trial.
  NIHR Research for Patient Benefit (RfPB) Programme, NIHR-201588

  David Stephensen, Melanie Bladen, Liz Carroll, Ferhana Hahsem, Tracy Pellat-Higgins, Eirini Saloniki

The annual meeting includes a half-day session focussed on sharing and developing research activity, as well as a free papers session for members to showcase their work in the format of a five-minute assessed oral presentation. This will take place again next year 2023 as we intend to host this meeting face to face.

The HCPA encourages collaboration and members continue to initiate, present and publish key papers on an international level. Melanie Bladen was invited to join the International Prophylaxis Study Group (the IPSG), a collaborative group of health care professionals involved with the assessment and care of individuals with inherited bleeding disorders, which is currently exploring the utility and modification of the Haemophilia Joint Health Score (HJHS) this is ongoing.

At EAHAD in February 2022, despite the challenges faced HCPA members contributed to numerous poster presentations and 5 presentations three of which were in the main programme. In the Physiotherapy SLAM Oral presentation session two of the six abstracts selected were from HCPA members.

- Oral presentation at EAHAD congress, Feb 2022. Stakeholder involvement in the development of a programme theory for a novel physiotherapy intervention for pain management in haemophilia.

Publications in 2021/22:

1. Wells AJ, Whitaker S, Gray D, Mangles S, Hislop-Lennie K, Stephensen D. Pain memories: A new concept to consider in the management of chronic pain in people with haemophilia. Haemophilia. 2022 Mar;28(2):e46-e48. doi: 10.1111/hae.14480. Epub 2021 Dec 24. PMID: 34951513. https://doi.org/10.1111/hae.14480
2. Wilkins R.A, Siddle HJ, Chapman GJ, Horn E, Walwyn R, Redmond AC. UK haemophilia consultant access to foot and ankle services and concurrent patient

impact questionnaire responses to foot and ankle interventions. Haemophilia. 2022 Jul 13. doi: 10.1111/hae.14625. Epub ahead of print. PMID: 35830681.

3. Wilkins, R.A., Chapman, L.S., Emmel, J.C., Flannery, T., Chapman, G.J., Walwyn, R.E., Redmond, A.C. and Siddle, H.J., 2022. A systematic review and narrative synthesis of footwear and orthotic devices used in the management of ankle haemarthrosis and haemarthropathy in haemophilia. *Haemophilia*, *28*(3), pp.422-436.

4. Wilkins, R.A., Stephensen, D., Siddle, H., Scott, M.J., Xiang, H., Horn, E., Palmer, B., Chapman, G.J., Richards, M., Walwyn, R. and Redmond, A., 2022. Twelve-month prevalence of haemarthrosis and joint disease using the Haemophilia Joint Health score: evaluation of the UK National Haemophilia Database and Haemtrack patient reported data: an observational study. *BMJ open*, *12*(1), p.e052358.
5. Talbott, H.G., Wilkins, R.A., Redmond, A.C., Brockett, C.L. and Mengoni, M., 2021. Morphological variation of the hemophilic talus. *Clinical Anatomy*, *34*(6), pp.941-947.
6. Talbott, H.G., Wilkins, R.A., Redmond, A.C., Brockett, C.L. and Mengoni, M., 2022. The relationship between subchondral bone cysts and cartilage health in the Tibiotalar joint: A finite element analysis. Clinical Biomechanics, p.105745.
7. Khair K, Holland M, Dodgson S, McLaughlin P, Fletcher S, Christie D. Fitness enhances psychosocial well-being and self-confidence in young men with hemophilia: Results from Project GYM. Research and Practice in Thrombosis and Haemostasis. 2021;5(8):e12622.
8. McLaughlin P, Holland M, Dodgson S, Khair K. Project GYM: A randomized feasibility study investigating effect on motivation of personal trainer-led exercise in young men with hemophilia. Research and Practice in Thrombosis and Haemostasis. 2021;5(8):e12613.
9. McLaughlin P, Hurley M, Chowdary P, Stephensen D, Khair K. The experiences and beliefs of people with severe haemophilia and healthcare professionals on pain management, and their views of using exercise as an aspect of intervention: a qualitative study. Disability and Rehabilitation. 2021:1-9.
10. McLaughlin P, Hurley M, Chowdary P, Stephensen D, Khair K. How does a lifetime of painful experiences influence sensations and beliefs about pain in adults with severe haemophilia? A qualitative study. Disability and Rehabilitation. 2021:1-8.
11. Lobet S, Timmer M, Königs C, Stephensen D, McLaughlin P, Duport G, et al. The Role of Physiotherapy in the New Treatment Landscape for Haemophilia. Journal of Clinical Medicine. 2021;10(13):2822.
12. Kleijn P, Duport G, Jansone K, Marinić M, McLaughlin P, Noone D, et al. European principles of care for physiotherapy provision for persons with inherited bleeding disorders: Perspectives of physiotherapists and patients. Haemophilia. 2022.
13. St-Louis J, Abad A, Funk S, Tilak M, Classey S, Zourikian N, McLaughlin P et al. The Hemophilia Joint Health Score version 2.1 Validation in Adult Patients Study: A multicenter international study. Res Pract Thromb Haemost. 2022;6(2):e12690.
14. Matlary RED, Grinda N, Sayers F, Versloot O, McLaughlin P. Promoting physical activity for people with haemophilia in the age of new treatments. Haemophilia. 2022.
15. Taylor S, David J, Partington K, Pemberton S, Mangles S, Wells A, Curry N. A single centre, open label, pilot study evaluating the effect of intra-articular hyaluronic acid injection on pain and functionality when injected into the ankle (tibio-talar and sub-talar) joint in patients with haemophilic arthropathy. Haemophilia. 2022 Jul 29. doi: 10.1111/hae.14639. Epub ahead of print. PMID: 35905300.
16. Taylor S, Pemberton S, Barker K. Validity of the four-square step test in persons with haemophilia. Haemophilia. 2022 Mar;28(2):334-342. doi: 10.1111/hae.14482. Epub 2022 Jan 12. PMID: 35020243.
17. Berntorp E, Fischer K, Hart DP, Mancuso ME, Stephensen D, Shapiro AD, Blanchette V. Haemophilia. Nat Rev Dis Primers. 2021 Jun 24;7(1):45.
18. Minno MNDD, Martinoli C, Pasta G, la Corte-Rodriguez H, Samy I, Stephensen D, Timmer MA, Winburn I. How to assess, detect, and manage joint involvement in the era of

transformational therapies: Role of point-of-care ultrasound. Haemophilia. 2022 Sep 26. doi: 10.1111/hae.14657.

Awards

- PhD, Wilkins, R.A., 2021. Haemarthrosis of the ankle in haemophilia A and B: prevalence, impact and intervention (Doctoral dissertation, University of Leeds), https://etheses.whiterose.ac.uk/29745/
- NIHR Development and Skills Enhancement award (clinical trials) 2021
- Paul McLaughlin 2022 - British Society Haematology/ NIHR Researcher of the year (AHP/Nursing category).

Peer Review 2023

HCPA members have volunteered to take part in the next peer review of haemophilia services across the UK. Many members wish to take part in this to promote the benefits of the physiotherapist as a active member of the haemophilia MDT.

Project Phoenix

Haemnet running 'Project Phoenix' – looking at service provision & keen to work with us to overcome barriers in places where we are struggling with physio provision. Results released at EAHAD 2022, HCPA physiotherapists involved in this process.

Gene Therapy Working Party

HCPA members (David Hopper & Stephen Classey) have also been involved in the gene therapy working party alongside the UKHCDO. This work is ongoing and due to be finalised at the end of 2022.

EAHAD 2023

At the AGM in June 2022 the committee were encourage attendance and abstracts submissions to next year's EAHAD.

WFH Comprehensive Care Summit 2023

At the AGM in June 2022 the committee were encourage attendance and abstracts submissions to next year's WFH event.

HCPA Meetings

- June 2022 AGM and Educational meeting
- Northern Physiotherapy Group – Monthly CPD sessions 2022 and Northern face to face meeting September 2022.
- Southern Physiotherapy Group – Monthly CPD sessions 2021

Future Meetings

- April 2023 – HCPA AGM (Face to Face)

UK Standards of Care

- http://www.ukhcdo.org/wp-content/uploads/2020/06/2020v1-Children-Service-Provision-of-Physiotherpay-in-Haemophilia.pdf
- http://www.ukhcdo.org/wp-content/uploads/2020/06/2020v1-Adult-Service-Provision-of-Physiotherapy-in-Haemophilia.pdf

HCPA Constitution

- http://www.ukhcdo.org/wp-content/uploads/2019/01/FINAL_HCPA_Constitution.pdf

David Hopper,
Chair, Haemophilia Chartered Physiotherapists' Association
November 2022

22. British Society for Haematology Haemostasis & Thrombosis Task Force

Membership

Dr Keith Gomez	Chair
Dr Will Lester	Vice-Chair
Dr Ian Jennings	UK NEQAS representative
Dr Stella Williams	NIBSC representative
Dr Karen Breen	
Dr Lara Roberts	
Dr Jayashree Motwani	
Dr Deepa Arachillage	
Dr Julia Anderson	UKHCDO representative
Mr Sean Platton	
Mr Peter Baker	
Dr Renu Riat	
Dr Khalid Saja	

Meetings

T Dr Gomez chairs the BSH H&T Task Force, and Dr Lester is Vice-Chair. The Task Force met on 25 January 2022, 22 April 2022, 8 July, 2022, 10 October 2022.

UKHCDO Guidelines and other publications published 2021/2022

Laboratory coagulation tests and recombinant porcine factor VIII: A United Kingdom Haemophilia Centre Doctors' Organisation guideline. A Bowyer, E Gray, P Murphy et al. Haemophilia 2022 May 28 (3) 515-519

Twelve month prevalence of haemarthrosis and joint disease using the Haemophilia Joint Health Score: evaluation of the UK National Haemophilia Database and Haemtrack patient reported data: an observational study. R Wilkins, D Stephensen, M Scott et al.

Immune tolerance induction in severe haemophilia A: A UKHCDO inhibitor and paediatric working party consensus update. D Hart, J Alamelu, N Bhatnagar, et al. Haemophilia 2021 Nov;27(6):932-937

Factor VIII/IX inhibitor testing practices in the United Kingdom: Results of a UKHCDO and UK NEQAS national survey. P Batty, A Riddell, S Kitchen et al. Haemophilia 2021 May 27 (3) 490 – 499

BSH Guidelines Published 2021/2022

Haematological evaluation of bruising and bleeding in children undergoing child protection investigation for possible physical maltreatment: A British Society for Haematology Good Practice Paper. T Biss, K Sibson, P Baker et al. B J Haem 2022 Oct; 199(1) 45-53

Guidelines in Preparation

The laboratory diagnosis of von Willebrand disease (Joint BSH/UKHCDO guideline, writing group chair: Mr Sean Platton)

Diagnosis and Management of Acquired Coagulation Inihibitors (Joint BSH/UKHCDO guideline, writing group chair: Dr C Percy)

Guidance on the Dental Management of Patients with Haemophilia and Congenital Bleeding Disorders (UKHCDO guideline, chair Dr J Anderson)

Guidance on the Management of Patients with Congenital Bleeding Disorders in Emergency Medicine (UKHCDO guideline, chair Dr E Horn)

Dr Julia A M Anderson
UKHCDO Representative for BSH Haemostasis & Thrombosis Task Force
November 2022

23. Haemophilia Society

The last financial year has been a year of change and progress. The Haemophilia Society went through an important re-branding exercise – the first in over 70 years. This enables us to market ourselves in a more modern way to our community and beyond. We remain very much the bleeding disorder community's organisation and this is encapsulated in our new mantra "together for life".

As we emerged into a post -pandemic world we have been able to hold more in person events. Our first Talking Red Live event- postponed from 2020 – for women with bleeding disorders was held in York in March 2022. Regular events such as Youth Camp and Newly Diagnosed Weekends have returned and we are grateful to the doctors, nurses, physiotherapists, psychiatrists, play specialists and other volunteers who give up their time to help make these events so successful. We have created new events such as Haemfest, a weekend of camping with activities for all ages.

Our work on supporting innovations in treatment and diagnosis continues. We launched a unique symptom checker, designed to help women and girls understand the signs of a bleeding disorder and encourage them to seek specialist medical advice if needed. The campaign was seen online by over 111,000 people and received national media coverage. We move ever closer to the licensing of gene therapy and continue to monitor the safety of such products whilst working with the NHS to ensure payment models are in place when these products come to market.

Five years after the Infected Blood Inquiry was announced, the end of the hearings is in sight with the report due in the middle of 2023. It has undoubtedly taken longer than expected and taken a great toll on many people involved. At the time of writing, the interim compensation of £100,000 announced by government in August is due to be paid to all those currently registered on support schemes. In the years ahead we need to ensure that all those infected and affected receive full and fair compensation.

We are living in uncertain and volatile times. The demand for our support and services has never been higher but we face some of the most challenging fundraising conditions in our history. We need to ensure that the Haemophilia Society can survive and thrive to support the next generation of the bleeding disorder community. Thank you to the UKHCDO for all your support.

Kate Burt,
CEO, The Haemophilia Society
October 2022

The Haemophilia Society

24. NHD technical development

The National Haemophilia Database (NHD) is currently undergoing an organisational IT transformation project. The project encompasses all aspects of the running of the organisation. Including staffing, operational and database IT systems. Once complete the project will ensure the NHD is fit for purpose for many years to come.

Hosting

In recent years there has been a move to the provision and adoption of cloud hosting across organisations. This offers multiple benefits for organisations, including performance, reliability, scalability and stability.

A considerable amount of work has been undertaken and completed to migrate the entire organisational IT infrastructure to an Azure cloud hosting environment. An important element in the move to this approach has been to maintain security standards for patient data. This has been achieved by encapsulating patient data within the NHS Health and Social Care Network (HSCN) which is not accessible from the Internet.

Haemophilia Clinical Information System (HCIS)

The HCIS system has bean successfully operating throughout UK haemophilia centres since 1998 providing operational support for haemophilia centres and providing the NHD with its main source of data. Throughout this time it has undergone numerous revisions and updates, with the most recent being the development of a new version of HCIS designed and built in new technology to facilitate easier updates and closer alignment with the NHD dataset.

The new version of HCIS is currently ready for rollout to centres and we would ask centres to support us with this process whilst working with local IT departments to implement the necessary IT requirements for the upgrade.

Haemtrack

The Haemtrack system has had over 2.3 million entries recorded by patients onto the system. Currently there are phone Apps (iPhone and Android) and a website version of Haemtrack. We will soon be introducing a new version of Haemtrack that will operate on a single platform for all devices. This will simplify the ongoing management of the system and the ability to add any future updates to the data collection. This new version has been subject to extensive user consultation to ensure that it meets the needs of all stakeholders.

Before go-live of the system there will be a communications plan to guide all stakeholders as to the requirements and timing of the implementation. Ultimately this will see the withdrawal of the current natively installed patient apps.

National Haemophilia Database

The NHD administrative and analysis functions are also being re-developed as part of the IT re-development process. The main aim is to simplify the management of core functions for NHD and haemophilia centres. These include data capture, validation and data chasing, together with research, audit, surveillance and data supply.

The finished solution will see increased automation of currently manual validation to reduce the burden required to carry this out and improve accuracy of data collected. The datasets of NHD and haemophilia centres will also be more closely linked, with improved connectivity between all the systems in the UK Haemophilia IT Strategy. This will result in better visibility to centres of data held by NHD, again helping to improve the overall accuracy of information within centres.

Dr Rob Hollingsworth,

CEO, MDSAS

November 2022