Witness Name: Prof Michael Makris

Statement No.: WITN4033001

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Dated: 20 October 2020

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF PROFESSOR MICHAEL MAKRIS

I provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 19 June 2020

I, Professor Michael Makris, will say as follows: -

Section 1: Introduction

1. Please set out your name, address, date of birth and professional qualifications.

1.1. My name is Michael Makris and my professional address is Department of Haematology, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF. My date of birth is GRO-C 1959. My professional qualifications are MB BS, MA, MD, FRCP, FRCPath.

2. Please set out your employment history including the various roles and responsibilities that you have held throughout your career, as well as the dates. In particular please set out the dates when you were director of the Sheffield Haemophilia and Thrombosis Centre.

2.1 1984-1985 House Officer, The London Hospital and Oldchurch Hospital, London (Whilst a house officer at The London Hospital I covered the Haematology patients as well as medicine)

1985-1987 Senior House Officer in Medicine, Morriston Hospital, Swansea (For six months as a Senior House Officer, the rotation was with Haematology)

1987-1989 Registrar in Haematology, Royal Hallamshire Hospital, Sheffield

1989-1994 Lecturer in Haematology, University of Sheffield (During this time, I spent 6 months at the Sheffield Children's Hospital and 6 months at the Regional Transfusion Centre)

1994-2002 Senior Lecturer in Haematology, University of Sheffield

2002-2012 Reader in Haematology, University of Sheffield

2013-todate (current role) Professor of Haematology, University of Sheffield

1994-todate (current role) Honorary Consultant Haematologist, Sheffield Teaching Hospitals NHS Trust (For a period of approximately 3-5 years around 20 years ago, I did some of the Haemophilia on-call cover at the Sheffield Children's Hospital)

2000-2018 Director of the Sheffield Haemophilia and Thrombosis Centre

3. Please set out your membership, past or present, of any committees, associations, parties, societies or groups relevant to the Inquiry's Terms of Reference, including the dates of your membership and the nature of your involvement.

3.1 Royal Hallamshire Hospital Transfusion Committee 1997-2003
UKHCDO Transfusion Transmitted Disease working group member 1998-2003
UKHCDO Advisory committee member 1998-2018
UKHCDO Morbidity and Mortality working party chairman 2009-2012
UKHCDO Data Management Working group member 2009-2012
UKHCDO Comorbidities Working Party Member 2019-ongoing
EUHASS co-ordinator since 2008
World Federation of Hemophilia (WFH), Coagulation Product Safety, Supply and Access Committee (CPSSAC) member since 2017
EAHAD executive committee member 2016-2022, President 2018-2020
EHC Medical Advisory Group member 2013-2020, Chairman 2020+,

(EUHASS is the European Haemophilia Safety Surveillance System and was set up under the auspices of the European Association for Haemophilia and Allied Disorders [EAHAD] and the European Haemophilia Consortium [EHC] in 2008.

4. Please confirm whether you have provided evidence to, or have been involved in, any other inquiries, investigations, criminal or civil litigation in relation to human immunodeficiency virus ("HIV") and/or hepatitis B virus ("HBV") and/or hepatitis C virus ("HCV") infections and/or variant Creutzfeldt-Jakob disease ("vCJD") in blood and/or blood products. Please provide details of your involvement. Please also provide copies of any statements or accounts that you provided to the inquiries etc., if you are still in possession of such statements.

4.1 Department of Health Ministerial Contaminated Blood Review working party member 2010. See answer to question 120. I was representing the UKHCDO (together with Professor Charles Hay) on the Expert Working Group on the Natural History of Hepatitis C. My role was to comment on a document written by the Advisory Group on Hepatitis (which I did not belong to).

Section 2: Decisions and actions of those treating patients with haemophilia at the Royal Hallamshire Hospital

5. Please describe the roles, functions and responsibilities of the Sheffield Haemophilia and Thrombosis Centre at the Royal Hallamshire Hospital ("the Centre") during the time that you have worked there and how they have changed over time.

5.1 The Sheffield Haemophilia and Thrombosis Centre provides 24/7 care to the population of South Yorkshire. There is a dedicated small centre at the Royal Hallamshire Hospital which is part of the Sheffield Teaching Hospitals NHS Foundation Trust (STHFT). It is an adult only haemophilia centre and children are cared for at the Sheffield Children's Hospital (SCH) which is a separate hospital and Trust, located close to the Royal Hallamshire Hospital. The current consultant medical staff are five individuals working for 3.8 Whole Time Equivalent (WTE) contracts. There is also a team of 4.6 WTE nurses. Patients with haemophilia have their care transferred to the adult centre from the Children's Hospital between the ages of 16 and 18 years, and they remain under the care of the adult haemophilia centre thereafter.

5.2 Because the maternity service in Sheffield is part of adult health care services (STHFT), the haemophilia team participate in the care of pregnant haemophilia carriers by providing combined obstetric haematology clinics and in the care of new-born babies with haemophilia, until their discharge within a few days of their birth.

5.3 Care of newborn babies by neonatal services access support from specialist paediatricians at SCH, as well as from clinicians at STHFT. Haematology consultants at SCH are therefore asked for advice regarding the management of neonates who are being cared for at STHFT. Guidelines for the care of neonates with bleeding disorders were jointly authored by adult and paediatric haematologists from STHFT and SCH.

5.4 We provide all the services expected from a comprehensive care haemophilia centre including support for home treatment, home delivery of concentrates, support for surgery, clinic reviews etc. Prophylactic treatment by the patients at home is standard of care at our centre. We participate in clinical trials of new haemophilia therapies including gene therapy.

5.5 We have a state of the art haemophilia coagulation laboratory, as well as dedicated physiotherapy and social work support. All medical services (except liver and cardiac transplantation) are provided by the Trust which has two large hospitals, the Royal Hallamshire and Northern General Hospitals.

5.6 Two of the current consultants and two of the nurses have worked at the haemophilia centre for more than 30 years each.

5.7 As expected, the service evolved over the years. When I started in July 1987 as a general haematology trainee, although the name of the Sheffield Haemophilia Centre existed, this was a virtual rather than a physical entity. Patients were seen and clinics were held on the haematology ward (Ward P2). There was one nurse, Sister Joy Farnsworth, and haemophilia care was delivered and overseen by two haematology consultants who specialised in haemostasis and thrombosis. Professor Eric Preston was the Director of the Haemophilia Centre and was the consultant in charge of haemophilia. Dr Mike Greaves covered haemophilia when Professor Preston was not available, but otherwise concentrated on thrombosis and general haematology. There were no junior staff dedicated to haemophilia but the team of haematology juniors covered the service in the same way as they covered the patients with leukaemia.

6. Please identify senior colleagues and the roles and responsibilities that they had during the time that you have worked at the Centre.

Doctors

6.1 The Haemophilia Centre Director from the late 1970s until 2000 when he retired, was Professor Eric Preston.

6.2 During the 1980s and early 1990s the second haematologist specialising in haemostasis and thrombosis was Professor Mike Greaves. Although they cross-covered, Professor Preston was responsible for haemophilia and Professor Greaves for thrombosis and general haematology.

6.3 Dr Kingsley Hampton started as a trainee haematologist in Sheffield in August 1989 and after a brief time as Haemophilia Centre Director in Cardiff in the mid-1990s, he returned to Sheffield in May 1996 as a consultant in Haemostasis and Thrombosis, a position he still holds in 2020.

Nurses

6.4 Sister Joy Farnsworth who is still working in the Haemophilia Centre, has been the senior haemophilia nurse since November 1985.

6.5 Sister Caryl Lockley, our other senior haemophilia nurse and who is still working as a haemophilia nurse, joined our team in November 1990.

7. *Please* describe your role and responsibilities at the Centre and how those have changed over the years.

7.1 I started in Sheffield as a junior doctor (Haematology Registrar) in July 1987, intending to specialise in the treatment of leukaemia and bone marrow transplantation. Soon after I started, one of the other haematology registrars who was in charge of a clinical trial that was about to commence (liver biopsy interferon trial in haemophilia) moved to Australia and I was asked to be responsible for the trial. This was a parallel activity whilst training and working

as a haematology registrar. After 2-3 years I was appointed as lecturer at the University of Sheffield, which allowed me to undertake more research whilst continuing my clinical training.

7.2 The research was directed by Professor Preston who was my supervisor. Professor Preston had an international reputation in haemophilia and I felt he would be a good supervisor.

7.3 The haematology training was mainly at the Royal Hallamshire Hospital, but in the early 1990s I spent 6 months at the Sheffield Children's Hospital training in paediatric haematology and 3-6 months at the Regional Centre in Longley Lane Sheffield, training in Blood Transfusion.

7.4 I became a Senior Lecturer at the University of Sheffield and Honorary Consultant Haematologist in December 1994. My role was caring for patients with bleeding and thrombotic problems.

7.5 In 2000 Professor Preston retired and I took over as Director of the Sheffield Haemophilia and Thrombosis Centre.

7.6 In 2018 the position of Director of the Centre was taken over by a consultant colleague, Dr Rhona Maclean.

7.7 I am currently working 50% for the University of Sheffield and 50% for the NHS clinical service, covering haemostasis and thrombosis.

8. Approximately how many individuals with bleeding disorders were under the care of the Centre when you first started working there and over the years that followed? Approximately what proportion were adults and what proportion were children? (If you are able to give exact rather than approximate figures, please do so).

8.1 Following a direct request, the National Haemophilia Database (NHD) staff have indicated that 1814 patients with inherited bleeding disorders were registered from Sheffield Adult Haemophilia Centre during the period of 1987-2019.

8.2 The earliest Sheffield registration data I found held at our centre are from 2005 and I have also included the most recent 2020 data as well. The 1987 data by diagnosis were provided by the NHD.

8.3 The Sheffield Haemophilia Centre based at the Royal Hallamshire Hospital cares only for adult patients. Children with haemophilia are cared for at the Sheffield Children's Hospital which is an independent organisation.

Diagnosis	1987	2005	2020
Haemophilia A	152	162	236
Haemophilia A carrier	2	74	140
Haemophili B	28	27	34
Haemophilia B carrier	6	16	24

Von Willebrand disease	60	303	603
Factor V deficiency	0	23	32
Factor VII deficiency	0	22	66
Factor X deficiency	1	17	32
Factor XI deficiency	1	85	262
Fibrinogen disorders	0	4	41

9. *To the best of your knowledge, what responsibility did the Centre have for the selection and purchase of blood products (in particular factor concentrates)? What policies were formulated and what decisions were taken as to which products to purchase and use? In addressing these issues, please answer the following questions:*
a. How, and on what basis, were decisions made about the selection and purchase of blood products?
b. What particular products were used for treating patients at the Centre, over what period of time and for which categories of patients?
c. What were the reasons or considerations that led to the choice of one product over another?
d. Where were products used at the Centre sourced?
e. What role did commercial and/or financial considerations play?
f. What was your involvement in this process?
g. What involvement did other clinicians at the Centre have in making these decisions?

9.1 I have only been involved in selection of products for our haemophilia patients since I have been the Centre director in 2000. I had no involvement in product selection whilst I was a trainee haematologist during 1987-1994. Even after I became an honorary consultant, I do not believe I was involved in the process, until I became the Director of the Haemophilia Centre.

9.2 I will answer your specific questions first and then provide some information about local practice before and after the time I became centre director.

9.3 a) I do not know before 1995, other than patients were kept on the same product for as long as possible. For decisions after 2000 see below covering the period since I have been the director of the centre.

9.4 b) Both NHS and commercially produced products were used for severe haemophilia A and all haemophilia B. For mild haemophilia A and for von Willebrand disease desmopressin was primarily used.

9.5 c) I do not know why initial decisions were made but patients were changed when a product was no longer being manufactured or when a purer or a recombinant product was introduced.

9.6 d) Both NHS and commercially produced concentrates were used

9.7 e) I do not believe these played a significant role directly at the local level. We were directed by the Department of Health centrally about what products we could use.

9.8 f) No involvement in purchasing of products before 2000. After 2000 decisions were made by the centre multidisciplinary team.

9.9 g) Prior to 2000 the centre director was responsible, and I am not aware of any other clinicians being involved. After 2000 all haemophilia consultants had the same input as the issues were discussed at the multidisciplinary meetings.

The time when Professor Preston was the centre director (1974-1999)

9.10 I am aware of some principles that the previous Director, Professor Preston, held and used because he told us many times. He always insisted on "not putting all the eggs in one basket" in case something happened with the supply chain. Throughout my time in Sheffield, multiple products were used at the same time (although individual patients were kept on the same concentrate, and the same "batch" for as long as possible to minimise exposure to different blood donations). Professor Preston was one of the early adopters of the use of desmopressin (DDAVP) in patients with mild haemophilia A and von Willebrand disease, but I do not know precisely when this was introduced in Sheffield. In a letter to the Lancet in 1982, Professor Preston mentioned that the liver biopsy he was reporting on was covered with desmopressin, so the introduction was by 1982 at the latest.

9.11 By 1987 when I started in Sheffield, desmopressin was widely used. Professor Preston also believed that heat treatment of blood products was the answer to the HIV and NANB hepatitis problem and introduced them early. Unfortunately, non-A, non-B hepatitis was not eliminated by the first two heat treated products that were introduced in the UK and used in Sheffield.

9.12 In a publication in the Lancet in July 1985 Professor Preston described three patients from Sheffield who received "Armour Factorate" heat treated (dry heat 60°C for 32 hours) FVIII concentrate. Although this was shown to be effective in not transmitting non-A, non-B hepatitis to chimpanzees, two of the three Sheffield patients developed acute hepatitis within 4 weeks of exposure and became ill with it – one requiring hospital admission. The reference to the paper is:
Preston FE, Hay CRM, Dewar MS, Greaves M, Triger DR. Non-A, non-B hepatitis and heat-treated factor VIII concentrates. The Lancet 1985; ii: 213

9.13 In a second publication in the Lancet in September 1985, Kernoff described the initial results of wet heat treatment (wet heat 60°C for 20 hours) of concentrates using a product called "Profilate Heat Treated" from Alpha Therapeutics. This was an ongoing study from Sheffield, London and a centre in Italy. The report was on the first 18 patients treated and 4 who received the same batch of FVIII, developed non-A, non-B hepatitis. The reference to the paper is:
Kernoff PBA, Miller EJ, Savidge GF, Machin SJ, Dewar MS, Preston FE. Wet heating for safer factor VIII concentrate? The Lancet 1985; ii:721

The final results of this study were published in 1987. The total number enrolled was 18 with 5 developing non-A, non-B hepatitis. The final reference is:
Kernoff PBA, Miller EJ, Savidge GF, Machin SJ, Dewar MS, Preston FE. Reduced risk of non-A, non-B hepatitis after a first exposure to "wet heated" factor VIII concentrate. British Journal of Haematology 1987; 67: 207-211

9.14 In the early 1990s there were some publications suggesting that the CD4 count of HIV positive patients with haemophilia remained stable if they were using monoclonally purified FVIII rather than intermediate purity concentrates, so HIV positive patients were switched to these products.

The time after I was the centre director (2000)

9.15 I was ultimately responsible for product selection and usage when I took over as Centre Director in 2000 but several factors meant that the decision on product selection was not left to a single individual. The consultant body introduced weekly haemophilia multidisciplinary team meetings (with all the consultants, the haemophilia clinical nurse specialists, social worker, physiotherapist and junior doctors) to discuss patients and make policy decisions. Although initially these were not minuted, over time these became more formalised with minutes recorded for every meeting. The other major change that took place was the introduction of national tendering. The result was that we are told which products to use, and what quantities of each product to use. Sometimes as a result of the process we had to change products for patients, but we always had a discussion with the patients as to why this was being done and most were happy to change. All the medical and nursing staff in Sheffield shared the opinion that there was no difference in terms of efficacy or safety between the different recombinant FVIII and FIX products. Where a patient expressed a concern regarding a product switch, this was documented and discussed at the weekly multidisciplinary team meeting. No patient was forced to switch product if they had concerns.

9.16 More recently with the introduction of extended half-life (EHL) products, there was again a choice but, in our view, no significant difference in efficacy or safety between the different (EHL) products. Since we did not believe there was a difference, patients who did not express a preference were changed alternately to different products.

10. What, if any, was the relationship between the Centre and the pharmaceutical companies manufacturing/supplying blood products? What influence did that relationship have on the Centre's decisions and actions?

10.1 There was no relationship between the Centre and the Pharmaceutical companies which would influence product selection and certainly not since I have been Director of the Centre.

11. If the responsibility for the selection and purchase of blood products lay with an organisation other than the Centre, please specify which organisation and provide as much information as you can about its decision-making.

11.1 The UK started national tenders around 15-20 years ago for coagulation factor concentrates and the result was that we were allocated volumes of different concentrates to use. The UKHCDO which was involved in the negotiations with the national authorities, informed us of the decisions on volumes of products we had to use, as this was based on the number of patients we had registered and the volume of products our patients were using. We tried to maintain patients on the same product for as long as possible. Where a change was necessary, we saw the patients, explained the reason for the change, and if they agreed we documented the discussion and change in the medical notes. No switch was undertaken where the patient did not consent to a switch.

12. How were decisions taken as to which products to use for particular patients? What role did you have in such decisions? Were patients given any choice or involved in any discussions as to which products to receive?

12.1 We tried to keep patients on the same product for as long as possible. When a patient was one of a group that needed to change, they were seen by one of the haemophilia consultants and we explained the process. The decision was documented in the notes. On rare occasions when patients did not wish to change, we accepted the patient's wish as long as the product was still sold in the UK, which was not always the case.

13. What alternative treatments to factor concentrates were available for people with bleeding disorders?

13.1 The alternative treatments would have been:
a) Desmopressin
b) Fresh frozen plasma
c) Cryoprecipitate
d) Tranexamic acid

14. What were, in your view, the advantages and disadvantages of those alternative treatments? What use was made of them at the Centre? Do you consider that they should have been used in preference to factor concentrates so as to reduce the risk of infection. If not, why?

Desmopressin

14.1 The main advantage of desmopressin (DDAVP) is that it is not a blood product and is effective in mild haemophilia A, in mild and moderate von Willebrand disease and in patients with mild platelet function disorders. It is ineffective in severe haemophilia A and in haemophilia B of any severity.

14.2 The disadvantages are that in the period from the early 1980s to around 2005 it could only be used intravenously, and many patients developed headaches and facial flushing. It causes fluid retention so fluid restriction is required and

also if given daily for more than 3-4 days it stops being very effective (tachyphylaxis). Due to reports of myocardial infarction associated with its use, it is avoided in patients with uncontrolled hypertension, those with heart disease and in the elderly. It can cause hyponatraemia due to water retention and seizures should that occur, therefore care must be taken in patients with electrolyte dysfunction and young children.

Fresh frozen plasma

14.3 The main advantage is that each unit is made from one blood donation, so a recipient is exposed to a very small number of donors. Normally 4 units would be infused which would mean 4 donor exposures, in contrast to concentrates where 20,000 donor exposure with the use of a single vial of concentrate was possible. Because fresh frozen plasma is not fractionated, it contains all the clotting factors but in a very dilute form so it will in theory be effective in haemophilia A and B as well as in von Willebrand disease if sufficient volume is given.

14.4 The main disadvantages are that a large volume of fluid would need to be given, it would need to be administered in hospital and some patients develop allergic reactions to it. In practice it is less effective than other treatments as the volume of plasma required to be given to normalise factor VIII or IX levels, or von Willebrand factor is very significant, and usually precludes its use due to the risk of fluid overload. It is not usually virally inactivated, although virally inactivated forms are available (eg Octaplas). In patients with inherited bleeding disorders in the UK, virally inactivated fresh frozen plasma is used whenever feasible.

Cryoprecipitate

14.4 This is prepared from blood donations and each unit of cryoprecipitate is a small volume containing concentrated FVIII and von Willebrand factor but not factor IX. Normally 10 units are given at the time resulting in only 10 donor exposures.

14.5 The disadvantages are that it has to be given in hospital, it has to be infused rather than injected and allergic reactions can result. For patients requiring surgery the number of bags of cryoprecipitate required could be rather high. It is not usually virally inactivated.

Tranexamic acid

14.6 This is a chemical drug not derived from blood. It will not stop a joint or muscle bleed, but it is good as an adjunct for stopping gum bleeding after dental extractions, and to help in the management of other mucosal bleeding such as menorrhagia and epistaxis.

14.7 As I have indicated elsewhere, by the time I started in Sheffield in 1987, safe virally inactivated clotting factor concentrates (both FVIII and FIX) were available and in my opinion in 1987, it was better to use the virally inactivated concentrates rather than fresh frozen plasma or cryoprecipitate (which were not virally inactivated). In 1987, however, as a junior doctor I had no input in what product was to be used to treat each patient.

14.8 By 1987, desmopressin (DDAVP) was widely used for mild haemophilia and von Willebrand disease (type 1 and some type 2 where the patients responded to DDAVP) and for these patients it was used in preference to concentrate. Tranexamic was widely used but is rarely effective when used in isolation, so it rarely would have replaced concentrates.

14.9 I do not know when DDAVP was introduced to haemophilia treatment in Sheffield, but it must have been in 1982 or earlier as its use was reported in a publication from Sheffield that year. DDAVP use rather than non-virally inactivated clotting factor concentrates clearly eliminated any infection risk.

14.10 I am aware that some centres, especially paediatric ones used cryoprecipitate rather than non-virally inactivated FVIII concentrate to reduce the infection risk. I do not know how widespread this practice was and I do not know how systematic it was. I have no information on cryoprecipitate use at the Centre. It was not used to treat haemophilia A when I started in 1987.

15. What was the Centre's policy and approach as regards the use of cryoprecipitate for the treatment of individuals with bleeding disorders? How did that policy and approach change over time?

For patients with haemophilia A or von Willebrand disease

15.1 I started in Sheffield as a junior doctor in 1987 and by that time safe virally inactivated concentrates were available. During my time in Sheffield only virally inactivated FVIII has been used and cryoprecipitate was not used to treat patients with haemophilia or von Willebrand disease.

15.2 I do not know what the policy was in the early 1980s as there was no local written policy, as far as I know.

For patients with fibrinogen disorders

15.3 These patients have traditionally been treated with cryoprecipitate. For the last 5-10 years we have been treating patients with inherited fibrinogen disorders and women with major bleeding during delivery of pregnancy with fibrinogen concentrate. All other patients with acquired reduction in fibrinogen levels are still being treated with cryoprecipitate.

16. What was the Centre's policy and approach in relation to prophylactic treatment? Did that policy and approach change over time and if so how?

16.1 We believe all patients with severe haemophilia will be better off on prophylaxis and this has been offered to all for some years. A small minority of patients continue to make the choice not to start prophylaxis but instead to treat bleeds on demand.

16.2 Prophylaxis in children in the UK started in the early 1990s so most children transferring to us after the age of 16 years were already on prophylaxis and we continued it. For adults the introduction of prophylaxis was more gradual. Three events that contributed to the increased uptake of prophylaxis were:

a) A clinical trial in which we participated. Patients receiving on-demand therapy were prospectively followed for 6 months and then were given 6 months of FVIII prophylaxis three times a week. Whilst on on-demand therapy the median annual bleed rate was 15.0 but when on prophylaxis it was zero. (Collins P. Journal of Thrombosis and Haemostasis 2010; 8:83-89)
b) The introduction of the extended half-life products which meant fewer intravenous injections
c) The introduction of Emicizumab which allows prophylaxis with one subcutaneous injection every two weeks.

17. What was the Centre's policy and approach in relation to home treatment? Did that policy and approach change over time and if so how?

17.1 Home treatment started relatively early in Sheffield. A typed list I located indicates that in March 1980, there were 27 patients with severe haemophilia on home treatment.

17.2 Since I started in Sheffield all severe haemophilia patients have been encouraged to start home treatment as early as possible. In practice almost all children transferring from the Sheffield Children's Hospital at the age of 16 years were already on home treatment.

17.3 In the last 20-30 years any patient who required treatment more than a few times a year was trained on home treatment, even if they did not have severe disease according to their baseline clotting factor level.

18. If children were treated at the Centre, what was the Centre's policy and approach in relation to the use of factor concentrates for children? Did that policy and approach change over time and if so how?

18.1 The Centre does not treat children.

19. To what extent, and why, were people with mild or moderate bleeding disorders treated at the Centre with factor concentrates?

19.1 This question largely applies to haemophilia A and von Willebrand disease which can be treated with desmopressin, since for haemophilia B there is no real alternative to concentrate. For haemophilia B the decision was whether or not to treat a bleed, and if to treat, or to cover surgery, whether to use FIX concentrate or FFP (which requires a very large volume of intravenous fluid).

19.2 If a patient with non-severe haemophilia A or von Willebrand disease had a bleed that required treatment, or required surgery or an interventional procedure, the reasons for using concentrate rather than desmopressin include:

a) They had moderately severe disease. Most patients with levels of <5% rarely respond sufficiently to desmopressin. Even with a 2-5 fold increase in

levels post desmopressin, it is unlikely the coagulation factor levels will get to the lower end of the normal range (i.e. 50%), and that adequate clinical haemostasis will be achieved.

b) They have had a test dose of desmopressin and have achieved an inadequate response

c) They are children less than 2 years of age

d) They have had an adverse reaction to desmopressin

e) It is anticipated the patient will need many days of treatment, such as in the context of major surgery, where desmopressin tachyphylaxis will mean that after 3-4 days it stops working sufficiently well and side effects of treatment will be troublesome (ie hyponatraemia)

f) Some variants of von Willebrand disease such as types 2A, 2B, 2N, 1 with high clearance where the response will be (or has been demonstrated previously to be) inadequate

g) Patients with ischaemic heart disease or uncontrolled hypertension where desmopressin is considered contraindicated (has been reported to cause myocardial infarction)

h) In the elderly who cannot tolerate fluid retention or restriction

i) Patients treated before the introduction of desmopressin to the UK (in the early 1980s)

j) There was a current or past clinical treatment failure with desmopressin.

19.3 It is our practice in Sheffield that for patients with mild haemophilia and von Willebrand disease, wherever possible, desmopressin is used unless there is a specific reason not to.

19.4 I do not have any information on why this would not have been followed especially during the period before the introduction of viral inactivation of concentrates in 1985.

20. What if any viruses or infections, other than HIV, HCV and HBV, were transmitted to patients at the Centre in consequence of the use of blood products?

20.1 I am not aware of any other viral transmissions. There were no patients with hepatitis D in Sheffield and there were no concentrate related episodes of hepatitis A. Although some patients had hepatitis A antibodies, it was believed that their infection was faeco-oral like in the general population. One patient with Hepatitis E infection was believed to have acquired it in the community as the patient did not receive blood products in the 10 years before the infection.

Section 3: Knowledge of, and response to, risk

General

21. When you began work at the Centre, what did you know and understand about the risks of infection associated with blood and/or blood products? What were the sources of your knowledge? How did that knowledge and understanding develop over time?

21.1 I started in Sheffield in July 1987 and at that stage although the term haemophilia centre was used, there was no actual physical centre. I completed the Membership of the Royal College of Physicians examination just before I started in Sheffield, so I had a good general medicine knowledge. The concept that viruses could be transmitted by non-virally inactivated concentrates was well accepted by the time I started. By reading the literature I was able to remain up to date.

22. What advisory and decision-making structures were in place, or were put in place, at the Centre and/or within the area covered by the Centre, to consider and assess the risks of infection associated with the use of blood and/or blood products?

22.1 By 1987 when I started, the risk of new concentrate transmitted infection was small. There had been no new cases of HIV in haemophilia in Sheffield for at least 2 years at the time. Desmopressin was already widely used and exposure to concentrate was only when considered essential. Patients were kept on the same batch of concentrate for as long as possible; if it was not possible to maintain them on the same batch of product, they were kept on the same brand of product. The intention was to minimise the patient's exposure to different donors wherever possible. Decisions were made regarding the choice of concentrate, and treatment "ethos" (ie to treat with concentrate only when considered essential) was established by the centre director (Professor Preston).

23. What was your understanding of the relative risks of infection from (i) the use of commercially supplied blood products, and (ii) the use of NHS blood products? How did this understanding change over time? How, if at all, did this inform or influence the Centre's decisions as to which blood products to use in treating patients?

23.1 By the time I started in Sheffield the risk of infection through concentrates was the same for both commercial and NHS blood products because the viral inactivation procedures for both types of product were quite effective.

23.2 Through my academic interest in transfusion transmitted infection, I gradually formed an opinion about the infection risk of the commercial (largely US plasma sourced) vs NHS (UK plasma sourced) blood products that were used before viral inactivation in 1985. I believe:

a) The commercial products carried a higher risk of HIV infection than the NHS ones because the rate of infection in the donors was higher in the US commercial donor plasma collection facilities, than in the UK blood donors.

b) For hepatitis C I believe the risk with the commercial products was higher than the NHS ones before 1980 or so, but after this period I am not convinced there was much difference, because the UK donor pools used to manufacture the concentrates were much larger.

23.3 I would like to make two points to explain my opinion on the risk of transmission of infection by concentrates. Firstly, the risk of transmission of infection by a concentrate depends on the prevalence of the relevant chronic infection in the donor population, the viral load of the infected donations and the number of donations that were pooled to make a batch of concentrate. Secondly the risk is reduced if a viral inactivation procedure is used. Both HIV and hepatitis C are sensitive to heat and although the first viral inactivation procedures in 1984 were not as effective, by 1985 these improved significantly hence my view that after effective viral inactivation, there was no difference between commercial and NHS concentrates.

24. What decisions and actions were taken by the Centre and/or by you to minimise or reduce exposure to infection?

24.1 Patients were maintained on the same concentrate for as long as possible and exposure was limited to the same batch of product wherever feasible. If a patient was having surgery only one batch of concentrate was used. Desmopressin was routinely used in patients who responded to it. Patients were treated with concentrate only when felt essential.

Hepatitis

25. When you began work at the Centre, what was your knowledge and understanding of the risks of the transmission of hepatitis (including HBV and NANB hepatitis/HCV) from blood and blood products? What were the sources of your knowledge? How did that knowledge and understanding develop over time?

25.1 Although I was aware that patients with haemophilia, treated with concentrate, were at risk of HIV and NANB hepatitis, I did not appreciate how many patients had NANB hepatitis. I rapidly learned a lot by working in the haematology department in Sheffield, from Professors Preston and Triger as well as from managing patients. Professors Preston (Haematologist) and Triger (Hepatologist) were working on haemophilia and chronic liver disease due to NANB hepatitis for more than 10 years by the time I started in Sheffield.

26. What was your understanding of the nature and severity of the different forms of blood borne viral hepatitis and how did that understanding develop over time?

26.1 I quickly learned after starting in Sheffield that most of the hepatitis was NANB and that HBV, HAV and HDV were not really a major ongoing issue. I was aware that the NANB related liver disease could be serious because:

a) I read the papers by Professor Preston on liver biopsies in patients with haemophilia from Sheffield. Some of the patients had serious liver disease. [Preston FE, et al. Percutaneous liver biopsy and chronic liver disease in haemophiliacs. Lancet 1978; ii:352-354]

b) We were doing quite a few liver biopsies when I started in Sheffield and some patients had evidence of significant liver disease.

c) Soon after starting in Sheffield on a day when I was on call, I admitted a patient with bleeding oesophageal varices and haemophilia A with NANB hepatitis. As a result of the liver disease the veins in the gullet dilate and when one ruptures the patients vomit fresh blood. This is one of the most frightening scenarios you ever encounter as a doctor and I have never forgotten that day.

27. Did you take steps to ensure that patients were informed and educated about the risks of hepatitis? If so, what steps?

27.1 Initially because I was running the interferon trial during 1987-1989, I would talk to patients about what I knew about hepatitis and haemophilia. When I did the haemophilia outpatient clinic I would talk to patients and explain the reasons for treatment. In terms of wider education, I have given lectures on liver disease and haemophilia at national and international meetings organised by the UK Haemophilia Society, the World Federation of Haemophilia and the European Haemophilia Consortium.

28. Please explain your work in relation to investigating antibodies to HCV i n Hepatitis C Antibody and Chronic Liver Disease in Haemophilia: Clinical and Histological correlates, of which you were the lead author, (Seventh Draft, 20 December 1989) based on patients attending the Sheffield Haemophilia Centre [NHBT0000188_137] and Makris et al, Hepatitis C antibody and chronic liver disease in haemophilia, the Lancet 1990 May 12; 335 (8698) 1117-1119 [OXUH0000024_002]. In relation to these papers:

a. Why did you and your colleagues decide to conduct this research?
b. What were your conclusions?
c. How was the paper received by haemophilia clinicians within the United Kingdom?
i. In your opinion, were conclusions given appropriate respect and weight by your peers?
ii. If not, why do you think that was?
iii. What, if any, changes in practice did this work prompt (i) in the practices adopted at the Centre; and (ii) to the extent that it is within your knowledge, elsewhere?

28.1 Please note that the two documents referred to in this question, NHBT0000188_137 and OXUH0000024_002, are the same manuscript. I do

not know if the Seventh Draft was the final manuscript, but it must be close to the final version. Around this time there was often delay between acceptance of a manuscript by a journal and appearance of the paper in print. Sometimes authors sent accepted manuscripts to others who would be interested in the findings.

a) The idea for this study came from Professor Eric Preston. He met some of the researchers from the Chiron corporation at a scientific meeting in Germany and wondered if their new antibody test was the explanation for the cases of NANB hepatitis in haemophilia. He agreed a collaboration with them so that they would test samples from Sheffield patients with inherited bleeding disorders.

b) The conclusions were that 59% of haemophilia patients treated with FVIII or IX concentrate were positive for HCV using the Chiron assay. No patient who did not receive concentrate was positive. HIV positive patients were more likely to be HCV positive, as were patients with previous exposure to HBV. The conclusion was that HCV appeared to be the major factor causing NANB hepatitis. It was not clear why not all NANB hepatitis patients were positive, and possible reasons were either that the test was not sensitive enough or that other, yet unidentified, viruses were responsible for some of the cases.

c) I believe that other clinicians would have become aware that the major cause of NANB hepatitis was HCV. However, it must be appreciated that when this paper was published, I was a junior doctor and did not go to national meetings where other haemophilia doctors would be present and likely to discuss this issue. Also, I did not attend the UKHCDO meetings where data would be discussed, and decisions were being made.

i) I believe the answer was yes, because although the Chiron test was not available, other assays started appearing and the prevalence of hepatitis C in different cohorts started being reported.
ii) I do not know
iii) We already knew that the majority of concentrate treated patients had NANBH and that it was likely one or more viruses were involved, so the findings of this paper were not really that surprising to us. Once a validated test became available on the NHS, patients started to be tested using the validated test.

29. *In the paper The Impact of HIV on Mortality Rates in the Complete UK Haemophilia Population (AIDS 2004, Vol 18 No 3) [PRSE0001165], in relation to which you are listed in the Analysis and Writing Committee, it is noted at p526 that "before the mid-1980s, haemophilia treatment also carried a near certain risk of hepatitis C virus (HCV infection) and the majority of this population, including almost all those with severe haemophilia, were infected." The same paper goes on to note at p527 that "the UKHCDO database indicated that all but 10 of the HIV infected individuals had received very high HCV risk products, as had 895 of the HIV-uninfected individuals with severe haemophilia (92% of those born before 1985) and 2497 of the HIV uninfected individuals born with moderate/mild haemophilia (64% of those born before*

1985). Enquiries at haemophilia treatment centres showed that UKHCDO treatment records were not comprehensive…" Please explain:

a. The degree of involvement that you had in the writing of the paper.
b. When you first became aware that there was a "near certain" risk of transmission of HCV through haemophilia treatment before the mid-1980s. What was the basis for this conclusion?
c. Why treatment records were considered not to be comprehensive and whether and if so how this affects the conclusions drawn in the paper.
d. The main conclusions to be drawn from the paper.

29.1 a) This paper was produced by the Transfusion Transmitted Infection Working Party on behalf of the UKHCDO. The data analysis was carried out by Professor Darby, Dr Kan and Ms Spooner. The rest of the members of the writing committee of the paper (Giangrande, Lee, Makris, Sabin, Watson, Wilde and Winter) were the members of the working party. Professor Sarah Darby was the lead for the project and wrote the first draft of the paper. Professor Lee was the chair of the working party. My own role on this paper involved discussing the work at the working party meetings and revising the manuscript.

29.2 b) Because non-virally inactivated pooled products have donations from thousands of donors, it was inevitable that most pools will be contaminated with HCV positive donations. The problem was exacerbated by the fact that 85% of the HCV antibody positive individuals were PCR positive i.e. had active virus in their blood. As the donors felt very well and had no symptoms and since there was no test for HCV before the early 1990s, these infected donors contributed to the pools of plasma.

29.3 The plasma pools were often made of pools of 20,000-30,000 donations. The prevalence of HCV in the blood donor population in the early 1990s in Sheffield was approximately 1 in 2000 in the Sheffield area but I suspect this prevalence would be dramatically higher in US prisons where some commercial manufacturers collected their plasma from [Weinberg E & Shaw D. Blood on their hands. 2017, Rutgers University Press]. The 1 in 2000 figure for HCV prevalence in Sheffield blood donors was provided to me by Dr Virge James, the Director of the Regional Blood Transfusion Centre in 1995 and I quote it in my paper on the natural history of HCV in haemophilia (Makris et al. British Journal of Haematology 1996; 94:746-752)

29.4 Even with the low prevalence of 1 in 2000 donors being infected, it can be seen that it is inevitable that almost all plasma pools would be contaminated with hepatitis C.

29.5 Furthermore, a study from Oxford reported that 9 out of 9 patients with haemophilia treated with concentrate for the first time developed NANB hepatitis [Fletcher ML, et al. Non-A, Non-B hepatitis after transfusion of FVIII in infrequently treated patients. British Medical Journal 1983; 287:1754-1757].

29.6 In another study from London 19 of 21 patients with haemophilia treated for the first time developed NANB hepatitis. All nine patients who received commercial FVIII and 10 of the 12 who receive UK donor FVIII concentrate developed NANB hepatitis [Kernoff PBA, et al. High risk of non-A, non-B hepatitis after a first exposure to volunteer or commercial clotting factor concentrates: effect of prophylactic immune serum globulin. British Journal of Haematology 1985; 60:469-479].

29.7 It is due to this evidence that I believed that infection was near certain with the first dose of a pooled non-virally inactivated concentrate. It is difficult to say the precise date that I was personally aware of the near certainty of infection after exposure to pooled plasma concentrates but it was in the early 1990s.

29.8 c) I do not know the precise reason this was said. My speculation is that very few haemophilia centres in the UK will have complete data of all the doses of clotting factor concentrate used.

29.9 d) The main conclusions of the paper were the provision of mortality rates for HIV positive haemophilia patients and to show the dramatic fall in this mortality in 1996 after the introduction of Highly Active Antiretroviral Therapy (HAART).

HIV and AIDS

30. When you began work at the Centre, what was your knowledge and understanding of HIV (HTLV-III) and AIDS and in particular of the risks of transmission from blood and blood products? How did your knowledge and understanding develop over time?

30.1 By the time I started in Sheffield in July 1987, the link between HIV and blood products was well established. Knowledge about HIV was developing but the link with non-virally inactivated blood products and the fact that the virus was susceptible to elimination by heat treatment were clear.

31. How and when did you first become aware that there might be an association between AIDS and the use of blood products? If you were clinically involved with the treatment of patients with bleeding disorders at that time, what steps did you then take in light of that awareness?

31.1 I was aware of the transmission of HIV by clotting factor concentrates before I started in Sheffield by reading the journals and listening to the news. I was not involved in treatment of patients with bleeding disorders at the time.

31.2 In 1986 whilst I was a senior house officer in medicine in Swansea, I rotated through haematology for 6 months but I only ever recall giving clotting factor concentrate to a single patient who actually did not have an inherited bleeding disorder (FIX concentrate was given to reverse warfarin over-anticoagulation).

32. Did you take steps to ensure that patients were informed and educated about the risks of HIV? If so, what steps?

32.1 In the early stages when I started in Sheffield, I did not do any of the outpatient clinics, so the HIV education was provided by Professor Eric Preston and Sister Joy Farnsworth.

Response to risk

33. Were you involved in treating patients with factor concentrates prior to heat-treated products becoming available? If so:

a. What if any actions did you take to reduce the risk to your patients of being infected with HIV?
b. Did you continue to use blood products to treat patients, after becoming aware of the possible risks of infection of HIV? If so, why, which products did you use and what were your reasons for choosing those products over others?

33.1 I started in Sheffield in 1987 and was not involved in using factor concentrates prior to heat treated products becoming available.

34. Do you consider that heat-treated products should have been made available earlier? If not, why?

34.1 Obviously with hindsight the earlier heat treatment was introduced, the better it would have been, because the number of infected patients would have been a lot less. One point to appreciate, however, is that the early forms of heat treatment of clotting factor concentrates were not completely successful in eliminating viruses.

35. To the best of your knowledge, what (if any) actions did the Centre take to reduce the risk to patients of being infected (a) with hepatitis (of any kind) and (b) with HIV?

35.1 The centre was one of the first in the UK (and the world) to start using virally inactivated concentrates. Desmopressin was being used by 1982 to avoid concentrate exposure. Patients were kept on the same batch of concentrate for as long as possible.

35.2 After I started in Sheffield in 1987, the risk of hepatitis associated with concentrates was clearer. Only virally inactivated products were used, concentrate exposure was minimised by using desmopressin and patients were kept on the same batch and type of concentrate for as long as possible. All patients were vaccinated against hepatitis B and hepatitis A. As part of my response to the rule 9 letter, I found the book recording all the HBV vaccinations between 15 September 1986 and 2012. The systematic recording for hepatitis A vaccinations covers the period 1992-2012. Furthermore, as soon as we were allowed to use recombinant concentrates which did not have any infection risks, these were introduced into clinical practice.

36. Do you consider that the decisions and actions of the Centre in response to any known or suspected risks of infection were adequate and appropriate? Please explain your answer.

36.1 I do not have access to documents about how decisions before 1985 were made, so I cannot comment on these decisions. I am not aware of any inappropriate decisions having been made that surfaced in later years.

37. Looking back now, what decisions or actions by the Centre could and/or should have avoided, or brought to an end earlier, the use of infected blood products?

37.1 I was told that the haemophilia centre started using virally inactivated concentrates as soon as they became available. Clearly earlier availability of virally inactivated concentrates would have made the biggest difference.

38. What decisions or actions or policies of other clinicians or other organisations, within your knowledge, played a part in, or contributed to, the scale of infection in patients with bleeding disorders?

38.1 There are three dimensions to this answer:

Local Centre level decisions

38.2 The key issues here are whether local decisions were consistent with the national/international knowledge, recommendations and actions at the time. Important issues (that I have no evidence for but could have contributed to the size of the problem) are:
Late introduction of virally inactivated concentrates
Use of non-virally inactivated concentrates when virally inactivated ones were available
Late introduction and non-preferential use of desmopressin
I do not believe these were issues applicable to the Sheffield Centre.

National issues

38.3 The dependence on imported clotting factor concentrates. I believe that, had the UK been self-sufficient in concentrates, the number of HIV infections in haemophilia patients would have been a lot less. The main reason I say this, is the low prevalence of HIV infection in the UK blood donor population during the 1980-1984 period.

38.4 It is less clear that had the UK been self-sufficient in concentrates there would have been a major impact on the number of hepatitis C infections. The evidence in my view is less convincing, unless donors would have been excluded on the basis of testing for ALT and anti-HBc.

38.5 Clearly a major impact would have resulted, if the UK had been self-sufficient in concentrates and it introduced viral inactivation earlier than the commercial manufacturers.

International issues

38.6 Although the Infected Blood Inquiry addresses the issues that resulted in so many UK persons with haemophilia being infected with HIV/HBV/HCV, it cannot be considered in isolation. Equal and often greater frequencies of HIV and HCV infections have been reported from many countries with advanced health care systems such as the USA, Canada, France, Germany, Italy, Japan, Australia etc. The reasons that led to the UK disaster, include the systemic international ones and not just the local ones.

38.7 Among the international reasons that contributed in a major way are:

a) The contaminated donor pools used for commercial concentrates. I have read in books e.g. by Weinberg & Shaw and by Cees Smit and saw in television programs such as the BBC Panorama examples of poor practice, such as collection of plasma from prisons where prisoners were paid for plasma donation and could donate twice weekly. [Weinberg E, Shaw D. Blood on their hands. 2017 Rutgers University Press] [Smit C. Surviving Hemophilia. Eburon Publishers 2020]

38.8 b) The failure to recognise the serious nature of NANB hepatitis. I believe that doctors knew that NANB hepatitis was a problem post concentrate use. I do not believe anybody will argue ***now*** that HCV is not a serious disease. Unfortunately, this was not the case in the late 1970s and early 1980s. This was not the case everywhere and Sheffield was a centre that tried to convince people that NANB hepatitis was a serious issue.

38.9 In 1978 Professor Preston and colleagues from Sheffield published a paper in The Lancet on liver disease in patients with haemophilia. They analysed the data on 36 patients and found persistently abnormal liver function tests in 70%, with ALT elevation at some point in 100% of the patients. They went on to do liver biopsies in 8 asymptomatic patients and found 2 had cirrhosis and 2 chronic aggressive hepatitis. Although 2 patients had chronic hepatitis B, many of the patients showed evidence of past infection to HBV. The conclusion of the paper was "The high incidence of chronic liver disease seems to be a recent development and is probably related to factor concentrate replacement therapy" [Preston FE, Triger DR, Underwood JCE, Bardhan G, Mitchell VE, Stewart RM, Blackburn EK. Percutaneous liver biopsy and chronic liver disease in haemophiliacs. Lancet 1978; ii:592-594].

38.10 In 1982 Professor Preston and colleagues published in The Lancet a letter to the editor demonstrating the clear progressive nature of NANB hepatitis. In the letter they state that NANB hepatitis viruses have been implicated in the chronic liver disease of patients with haemophilia and that the chronic liver disease was well established. They performed serial liver biopsies in a patient with von Willebrand disease 2.5 years apart and showed liver disease progression [Preston FE, Triger DR, Underwood JCE. Blood product concentrates and chronic liver disease. Lancet 1982; i:565].

38.11 In 1985 in a third paper from Sheffield, Dr Charles Hay, Professor Preston and colleagues published in The Lancet data on the severity of the liver disease in Haemophilia. Data of 79 unselected patients were included and

progressive liver disease was demonstrated in 21%, with cirrhosis in half of these [Hay CRM, Preston FE, Triger DR, Underwood JCE. Progressive liver disease in haemophilia: An understated problem? Lancet 1985; i:1495-1498].

38.12 By 1985, 115 patients with haemophilia internationally have had liver biopsies and Louis Aledort from New York reported in the journal Blood that 15% of them had evidence of cirrhosis [Aledort L, et al. A study of liver biopsies and liver disease among haemophiliacs. Blood 1985; 66:367-372].

38.13 At least in Sheffield the issue that chronic liver disease in haemophilia was common and serious was known by the late 1970s. Had these observations been accepted and acted on, via the introduction of viral inactivation of concentrates we may be in a different position today.

38.14 Centres that did not do liver biopsies were not convinced of the severity of liver disease. Even centres who did biopsies believed the low rate of advanced disease was not such a problem and the issue may have been overestimated.

38.15 In a publication in the British Journal of Haematology in 1983 from Manchester in the UK, Stevens and colleagues reported that 79 (52%) of 153 patients with haemophilia had abnormal liver function tests. The went on to do 12 liver biopsies and because only one patient had cirrhosis, they concluded that this meant that liver disease in haemophilia was not such a big issue [Stevens RF, et al. Liver disease in haemophiliacs: an overstated problem? British Journal of Haematology 1983; 55;649-655].

38.16 c) Failure to introduce screening of blood donors with the surrogate tests of ALT and anti-HBc testing. Had this been done, a large number of HIV and HCV positive donors would have been excluded from the plasma pools. In a study published in 1981 by Aach and colleagues which followed 1513 blood transfusion recipients between 1974-1979, they showed that ALT screening of donations would have significantly reduced the incidence of NANB hepatitis in the recipients (New England Journal of Medicine 1981; 304:989-994].

38.17 d) The failure to introduce viral inactivation earlier. The World Federation of Haemophilia in 1977 called on the makers of clotting concentrates to kill viruses in their products for the sake of future generations of persons with hemophilia [Page 38, Weinberg & Shaw. Blood on their hands].

38.18 Dr Shohachi Wada testified that he conducted viral inactivation experiments using heat whilst working for Cutter (one of the FVIII manufacturers) in 1972 [Page 194, Weinberg & Shaw. Blood on their hands]. Behringwerke AG was testing heat treatment of concentrates in 1979 and their product was licensed in Germany in 1981 [Page 193, Weinberg & Shaw. Blood on their hands].

38.19 In 1980 Dr Shanbrom submitted a patent application for the solvent detergent method of viral inactivation [Page 95, Weinberg & Shaw. Blood on their hands].

38.20 I believe the decisions not to introduce viral inactivation of clotting factor concentrates earlier were commercial and political rather than scientific.

38.21 Had viral inactivation been introduced earlier, the number of patients with haemophilia infected with HIV and HCV throughout the world is likely to have been a lot lower.

39. The Inquiry draws your attention to a publication from the Haemophilia Society, "The Bulletin" No.4. (1991), at page 6, [HSOC0022977], where you provided your opinion on the purity and viral safety of blood products and urged "caution", suggesting that "people with haemophilia should be aware of the lack of evidence for a clinically important immunomodulatory effect by intermediate products with a long safety record such as 8Y, before they consider changing to a purer product that comes from paid donors and costs twice as much". Please explain your views, as expressed in the article, and set out what you recall about this issue.

39.1 The FVIII products used during 1985-1990 were all intermediate purity concentrates because they contained FVIII and von Willebrand factor (VWF). VWF circulates in the blood attached to FVIII and protects the degradation of FVIII.

39.2 In the early 1990s a new type of FVIII concentrate was introduced from America. After viral inactivation it underwent purification using monoclonal antibodies so the final product in the bottle contained FVIII but almost no VWF. The new monoclonally purified products were being pushed as being better than the older intermediate purity products.

39.3 I was personally not convinced about the superiority of these products and felt that this was a marketing exercise to persuade people to change concentrate use. I was impressed by the safety record of 8Y FVIII (dry heat 80°C for 72 hours) which was made from volunteer UK blood donors and was not ever associated with any viral infections.

39.4 I saw no significant advantage to changing to a purified product made from American paid plasma, especially as there was a case in Sweden of hepatitis C infection in an one year old boy with haemophilia, following the use of one of the new monoclonally purified FVIII concentrates [Berntorp E, et al. Hepatitis C virus transmission by monoclonal antibody purified factor VIII concentrate. Lancet 1990; 335:1531-2].

39.5 Although the Sheffield Centre did eventually move to using some of these monoclonally purified products, the history since then is interesting:
a) The story that intermediate purity concentrates suppress the immune system was never shown convincingly
b) The intermediate purity FVIII concentrates are still being used because they cause less antibodies to FVIII (inhibitors). In many parts of the Western World and especially Germany, new-born babies with severe haemophilia are currently treated on the first 50 occasions with intermediate purity FVIII concentrates rather than recombinant or monoclonally purified concentrates.

39.6 The superiority of the intermediate FVIII concentrates over the recombinant ones was shown in the randomised SIPPET trial [Peyvandi F, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. New England Journal of Medicine 2016; 374:2054-2064]. In the SIPPET trial, 264 previously untreated (PUPs) boys with severe haemophilia A were randomised to be treated with plasma derived or recombinant FVIII on the first 50 occasions. Inhibitors developed in 26.8% of the plasma derived FVIII treated patients and 44.5% of the recombinant FVIII treated group.

39.7 c) 8Y FVIII has the best safety record of any FVIII treatment developed anywhere in the world. Actually, in Sheffield we still use 8Y FVIII in 2020, 35 years after its introduction, for a very rare condition called congenital thrombotic thrombocytopenic purpura (TTP). Over a 35-year period no viral infections have ever been reported with the use of the 8Y FVIII concentrate.

Section 4: Treatment of patients at the Centre

Provision of information to patients

40. What information did you provide or cause to be provided to patients with a bleeding disorder:

a. about the risks of infection in consequence of treatment with blood products (in particular factor concentrates) prior to such treatment commencing?
b. about alternatives to treatment with factor concentrates?

40.1 a) Please also see my answers to questions 32 and 33.

40.2 I started in Sheffield in July 1987 by which time concentrates were virally inactivated and relatively safe in terms of infection. I was responsible for very few patients requiring treatment, other than for liver biopsies where patients knew both about the infection risks (as they had been infected already), were using concentrates at home, and there was a clear need for concentrate use before the liver biopsies. These patients who were being admitted for liver biopsies, were well informed of the infective risks of concentrates because it was discussed with them at length.

40.3 b) Despite the safety of clotting factors by 1987, desmopressin was widely used in Sheffield.

41. How (if at all) did this change over time?

41.1 The major infection risks took place before I started in Sheffield. After I started, we always considered the issue of whether concentrate was required and whether it could be replaced by desmopressin. As soon as we were allowed to use recombinant concentrates, we rapidly changed patients over to these products because of the increased potential safety, even though we did not have an infection issue with the plasma derived concentrates we were using for the previous 10 years.

HIV

42. When did you first discuss AIDS or HIV (HTLV-III) with any of your patients? What did you tell them?

42.1 I started in Sheffield in July 1987 and by that time all relevant patients were aware that they were HIV positive. I did not have to give the HIV positive diagnosis to any person with an inherited bleeding disorder.

43. How many individuals at the Centre were infected with HIV? Of those infected:

43.1	Total Infected	38
	a. How many had severe haemophilia A?	28
	b. How many had moderate haemophilia A?	1
	c. How many had mild haemophilia A?	5
	d. How many had haemophilia B?	4
	e. How many had von Willebrand's disease?	0
	f. How many were children?	8*

43.2 * 8 of the 38 HIV positive patients that the centre cared for were infected as children, prior to their transfer to the adult service. The Sheffield Haemophilia Centre at the Royal Hallamshire Hospital is an adult centre and does not care for children under the age of 16.

44. Was work undertaken at the Centre to establish the time period during which patients seroconverted? If so please describe what work was undertaken and what if any conclusions were reached?

44.1 This predates my joining the haematology department in Sheffield, but there is an early computer printout in the Centre with the HIV results of all the Sheffield patients. The testing for HIV probably took place in1985 (possibly late 1984) when it was first introduced in the UK. It is clear that stored frozen samples were tested for many of the patients to establish the date of their HIV seroconversion. Some patients had HIV tests going back to 8.8.1979 (the test was negative). One of the first positive samples was from 10.6.1981. Up to six samples spanning up to 6 years were tested per patient, although in some cases there was just a single test on a sample from 1985.

HBV

45. Were patients infected with HBV informed of their infection and if so how?

45.1 I do not know how the 4 patients with active HBV were informed. One of these was a patient who transferred from another part of the UK and the patient knew on transfer, whilst another was infected as a child at the Sheffield Childrens' Hospital.

46. What information was provided to patients infected with HBV about the infection, its significance, prognosis, treatment options and management?

46.1 The patients with chronic HBV were all referred to hepatology at periodic intervals, but the conclusion after each hepatology review was that none of them required hepatology follow-up or treatment for their HBV.

47. How many patients at the Centre were infected with HBV?

47.1 In our 1996 paper on natural history of chronic hepatitis C in haemophilia, it is stated that three patients were hepatitis B surface antigen positive ie have active infection. Furthermore, 65 of 135 (48.1%) of the patients showed previous hepatitis B infection with spontaneous clearance. [Makris M, Preston FE, Rosendaal FR, Underwood JCE, Rice KM, Triger DR. The natural history of chronic hepatitis C in haemophiliacs. British Journal of Haematology 1996; 94: 746-752].

NANB Hepatitis/HCV
48. Were patients infected with NANB hepatitis informed of their infection and if so how?

48.1 I believe they were, but this was before I started in Sheffield. The patients I saw when I first started, had already agreed to have two liver biopsies in one year and to be randomised to take Interferon for a year, so they most certainly knew they had NANB hepatitis. I do not know how they were informed.

49. What information was provided to patients infected with NANB hepatitis about the infection, its significance, prognosis, treatment options and management?

49.1 I can only comment on the patients that I saw after I started. The patients knew that this could be serious, progressive and that it affected the majority of the patients with haemophilia treated with concentrate. Patients were aware that the route of infection of their NANB hepatitis was through their treatment with clotting factor concentrate. Patients were offered the option of participating in the Interferon trial as a potential treatment for NANB hepatitis.

50. When did the Centre begin testing patients for HCV? Over what period of time was testing for HCV carried out after a test became available? How and when were patients told of their diagnosis of HCV? Where they told in person, by letter or by phone?

50.1 I believe the main testing was during 1989-1992 using the different tests that were available. Testing was done through the outpatient clinics and the patients were informed of the results in person in the clinic. At the time I was a trainee haematologist covering all areas of haematology and spent time at the Sheffield Children's Hospital as well as the regional blood transfusion service. Professor Preston as the Director of the Haemophilia Centre and the patients' consultant was ultimately responsible for the process.

50.2 The haemophilia outpatient clinic was conducted by Professor Preston or one of the haematology trainee doctors. There were 6-8 different haematology trainee doctors working in Sheffield at any one time and could have done the clinic.

51. What information was provided to patients who had tested positive for HCV about the infection, its significance, prognosis, treatment options and management?

51.1 By the time patients were tested most already knew they had NANB hepatitis, were being followed up for this, many had had liver biopsies, some participated in the Interferon treatment trial in 1987-1989 and were informed that their liver disease was due to NANB hepatitis. A number of doctors did the haemophilia clinic (see answer to question 50), so it is not possible to say what was said to individual patients. The knowledge of doctors about hepatitis and haemophilia may have varied significantly but I believe most Sheffield Haematology trainees knew about the seriousness of the condition because they were aware of Professor Preston's long-term interests in the disorder. Furthermore, they could see haemophilia patients were often inpatients on the ward for liver biopsies and that patients were being treated with Interferon. Unlike the situation today when the haemophilia and leukaemia haematology teams are very separate, during the 1980s and 1990s there was a single haematology ward round, in which all doctors participated and all patients including those with haemophilia and leukaemia were assessed on the ward round.

52. Were the results of testing for HCV notified to patients promptly or were there delays in informing patients of their diagnosis? If there were delays in informing patients, please explain why.

52.1 As far as I know patients were notified of their results promptly. I do not know if there were any delays because I was not doing the haemophilia clinic regularly.

53. The Inquiry draws your attention to the information provided by you in the Bulletin (1994) No.3 at page 7, where you expressed the view that there is "no reason" why a patient should not be told that they are HCV positive, and whereas perhaps young children should not be told, their parents should be [HSOC0023000]. Did you follow this in practice?

53.1 This was a Question and Answer article that was published in the Haemophilia Bulletin in October 1994. The specific question was: "Are there any reasons why a person should not be told they are hepatitis C positive?"

53.2 My answer was: "No, but in young children it may be preferable to wait until they understand more about their health – the parents of the affected child should of course be told". I believe I followed this in practice.

54. How many patients at the Centre were infected with HCV?

54.1 We have 179 patients with hepatitis C in our records. Some of these, however, were not infected in Sheffield, but moved to our centre for various reasons including, in some cases, our interest in haemophilic liver disease.

54.2 As a city with two large Universities, we have had many students from all over the UK register with our centre for 3-4 years whilst they studied at the Universities and the HCV positive ones are included in this number.

55. The Inquiry understands that in 1993 you and Professor Preston studied 183 haemophiliac men and boys who attended the Centre and found that as many as 29% of HCV infected haemophiliacs at the Centre had cirrhosis or end stage liver disease. Please provide details of this study and explain your findings.

55.1 I do not know which publication you are referring to. Our main natural history of chronic hepatitis C in persons with haemophilia paper was published in 1996 in the British Journal of Haematology. Full reference is: [Makris M, Preston FE, Rosendaal FR, Underwood JCE, Rice KM, Triger DR. The natural history of chronic hepatitis C in haemophiliacs. British Journal of Haematology 1996; 94: 746-752].

55.2 Soon after the discovery of the hepatitis C virus and the introduction of the antibody test for its detection, a number of studies were published showing the prevalence of the infection in patients with haemophilia. We believed they underestimated the real impact of the disease because follow up was short, most centres did not perform liver biopsies in these patients and few autopsies were requested.

55.3 Another big issue at the time was whether the natural history of patients with HCV and haemophilia was the same as that in patients without haemophilia. There was debate as to whether the recurrent HCV exposure of haemophilia patients with multiple genotypes could have led to a different severity of liver disease.

55.4 We felt we were in a unique position to report on the morbidity and mortality of the HCV in haemophilia because the Centre had a long interest in the disease, maintained good records, performed liver biopsies, tested all patients and tried to request autopsies in most patients that died.

55.5 In this paper we reported on all 138 patients diagnosed with hepatitis C in Sheffield up to January 1995. Patients were followed in the Haemophilia Centre for up to 28 years since the date of presumed infection. An unusual feature of this cohort of patients was that 63 of them had a total of 116 liver biopsies between them and included 13 patients who had autopsies. Among the findings were:

55.6 a) The route of infection was though to be treatment with non-virally inactivated concentrates prior to 1985 in 132 (95.6%). Four (2.9%) of the patients were infected by early forms of virally inactivated concentrates, and two (1.4%) of the patients were infected through the use of cryoprecipitate.

55.7 b) 36 (26.1%) of the patients were HIV positive. This was a lower rate than other cohorts. A study from London reported their HIV positive rate to be 40.4% and one from the USA the rate was 62.8%.

55.8 c) Previous infection with hepatitis A and B (i.e. not due to vaccination) was seen in 37.2 and 48.1% of the patients respectively. Hepatitis A does not give rise to chronic disease. Although hepatitis B can lead to chronic disease, only 3 of 135 (2.2%) had evidence of continuing infection.

55.9 d) 82.6% of the patients had abnormal liver function tests.

55.10 d) 11 of 15 patients with persistently normal liver function tests (based on blood tests) had evidence of chronic hepatitis C because they were HCV PCR positive.

55.11 e) Cirrhosis was diagnosed on liver biopsy in 19 patients and 9 patients developed liver failure. The incidence of cirrhosis increased significantly 15 years after infection. Liver failure tended to occur 5-10 years after the diagnosis of cirrhosis.

55.12 f) Liver failure and cirrhosis were more likely to occur in persons who were HIV positive, those who were older (>45 years) at the time of the hepatitis C infection and in those who were infected for the longest period since infection.

55.13 The conclusions of this paper were that chronic hepatitis C in haemophilia was associated with a major impact in morbidity and mortality.

Other information

56. What information was provided to patients about the risks of other infections?

56.1 The possibility of transmission of hepatitis A and B was discussed and as per UKHCDO guidelines all persons with an inherited bleeding disorder likely to be treated with blood products were vaccinated.

56.2 In the mid-1990s vCJD was discussed and recombinant concentrates were used as soon as we were allowed to.

56.3 With some patients the concept of unknown viruses that could potentially come through the viral inactivation procedures was also discussed.

57. What information was provided to patients about the risks of infecting others?

HIV

57.1 This was a major issue with all sexually active patients. We provided information about not sharing personal items such as razors, toothbrushes, about proper disposal of needles and syringes post factor concentrate administration. We advised the use of protected sexual intercourse and provided condoms free of charge from the haemophilia centre.

57.2 In Sheffield we have had two partners of HIV positive persons with haemophilia acquire the infection sexually before 1985. We have had no sexual or other household contact transmissions since.

57.3 Sister Joy Farnsworth, a clinical nurse specialist, was appointed to provide support to HIV positive patients and their families and the issue of sexual and family transmission was frequently discussed when patients and their partners visited the haemophilia centre.

HBV

57.4 The main difference here is the efficacy of vaccination of partners and household contacts against hepatitis B. As well as offering vaccinations to them through the haemophilia centre, we also tested their antibody response to confirm immunity and offered revaccination, if appropriate.

HCV

57.5 The information for this evolved over the years. Because of our interest in HCV in haemophilia, this literature in this area was very closely followed both by me and Sister Joy Farnsworth. The low transmission rate and the uncertainty of the information available was made clear to our patients. Despite the low rate we advised protected sexual intercourse as a safety measure.

57.6 We have had no HCV transmissions to partners or household contacts in Sheffield.

Consent

58. How often were blood samples obtained from patients attending the Centre and for what purposes? What information was given to patients about the purposes for which blood samples were taken? Were samples stored for prolonged periods and if so why? Did the Centre obtain patients' informed consent to the storage and use of those samples?

58.1 Samples were obtained from patients for many reasons such as to see if they are anaemic, if they had liver inflammation, what clotting factor levels they achieve after treatment, to see if they have inhibitors etc. All of these tests were and still are done as part of the ongoing delivery of clinical care and monitoring of long-term conditions. All the tests are either performed on the day of sample collection or for some more specialised tests, samples are stored and tested over the subsequent few weeks. Samples are not collected and stored in case they are of some use in the future.

58.2 There are three areas not covered by the above:
a) Patients participating in clinical trials of new products or gene therapy. Lots of samples are taken from these patients and analysed centrally in laboratories based usually in Europe or the USA. Some of these samples are stored long term but the consent form to participate in the clinical trial makes this explicit. Long term storage of samples does not take place locally, other than to facilitate transfer to the central facility as transportation takes place using special boxes containing dry ice (and therefore easier to make as few postings as possible).

58.3 b) Patients participating in research studies

Samples from patients participating in research studies are stored for testing at a later date. The reason for the storage and the testing to be done is stated in the patient information sheet provided to every participant and the consent form also indicates if samples are to be stored. All of these studies are approved by the relevant research ethics committees.

58.4 c) In the 1980s it was routine to store a frozen sample from every patient at every visit when they had blood samples taken for another reason. It is unclear why or when this started but as part of completing this response, I found out that it must have started by 1979, because this was the date of the first negative HIV test result (1979 sample was tested in 1985 – see my answer to question 44). I also consulted with the current Lead Scientist of the Coagulation laboratory, Dr Steve Kitchen, and he mentioned that when he started at the Royal Hallamshire Hospital in Sheffield in February 1986, the serum save process was already well underway and there were several years of samples frozen down. I do not know what information was given to patients when this was first introduced, especially since the first haemophilia nurse was not employed in Sheffield until November 1985. The process of saving samples was still in place in the late 1980s. It is not clear when it was stopped.

58.5 These samples were the ones used to test for HIV infection when the test was introduced either late in 1984 or in 1985. The stored samples were able to identify the time of infection more precisely. These samples were also used when they were tested with the Chiron first generation test for hepatitis C.

58.6 I do not know how patients were informed that this serum storage was taking place.

59. Were patients under your care and/or at the Centre treated with factor concentrates or other blood products without their express and informed consent? If so, how and why did this occur? What was the approach to obtaining consent to treatment?

59.1 To this day, there is no signed informed consent process to treat patients with concentrates for procedures. Patients will have received extensive information in clinics with haematology staff, regarding their condition and options for treatment, and developments in treatments over the course of their illness. This information would include any generally known heightened risks and any specific risks for the individual patient associated with surgical procedures and specific medical conditions.

59.2 Most patients are on home treatment with the same products, so when they are admitted and treated for surgery or for management of major bleeds, there is implied consent to treatment. Clinicians relied on expressed verbal or implied consent by the fact that patients attended for treatment.

59.3 For patients with mild haemophilia, we do discuss the specifics of treatments because of the risk of developing a FVIII inhibitor (alloantibody), not because we feel there is any infective risk with the current treatments. We use

desmopressin if we can and explain to patients the risks if they need to be treated with concentrate. For elective procedures this process is discussed and documented in the letters we send to general practitioners. For a few years now, all letters to general practitioners are copied to the individual patients as well.

59.4 The last 5 years or more have seen the introduction of two main treatments, extended half-life concentrates (EHLs) and Emicizumab. Currently these two groups of products are used by around 75% of all our patients. When EHLs and Emicizumab were introduced all patients were seen, informed of advantages and disadvantages of the new treatments and they all signed an informed consent and agreement for changing concentrate treatment. This consent form is in the medical notes and patients are also given a copy.

59.5 We do not ask for individual consent every time we use these products to treat a patient in hospital when they are bleeding or before surgery. As standard practice for all patients, persons with haemophilia do sign a consent form before having surgery.

60. Were patients under your care and/or at the Centre tested for HIV and/or for HCV and/or for any other purpose without their express and informed consent? If so, how and why did this occur? What was the approach to obtaining consent to testing?

HIV

60.1 I cannot comment on the situation with HIV because all HIV positive patients were tested before I started in Sheffield in 1987.

60.2 When patients post 1987 were tested for HIV, they were always informed that the testing was being done and we organised for them to come back and get the result in person a few days later.

60.3 We have also had a program of testing all the partners of our HIV positive patients and this was run by Sister Joy Farnsworth. The partners would come and see Sister Farnsworth separately from clinics; they would not see any doctors and would be tested, and the result communicated to them. Although the purpose of the visits was to perform the HIV testing, it was used as an informal counselling session because Sister Farnsworth knew the partners and the families very well.

HCV

60.4 The first tests performed with the Chiron assay were done on stored sera and no specific consent was obtained.

60.5 For the early Elisa antibody test, an application to the local research ethics committee was made to test the stored sera. This was approved without the requirement to go back to patients for individual consent.

60.6 Subsequently, when the testing was available on the NHS, the tests were requested when patients were seen in clinic and fresh blood samples were

obtained for HCV testing. A number of doctors did the haemophilia clinic and I cannot be certain that the same process was carried out. Professor Preston was the consultant in charge and Director of the Haemophilia centre. Patients were informed of the result next time they were seen in the haemophilia clinic.

Research

61. Other than is set out in response to earlier questions, please list all the research studies that you have been involved with during your time working at the Centre (insofar as relevant to the Inquiry's Terms of Reference) and:
a. Describe the purpose of the research;
b. Explain the steps that were taken to obtain approval for the research;
c. Explain what your involvement was;
d. Identify what other organisations or bodies were involved in the research;

61.1 You ask me to answer these questions by referring to the studies in Question 62.

Makris M, Preston FE, Triger DR, Underwood JCE, Choo QL, Kuo G, Houghton M. Hepatitis C antibody and chronic liver disease in haemophilia. Lancet 1990:335:1117-1119.

61.2 The purpose of this research was to see if the antibody identified by the researchers at the Chiron Corporation was the agent causing NANB hepatitis in haemophilia.

61.3 The work was carried out in 1989 and as far as I know there was no specific approval obtained. The work was agreed between the researchers at the Chiron Corporation and Professor Eric Preston.

61.4 The samples used were the frozen serum save samples and the anonymised samples were sent to the Chiron laboratories on dry ice by the coagulation laboratory staff.

61.5 My main role was to analyse the data and with the co-authors wrote the the paper.

61.6 The only organisations involved were the Haemophilia Centre in Sheffield and the Chiron Corporation.

Makris M, Preston FE, Rosendaal FR, Underwood JCE, Rice KM, Triger DR. The natural history of chronic hepatitis C in haemophiliacs. British Journal of Haematology 1996; 94:746-752

61.7 The purpose of this research was to describe the natural history of the 138 patients with haemophilia who were found to be HCV positive in Sheffield. The study is described in more detail in answer to question 55.

61.8 This work was a review of the medical notes and as it did not require to go back to the patients for any tests or information, no approval was sought. I

collected all the data from the medical notes, did the analysis and co-wrote the paper. No other organisation was involved in the performance of the work.

e. State how the research was funded and from whom the funds came;

61.9 All my research grants relating to haemophilia are listed in Appendix 2. The list includes when the grant was awarded, the title of the project, the amount of funding and who provided the funding.

61.10 The two studies described in 61a-d above did not have specific funding from anywhere.

f. State the number of patients involved;

61.11 This varied depending on the study. The number of patients involved is reported in each publication.

61.12 For the studies in 61a-d, the first study (Chiron antibody) had 154 and the second (natural history) 138 patients.

g. Provide details of steps taken to inform patients of their involvement and to seek their informed consent; and

61.13 This has changed over the years. Now all studies are approved by the research ethics committees, patients receive the patient information sheet before they attend, and the study is explained to them when they are seen in person. If they are happy to participate, they sign the relevant consent form. A copy of the consent form is given to the patient and one is filed in the patient's notes, as well as in the research file.

61.14 In the past, studies were mentioned to the patients in clinic and they were given the study patient information sheet. Although the intention was usually to formally enrol them at the next clinic visit, provided all that was required was a blood sample that did not require another venepuncture, most patients were keen to proceed with participation that day.

61.15 In terms of the natural history studies, these only required to look at the patient's medical notes. Although for the last 20 years individual patient consent to do this was obtained, this did not happen in the early 1990s because this was not required then for this type of study.

61.16 The original Chiron antibody study used stored serum samples from the 1980s and specific consent was not obtained. After Chiron antibody study we applied to the Local Research Ethics Committee to test the stored frozen samples using an Elisa assay locally. The Ethics committee approval to use these samples did not require us to go back to the patients to obtain individual consent.

h. Provide details of any publications relating to the research.

61.17 Please see Appendix 1 for all my publications on haemophilia and infections

62. In answering the above question, please include the following studies/research:
a. M. Makris, MS Dewar, FE Preston, Q-L Choo, G Kuo, M Houghton, The Relation of Hepatitis C Antibodies to Acute Non-A Non-B Hepatitis (NANBH) in previously untreated Haemophilia Patients [BAYP0000035_019].
b. Makris et al, The Natural History of Chronic Hepatitis in Haemophiliacs (1996) British Journal of Haematology vol 94 746 – 752 [NHBT0045517].
c. Makris et al, Hepatitis C antibody and chronic liver disease in haemophilia Lancet 1990 May 12;335(8698) 1117-1119 [OXUH0000024_002] and comments in The Lancet, "Prevention of hepatitis C infection in haemophiliacs", July 1990 (page 2) [NHBT0000030_045].
d. Work with Scientists from the Chiron Corporation in tests for HCV antibody status (see page 4) [ARCH0001716].

62.1 I need to clarify these four references because they are two not four different studies. 62a [BAYP0000035_019] is a conference abstract reporting the findings that were published in the full Lancet paper referred to in 62c [OXUH0000024_002]. The second reference in 62c [NHBT0000030_045] is correspondence published in the Lancet in response to our paper. In our paper we said: "There is an urgent need to eliminate HCV from clotting factor concentrates by screening…….". Although we did not specifically state it, the implication was the this was HCV screening of plasma donors.

62.2 John Barbara and Marcella Contreras from the National Blood Transfusion Service disagreed with us on the urgency and questioned the cost effectiveness of our proposal. They started their letter by saying "Dr Makris and colleagues (May 12, p 1117) urge rapid implementation of anti-HCV screening of blood donations." They pointed out that there have been no cases of hepatitis with NHS 8Y concentrate. They also suggested that because some of our HCV antibody positive patients did not have significant liver disease on liver biopsy, this could reflect non progressive nature of HCV or that the HCV antibody results were false positive.

62.3 We did not accept their arguments and said so in our response to their letter. We said: "It seems to us important to ensure safe products through the combined effects of donor selection and viral inactivation/elimination. This dual approach should greatly reduce the risk of unexpected HCV transmission, such as happened with Scottish National Blood Transfusion Service intravenous IgG preparation and with a batch of wet-heated commercial factor VIII concentrated. Although the immunoglobulin was produced by a different manufacturing process, it is likely that the transmission of HCV by these two products resulted from a heavy viral load in the starting plasma. In our view, the current safety record of 8Y should not influence decisions on donor screening in the UK."

62.4 62d is a report written by Professor Eric Preston responding to a series of question by Dennis Whalley Associates (? a law firm) but the questions are not listed. Although the 62d document [ARCH0001716] refers to work with

the Chiron corporation, the actual work is the one described in the Lancet paper i.e. 62c.

62.5 62b [NHBT0045517] is a separate study on the natural history of chronic hepatitis in Haemophilia. See answer to question 55 which discusses this study in detail.

63. In a letter dated 12 September 1990 in a letter from you to Dr Rizza, regarding an NHS 8Y 'Virgin Patient' study, you refer to a mistake made regarding notification of treatment with cryoprecipitate [OXUH0002132_007]. Please answer the following questions:
a. What was the 'Virgin Patient' Study?
b. What was your involvement in this study?
c. How many patients were part of the study?
d. What was your approach to obtaining their consent?
e. What were the conclusions or findings of the study?

63.1 Clarification: The term "virgin patient" was the term used in the 1980s to refer to patients with haemophilia who had never been exposed to clotting factor concentrate. The term that replaced it, is Previously Untreated Patient (PUP)

63.2 a) I believe that this was a study that collected data from patients whose first ever exposure to concentrate was to BPL 8Y FVIII concentrate. The intention was to document that this product was safe as it was widely used in the UK. The study has been published and the full report is: [Rizza CR, Fletcher ML, Kernoff PBA. Confirmation of viral safety of dry heated factor VIII concentrate (8Y) prepared by Bio Products Laboratory (BPL): a report on behalf of the UK Haemophilia Centre Directors. British Journal of Haematology 1993; 84:269-272]

63.3 b) I was not involved in this study, which was carried out by the UKHCDO and run from the Oxford Haemophilia Centre. On this occasion I was asked to complete the follow-up forms for the Sheffield patient that was participating in the study.

63.4 c) A total of 27 patient from throughout the UK were included.

63.5 d) I do not know

63.6 e) None of the patients was infected with HIV, HBV or HCV as a result of 8Y concentrate use, confirming the safety of this concentrate and the fact that viral inactivation using dry heat at 80°C for 72 hours was effective in eliminating viral transmission by concentrates.

64. The minutes of a meeting of the UKHCDO Transfusion Transmitted Infection Working Party of 28 June 1999 state that you requested that the Working Party consider the feasibility of a randomised trial of combination therapies for the treatment of HCV, and that you had been approached by Roche. The Working Party concluded that it would be unlikely that there would be sufficient numbers of patients that could be recruited to enable the study to

succeed [BART0002243]. Why did you make this suggestion? Please explain how, if at all, this project progressed following this discussion.

64.1 I do not have any details on this and cannot recall what the arms of the randomisation were. This trial did not progress in haemophilia. As far as I know there has only ever been one randomised clinical trial of treatment of hepatitis in haemophilia and this was the one we performed in the late 1980s and which is discussed in question 65.

65. The Inquiry understands that patients at the Centre were involved in an Interferon trial (and see further, Makris et al. – Blood Vol 78, A Randomised Controlled Trial of Recombinant Interferon-Î± i n Chronic Hepatitis C in Haemophiliacs [PRSE0004466]).
a. Please describe the trial.
b. What led you to undertake this study?
c. How many patients were part of the study?
d. What was your approach to obtaining their consent?
e. What were the salient conclusions to be drawn from the trial?
f. Was the use of Interferon considered controversial at the time of the trial? If so, why?

65.1 I will answer part (b) of the question first because this gives the background to why the study was undertaken.

65.2 b) Earlier published research from Sheffield showed that NANB hepatitis can be severe, is progressive and is common. With this background it was clear that patients should be treated when a treatment became available. Interferon alfa-2b was being studied in patients with NANB hepatitis without haemophilia, so it was decided to study it in this group of patients. Because there is fluctuation in the condition it was decided to have a control group, use randomisation, and to have a liver biopsy at the start and end of the trial. Although these principles in trial design are common now, they were rare then. Furthermore, during this trial 35 liver biopsies were performed which were rarely done in haemophilia at the time. In 1985 Aledort reported on the world experience of liver biopsies in haemophilia and he estimated that 200 have been performed in total. Each liver biopsy required a 4-day hospital inpatient stay.

65.3 a) Patients with haemophilia and NANB hepatitis had a liver biopsy on entry into the study. After this, they were randomised to receive Interferon alpha-2b for 1 year or to act as a control group and not receive any treatment for their hepatitis. After 12 months all patients, including those in the control group had a second liver biopsy. After the second liver biopsy, the control group patients were offered Interferon for 6 months. This study was approved by the local research ethics committee.

65.4 c) 18 patients participated

65.5 d) The trial was discussed with the patients in the haemophilia clinic by the doctor doing the haemophilia clinic, which was usually not me as I only just

started in Sheffield. I would meet the patients when they were admitted to hospital for their first liver biopsy. I would explain the process of what having a liver biopsy and being treated with Interferon involved. I would discuss the advantages and side effects of interferon, bearing in mind this was a very new treatment and little was known about it, at least initially. Patients would always be reconsented before their second liver biopsy.

65.6 e) 18 patients were enrolled.
The first liver biopsy showed chronic active hepatitis in 9, chronic persistent hepatitis in 7 and cirrhosis in 2.
10 patients were randomised to Interferon Alpha 2b and 8 to the control group
After 12 months a second liver biopsy was performed in 17 patients.
Four of 10 patients in the Interferon group normalised their liver enzymes versus none in the control group.
After the second liver biopsy six patients in the control group received Interferon for 6 months. Five of these 6 patients who received 6 months of Interferon normalised their liver enzymes.
The liver biopsies were scored by an expert histopathologist that did not know whether the patients were treated with Interferon or not and whether it was the first or second liver biopsy he was reporting on.
The result was that there was significant histological improvement in patients treated with interferon.

65.7 I saw these patients for most of their hospital visits and in addition to these published observations, in 1988 I became convinced of the association of chronic fatigue with chronic NANB hepatitis/HCV. One patient who always complained of severe tiredness, told me at one visit that the tiredness had gone and that coincided with normalisation of his liver enzymes; this was before either of us knew the blood test results that day, confirming normalisation of the liver enzymes. Some weeks/months after he stopped the interferon, I saw him at a clinic visit again and he told me his tiredness returned; after he went home, I got the results of his blood tests and he relapsed with the NANB hepatitis returning.

65.8 The experience of a second patient convinced me even more of the association. He never complained or believed he had chronic tiredness, but after a few weeks on interferon he spontaneously mentioned that he had so much energy and he never realised that he was tired before going onto Interferon; after the visit the blood tests confirmed that his liver enzymes normalised.

65.9 Two of the original cohort of the 1987-1989 Interferon treated patients from this study continue to be in remission from their HCV/NANB hepatitis to this day, more than 32 years after treatment.

65.10 f) The problems with Interferon were the side effects especially flu-like symptoms and the fact that not all patients responded. Since the large majority of haemophilia patients were well and as most centres did not do liver biopsies, the need to treat to eliminate the hepatitis was not so clear to many haematologists.

66. What do you understand to be the ethical principles that should guide research? Did you apply those principles to the research studies referred to above and if so, how? If not, why?

66.1 This is a large area but the guiding principles of research ethics are that the participants are given full information and have a right to:
Consent to participate, withdraw or refuse to participate in research projects,
Confidentiality in not disclosing personal information without consent,
Security of data and samples, and
Safety in not exposing subjects to unnecessary levels of risk.

66.2 The researchers have an obligation to ensure that their research is conducted with honesty, integrity, with minimal possible risk to participants and to observe cultural sensitivity.

66.3 The ethics requirements for conduct of research have changed over the last 35 years but I believe I applied these principles to my research.

67. Were patients involved in research studies without their express consent? If so, how and why did this occur?

67.1 In the large majority of studies an application to the ethics committee was made and where required, the express consent of the patients was obtained. The exception to this was the initial testing of the frozen serum samples in 1989 using the Chiron test, as explained in the earlier answers.

68. Was patient data (anonymised, de-identified or otherwise) used for the purpose of research or for any other purpose without their express consent? If so, what data was used and how and why did this occur?

68.1 For at least the last 25 years, anonymised patient data for the purpose of research was only shared with patient consent.

69. Was patient data (anonymised, de-identified or otherwise) shared with third parties (e.g. UKHCDO or Oxford Haemophilia Centre) without their express consent? If so how and why did this occur, and what information was provided to whom?

69.1 I need to clarify the separation between the Oxford Haemophilia Centre and the UKHCDO. In the early days both were based in the same building, but they were two separate entities. Almost all our communications were with the UKHCDO based in Oxford rather than with the Oxford Haemophilia Centre per se.

69.2 The UKHCDO National Haemophilia Database (NHD) was set up in 1968 and was based in Oxford until it moved to Manchester in 2002. We had an obligation to submit data to the NHD, which we did on an annual basis – this

was done by all haemophilia centres in the UK. The data submissions were performed by the data managers. Although communications with the electronic National Haemophilia Database are now coded, it was not always the case when the database was housed in Oxford and the annual returns were on paper. We have followed the UKHCDO rules for data submission at all times.

70. Please provide details of any articles or studies that you have published (other than those already referred to) insofar as relevant to the Inquiry's Terms of Reference.

70.1 These are listed in Appendix 1

Previously Untreated Patients

71. Detail all decisions and actions taken at the Centre by you or with your involvement with regard to a category of people referred to as 'previously untreated patients' (PUPS).

71.1 The definition of PUPs is patients with severe haemophilia who have had less than 50 exposures to clotting factor concentrate. These patients are almost exclusively children and as an adult centre, the Sheffield Haemophilia Centre at the Royal Hallamshire Hospital does not see or treat PUPs.

Treatment of patients at the Centre

72. How was the care and treatment of patients with HBV managed at the §Centre? In particular:
a. What steps were taken to arrange for, or refer patients for, specialist care?
b. What treatment options were offered over the years?
c. What information was provided to patients about the risks and benefits of specific treatments and about side effects?
d. What follow-up and/or ongoing monitoring was arranged in respect of patients who were infected with HBV?

72.1 We have only ever had 4 patients with chronic hepatitis B. All were referred to hepatology, all were reviewed, and the advice was that they did not require treatment.

73. How was the care and treatment of patients diagnosed with NANB hepatitis managed at the Centre? In particular:
a. What steps were taken to arrange for, or refer patients for, specialist care?
b. What treatment options were offered over the years?
c. What information was provided to patients about the risks and benefits of specific treatments and about side effects?
d. What follow-up and/or ongoing monitoring was arranged in respect of patients who were infected with NANB hepatitis?

73.1 a) Patients with NANB hepatitis were managed by the haemophilia centre with the help of Professor Triger the hepatologist, who had a special interest in the diagnosis and management of hepatitis C in haemophilia.

73.2 b) Options for treatment of NANB hepatitis were limited but patients were advised to reduce their alcohol intake.

73.3 c) The first haemophilia Interferon trial to treat NANBH was carried out in Sheffield. Patients were informed of the Interferon side effects which were significant.

73.4 d) I believe that in the 1980s the centre had a policy to review persons with haemophilia and NANB hepatitis every 4 months in the outpatient clinic.

74. How was the care and treatment of patients once they were diagnosed with HCV managed at the Centre? In particular:
a. What steps were taken to arrange for, or refer patients for, specialist care?
b. What treatment options were offered over the years?
c. What information was provided to patients about the risks and benefits of specific treatments and about side effects?
d. What follow-up and/or ongoing monitoring was arranged in respect of patients who had been diagnosed with HCV?

74.1 a) Because Sheffield had a special interest in liver disease in haemophilia, until around 2010 the hepatitis treatments were delivered through the haemophilia centre. Patients with advanced liver disease were referred to hepatology.

74.2 b) All the available treatments were offered to patients as they became licensed including interferon, pegylated interferon, pegylated interferon and ribavirin as well as other more recent therapies.

74.3 c) The advantages and disadvantages of treatment and the relevant side effects were discussed before any treatment was commenced.

74.4 d) Follow up when HCV RNA positive is every 4 months. Once patients have gone one year after treatment and they remain HCV RNA negative i.e. achieved sustained virological response, follow up is annual. Patients with advanced fibrosis or cirrhosis have 6 monthly alfa fetoprotein estimation and liver ultrasound scans.

74.5 As of August 2020, only one patient in Sheffield continues to be HCV RNA positive because they have repeatedly refused treatment. We have tried very hard to persuade them, but we have not been successful.

75. How was the care and treatment of patients with HIV/AIDS managed at the Centre? In particular:
a. What steps were taken to arrange for, or refer patients for, specialist care?
b. What treatment options were offered over the years?
c. What information was provided to patients about the risks and benefits of specific treatments and about side effects?
d. What follow-up and/or ongoing monitoring was arranged in respect of patients who had been diagnosed with HIV?

75.1 a) Initially patients were managed from the haemophilia centre because the infectious diseases department in Sheffield did not have many more patients than us. We had the same access to anti-retroviral therapy. All patients have had 3 monthly measurements of their CD4 counts and HIV viral load for as long as these tests have been available. When in the early days patients had infectious complications, they were managed in consultation with the infectious diseases team on the haematology ward.

75.2 b) Most patients who were alive in 1996 went onto highly active anti-retroviral therapy (HAART) at that stage, but a minority who maintained good CD4 counts and low viral loads started HAART later. Before HAART was available, patients were given pneumocystis prophylaxis with nebulised pentamidine, and this was administered by the haemophilia nurses.

75.3 c) Patients were informed of the benefits and side-effects of treatments both before initiation of HAART but also at clinic visits during monitoring.

75.4 d) For the last 20 years or so we have had 1-3 monthly formal meetings between the haemophilia team and one of the HIV consultants. The data and histories of all patients are reviewed at each meeting and decisions on their treatment are made. The haemophilia consultants who see the patients at every clinic visit convey the decisions to the patients. Patients are offered the opportunity for a review by the HIV consultant in their outpatient clinic which some accept periodically.

75.5 Currently all our HIV positive patients have normal CD4 counts and their HIV viral load is fully suppressed.

75.6 Two of the haemophilia consultants and two of the nurses have worked in the haemophilia centre for more than 30 years and as might be expected we know all the patients and their families very well. In our experience, patients who express a preference, prefer to receive their HIV treatment together with their haemophilia treatment from the haemophilia centre.

76. What if any involvement did you and/or colleagues at the Centre have with clinical trials in relation to treatments for HIV and HCV? Please provide details.

76.1 We participated in some of the early trials of HIV treatments such as AZT. This was a national trial and we entered a number of haemophilia patients from Sheffield. The treatment was not really that effective, but patients were keen to try because it was the only treatment available.

76.2 We have done two trials on NANB/HCV, the first was a randomised trial of interferon monotherapy vs no treatment whilst the second was a cohort trial using another interferon therapy.

77. What arrangements were made for the care and treatment of children infected with HIV and/or hepatitis? How did those arrangements differ (if at all) from the arrangements made for adults?

77.1 As the centre is an adult haemophilia centre, it does not manage the treatment of children. Children transferred to the adult service after the age of 16 years and after that age they received the same treatment as the adult patients.

78. What if any arrangements were made at or through the Centre to provide patients infected through blood products with counselling, psychological support, social work support and/or other support?

78.1 The following information was told to me by Sister Joy Farnsworth. She was employed in November 1985 to provide counselling for the HIV positive patients. By the time she started, most of the patients were already informed they were HIV positive by Professor Eric Preston. Sister Farnsworth made the point that she had little knowledge about HIV initially but found the following meetings she attended incredibly useful in providing information/knowledge:

a) A haemophilia HIV conference in Newcastle in February 1986
b) The World Federation of Hemophilia Congress in Milan, Italy in 1986
c) An AIDS course at the Royal College of Nursing in London in 1987
d) An HIV counselling course at St Mary's Hospital in London in 1987
e) An one week attachment at the Newcastle Haemophilia Centre to visit Sister Maureen Fearn in 1986

78.2 Sister Farnsworth and Professor Preston set out to provide information and support which included:

a) In 1986 organised meetings in the evenings in the hospital board room for patients and their families to be informed about HIV. These meetings were open to all patients both HIV positive and HIV negative.
b) Sister Farnsworth set up a support group for the wives and partners of the HIV positive patients with haemophilia.
c) Sister Farnsworth met and talked to all the HIV positive patients at every clinic visit.
d) Sister Farnsworth at the time gave her personal home telephone number to all the HIV positive patients and asked them to telephone her at any time, day or night, when they wanted to discuss anything.
e) Joy Farnsworth also attended weekend support meetings organised by the haemophilia society.

79. Was the Centre allocated (whether by the DHSS/it's successors or another source) any funding to help with the counselling of patients infected with HIV?

79.1 Yes, this happened in 1985. Sister Joy Farnsworth was employed with government funding to provide counselling to HTLVIII positive patients. This was initially a one month contract, which was extended by 3 months and then by 6 months. After this the hospital took over the employment of Sister Farnsworth who was the first dedicated haemophilia nurse in Sheffield. She is still working in the haemophilia centre 35 years later.

80. What if any difficulties did you/the Centre encounter in obtaining sufficient funding for the treatment of people who had been infected with HIV and/or HCV?

80.1 I do not have any information on this. One position we felt we needed for some time but it was not funded has been a dedicated clinical psychologist to care for the HIV and HCV positive patients. We could access psychology services in the main hospital but these were not dedicated and access was difficult.

Records

81. What was the Centre's policy or practice as regards recording information on death certificates when a patient had been infected with HIV or hepatitis?

HIV

81.1 Some families felt very uncomfortable with a death certificate stating that their deceased relative died from HIV. In view of this, we completed the death certificate stating that further information may be available later. The relevant authorities would then contact us some weeks later and the exact cause of death was reported to them.

HCV

81.2 I do not recall the same stigma being attached to a deceased person dying from liver disease due to NANB hepatitis or HCV, but as the above was our policy for HIV I am sure we would have complied if asked.

82. What were the retention policies of the Centre in relation to medical records during the time you have worked there?

82.1 The policy was to retain the notes of all the HIV or HCV positive patients. For a long time these were kept in the Haemophilia centre, including those of the deceased. Due to space issues some of the records were microfilmed some time ago. Destruction of the paper copies of the medical notes of HIV and HCV positive patients stopped the day the Infection Blood Inquiry was announced in Parliament.

83. Did you maintain separate files for some or all patients? If so, why; where were those files located; and where are those files now?

83.1 Most of the notes were in a single file stored in the Haemophilia Centre at the Royal Hallamshire Hospital. There are three other possible locations for files.

a) The records before the age of 16 years are maintained at the Sheffield Children's Hospital as that is a separate hospital and Trust.
b) For HIV positive and HCV positive patients, the Infectious Disease department in Sheffield maintain their own records that are separate from the main hospital records. Patients with HIV/HCV were rarely admitted by the Infectious Disease department, as the haemophilia team dealt with all the complications – patients would be admitted under the haemophilia team and the other teams would visit and give advice.

c) Before the mid 1990s the Northern General Hospital was a separate Trust and kept their own notes. The Northern General and Royal Hallamshire Hospitals were merged into a single Trust and from then on, a single set of notes exists.

84. Did you keep records or information (e.g. information being used for the purpose of research) about any of your patients at your home? If so, why, what information and where is that information held now?

84.1 I did not keep patient information at home.

85. Do you still hold records or information about any of your patients? If so, explain why and identify the records or information that you still hold.

85.1 All the available information is held by the Sheffield Teaching Hospitals NHS Foundation Trust.

86. What system was followed for keeping records of the blood or blood products used in the Centre (both in relation to source and use)?

86.1 The Sheffield Haemophilia Centre at the Royal Hallamshire Hospital has maintained good records of all treatments given in hospital since 1st January 1976. Every single dose of clotting factor concentrate given since this time at the Royal Hallamshire Hospital is recorded. The information recorded includes the date, patient name, indication for treatment, the dose given, the name of the concentrate and the individual batch number. Furthermore, treatments were often also recorded in the patients' medical notes.

Section 5: Blood transfusion services and BPL

87. Please set out any interactions and dealings you had in relation to the blood services in your role at the Centre, insofar as relevant to the Inquiry's Terms of Reference.

87.1 I am aware that in the past the Blood Transfusion Services provided clotting factor concentrates to hospitals, but this was before I started training as a haematologist.

87.2 During training, all haematologists spend 3-6 months at the regional transfusion centre, but this is largely to do with blood transfusion training and did not involve clotting factor provision. I did my blood transfusion training in the early 1990s at the Regional Blood Transfusion Centre at Longley Lane in Sheffield.

88. Please set out any interactions and dealings you had in relation to BPL in your role at the Centre, insofar as relevant to the Inquiry's Terms of Reference.

88.1 My dealings with BPL have been similar to those I had with any other manufacturer that produces blood products that we used clinically. I have

never worked for them, nor on any project with them. As a Centre we participated in a clinical trial of one of their pure FVIII concentrates called Optivate.

88.2 Recently I wrote two reports in support of a NICE application of a product BPL produces called Coagadex. I was not paid and was not offered any inducements to write these reports. I wrote them because I believe this product is safer and is superior to the products we currently use to treat severe factor X deficiency. The NHS initially refused to fund its use but recently it has allowed limited use for prophylaxis.

Section 6: UKHCDO

89. Please describe your involvement with UKHCDO (including any of its working parties, committees or groups). [1]

89.1 My main involvement with the UKHCDO started in 1998 when I became a member of the advisory committee. This is the main committee of the UKHCDO and it has one representative from each of the comprehensive care haemophilia centres in the UK. Prior to 1998 Professor Eric Preston was the Sheffield representative on UKHCDO activities but as he was planning to retire in 2000, I started to represent Sheffield in 1998.

89.2 I have been a member of the UKHCDO adverse event committee while it has been active since 1998. The name of this committee has changed over the years, starting with Transfusion Transmitted Infection committee, then Morbidity and Mortality working party, and more recently Comorbidities working party. I was the chair of this committee during 2009-2012 when its name was Morbidity and Mortality working party.

89.3 Because I was chair of the Morbidity and Mortality working party during 2009-2012, I was automatically a member of the Data Management working group, which consisted of the chairs of all the UKHCDO committees.

89.4 Whilst I was a member of the UKHCDO advisory committee I was one of three authors who wrote the Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary disorders (Keeling D, Tait C, Makris M. Haemophilia 2008; 14:671-684)

89.5 The UKHCDO introduced an orange card system for reporting concentrate related adverse events in the early 1990s. In 2008, I and some European Colleagues developed an electronic haemophilia adverse event reporting system for Europe called EUHASS. The EUHASS software was written and maintained by MDSAS Ltd who are based in Manchester. MDSAS Ltd are also the IT company who maintain the National Haemophilia Database and about 8-10 years ago the UKHCDO moved from the orange card reporting to the electronic reporting system software developed by EUHASS. For the last few years, I get an automatic email with details of every adverse event reported (from Europe as well as the UK) as soon as an event is reported. In

this way I can alert the relevant people and the UKHCDO can make rapid decisions if required.

90. During the period that you were involved with UKHCDO, please outline:
a. The purpose, functions and responsibilities of UKHCDO, as you understood them;

90.1 The UKHCDO is the association of doctors working in haemophilia centres in the UK. The stated aims of the organisation are:
To preserve, protect and relieve persons suffering from Haemophilia and other inherited bleeding disorders.
To advance the education of the medical profession, the nursing profession, professions allied to medicine and the general public in the knowledge of Haemophilia and other inherited bleeding disorders and their treatment.
To promote or assist in the promotion of audit and research into the causes, prevention, alleviation and management of Haemophilia and other inherited bleeding disorders and their treatment.

90.2 I have been involved with the UKHCDO since 1998, when I followed Professor Eric Preston in representing Sheffield on the advisory committee. I believe during my association with the UKHCDO it has been an effective organisation in bringing the haemophilia medical community together. I believe the UK haemophilia medical community in the last 20 years has been the most well organised and effective internationally.

b. The structure, composition and role of its various committees or working groups;

90.3 The organisation has its secretariat in Manchester, and this is where the National Haemophilia Database is also held. There is an elected chair and vice chair as well as a secretary and a treasurer. The main working committee of the organisation is the advisory committee where each comprehensive care haemophilia centre in the country is represented. The advisory committee meets every 3-4 months and makes all the important decisions. There are also various committees and working groups such as paediatrics, inhibitor, musculoskeletal, von Willebrand disease, rare bleeding disorders, and comorbidities working party.

c. The relationships between UKHCDO and pharmaceutical companies;

90.4 I can only comment for the last 20 years. The UKHCDO has to raise its own funding to employ its staff and run the National Haemophilia Database. As it only has around 100 members, it cannot raise the required funding from its membership. The NHS pays for part of the upkeep of the database because it is used to make national concentrate purchasing decisions. In terms of pharmaceutical company funding this is provided in two ways:

90.5 The different companies have display stands at the annual general meeting but although they attend, they have no input into the content of the program. The UKHCDO uses the database to carry out analysis that the pharma

industry would like but this only relates to the use of their products in the UK. The pharma industry has no input on how the work is done, analysed or presented.

d. How decisions were taken by UKHCDO;

90.6 The advisory committee is the main body of the UKHCDO that makes all the decisions and has a representative from every comprehensive care haemophilia centre. In my experience, all decisions usually follow extensive discussions among the representatives present. Usually the advisory committee will provide direction about how the chairperson should act to carry out its decisions.

e. How information or advice was disseminated by UKHCDO and to whom;

90.7 Information and advice are usually disseminated by the Chairperson on behalf of the organisation. The advice disseminated will usually have been discussed at the advisory committee. All members of the organisation will get the disseminated information.

f. Any policies, guidance, actions or decisions of UKHCDO in which you were involved and which relate to:
i. the importation, purchase and selection of blood products;
(In answering this question, you may be assisted by the bundle of minutes of UKHCDO meetings at item 2 of this request and the 'Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders', by Keeling et al, published in Haemophilia (2008). Haemophilia (2008), 14, 671-684 [ABMU0000031_009].)

90.8 I have not been involved in any decisions relating to the importation or purchasing of blood products. I was one of three authors on the 2008 UKHCDO guideline on the selection of products to treat inherited bleeding disorders. Although this guideline was written by the three authors, there was extensive discussion about different aspects at the UKHCDO advisory committee. The key features of the guideline were:

- Discuss with the patient the advantages and disadvantages of any new treatment, and following an informed decision, document the consent in the notes.
- Avoid exposure to concentrates, blood products and animal proteins if possible
- Select a licensed product over an unlicensed one
- Select a recombinant concentrate over a plasma derived one
- Select a pure single factor product rather than a product which is a mixture of several factors
- Select a concentrate that has undergone two different viral inactivation procedures over a product that has had one viral inactivation step

90.9 The guideline recommended specific treatments for each individual bleeding disorder. Although in the haemophilia community the risk of infection transmitted by the product has been the main safety concern and was considered, the additional safety issues of inhibitor development and thrombosis featured highly in what the guideline ended up recommending.

ii. alternative treatments to factor products for patients with bleeding disorders;

90.10 The guideline referred to above stated that "Desmopressin, a synthetic analogue of the non-peptide arginine vasopressin, remains the treatment of choice in the prophylaxis and treatment of haemorrhagic episodes in patients with mild haemophilia A or VWD". Although the suggestion of using Desmopressin was clearly stated in this guideline, in my experience this was routinely used for at least the last 20-30 years. A significant advance has been the introduction of the high concentration desmopressin (15 micrograms/ml) that can be given subcutaneously, and which has significantly less side effects in terms of headache and facial flushing.

90.11 The guideline also recommended the use of tranexamic acid, which was already widely used by the haemophilia community for mouth bleeding and in relation to dental extractions.

iii. the risks of infection associated with the use of blood products;

90.12 I am not aware of any published UKHCDO guidelines during the 1980s. I have seen references to guidelines during this period, but they were not published in journals and I have never seen them.

90.13 As I have indicated in answers to earlier questions blood products were safe from infections by the time I started in haemophilia in 1987.

90.14 There was advice to vaccinate patients against hepatitis A and B and to use Desmopressin rather than blood products. There was pressure on the health authorities to allow haemophilia centres to use recombinant concentrate after these were licensed.

iv. the sharing of information about such risks with patients and/or their families;

90.15 I do not know how this was dealt with as it was before I started in haemophilia. Although concentrates were "safe" from infection by 1987, we always used Desmopressin if possible, kept patients on the same concentrate for long periods and in some cases avoided treatment altogether. Some patient were very anxious about receiving even virally inactivated concentrates and often avoided contacting us about treatment of bleeds.

v. obtaining consent from patients for the testing and storage of their blood, for treatment and for research;

90.16 I am not aware of what the UKHCDO recommendations for these issues were in the 1980s, if there were any. The recommendations for getting consent for testing was limited to genetic testing and has been in place for 10-20 years. Research consent has been in place for many years, but this was based on general national policies rather than specifically directed by the UKHCDO.

vi. measures to reduce risk;

90.17 Most relevant measures are included in the guideline document referred to in f(i) above. The full reference is:

Keeling D, Tait C, Makris M. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. Haemophilia 2008; 14:671-684

90.18 The UKHCDO working parties on Transfusion Transmitted Infection and Morbidity and Mortality, also published two guidance documents on vaccination of persons with inherited bleeding disorders. Although these give advice for vaccination for all infectious diseases, they also deal with vaccinations against hepatitis A and B to reduce any blood product transmission. The references are:

Makris M, Conlon C, Watson HG. Immunization of patients with bleeding disorders. Haemophilia 2003; 9:541-546

Watson HG, Wilde JT, Dolan G, Millar C, Yee TT, Makris M. Update to UKHCDO guidance on vaccination against hepatitis A and B viruses in patients with inherited coagulation factor deficiencies and von Willebrand disease. Haemophilia 2013; 19:e174-e192

vii. vCJD exposure;

90.19 The UKHCDO has largely followed the advice of the national bodies such as the CJD Incidents Panel. The only exception was the decision in 2001 to inform patients who were treated with concentrate from implicated batches; whilst the Department of Health advice was not to tell the patients, the UKHCDO decision was that patients should be informed.

90.20 The UKHCDO had been pushing for recombinant concentrates even before the issues with implicated batches of blood derived concentrates. The UKHCDO helped in the gradual introduction of concentrates in the UK.

viii. treatments for HIV and HCV.

HIV

90.21 I am not aware of the UKHCDO producing guidelines or advice on the treatment of HIV infection. The management of HIV infection was local. In the larger haemophilia centres it was carried out primarily through the haemophilia centres, whilst in the smaller centres this was devolved to the infectious diseases or HIV departments.

HCV

90.22 The UKHCDO produced two guideline documents on the diagnosis, follow-up and treatment of hepatitis in haemophilia. I was the first author of the 2001 guideline and last author on the 2011 guideline. The published references are:

Makris M, Baglin T, Dusheiko G, Giangrande PLF, Lee CA, Ludlam CA, Preston FE, Watson HG, Wilde JT, Winter M. Guidelines on the diagnosis, management and prevention of hepatitis in haemophilia. Haemophilia 2001; 7:339-345

Wilde JT, Mutimer D, Dolan G, Millar C, Watson HG, Yee TT, Makris M. UKHCDO guidelines on the management of HCV in patients with hereditary bleeding disorders 2011. Haemophilia 2011; 17:e877-883

Section 7: Pharmaceutical companies/medical research/clinical trials

91. Have you ever provided advice or consultancy services to any pharmaceutical company involved in the manufacture and/or sale of blood products? If so, please list the names of the companies and give details (including dates) of the advisory or consultancy services that you provided.

90.1 I do not have records from the earlier period. The list below lists my involvement with blood product manufacturers for consultancy or advisory activities or research funding for the last 10 years. I specifically do not get involved in terms of consultancy or advisory board meetings if they are about marketing of a company's products.

91.2 In addition to the events listed below, for the last 10 years or so I have been on a Data Safety Monitoring Board (DSMB) for two clinical trials for CSL Behring. My involvement is compensated by the hour spent on it and paid to the University of Sheffield. The value is less than £1000 per year.

91.3 During 2008-2020, I have been the lead of the European Haemophilia Safety Surveillance System (EUHASS) which receives funding from the pharmaceutical industry. EUHASS is a not for profit project and is run on behalf of the European health professionals (EAHAD) and the patients' (EHC) organisations. For the period 2008-2015, 60% of the funding was provided by the European Commission. During 2008-2015, 40% of the funding was provided by Industry, whilst since 2015 the project is entirely funded by the Pharmaceutical Industry who have no input in how the project is carried out or reported. The companies supporting the project provide funding for an equal amount. The companies supporting EUHASS financially are Bayer, BPL, CSL Behring, Kedrion, NovoNordisk, Octapharma, Pfizer, Roche, SOBI and Takeda. In the past Grifols, LFB and Biotest supported EUHASS but they no longer do so.

91.4 2020
Consultancy: Membership of the Jury of the Annual Martin Villar Research Grant Awards 2020 (Activity involves scoring research grant applications over 2 rounds)
Company sponsoring the activity: Grifols
Payment: £2,002

2019
Consultancy: Membership of the Jury of the Annual Martin Villar Research Grant Awards 2019 (Activity involves scoring research grant applications over 2 rounds)
Company sponsoring the activity: Grifols
Payment: £2,012

2017
Advisory Board Meeting participation
Company: Shire
Payment: £1,150

2016
Participation at a company symposium at the EAHAD meeting
Company: Grifols
Payment: £1,300 to the University of Sheffield

2014
Sponsorship to attend the World Federation of Haemophilia meeting in Melbourne
Company: Bayer
Value: Flight, hotel and meeting registration. No fee

2013
Chairing of a session at an educational meeting
Company: Bayer
Value: Train ticket to Birmingham. No fee

Consultancy: Participation in a research meeting on inhibitors in New York
Company: Baxter
Value: Flight, hotel and fee of £900 to the University of Sheffield

Consultancy: Participation in a research meeting in Dublin
Company: Baxter
Value: Flight and hotel. No fee

Consultancy: Lecture at a company symposium at a WFH meeting, Dubai
Company: Biotest
Value: Flight, hotel and fee to the University of Sheffield

Consultancy: Lecture at the German Haemostasis meeting, Hamburg
Company: Baxter
Value: Flight and hotel. No fee

2012
Consultancy: Participation in a Research meeting in Miami
Company: Baxter
Value: Flight and hotel. No fee

Consultancy: Lecture at a meeting in Sweden
Company: Octapharma
Value: Hotel, flight and fee of £793 to University of Sheffield

Consultancy: Lecture at a meeting in Italy
Company: Biotest
Value: Hotel, flight and fee of 1000 euro to University of Sheffield

Advisory Board meeting participation
Company: BPL
Payment: £1,250 to University of Sheffield

Consultancy: Lecture at meeting in Birmingham
Company: Bayer
Payment: £750 to University of Sheffield

2011
Consultancy: Attendance at an educational meeting in Birmingham
Company: Bayer
Value: Train fare and hotel. No fee

Consultancy: Attendance at an educational meeting in Barcelona
Company: Baxter
Value: Flight and hotel. No fee

Consultancy: Lecture at a symposium at the ISTH meeting
Company: Bayer
Value: Flight, hotel, registration. No fee to me.

Consultancy: Lecture at the EHC meeting Budapest
Company: Octapharma
Value: Flight and hotel. No fee.

2010
Consultancy: Participation at an educational meeting in Birmingham
Company: Bayer
Value: Train fare and hotel. No fee.

Consultancy: Sponsorship to attend the World Federation of Haemophilia meeting, Buenos Ayres
Company: Bayer
Value: Flight, hotel and registration. No fee.

Consultancy: Participation in educational meeting in Oxford
Company: Biotest
Value: Train fare and hotel. No fee.

92. Have you ever received any pecuniary gain in return for performing an advisory/consultancy role for a pharmaceutical company involved in the manufacture or sale of blood products? If so, please provide details.

92.1 See answer to question 91

93. Have you ever sat on any advisory panel, board, committee or similar body, of any pharmaceutical company involved in the manufacture or sale of blood products? If so, please provide details of your involvement (including dates) and of any financial or other remuneration you received.

93.1 See answer to question 91

94. Have you ever received any financial incentives from pharmaceutical companies to use certain blood products? If so, please provide details.

94.1 No, I have not.

95. Have you ever received any non-financial incentives from pharmaceutical companies to use certain blood products? If so, please provide details.

95.1 No, I have not.

96. Have you ever received any funding to prescribe, supply, administer, recommend, buy or sell any blood product from a pharmaceutical company? If so, please provide details.

96.1 No, I have not.

97. Please explain the nature of any relationship which you had with the pharmaceuticals companies Bayer, Aventis and Baxter. The Inquiry refers you to the document at [HCDO0000110_165].

97.1 This was a questionnaire sent out by the UKHCDO in 2003. The UK was purchasing FVIII concentrate nationally and there were several products on the market. We were not asked to choose which concentrates we wanted to use. The question was regarding what proportion should be available e.g. only select the two cheapest and go with those only or give the majority to the two cheapest and allow some patients to use other products. My choice here for 70% of the contract to go to the two cheapest and 30% to the others, was because it allowed choice for patients who did not wish to change product based on price alone.

97.2 The form asked to declare interests with the pharmaceutical industry, and I declared:

Bayer: Sponsored me in 2002 to attend the World Federation of Haemophilia meeting in Seville, Spain. I also attended one dinner hosted by Bayer during the International Society of Thrombosis and Haemostasis (ISTH) meeting in 2003.

Aventis: I attended two dinners hosted by Aventis during the ISTH 2013 meeting and during the American Society for Haematology meeting.

Baxter: I gave 2 lectures and chaired a meeting for which I received a fee, but I do not have details of this.

98. What regulations or requirements or guidelines were in place concerning declaratory procedures for involvement with a pharmaceutical company? If you were so involved, did you follow these regulations, requirements and guidelines and what steps did you take?

98.1 The regulations have changed several times over the last 33 years. My primary employer is the University of Sheffield that allows me to conduct up to 35 days of consultancy per year, as long it is approved by the head of department. All my consultancies and other activities with pharmaceutical companies are approved by the head of department. I also declare the relevant activities to the Trust when it involves a company that sells products to the Trust.

99. Have you ever undertaken medical research for or on behalf of a pharmaceutical company involved in the manufacture or sale of blood products? If so, please provide details.

99.1 In 2002 we participated in a commercial study of a new FVIII concentrate by BPL.

100. Have you ever provided a pharmaceutical company with results from medical research studies that you have undertaken? If so, please provide details.

100.1 In 2002 we participated in a study of a new FVIII concentrate called Optivate from BPL. This was a commercial sponsored study and the data were provided to the company.

100.2 Since 2008 I have been running the European Safety Surveillance System. Every year we produce a safety report for every concentrate used in Europe (approx. 70) and the cumulative reports are passed onto the companies that make the products.

101. If you did receive funding from pharmaceutical companies for medical research, did you declare the fact that you were receiving funding and the source of the funding to your employing organisation?

101.1 All research funding including from pharmaceutical companies is paid to my employer, the University of Sheffield.

Section 8: vCJD

102. When and in what circumstances did you become aware of the risks of transmission of vCJD associated with the use of blood and blood products?

102.1 There was no single point in time when I was made aware of the risks of transmission of vCJD associated with blood and blood products. Clearly in the early 1990s living in the UK, the importance and information about Bovine Spongiform Encephalopathy (BSE) was ubiquitous in the news. The paper describing the cases of variant CJD in the Lancet (Will RG, et al. Lancet 1996; 347:921-925) and linking them to BSE was key because it made the jump from species to species clear. It was after this that I and other UK haemophilia doctors started wondering whether it could be transmitted by blood transfusion. The concern increased when BPL released information in 1997 that plasma from two blood donors who subsequently developed vCJD, went into the pool from which clotting factors were manufactured. Recombinant FVIII concentrate which did not have any infection risks was available but not used in the UK which was rather frustrating. In a letter to the Lancet Professor Ludlam (Ludlam CA. Lancet 1997; 350:1704) expressed the views of the UK haemophilia medical community at the time.

103. How and by whom were decisions taken (either nationally or locally or both) as to the information that should be provided to patients about vCJD and as to any steps which should be taken in relation to patients and their care and treatment?

103.1 We followed national advice and guidance at every step.

103.2 In 2001 BPL informed us that another blood donor, whose plasma was used to manufacture coagulation factor concentrates, subsequently developed vCJD and gave us the batch numbers to which our patients were exposed. Although the Department of Health advised that the patients who received the relevant batches ("notified batches") should not be told, I along with the rest of the UKHCDO centre representatives disagreed and decided to inform the patients. A national policy was quickly developed and Professor Frank Hill on behalf of the UKHCDO provided templates for letters to be sent to patients. These letters were sent to all patients who received UK plasma sourced concentrates. The letter was one page with a list of eight bullet points about vCJD and a reply sheet asking the patient to tell us if they wanted to discuss this further in person or on the telephone and if they wanted to know whether they had received any of the notified batches. Patients who wanted to know by letter received notification as to whether they did or did not receive any notified batches of concentrate.

103.3 On 9th September 2004 we received a letter from Professor Frank Hill, on behalf of the HPA and UKHCDO asking us to send out letters by first class post to all patients registered with us who received treatment with concentrate between 1980-2001. At the same time, we were provided with a list of batches of concentrate that were made from plasma of persons who subsequently developed variant CJD. We were told to send the letters to all patients treated with concentrate not just those at risk. We were not very happy with this

because lots of unaffected patients would get the letters but as this was a national policy we agreed to comply.

103.4 On 20th September 2004 we sent out 731 letters to patients treated with concentrate between 1980-2001 at the Sheffield Haemophilia Centre at the Royal Hallamshire Hospital. The letter was the template provided by the UKHCDO, was four pages long and it was signed by me and the two other haemophilia consultants, Drs Kingsley Hampton and Rhona Maclean. The letter included a patient reply sheet which asked if they would like to know:
a) if they received UK sourced plasma derived clotting factor
b) if they received an implicated batch
c) if they would like a specific consultation with one of the consultants to discuss the issue

103.5 The last sentence of the letter mentioned that they could telephone the Haemophilia Centre to discuss the issue with us. The consultants and nurses remained available in the haemophilia centre for several days (including in the early evening and on Saturday morning) but we received very few telephone calls about it.

103.6 For those patients who returned the reply sheet, we followed their wishes as to whether they wanted to be informed or have a consultation with us.

103.7 We formally saw for counselling 49 patients, and in addition the issue was discussed in more detail with all relevant patients when they attended for their regular outpatient visits to the haemophilia centre.

103.8 The adult Sheffield Haemophilia centre at the Royal Hallamshire Hospital had a total of 128 patients who received UK sourced plasma concentrates between 1980-2001 and 27 of these received implicated batches.

103.9 By December 2004, we went through the notes and our infusion records for all the 731 patients who received the letter on 20th September 2004. Those who did not receive a UK plasma sourced concentrate were written to and informed of the fact. For patients who received an implicated batch and did not respond to our letter, we wrote to their General Practitioners explaining the situation.

103.10 On 17th February 2009 we received a letter from the UKHCDO about a patient with haemophilia who died and at autopsy was found to have prions in the spleen. We were asked to send out a letter based on a template provided, informing patients who received UK plasma products between 1980-2001 about the patient with haemophilia who died and found to have prions in their spleen. The two-page letter that went out included a six-page information letter from the Health Protection Agency.

103.11 In September 2013 when the advice about the risk period changed from 1980-2001 to 1990-2001, we wrote to the relevant patients i.e. those who received UK source plasma concentrates only during 1980-1989, informing them that they were no longer at risk.

104. What was the process at the Centre for informing patients about possible exposure to vCJD?

104.1 See answer to question 103 above.

105. How and when were patients told of possible exposure to vCJD?

105.1 See answer to question 103 above.

106. What information was provided to patients about the risks of vCJD?

106.1 We provided the written information that was supplied to us from the UK national bodies and/or the UKHCDO.

107. What counselling, support and/or advice was offered to patients who were informed that they might have been exposed to vCJD?

107.1 Some patients telephoned the haemophilia centre and spoke to our haemophilia clinical nurse specialists. Others were seen in person by myself, or one of my consultant colleagues and/or haemophilia clinical nurse specialists. In general, we explained the uncertainty, the meaning of being "at risk for public health purposes", the fact that no person with haemophilia had developed vCJD despite having over 3000 patients at risk in the UK. Most of the patients in the at-risk group were patients who we know very well, as we have cared for them for over 20 years at the time. Patients were invited to contact us again to discuss it at any time.

108. What measures were put in place, from a public health perspective, in relation to the care and treatment of patients who had or might have been exposed to vCJD?

108.1 All at-risk patients were informed not to donate blood or tissue and to tell the surgeons about their at-risk category. They were also advised to tell their relatives in case they were not able to convey the information themselves.

108.2 We maintained an up-to-date list of the patients at risk in Haemophilia Centre so we could quickly check about patients having surgery or procedures who may have not remembered to tell the surgeon or operator. Because of the need for blood product support the haemophilia centre is informed about all patients having procedures or surgery.

108.3 We used the information about different types of surgery or procedures from the CJD Incidents Panel to decide on the management of the surgery/procedure.

108.4 For all patients at-risk having procedures or surgery we informed Dr CJ Bates, Director of Infection Prevention and Control and consultant microbiologist at our hospital, who provided individual advice using individual letters addressed to the relevant surgeon or operator.

109. What steps were taken at the Centre following notification from BPL in 2001 that a plasma donor had been diagnosed with vCJD? (In answering this question, you may find it helpful to refer to the Centre Doctors' Questionnaire from The Haemophilia Society at [HSOC0004244] and the letter from you dated 16 January 2001 to CSUH [DHSC0004494_047 and DHSC0004494_048.)

109.1 This was partially answered in my response to question 103.

109.2 On 15 January 2001, I attended a meeting of the UKHCDO where the BPL notification that a plasma donor was diagnosed with vCJD was discussed. The Haemophilia Society had written a letter and were about to send it to their members hence the need for urgent action. The advice from the Department of Health (based on a letter by Graham Winyard dated 6 February 1998) was not to inform the patients, but those present at the meeting felt that this was not right and that the patients should be informed. There was discussion about how to implement this, and it was decided to have a national approach in which patients who received UK concentrate will be written to and asked if they want to know if they received an implicated batch.

109.3 The letter was one page with a list of eight bullet points about vCJD and a reply sheet asking the patient to tell us if
a) they wanted to discuss this further in person or on the telephone,
b) whether they wanted to know if they received any of the notified batches.

109.4 In Sheffield the letter went to all the concentrate treated patients and were offered an appointment. Patients who wanted to know by letter, were written to notifying them as to whether they did or did not receive any notified batches of concentrate.

109.5 Patients who attended in person were seen by a consultant and on average it took 30 minutes per patient.

110. Why was the view of the UKHCDO not to introduce a risk score to patients to inform the approach to patient counselling and did you agree with it? (See, Minutes of the Thirteenth Meeting of UK Haemophilia Centre Doctors' Organisation Advisory Committee, 16 February 2004, [BART0000930]).

110.1 The Chairman of the UKHCDO, Dr Frank Hill, commented on this but details of the risk score were not presented at the meeting. I have not seen the risk score in question. I am not aware of a haemophilia specific risk score ever being developed, and I am not aware that the risk score referred to related to haemophilic risk factors as well. Although desirable to know the level of risk, the uncertainty was too great to develop a risk score. Furthermore, the information was developing and concepts of risk were changing.

111. Where certain patients were initially incorrectly marked as "at risk" of variant CJD, and this status changed, was this communicated to those patients? [HCDO0000616_001]. How long did it take for these patients to receive correct information regarding the risk?

111.1 The unredacted version of [H CDO0000616_001] was located and I can confirm prompt communication of the correct information. My letter [H CDO0000616_001] to Mrs Dewhurst at the National Haemophilia Database asking for more information was dated 1 September 2010 (although was dictated 30 July 2010). She must have replied but I do not have her response. We do have correspondence in all the patients' notes regarding these events and how the information was communicated.

111.2 A) All patients in section A were only treated with this batch of concentrate in Sheffield and were therefore not at risk. I wrote to all three of them to inform them they were no longer considered to be at risk on 4th October 2010. The letters were typed between 7-20 October 2010.

111.3 B) The patient in section B was a Royal Free Hospital patient who was in Sheffield as a visitor when she was exposed to this concentrate. I wrote an explanatory letter to Professor E Tuddenham at the Royal Free Hospital regarding this patient on 4th October 2010.

111.4 C) These two patients were students at Sheffield University. They received multiple other batches made from UK plasma (at their local haemophilia centres before moving to Sheffield to study) so they would still be considered to be at risk. I wrote to their local haemophilia centres on 1st October 2010 regarding this issue to clarify the position.

111.5 I consider that this information was communicated promptly despite the varied circumstances of the three different groups.

Section 9: Financial Support Schemes

112. What if any involvement did you have with any of the trusts or funds (the Macfarlane Trust, the Eileen Trust, the Macfarlane and Eileen Trust, the Caxton Foundation, the Skipton Fund, the English Infected Blood Support Scheme 'EIBSS') set up to provide financial assistance to people who had been infected. If you have been involved with one or more of the trusts or funds, please address the following matters:
a. How you came to be involved in the trusts or funds, whether you held any formal position and, if so, for how long you held that position.
b. What if any involvement you had in the development of any criteria or policies relating to eligibility for financial assistance.
c. Any advice you provided to any of the trusts or funds.
d. Whether you were involved in the assessment of any applications to the trusts or funds by people who had been infected.

112.1 a) I came to be involved via my position as a Haemophilia Centre director. I have never held any formal position in any of these Trusts.

112.2 b) I have not been involved directly in the development of the criteria other than commenting on the more recent criteria. More recently, I felt there was a

reliance on subjective responses which the haemophilia staff completing the application had to support and I pointed this out. In my view the assessors at the Trusts should have considered the patient's written statements of the impact of hepatitis C, rather than getting the haemophilia centres to comment on whether they believed their patients or not.

112.3 c) Not as far as I can recall

112.4 d) I was the Sheffield Haemophilia doctor that completed both the stage 1 and stage 2 Skipton Fund applications and the later applications under the EIBSS Special Category Mechanism.

113. To what extent did the Centre and its staff, including you, inform patients about these different trusts and funds?

113.1 We took a proactive approach. Since we knew who were infected, we contacted, usually by letter, everybody who was eligible for payments from the Skipton Fund, Macfarlane Trust and the EIBSS. This included contacting families of the deceased.

114. Did the Centre have any policy or guidance for staff members in relation to referring patients to the trusts and/or schemes for support?

114.1 We had a blanket policy to refer all eligible patients to the trusts/schemes.

114.2 Essentially this was a three-person team responsibility. Primarily Sister Joy Farnsworth, supported by Sister Caryl Lockley, contacted all the patients. Those who wished to apply, sent their partially completed forms to the Sheffield Haemophilia Centre. These were passed onto me who located the data, completed the forms and posted them to the Trusts.

114.3 The later applications which required a statement on the basis of psychological impact or chronic fatigue, were dealt with differently. Patients were contacted and offered an appointment with Sister Lockley and the haemophilia social worker, Sarah Bowman. Patients were assisted in completing the form and Sister Lockley wrote a supporting statement. I reviewed all these and I completed my part before sending them off.

115. What kind of information did the Centre (whether through you or otherwise) provide to the trusts and funds about or on behalf of patients who were seeking assistance from them?

115.1 We completed the relevant forms.

116. Did the Centre or any of its staff, including you, act as a gateway for determining whether a particular patient met the eligibility criteria for the receipt of assistance from any of the trusts and funds?

116.1 Only in as far as advising the patients whether they were eligible to apply. For example, we advised patients who were HCV antibody negative, not to apply

as they were ineligible. We did not feel it was our role to act as "gate keepers".

117. Was the Centre or any of its staff, including you, involved in assessing or determining applications made by patients for assistance from the trusts and funds? If so please describe that involvement.

117.1 No, we did not. We felt this was not our job to judge and we completed all forms that our patients sent us. I do not recall refusing to support any application from an HCV positive patient. We have supported 55 applications to the EIBSS for stage 2 payments so far, all of which have been successful.

118. Please consider the Report of the Hepatitis C Working Party to the Haemophilia Society [HSOC0028466]. Please describe your involvement and what the Working Party was seeking to achieve.

118.1 My involvement in this working party covered the medical parts. I wrote and revised some of the medical section at the start of the report. I was asked to provide data estimating where UK haemophilia patients were at the time, in terms of their hepatitis C natural history. My task was to provide the data shown in Appendix E, based on the best available estimates at the time. I had no involvement at all in the financial aspects of the report.

118.2 I believe this was a report by a working group organised by the UK Haemophilia Society, with the aim of putting pressure on the government to provide compensation to patients with haemophilia and hepatitis C.

119. In relation to the Skipton Fund,
a. You corresponded with the Skipton Fund about its request for supporting documentation to be supplied for all applications to the scheme (see [ABMU0000013]). Please set out what you can recall about this issue.

119.1 This is the first time I have seen ABMU0000013 as it was not copied to me. I do not have a copy of my letter to the Skipton Fund. The document I was given access to has an attachment (my letter) but this was not included on the scanned document. I was aware that the episode of fraud occurred at the Skipton fund and the application forms were altered as a result. Here I was simply asking the Skipton fund to write to Professor Charles Hay, who was the chairman of the UKHCDO, so he could alert other haemophilia doctors in the UK of the changes to the application form.

b. You wrote a paper dated August 2006 setting out your personal view of how to deal with the Skipton Fund and its appeal system (see [DHSC0011743]). Please explain your concerns.

119.2 My view was that when the Skipton Fund was set up, it would have been easier to pay the stage 1 payment to everybody who was HCV antibody positive. This did not happen, and I felt that the system used, unfairly affected some individuals. Haematologists who were not interested in chronic hepatitis C or how the Skipton application system worked, were unlikely to know the

intricacies of the system which is why I wrote this document and sent it to all haemophilia doctors in the UK.

119.3 As a doctor that has known the patients and their families for many years, I felt that in some cases they were unfairly dealt with by not being awarded the payment through no fault of their own.

119.4 For example, if the patient died before 29 August 2003 the families were not allowed any payment which appeared grossly unfair. This has since been rectified.

119.5 I was also hearing from our patients, that their friends in other centres could not apply because the relevant medical notes were destroyed years earlier.

119.6 Finally, the possibility of showing chronicity (i.e. abnormal liver function tests more than 6 months after first exposure to concentrate) was not known to most haematologists but in Sheffield we were able to successfully apply for some of our patients on the basis of this.

119.7 I never found out how many patient applications were rejected or how many appeals, if any, were successful.

120. Please consider the report entitled 'Reviewing the natural history of hepatitis C infection' [DHNI0000371] produced by the Expert Working Group in 2010. What was your involvement in the Group, what was its remit and what was the purpose of the report?

120.1 This is a largely academic paper on the current knowledge of chronic hepatitis C. I believe this Group was set up when new hardship payment regulations were being considered. As far as I recall, I only participated in one meeting by telephone conference call and the report was written by the Advisory Group on Hepatitis (I was never a member of this group). I believe they invited the UKHCDO to have two representatives on the writing group and Professor Charles Hay and myself participated. Our role was to comment on an advanced draft of the manuscript.

121. Based on your own dealings with any of the trusts and funds and/or based on your knowledge of the experiences of the Centre's patients in relation to them, do you consider that the trusts and funds were well run? Do you consider that they achieved their purpose? Were there difficulties or shortcomings in the way in which they operated or in their dealings with beneficiaries and applicants for assistance?

121.1 In general, I believe the trusts worked well, especially more recently. The most frustrating aspects in my experience have been:

121.2 a) Patients who are HCV antibody positive and who have cleared the HCV spontaneously are not able to get any financial support. The psychological impact of the HCV in many of them has been significant and for the different schemes to not recognise this, I feel is unfair. The lack of chronic liver disease

does not mean that patients who were infected with HCV have not suffered, and are not suffering, psychologically.

121.3 b) Because in Sheffield two of the doctors and two of the nurses worked in the haemophilia centre for over 30 years each, we know all the patients very well and have been able to support their applications. Many of our patients have told us very frustrating stories of their friends attending other centres who have not been able to find a doctor to support their application, even though their circumstances are very similar to our patients in terms of being infected. This does not seem to be fair or equitable.

121.4 c) There was no attempt by the funds to work with the local haemophilia centres to reach the patients or to educate the staff and doctors about the application processes either originally by the Skipton Fund or more recently by the EIBSS. After a UKHCDO advisory committee meeting in early 2011, it became clear to me that the majority of the new generation of haemophilia doctors knew little about HCV and haemophilia or about how the Funds worked. In an attempt to help I produced an information sheet that was sent to all UK Haemophilia doctors (Appendix 3).

Section 10: Current haemophilia care and treatment

(Please note that the questions in this section are aimed at enabling the Inquiry to understand how haemophilia care is currently provided and how the provision of care and treatment and the approach to patients may have changed over the years).

122. *Please describe:*
a. how the provision of care and treatment for bleeding disorders is currently organised at the Centre; and

122.1 The Sheffield Haemophilia and Thrombosis Centre provides comprehensive haemophilia care to all the patients with inherited bleeding disorders living in Sheffield and the surrounding areas. It also provides care to some patients living further afield who have requested transfer to and receive care from the Sheffield centre, or Sheffield patients who moved away but wish to continue to receive their care from the Centre. The centre is located within the Royal Hallamshire Hospital, next to the haematology unit and within walking distance of the attached obstetric hospital, Charles Clifford Dental Hospital (where the Special Care Dentists work), and the Sheffield Children's Hospital (allowing effective transition pathways and close working relationships with the haemophilia children's team). Care is provided for all patients across the trust sites (and the community when essential to do so).

122.2 All registered patients with inherited and acquired bleeding disorders have 24/7 provision of advice for bleeding concerns. During Monday to Friday 8:00am to 5:00 pm this is provided through the haemophilia centre via the Clinical Nurse Specialist team with attending haemostasis consultant cover and junior medical cover as needed. Outside of these hours, patients telephone the hospital switchboard and ask to be speak to the haematology registrar.

122.3 We have 5 consultants who are specialists in haemophilia and thrombosis, 6 Clinical Nurse Specialists whose main focus is bleeding disorders, 1 haemophilia physiotherapist, 0.5 WTE specialist social worker, 1.4 WTE data managers, secretarial and reception support, as well as a state-of-the-art NHS coagulation laboratory.

122.4 The Centre is a UK Comprehensive Care Centre, a certified European Comprehensive Care Haemophilia Centre and a World Federation of Hemophilia International Hemophilia Training Centre.

122.5 Patients are able to access our services on a 24/7 basis in an emergency.

b. your current roles and responsibilities at the Centre.

122.6 I am an honorary consultant haematologist, specialising in haemostasis and thrombosis. I work for the NHS on two days per week plus on 1 every 8 weeks I am the attending consultant when I am on call for 24 hours a day for 7 days in a row. During this time, I am responsible for all the haemostasis and thrombosis patients including all patients with inherited bleeding disorders in the Trust.

123. Please outline the treatments currently provided to patients with bleeding disorders at the Centre.

123.1 All treatments for patients with inherited bleeding disorders (except liver transplantation) are provided within this trust.

123.2 The centre team support direct provision of:
Prophylactic treatment with all available therapies on the NHSE framework
Home treatment and delivery through companies on NHSE framework
Support of Haemtrack use
Surgery provision and support (all types including orthopaedic)
Follow-up assessments
Specialist Physiotherapy provision including hydrotherapy
Specialist Social worker support
Access to research/drug trials
Special Care Dentist provision
Genetic testing and counselling
Hepatology and HCV treatment referral
HIV multidisciplinary team meetings

124. Please describe how you typically obtain your patients' consent to treatment. In particular:
a. What information do you give patients about the risks of the treatment?
b. What information do you give patients about the side-effects of the treatment?
c. What information do you give patients about the risks of not having the treatment?
d. What information do you give patients about the benefits of having the treatment?

124.1 This will depend on the situation and will be individualised to the specific patient. Each patient's bleeding risk will vary dependent on their diagnosis, and the reason treatment is required (e.g. dependent on bleeding risk of a surgical procedure).

124.2 All patients newly diagnosed with a bleeding disorder (or on transfer to the Sheffield comprehensive care haemophilia centre) will be comprehensively counselled by the consultant and clinical nurse specialist regarding the implications of their diagnosis, and the possible treatment options. This will include information regarding the use of blood products should these be a treatment option for their bleeding disorder. Written patient information is provided to the patient regarding the diagnosis and treatment options. Correspondence letters (to General Practitioners or other healthcare professionals) are copied to the patients.

124.3 For patients who have a known diagnosis of a bleeding disorder, who are already receiving regular treatment (i.e. patients with moderate or severe bleeding disorders), changes in treatment will usually be undertaken should there be side effects or considered to be a lack of efficacy of current treatment, or may be offered following changes in national procurements/tender. Treatment changes in such circumstances are discussed with the patient by a consultant haematologist at a clinic visit. The reason for the proposed change and the advantages and disadvantages of the new treatment, including potential side effects are explained. Further discussions regarding the advantages and disadvantages of changes of treatment options will be had with the haemophilia clinical nurse specialists. As new disruptive therapies are introduced such as emicizumab where there have been adverse events described in pre licensing trials and there are some unknowns, we have instigated a very clear checklist of discussion points with the patient to ensure all patients are informed and have opportunity to discuss any documented adverse events, any unknowns about the therapy and any guidance we have on the safe use of the product. As with other therapies the patient is provided patient information leaflets and multiple opportunities to ask for further information regarding the product before switching. The patients are asked to sign the checklist on starting this therapy to notify they have been informed and have understood all the information relayed to them. This is retained in the patient's records.

124.4 For patients with mild haemophilia and some von Willebrand disease patients who are not on regular treatment, where regular treatment may be beneficial to the patient, we discuss the advantages and disadvantages of prophylactic desmopressin (DDAVP) vs coagulation factor concentrate vs no treatment and accepting some bleeding, which can be treated when it occurs. This is documented in the patient's medical notes and in correspondence which is copied to the patient.

124.5 Should emergency treatment be required, patients whose treatment is managed remotely by the on-call consultant are not usually consented due to the remote aspect of the care. However, as above, at the time of diagnosis of

the bleeding disorder, or on transfer to the Sheffield Haemophilia centre, treatment options for their bleeding disorder and potential side effects are discussed.

124.6 For patients with factor XI deficiency (or other mild bleeding disorders such as dysfibrinogenaemia, who may require treatment with plasma derived blood products), who need an elective procedure, the advantages and disadvantages of prophylactic treatment with plasma derived blood products vs no blood product treatment and treating bleeding if it occurs are discussed with the patient either in an ad hoc clinic prior to a surgery plan is made or on the telephone and in conjunction with our weekly multidisciplinary team meeting. The discussions are documented in correspondence letters, which are now copied to patients.

125. *Please describe how you typically record your patients' consent to treatment*.

125.1 Where patients have signed a consent form to start a new treatment, such as emicizumab, this is filed in the patients notes. The consent form confirms that relevant information has been given to the patient.

125.2 Where we discuss a treatment for a procedure, this is recorded in the medical notes, but we do not obtain specific consent every time we give a treatment to a patient. The discussion with the patient will usually be documented in a letter to the relevant healthcare professional and a copy of that letter will be sent to the patient.

126. Are blood samples routinely taken from patients attending the Centre? If so, what information would you expect to be provided to patients about the purposes for which the samples are being taken. Does the Centre obtain patients' consent to the storage and use of the samples and, if so, how and in what way is that recorded?

126.1 Often, we obtain blood samples from patients to check their full blood count, kidney function, liver function, iron levels, clotting factor levels etc. Samples are also taken to monitor viral complications of treatment (e.g. HIV treatment, and to monitor liver function in those that have previously had hepatitis C). Samples are taken to investigate patients newly referred with possible bleeding disorders. Patients are informed regarding the purposes for which the samples are being taken. The results of each test are communicated to the patient, either at a subsequent clinic appointment or by telephone/ in a letter where appropriate.

126.2 In the case of monitoring treatment for HIV and for monitoring liver function in patients with hepatitis C, the patients are aware of the specific tests that will be performed on the samples taken.

126.3 We do not store samples other than in the case of highly specialised tests, for the brief period whilst they are waiting to be batch tested.

126.4 There are two situations where we get specific written informed consent for taking blood samples and that is for genetic testing and for research samples. For both of these indications a signed informed consent form is filed in the patient's notes and a copy is given to the patient.

126.5 When the blood samples are being taken by the CNS or support worker, direct consent is obtained verbally from the patient that is it OK to proceed and take the blood samples. If the patient declines, the requesting clinician would be informed to document this information in the medical records. Information about the blood samples, what they are is provided by the CNS too (although some patients would not want this full detail).

127. *Please describe how you typically (a) obtain and (b) record your patients' consent to testing (of any kind)*

127.1 As mentioned above, for routine testing no formal written consent is obtained other than by the member of the team performing the sampling seeking verbal consent that it is OK to proceed. Tests requested are documented in the correspondence to the GP/ other referring clinician, and a copy of that letter is sent to the patient. For genetic testing and for research samples written informed consent is obtained, is recorded in the notes and the patient gets a copy of the form.

128. *How many current patients at the Centre (a) were infected with HIV through blood products; (b) were infected with HCV through blood products; (c) were infected with HBV through blood products; (d) were co-infected with HIV and HCV through blood products?*

128.1	a) HIV positive	8	(All HIV RNA negative on HAART)
	b) HCV positive	86	(85 are HCV RNA negative)
	c) HBV positive	2	(Not requiring treatment)
	d) HIV and HCV	8	

129. What if any involvement do you have/does the Centre have in the treatment of the Centre's patients for HIV and/or HCV and/or HBV? Are there multi-disciplinary clinics (e.g. haematology and hepatology), and if not would such arrangements be feasible and beneficial?

129.1 a) For HIV we hold a bimonthly multidisciplinary team meeting in the haemophilia centre with an HIV specialist consultant and the haemophilia medical, nursing and social work team. All the HIV medications are home delivered under management of the haemophilia centre CNS team with direct guidance from the HIV/Sexual Health Consultant and with support from pharmacy. The haemophilia centre CNS and attending Consultant ensure appropriate follow up and monitoring is undertaken. Currently all our HIV patients have full suppression of their HIV viral load.

129.2 b) Patients who had HCV and now have advanced liver disease, are under the care of hepatology or infectious disease teams and have monitoring of their liver disease undertaken by those teams. Most patients without

advanced liver disease are under the care of the haemophilia centre for their bleeding disorder. A hepatic assessment including fibroscan of all bleeding disorder patients who had hepatitis C has been undertaken, and those who fulfil the criteria for monitoring of their liver disease (with ultrasound and alpha fetoprotein estimation) have this routinely scheduled.

129.3 One patient has repeatedly refused treatment despite encouragement and continues to be Hepatitis C RNA positive.

129.4 c) For HBV we have two patients who have intermittently been reviewed by the hepatology team, but they did not feel that treatment of their HBV or long term follow up by them was required.

130. *What, if any, psychological services are available at the Centre? Do you have a psychologist as part of the staff team? Is there psychological support specifically for those infected with HIV and/or hepatitis in consequence of infected blood products?*

130.1 We do not currently have a psychologist attached to the haemophilia centre; however, we have had approval to appoint a part time psychologist to the service. This post will be advertised imminently. In the past we have had variable levels of support from the general hospital psychology service.

130.2 The two longest serving clinical nurse specialists within the team both undertook the AIDS counselling course when they were appointed within the team. We have had Specialist Social Workers within the team and access to the trust's HIV/HCV psychologists as we have needed them, but this resource has only been accessible to those with acute HIV/HCV issues not for long standing issues.

130.3 The Specialist Social Worker and CNS team provide sign posting to primary care and other counselling services as needed and have links to services within the city for young adults seeking support for psychological wellbeing.

131. *What if any other support services are available at the Centre?*

131.1 We offer physiotherapy and specialist social work support.

132. *What has been the impact of the infection of patients with HIV and/or hepatitis through blood products:*
a. upon patients at the Centre (without identifying any individual patient);
b. the ways in which decisions about treatment and care are taken, and treatment and care are provided, at the Centre?

132.1 The impact of HIV and HCV on our patients has been enormous. We have seen great suffering not only clinically, but also emotionally, psychologically and financially. What is generally underestimated is the impact on patients' families and also the impact on patients who have cleared HCV spontaneously is underappreciated. Many patients have anxieties regarding changing treatments given their past experiences. There is also an impact on

family members' reproductive choices based on previous family experiences, especially relating to infected blood products.

132.2 When a new product is started all the potential advantages and disadvantages are discussed with the patients. Areas of uncertainty due to the lack of current evidence are also discussed. Written information is provided. Where appropriate, research papers have been provided to patients for information and discussion. We work in partnership with patients and decisions regarding treatment and care are made in conjunction with patients (and carers where appropriate) wherever possible.

133. *Has the infection of patients with HIV and/or HBV and/or HCV through blood products:*
a. Changed or influenced your professional practice and approach and if so how?
b. Changed or influenced the practice and approach of your colleagues and if so how?
c. Changed or influenced the way in which haemophilia care is nowprovided and if so how?

133.1 The infection of patients with HIV/HCV/HBV has had a profound impact on how haemophilia care is delivered. We are now all fully aware of the limitations of the evidence, and the potential risks of all therapies. We are fully aware that new is not always better and also that cheaper unit cost is not always the best value.

133.2 We advocate for haemophilia treatments at every level.

133.3 In my personal capacity I was part of a small group that founded the European Association of Haemophilia and Allied Disorders, an association for health professionals involved in haemophilia care with the aim of improving the scientific basis of Haemophilia care. I have also set up the European Haemophilia Safety Surveillance System which is now running in 26 European countries and serves as an early warning system in terms of safety.

133.4 Within Sheffield, the development of a formal weekly multidisciplinary team meeting where all patients who need a decision regarding a problem or change of treatment or management are discussed has been a great improvement in care; formal minutes are recorded during these meetings. We also undertake 3 monthly Morbidity & Mortality meetings to discuss adverse events, near misses, deaths and any governance issues relating to care provision.

133.5 The Sheffield Haemophilia Centre follows the nationally agreed Quality Standards of delivery of haemophilia care which can be found at: http://www.ukhcdo.org/wp-content/uploads/2019/03/Quality-Standards-IABD-QS-2018.pdf One of our CNS team & our Specialist Social Worker were involved in the development of these standards as part of a wider multidisciplinary working party.

133.6 The delivery of care through the Haemophilia centre is externally audited through the national audit of haemophilia centres by the West Midlands Quality Review Service. Our last external audit was in 2019, when we were visited by eight auditors. The report of our audit is now publicly available at: https://images.qualityreviewservicewm.nhs.uk/wp-content/uploads/2020/04/28113649/20190905-IABD-Sheffield-Adults-Final-Report-V1.pdf

Section 11: Other issues

134. Please provide details of any complaints made about you (insofar as relevant to the Inquiry's Terms of Reference) to your employer, the General Medical Council, the Health Service Ombudsman or any other body or organisation which has a responsibility to investigate complaints.

134.1 I am not aware of any complaints having been made against me.

135. Please explain, in as much detail as you are able to, any other matters that you believe may be of relevance to the Infected Blood Inquiry, having regard to its Terms of Reference and to the current List of Issues.

Are we using the safest possible products today?

135.1 One issue that has not been addressed by your questions to me is whether the products we currently use are the safest possible and whether there are alternatives, that are more expensive, but could be safer. I have always believed that we should be using the precautionary principle, but I am not convinced the UK Healthcare system allows us to do this.

135.2 I list some examples:

a) Cryoprecipitate. This is a non-fractionated, non-virally inactivated blood product used to provide fibrinogen. There is an alternative virally inactivated product, fibrinogen concentrate, that is more expensive. The whole of Western Europe has stopped using cryoprecipitate because of the concerns about vCJD, yet ironically the UK which has an issue with vCJD, continues to use cryoprecipitate. [Makris M. Is the continued use of UK plasma sourced cryoprecipitate justified? British Journal of Haematology 2015; 168:908-910].

b) Recombinant Von Willebrand factor concentrate. There is a recombinant von Willebrand factor concentrate licensed, but we are not allowed to use in the UK, as it is more expensive than the plasma derived concentrates. Since submission of my draft report, some limited use of this product will now be allowed.

c) Recombinant factor XIII concentrate. There is a licensed recombinant FXIII concentrate but in the UK, we continue to use plasma derived FXIII concentrate due to cost.

d) Fresh frozen plasma. In the UK, we continue to use non-virally inactivated fresh frozen plasma derived from UK donors, despite the availability of an

alternative virally inactivated (using solvent detergent method) fresh frozen plasma product made from non-UK donor plasma.

e) Pure factor X concentrate. There is a licensed pure factor X concentrate which is used for prophylaxis in severe factor X deficiency. We are, however, not allowed to use this concentrate to cover major surgery in severe factor X deficiency, even though it is the safest product to use; instead we have to use an older product that contains factors X as well as II, VII and IX. Because patients are not deficient in factors II, VII and X, the extra infused factors increase the risk of thrombosis.

The future of safety for patients with haemophilia

135.3 In the future, the treatment related safety risks for patients with haemophilia are unlikely to be due to infections since plasma derived concentrates are rarely used any more. In my opinion, the main treatment related risk for patients with haemophilia for the immediate future is thrombosis.

135.4 Because the rate of adverse events in the future will likely be low, international collaboration will be required to identify events early.

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed ___GRO-C_____

Dated _____20 October 2020_____