Witness Name: James Ironside

Statement No.: WITN7034001

Exhibits: WITN7034002-47

Dated: 28th April 2022

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF JAMES IRONSIDE

I provide this statement in response to a request under Rule 9 Request of the Inquiry Rules 2006 dated 15th October 2021.

I, James Ironside, will say as follows: -

Section 1: Introduction

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

   Name: James Wilson Ironside CBE

   Address: GRO-C, Edinburgh GRO-C, United Kingdom

   Date of birth: GRO-C 1954

   Professional qualifications:

   BMSc Pathology (2i): University of Dundee 1976

   MBChB (Merits in Basic Biological Sciences and Applied Pathological Sciences): University of Dundee 1979

   MRCPath (Neuropathology): Royal College of Pathologists 1987

   FRCPath (Neuropathology): Royal College of Pathologists 1997

FRCPEdin: Royal College of Physicians of Edinburgh 1999-2017

FMedSci: Academy of Medical Sciences 2002-2017

FRSE: Royal Society of Edinburgh 2011

MD: University of Edinburgh 2017

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.**

1979–1980 **Medical House Officer**, Ninewells Hospital, Dundee.

1980–1980 **Surgical House Officer**, Stracathro Hospital, Brechin.

1980–1981 **Senior House Officer in Pathology**, Ninewells Hospital, Dundee.

1981–1983 **Registrar in Pathology**, Ninewells Hospital, Dundee.

1983–1986 **Senior Registrar in Neuropathology**, Royal Hallamshire Hospital Sheffield, Honorary Tutor in Pathology, University of Sheffield.

1986–1987 **Lecturer in Pathology**, University of Leeds, and Honorary Senior Registrar in Neuropathology, The General Infirmary at Leeds.

1987–1990 **Senior Lecturer in Pathology**, University of Leeds and Honorary Consultant Neuropathologist, The General Infirmary at Leeds.

1990–1994 **Consultant Neuropathologist**, Western General Hospital, Edinburgh and Part-time Senior Lecturer in Pathology, University of Edinburgh.

1994–1998 **Senior Lecturer in Pathology**, University of Edinburgh and Honorary Consultant Neuropathologist, Western General Hospitals Trust, Edinburgh.

1998-2000 **Reader in Pathology**, University of Edinburgh and Honorary Consultant Neuropathologist, Western General Hospitals Trust, Edinburgh.

2000–2017 **Professor of Clinical Neuropathology**, University of Edinburgh and Honorary Consultant Neuropathologist, Lothian University Hospitals Trust, Edinburgh.

2017–present **Emeritus Professor of Clinical Neuropathology**, University of Edinburgh.

3. **In earlier correspondence with the Inquiry you provided a list of your relevant committee memberships. Please briefly describe the nature of your involvement in these committees. If there are any further associations, parties, societies or groups relevant to the Inquiry's Terms of Reference, also include them here.**
    a. **Advisory Committees**
        i. **Advisory Committee on Dangerous Pathogens TSE Working Group** (now the Advisory Committee on Dangerous Pathogens TSE Subgroup): Member 1995 - 2017. To advise on the Clinical Laboratory handling of tissues from patients with confirmed or suspected prion disease, including autopsy practices and tissue storage, and the tissue distribution of abnormal prion protein in all forms of human prion disease. I also provided similar advice to Subgroups of this Working Group, including the Decontamination Subgroup and the Risk Assessment Subgroup.
        ii. **WHO Working Group on International Reference Materials for Diagnosis and Study of Transmissible Spongiform Encephalopathies (TSEs)**: Member 1999 – 2017. To advise on the tissue distribution of abnormal prion protein in all forms of prion disease and to help provide reference materials for the assessment of novel diagnostic tests.
        iii. **Spongiform Encephalopathy Advisory Committee**: Member 1999-2005; Deputy Chairman 2001-2005. To advise on the neuropathological diagnosis of human prion diseases and the

tissue distribution of abnormal prion protein in human prion diseases.

iv. **CJD Incidents Panel**: Member 2000– 2012 (Ministerial Appointment). To provide advice on the tissue distribution of abnormal prion protein in all forms of human prion disease in relation to reported incidents of potential patient exposure to prion infectivity in a clinical setting.

v. **Commission on Human Medicines**: Biologicals Subcommittee: Member 2002 – 2005; Biological and Vaccines Expert Advisory Group: Member 2005- 2009. To advise on potential sources of prion exposure in vaccines and other biological therapeutics and the assessment of neuropathological assessment of data from safety studies.

vi. **Microbiological Safety of Blood and Tissue for Transplantation vCJD Subgroup**: Member 2003-2004. To advise on the tissue distribution of abnormal prion protein and infectivity in vCJD.

vii. **National Institute for Health and Care Excellence CJD Advisory Subgroup** 2004 - 2014. To advise on the tissue distribution of abnormal prion protein in all forms of prion diseases and its implications for the potential contamination of surgical instruments

b. Committees relevant to Research on Prion Disease

i. **Allen Sub-Committee on Human Spongiform Encephalopathies, Medical Research Council.** (Now the MRC CJD Epidemiology Committee): Member 1994-98. To provide expertise in the Neuropathology of human prion diseases in relation to research planning and funding.

ii. **Working Party on the Biology of Spongiform Encephalopathies Programme for the British Biotechnology and Biosciences Research Council**: Member 1995-2009. To provide expertise in the Neuropathology of human prion diseases in relation to research planning and funding.

iii. **MRC Steering Group on the Prevalence of Detectable PrP in Lymphoid Tissues**: Member 1998-2004. To provide expertise in the tissue distribution of abnormal prion protein in human prion diseases in relation to research planning on the use of lymphoid tissues to estimate the prevalence of vCJD infection in the UK.

iv. **UNESCO (Paris) Expert Advisory Group on "Man and Emerging Diseases"**: Member 1999- 2015. To provide expertise in the Neuropathology of human prion diseases and the tissue distribution of abnormal prion protein in human prion diseases in relation to research planning.

v. **INSERM (Paris) Member of the Advisory Group on research in Prion Diseases**: Member 2001- 2004. To provide expertise in the Neuropathology of human prion diseases and the tissue distribution of abnormal prion protein in human prion diseases in relation to research planning and funding.

vi. **MRC Advisory Board/MRC College of Experts**: Member 2001-2004. To provide expertise in the Neuropathology of human prion diseases and the tissue distribution of abnormal prion protein in human prion diseases in relation to research planning.

vii. **MRC Steering Group for the PRION-1 Trial**: Member 2003-2009. To provide expertise in the Neuropathology of human prion diseases and the tissue distribution of abnormal prion protein in human prion diseases in relation to the PRION-1 Clinical Trial.

4. **Please provide an outline of any relevant relationships you had, or initiatives you were involved in to ensure that the UK Government, Blood Services, UKHCDO, NHS bodies, medical profession and patients were informed and educated about the risks of vCJD transmission via blood and blood products. These documents may be of assistance to you (DHSC0004072_006; HCDO0000254_835; NHBT0007197).**

   a. **UK Government and NHS Bodies**

      i. Since I began work in 1990 with the National CJD Research and Surveillance Unit (NCJDRSU), my colleagues and I were in

regular contact with the Department of Health (DH), particularly Dr Ailsa Wight. DH funded the Unit, which was directed by Professor Robert Will, through a Research Contract with the University of Edinburgh. Since 1992, NCJDRSU has published an Annual Report describing our work and the results of our epidemiological, clinical and laboratory-based investigations.[1] When an Annual Report was ready to publish, a question about publication date was raised as a Parliamentary Question (recorded in Hansard) and details of the publication date and where the annual report could be found (Parliament Library and NCJDRSU Unit website) were given in the reply. DH then followed this with a Press Release.

ii. All the UK health departments are notified by email each time NCJDRSU diagnoses a case of vCJD. Regional epidemiologists in the 4 nations are updated quarterly on the number of vCJD cases per year split by year of death and strategic health authority (England) and by year of death and region (UK). There have been no new cases of vCJD in the UK since 2016, so no updates have been sent out since then.

iii. All newly diagnosed vCJD cases aged 17 and over (the age eligible to donate blood) are notified to all 4 blood services in the UK regardless of their donation history and an anonymised copy of this notification is mailed to each national health department.

iv. The contact between NCJRSU and DH became more frequent around the time we identified the first cases of vCJD, which Professor Will and I presented formally to the Spongiform Encephalopathy Advisory Committee on 8th March 1996. Our findings were announced in the House of Commons on 20th March 1996. This was immediately followed by a Press Conference in London that Professor Will and I attended to answer questions on our work, which was published in the Lancet on 6th April 1996 (HSOC0010099).

[1] http://www.cjd.ed.ac.uk/surveillance/data-and-reports

v. Since then, NCJRSU has been in regular and continuous contact with the Department of Health over a wide range of matters relating to the surveillance and diagnosis of all forms of CJD in the UK. My colleagues and I have also kept DH informed in a timely manner of results emerging from the various externally funded research projects undertaken in the Unit. Various DH representatives have visited NCJDRSU on numerous occasions to discuss the work of the Unit, funding levels and administrative matters, current research and future research in relation to DH policy needs.

vi. I had additional interactions with a wide range of DH and UK Government representatives for many years through my membership of the various Committees and related bodies listed above in section 3a, including the Advisory Committee on Dangerous Pathogens TSE Working Group and its various Subgroups (1995-2017), the BSE Inquiry (1998)(MHRA0011461), the Spongiform Encephalopathy Advisory Committee (1999-2005) and its reviews of the commissioned Risk Assessments from Det Norske Veritas on the Risk of Exposure to vCJD Infectivity in Blood and Blood Products in 1999 and 2004 (NHBT0008380 , DHSC0004424_052)), the CJD Incidents Panel (2000-2012) (HCDO0000254_119), the Commission on Human Medicines (2002-2009), the Microbiological Safety of Blood and Tissue for Transplantation vCJD Subgroup (2003-2006) (DHSC0038559_048, DHSC0004072_006, DHSC0004526_050) and the National Institute for Health and Care Excellence CJD Advisory Subgroup (2004-2014). I also provided written evidence to the Parliamentary Inquiry on blood, tissue and organ screening for vCJD (2013-2014) (TSTC0000050).

vii. I was a Member of the Human Tissue Authority (HTA) from 2005 – 2009. HTA is a regulatory body sponsored by DH created to implement the provisions of the Human Tissue Act 2004. I worked with fellow Members and HTA staff in the production of a series

of Codes of Practice to provide practical guidance to professionals carrying out activities within the scope of the HTA's remit, including post mortem examination and research. The fundamental principle of consent is covered in the overarching Code A, which contains information that is applicable to all establishments and professionals operating under the governing legislation (WITN7034035). During this period I was in contact with a range of DH staff in relation to this work.

viii. I also had longstanding interactions with Dr Philip Minor and his colleagues in the National Institute for Biological Standards and Control (now part of the Medicines and Healthcare products Regulatory Agency (MHRA)) over the requirements for and provision of a set of reference materials (including brain and spleen samples from sporadic CJD, vCJD and controls) to act as standards for developing and assessing novel assays for vCJD and other forms of CJD (DHSC0004526_050). This work was carried forward internationally through the WHO Working Group on International Reference Materials for Diagnosis and Study of Transmissible Spongiform Encephalopathies (TSEs) from 1999 onwards (WITN7034036).

ix. The reference materials produced under the auspices of the WHO Working Group were made available to researchers via the NIBSC Resource Centre.[2]

x. I was a member of the Commission on Human Medicines (CHM) Biologicals Subcommittee and then the Biological and Vaccines Expert Advisory Group from 2002-2005 and 2005-2009 respectively. My role was to advise on potential sources of prion exposure in vaccines and other biological therapeutics and on the assessment of neuropathological assessment of data from safety studies.

b. Blood Services

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[2] https://www.nibsc.org/science_and_research/virology/cjd_resource_centre/available_samples/who_reference_reagents.aspx

i. On 9th April 1996 I was invited to present our findings on vCJD at a meeting of the UK Transfusion Services and to answer the numerous questions arising concerning the possible implications for transfusion services in the UK. This was the first direct contact I had made with the UK Blood Services. After my presentation I answered questions from the attendees, but did not stay for the remainder of the meeting. Included in the actions agreed at this key meeting was the need to develop "an active collaboration with the CJD Surveillance Unit" in relation to the transfusion history of vCJD patients and the development of case control studies and lookback studies (NHBT0007197).

ii. This led to the establishment in 1997 of the Transfusion Medicine Epidemiology Review (TMER), which is a collaborative project between the NCJDRSU and the UK Blood Services that was funded by the National Blood Service and DH (now funded by DH as part of the NCJDRSU core funding). Its main purpose is to investigate whether there is any evidence that Creutzfeldt-Jakob disease (CJD) or vCJD may have been transmitted via the blood supply. My clinical colleague Professor Will was the principal investigator for NCJDRSU in this study. My role in this project was to provide a neuropathological diagnosis on the cases in the study and to study their pathological and biochemical features in relation to vCJD cases unrelated to blood transfusion. I continued to collaborate with the UK Blood Services in the TMER study until my retirement in 2017.

iii. I had additional interactions with a range of Blood Services representatives for many years through my membership of the various Committees and related bodies listed above in section 3a, including the Advisory Committee on Dangerous Pathogens TSE Working Group and its various Subgroups (1995-2017), the Spongiform Encephalopathy Advisory Committee (1999-2005), the CJD Incidents Panel (2000-2012), the Advisory Committee on Transfusion Transmitted Infection Working Group on vCJD (2002-2003) (JPAC0000029_108, JPAC0000114_018) and the

Microbiological Safety of Blood and Tissue for Transplantation vCJD Subgroup (2003-2005).

iv. I have also given a number of invited presentations on vCJD at scientific meetings attended by members of the Blood Services (WITN7034002) and have collaborated with individual Blood Services members in peer-reviewed publications and book chapters (WITN7034003).

c. UKHCDO

i. As recorded in NHBT0007197, the potential implications of the identification of vCJD for plasma donation and fractionation were also discussed. The first meeting I had with a member of the UK Haemophilia Centre Directors' Organisation (UKHCDO) was in 1997, when Dr Christopher Ludlam, Consultant Haematologist in the Royal Infirmary of Edinburgh and Chair of the UKHCDO met Professor Will and myself to discuss the potential implications of our recent findings in vCJD for haemophilia patients and services. During this meeting we discussed the possibility of a prospective study to collect blood and tissue samples taken with consent for research from haemophilia patients during life and at autopsy to help determine the extent to which the haemophilia patient population might have been infected by vCJD by testing for the presence of abnormal prion protein in lymphoid tissue. Such samples could potentially be retested by new and more sensitive methods, particularly if a blood-based assay became available. This suggestion raised complex considerations over issues of patient consent and study ethics, which Dr Ludlam agreed to discuss with UKHCDO members. Dr Ludlam subsequently published a letter "New-variant Creutzfeldt-Jakob disease and treatment of haemophilia" in the Lancet in 1997 (WITN7034006) and discussed the suggested study on tissue samples from haemophilia patients at the meeting of the UKHCDO Executive on 6th February 1998 (HCDO0000464).

ii. In 1998 my fellow Neuropathologists Professor Jeanne Bell (Edinburgh), Professor Margaret Esiri (Oxford), Dr James

McLaughlin (London) and I published a paper with Professor Christine Lee, Director of the Haemophilia and Haemostasis Unit, Royal Free Hospital, London and Dr Ludlam "Retrospective neuropathological review of prion disease in UK haemophilia patients. This study was based on a pre-existing collection of brain tissue samples from Edinburgh, Oxford and London that had been collected with consent for research as part of a MRC-funded study on HIV disease in the brain in haemophilia patients. These samples were re-examined microscopically using a technique to detect the abnormal form of prion protein that accumulates in the brain in CJD and vCJD. No evidence of prion disease or early prion infection was identified in the 33 cases examined (HCDO0000133_024).

iii. I had subsequent discussions on the project suggested to Dr Ludlam with Professor Christine Lee, who was the Chair of the Transfusion Transmitted Infections Working Party of the Advisory Committee of the UKHCDO. Professor Lee discussed possible funding for the suggested project with Dr John Stephenson in DH and wrote to NCJDRSU on 22nd December 1999 requesting confirmation of the Unit's participation in this project (provided by Professor Will, the Unit's Director) and details of the laboratory activities involved at NCJDRSU and the financial requirements to support this work, which I provided in a letter dated 5th January 2000.

iv. A 5-year prevalence study of patients with haemophilia was commissioned and funded by the DH in 2000 and coordinated by the UKHCDO following ethical approval from the London Multi-Centre Research Ethics Committee (MREC/01/2/11) to an application in 2001 by Professor Christine Lee on behalf of UKHCDO (HCDO0000718). The aims of this study were to determine the extent of exposure of individual patients with inherited bleeding disorders to implicated batches of clotting factor concentrate, to request consent to analyse tissue biopsies and autopsy material for the abnormal prion protein found in vCJD

in NCJDRSU and to notify possible and confirmed clinical cases of vCJD in the UK haemophilia population (WITN7034031).

v. I was a named collaborator for this project and was responsible for the laboratory work that would be carried out in NCJDRSU on the tissue samples collected in this project, but was not involved in the Ethics application.

vi. On 9th October 2001 I gave a presentation "Overview of vCJD prion disease" to the Joint Annual General Meeting of the British Society for Thrombosis and Haemostasis and the UKHCDO in Bath.

vii. In February 2003 Professor Frank Hill, Chairman of UKHCDO, wrote to members of the Organisation to confirm that DH had agreed to fund the UKHCDO vCJD prevalence study and encouraged members to participate (HCDO0000109_013). In 2004 I gave a presentation on the Blood Product Associated Risk of vCJD and progress on the DH-funded prevalence project to the UKHCDO Annual General Meeting in Edinburgh (HCDO0000254_835).

viii. I had additional interactions with a range of UKHCDO representatives for many years through my membership of the various Committees and related bodies listed above in section 3a, including the Advisory Committee on Dangerous Pathogens TSE Working Group and its various Subgroups (1995-2017), the CJD Incidents Panel (2000-2012) and the Microbiological Safety of Blood and Tissue for Transplantation vCJD Subgroup (2003-2005).

ix. I have also given a number of invited presentations on vCJD in the UK and overseas at scientific meetings attended by members of the UKHCDO (WITN7034002) and have collaborated with individual UKHCDO members in peer-reviewed publications and book chapters (WITN7034003).

d. Medical Profession:

i. As part of its surveillance work, NCJDRSU is in regular contact with individual members of the medical profession across the UK

in relation to patient referral and follow-up, investigations, diagnosis and consent for autopsy. I helped with the arrangements for autopsies through the network of Neuropathologists across the UK who had the appropriate mortuary facilities to allow autopsies on suspected CJD cases to be performed according to current Health and Safety guidelines. I provided protocols to the pathologists concerned to allow a standardised approach to the autopsy and tissue sampling in a variety of formats (fixed tissues, frozen tissues etc). My colleagues in the NCJDRSU Neuropathology Laboratory arrange the safe uplift and transport of these samples to NCJDRSU for investigation and diagnosis and I provided a report and representative microscopic slides to the referring pathologists for their records and to allow presentation and discussion of these cases at local medical meetings. Through the British Neuropathological Society, I was in regular contact with all the Neuropathologists across the UK and other pathologists with access to the necessary mortuary facilities to help ensure that every consent for autopsy could be respected and fulfilled no matter the geographic location of the patient. I also helped answer more general inquiries to NCJDRSU from the individual members of the medical profession and provided details of how to access further information, publications and advice from our website and other relevant websites (Department of Health, MRC Prion Unit, etc).

ii. In 2006, under the leadership of Dr Matthew Helbert, Consultant Immunologist in Manchester, I helped establish the Primary Immunodeficiency Surveillance (PID) study, a DH-funded project that aims to find out whether any evidence of abnormal prion protein can be found in antibody deficient patients (including children) who received certain UK-sourced immunoglobulin products between 1996 and 2000. The products were made from plasma from UK donors and patients treated with these products may have been exposed to vCJD. I was involved in the study

design, but was not involved in the Ethics application for this study. The study involves immunology teams and patients throughout the UK. Participants are followed over several years, testing any available tissue (from surgical biopsies) and blood (for when a suitable test becomes available) for the abnormal prion protein that causes vCJD. Participants and their relatives can also consent to donate tissues obtained from a post-mortem examination. All tissues are examined in NCJDRSU and the results are provided to Dr Helbert and his team in Manchester. Following Dr Helbert's retirement in 2015, management of the study transferred from Manchester to Edinburgh, and is now led by Professor Richard Knight and a team at NCJDRSU. To date, no primary immunodeficient patients have shown symptoms of prion disease, nor is there any evidence of prion infection in the tissues tested.

iii. I also collaborated in the Study of Progressive Intellectual & Neurological Deterioration (PIND), a DH-funded project led by Dr Christopher Verity, Cambridge and Professor Robert Will, NCJDRSU. PIND aims to use the mechanism of the British Paediatric Surveillance Unit to identify all cases of progressive intellectual and neurological deterioration in children in the UK, particularly those with features suggestive of vCJD. All cases are discussed and allocated to a diagnostic category by an Expert Neurological Advisory Group. My role was to examine any tissues available from surgical biopsies and post-mortem examinations for the abnormal prion protein that causes vCJD. The results of these investigations are reported to PIND through my colleague Professor Robert Will. As of 31st December 2019, 4633 patients with suspected PIND had been reported, including six cases of vCJD: four definite and two probable.

iv. Since I began work in NCJDRSU I have been invited to speak at numerous local and national meetings of medical professionals across the UK, including professional organisations with a special interest in prion diseases, e.g. the Society for General

Microbiology, the Hospital Infection Society, the Royal College of Pathologists, the Society of British Neurosurgeons (WITN7034002). At all of these meetings I answered numerous questions from the attendees on the complex subject of prion diseases and often provided further information outside the meeting. Some of the questions received were helpful in the work of the various committees and bodies on which I worked, particularly in terms of providing clearer guidance and advice with specific examples e.g. in guidelines for the decontamination of medical devices and appliances. I also met many members of the Medical Profession during my work as a Member of the HTA at presentations, consultation events and open days.

e. Patients:

i. As I am predominantly involved in Laboratory Medicine (as opposed to Clinical Medicine) I did not interact routinely with patients. However, I have attended several Family Support Day meetings of the CJD Support Network (CSN), at the request of the National CJD Co-ordinator, Gillian Turner. Some of these meetings were held in NCJDRSU, or in adjacent hospital premises. I have given short talks at these meetings on topics raised by the relatives of CJD and vCJD patients and answered further questions from individual relatives in face-to-face meetings or by telephone. I have also provided further support to the work of the CSN by contributing to a series of documents suitable for the general public on topics including "The autopsy in patients with suspected CJD". These are accessible on the CSN website.[3] Gillian Turner and I were in regular contact by telephone and at meetings of the CJD Incidents Panel (of which she was also a member) about questions she had received relating to the laboratory diagnosis of CJD. At her request I arranged to meet

[3] https://www.cjdsupport.net

individual relatives or groups of family members to try to answer their questions and provide help and advice whenever possible.

ii. I had no routine interaction with haemophilia patients, but did meet some UK haemophilia patients at national and international conferences on haemophilia at which I had given presentations on vCJD. I answered questions from individual patients both after my presentations and at informal meetings at other times during the conferences.

iii. I also interacted with a range of patients and their relatives during my work as a Member of the HTA at presentations, consultation events and open days.

5. The Inquiry is aware that you provided evidence to the Parliamentary Inquiry on blood, tissue and organ screening for vCJD in 2013/2014 (TSTC0000050; TSTC0000051). Please review the statements and views you expressed to the Inquiry and set out whether your views have changed in any way. If your views have changed since making the statement please explain how they have changed and why.

On review of the evidence I provided to the Parliamentary Inquiry on blood, tissue and organ screening for vCJD in 2013/2014 (TSTC0000050), my views have changed in light of the following subsequently available data:

a. **Updated vCJD epidemiology and modelling requirements**

i. Since 1995, 178 UK patients with definite and probable vCJD have been reported by NCJDRSU (WITN7034037), the last of whom died in 2016, alongside worldwide vCJD figures (WITN7034038). Early attempts at modelling the UK vCJD epidemic predicted possible future case numbers ranging from dozens to several millions (WITN7034007). This gave rise to concerns that infected individuals might spread the infection through surgical instruments or blood, tissue and organ donations, leading to a self-sustaining secondary epidemic of vCJD.

ii. Subsequent modelling in 2010 suggested "a potentially long but uncertain tail in the epidemic, with a peak annual incidence of

around 11 cases, but the 95% credibility interval is between 1 and 65 cases. These cases are predicted to be due to past food-borne transmissions occurring in previously unaffected genotypes and to transmissions via blood transfusion in all genotypes" (WITN7034008). However, no evidence of self-sustaining epidemics was identified. Since then there have been 5 cases of vCJD in 2011, none in 2012, 1 case in 2013, none in either 2014 or 2015, and 1 case in 2016. No UK cases of vCJD have been reported since. An updated modelling exercise to estimate future vCJD cases in light of the vCJD surveillance data since 2010 and the results of the Appendix 3 study in 2020 (WITN7034009) would therefore be helpful for current assessments of vCJD risks.

b. **Emergence of vCJD in a different genetic subgroup in the UK in 2016.**

    i. All but one of the genetically tested vCJD cases have occurred in prion protein gene (PRNP) codon 129 MM patients; however, the patient who died in 2016 had the PRNP codon 129 MV genotype (WITN7034010). The incubation period for vCJD in the MV genotype is likely to be longer than for the MM genotype, possibly extending to several decades (see the response to Question 11 below). To date, no cases of vCJD in the PRNP codon 129 MV genotype have been identified outside the UK. It remains the case that no vCJD cases in the PRNP codon 129 VV genotype have been identified in the UK or elsewhere.

c. **Results of the Appendix 3 vCJD prevalence study published in 2020.**

    i. Several studies exist on the prevalence of vCJD infection in appendix and tonsil tissues, the latest of which is the Appendix 3 study, which studied 29,516 samples from 2 populations thought to have been unexposed to BSE: individuals born between 1891 and 1965 who underwent appendectomy between 1962 and 1979 (pre-BSE); and individuals born after 1996 who underwent appendectomy between 2000-2014 (post-BSE) (WITN7034009). Seven appendix samples were positive for abnormal prion

protein, of which two were from the pre-BSE exposure era and five from the post-BSE period. None of the positive samples were from appendices removed before 1977, or from patients born after 2000.

ii. The overall results of the three Appendix studies indicate a prevalence of vCJD infection of around 240-500 per million UK population. All three possible PRNP codon 129 genotypes (MM, MV and VV) are represented in the positive cases. This finding is consistent with experimental evidence that all 3 PRNP codon 129 genotypes are susceptible to infection with vCJD. None of the positive samples in the three Appendix studies came from individuals later diagnosed with vCJD.

iii. Two possible interpretations of these results are suggested (WITN7034009): either there is a low background prevalence of abnormal PrP in human lymphoid tissues that may not progress to clinical vCJD; alternatively, all positive specimens are attributable to BSE exposure, requiring dietary exposure to BSE to have begun in the late 1970s and continued through the late 1990s. The authors state "whichever interpretation is preferred, the contrast between the prevalence of abnormal PrP and the number of clinical vCJD cases seen to date (mid-2020) strongly suggests that possibly none of those in whom abnormal PrP is detected through an ante-mortem lymphoid tissue survey will develop any symptoms of prion disease".

d. **Identification of 2 cases of sporadic CJD in UK plasma product recipients.**

i. Sporadic CJD (the commonest form of CJD that occurs worldwide) had not been reported in patients with clotting disorders requiring treatment with fractionated plasma products until 2017, when a report from NCJDRSU and the TMER study described two such cases in the UK. Both patients had been informed that they were at increased risk of vCJD because of past treatment with fractionated plasma products from the UK. However, both patients had clinical features characteristic of

sporadic CJD, which was confirmed on post mortem neuropathology and biochemical analysis of the abnormal prion protein in the brain (WITN7034011). A causal link between the treatment and the development of sporadic CJD could not be established; the possibility that these cases may simply represent a chance event cannot be excluded.

e. **My changed views can therefore be summarised:**

i. The absence of any new cases of vCJD since 2016 and the complex results of the Appendix 3 study indicate that the modelling predictions of 2010 may not now be applicable and a more up to date set of modelling predictions for the vCJD epidemic based on current data would be helpful for current and future risk assessments of potential vCJD transmission risks.

ii. The conclusions in the Appendix 3 study may be applicable to the previously reported case of abnormal prion protein detected in the spleen of a UK haemophilia patient who died with no evidence of clinical vCJD (HCDO0000799), raising further questions about the interpretation of this finding.

iii. The identification of two cases of sporadic CJD in long-term recipients of fractionated UK plasma products is unexplained and reinforces the need to continue the TMER study.

iv. The emergence of clinical vCJD in the PRNP codon 129 MV genotype and the potentially long incubation periods in this genetic subgroup suggest that future cases of this type may occur over a lengthy period.

v. Continuing surveillance of all forms of CJD in the UK is still required.

6. Please confirm whether you have provided any evidence or been involved in any other inquiries, investigations, criminal or civil litigation in relation to variant Creutzfeldt-Jakob Disease (vCJD) infections in blood and blood products. If so, please provide details of your involvement other than the Inquiry mentioned below.

Other than the Parliamentary Inquiry mentioned in paragraph 5 above, I have not been involved in any other inquiries, investigations, criminal or civil litigation in relation to vCJD infections in blood and blood products.

Section 2: What is currently known about vCJD?

7. Please provide an explanation as to what vCJD is.

a. Variant CJD is a unique form of human prion disease that was first reported in 1996 following the identification of a series of 10 individuals in the UK between 1995 and 1996 with a novel prion disease characterised by atypical demographic, clinical, radiological and neuropathological features (HSOC0010099). In contrast to sporadic CJD (the commonest form of human prion disease that occurs worldwide, most frequently in the 7-8th decades of life as a rapidly progressive dementia with a median duration of illness of 4 months), vCJD predominantly presents in the third decade of life and has a median duration of illness of 14 months. Early psychiatric symptoms are common, including withdrawal, anxiety and dysphoria. The onset of cognitive impairment, ataxia and movement disorders may be preceded or accompanied by thalamic pain.

b. vCJD has a unique neuropathology, with numerous florid plaques composed of prion protein in the cerebrum and cerebellum, thalamic gliosis and extensive accumulation of type 2B abnormal prion protein (in the brain (HSOC0010099). vCJD also differs from other human prion diseases in the widespread accumulation of PrP^{res} outside the central nervous system, particularly in lymphoid tissues such as the spleen, tonsil, lymph nodes, thymus and gut-associated lymphoid tissues, and in peripheral nerves (WITN7034012). PrP^{res} has been detected by high sensitivity biochemical analysis in blood from vCJD patients (WITN7034013, WITN7034014).

c. Most cases of vCJD have occurred in the UK (178 cases) and France (28 cases). As of 4th October 2021, 26 additional cases of vCJD have been identified worldwide in 10 other countries or territories across Europe, the USA, the Middle East and Asia (WITN7034038). vCJD is

causally linked to the epizootic of BSE, a novel prion disease affecting cattle, with the consumption of contaminated beef products being the likely primary source of vCJD infection. Experimental transmission studies from vCJD tissues have shown that the infectious agent in vCJD has biological properties that are closely similar to those of the BSE agent, but different from the transmissible agents causing sporadic CJD and scrapie (a prion disease of sheep and goats) (WITN7034015).

8. **Please provide an explanation as to how vCJD is transmitted and in particular what is known now about whether and if so how it is transmitted via blood and blood products.**
    a. **The extent of exposure a person requires to become infected.**
        i. vCJD is an acquired human prion disease resulting from transmission of the BSE agent to humans, most likely via the food chain. This implies that the BSE agent spreads from the gut to the brain, which is the target organ in prion diseases where prion replication causes nerve cell death and brain damage, resulting in neurological signs and symptoms. Evidence from experimental transmission of prions in animal models suggests that prion replication can occur in lymphoid tissues such as the spleen prior to invasion of the central nervous system (WITN7034016). Since the spleen is involved in the filtration of blood, the possibility that prions could also be present in blood was further studied experimentally. Since 2000, modelling studies in sheep have demonstrated the efficient transmission of BSE by intravenous transfusion of labile blood components including red blood cells, platelets and plasma. Infectivity can be transmitted in blood components from sheep in a preclinical stage of BSE infection and a recent study has found that variations in the donor prion protein genotype may influence transfusion transmission rates (WITN7034017).
        ii. The possibility that vCJD prions might be present in the blood of individuals infected with vCJD before the onset of clinical signs and symptoms, representing a risk of secondary vCJD

transmission via blood and blood products, was considered by the UK Blood Authorities at the meeting I attended in April 1996, very shortly after the publication of our article describing the first 10 cases of vCJD in the UK. One of the actions agreed at this meeting was the need to develop "an active collaboration with the CJD Surveillance Unit" regarding the transfusion history of vCJD patients and the development of case control studies and lookback studies (NHBT0007197). Consequently, the TMER study was established in 1997 as a collaborative project between NCJDRSU and the UK Blood Services to investigate whether there is any evidence that vCJD or other forms of CJD may have been transmitted via the blood supply. My clinical colleague Professor Robert Will was the principal investigator for NCJDRSU in this study.

iii. In the latest report of the results of the TMER study on the NCJDRSU website[4] dated 29th November 2019, it states: "Thirty-one vCJD cases were reported to have been blood donors. Four additional cases who were not reported to have been blood donors were found to be registered with UKBTS. One of these cases was found to have been a blood donor while the other three cases were registered as donors but never made any donations. Twenty-four of the cases have been traced at blood centres including the four additional cases mentioned above. Components from 18 of these individuals were actually issued to hospitals. It has been established that 67 components were transfused to named recipients (53 dead, 14 alive)".

iv. "Four instances of probable transfusion transmitted infection have been identified. The first recipient (Case 1) developed symptoms of vCJD 6½ years after receiving a transfusion of red cells donated 3½ years before the donor (Donor 1) developed symptoms of vCJD (NHBT0008743_013). The second recipient (Case 2) died from a non-neurological disorder 5 years after

[4] http://www.cjd.ed.ac.uk/projects/transfusion-medicine-epidemiology-review-tmer

receiving blood from a donor (Donor 2) who subsequently developed vCJD; protease-resistant prion protein (PrP^{res}) was detected in the spleen but not in the brain. This is the first recorded case in the UK of autopsy detection of presumed pre- or sub-clinical vCJD infection (DHSC0004215_039). The third recipient (Case 3) developed symptoms of vCJD 7 years, 10 months after receiving a transfusion of red cells donated about 21 months before the donor (Donor 3) developed symptoms of vCJD. The fourth recipient (Case 4) who also received a transfusion from the same donor as Case 3, developed symptoms of vCJD 8 years, 4 months after receiving a transfusion of red cells donated about 17 months before this donor (Donor 3) developed symptoms of vCJD".

v. "These findings strongly suggest that vCJD may be transmitted via blood transfusion. The identification of a third case of vCJD in this small cohort of known recipients of blood from persons incubating vCJD establishes beyond reasonable doubt that blood transfusion is a transmission route".

vi. "In the reverse study, 15 vCJD cases were reported to have received blood transfusions in the past. A further case received a blood transfusion after onset of illness. This case is excluded from the figures quoted. Checks revealed that of these 15 cases, one was not transfused, 4 had transfusions which pre-dated available records (pre1980), and 10 had records of transfusion which could be traced (see vCJD cases who received blood transfusion(s) in the past below). These 10 had received 209 donor exposures (with one patient given 103 components), which have been traced to 192 named donors (two of whom had vCJD as described above)."[5]

vii. Experimental transmission studies of tissue samples from Case 2 (described above) confirmed the presence of vCJD infectivity in the spleen, but not in the brain (NHBT0033619). These results

[5] http://www.cjd.ed.ac.uk/projects/transfusion-medicine-epidemiology-review-tmer

support the concept that asymptomatic individuals infected with vCJD harbour infectivity in lymphoid tissues, and presumably also in blood. vCJD prions were subsequently detected by highly sensitive biochemical assays in blood samples from vCJD patients and from samples taken from individuals infected with vCJD before their onset of clinical signs and symptoms (i.e. during an asymptomatic or preclinical infection) (WITN7034013, WITN7034014).

viii. On 7th September 2009 I reported to the HCDO the first positive result detecting the abnormal prion protein found in vCJD in a spleen sample from a patient included in the DH-funded prevalence study of vCJD infection in haemophilia (HCDO0000131_056). This positive result came from one region of the spleen of a haemophilia patient. Our findings were published in Haemophilia in 2010 (HCDO0000799). The finding of a single positive result from a single tissue sample was difficult to interpret and the possibility of accidental cross-contamination was investigated. Clinical, epidemiological and statistical analyses suggested that the most likely route of vCJD infection was the receipt of UK plasma products, but this could not be proven conclusively on independent review by the DH Health Protection Analytical Team (WITN7034039). No further positive cases in the DH-funded prevalence study have subsequently been identified to my knowledge.

ix. No instances of vCJD transmission in other healthcare settings e.g. via surgical instruments (including neurosurgical and ophthalmic surgical instruments) or via endoscopes have ever been identified as far as I am aware.

x. **The extent of exposure a person requires to become infected;** This question is difficult to answer, since a number of factors determine the risk of prion disease transmission, including the nature of the prion strain involved, the species of the donor and recipient, the amount of infectivity present in the material being transmitted, any interventions to reduce infectivity in the

material concerned prior to exposure and the route of exposure to infectivity. The possible determinants of the risk of vCJD transmission by transfusion of blood and plasma products are complex (HSOC0016641), but likely to include:

1. **Levels of infectivity in donor population**

a. Prevalence of sub-clinical infection – geographical variation

2. **Exposure of recipient to infected donors**

a. Infectivity of donation within incubation period

b. Quantity of plasma/leucocytes within component

c. Number of donors contributing towards component/size of plasma pool

d. Number of transfusions received/quantity of plasma product infused

e. Manufacturing process: e.g. leucodepletion, plasma fractionation, inactivation procedures

3. **Susceptibility of recipient**

a. Genotype e.g. codon 129 PRNP

b. Age

c. Immune function

d. Other factors

xi. An independent assessment of the risk to patients of exposure to vCJD infectivity in blood products was carried out on behalf of the Department of Health (DH) by Det Norske Veritas Consulting (DNV) and reported in 1999 (NHBT0008380). The report concluded "it is not possible to make any firm predictions about the level of risk from any vCJD infectivity that may be present in the blood of people incubating the disease. With our current level of knowledge....it has not been possible to estimate the absolute level of risk and the results have been presented in terms of the risks per infected donation". "If it is assumed that blood from a person infected with vCJD can carry infectivity.... the infectivity level in a full unit of red blood cells, platelets or plasma may be sufficient to cause infection."

xii. On the basis of the assumptions made in this report, an infected donation was estimated to result in up to 2.6 new infections, around half of which were predicted to be due to plasma derivatives. 80% of those infected were predicted to live long enough to develop vCJD. Subsequent data from a dose response model of CJD infectivity in a non-human primate model estimated a mean infection rate of 76% among human recipients who receive one unit of whole blood collected from an infected donor near the end of the incubation period (WITN7034018).

b. Whether everyone exposed to an infected batch of product will become infected;

i. I presume this question refers to plasma product batches. Plasma from many thousands of donations is pooled prior to fractionation. The impact of plasma processing technologies on the nature and distribution of vCJD infectivity in plasma products are unknown. Furthermore, the various determinants that influence prion transmission listed in the Response to 8a above indicate that a uniform recipient response (in terms of developing infection) to exposure to vCJD infectivity in plasma products might not be anticipated, particularly if individual recipients received different volumes of the product in question.

c. Whether repeated exposure to vCJD infected products increases the risk of a person becoming infected with vCJD.

i. The DNV report in 1999 (NHBT0008380) considered the available data from different experimental models on the dose-response relationship in prion infections and concluded with the assumption that the dose-response function for vCJD is linear without any threshold. This assumption has been questioned and was subsequently described as "likely to be a simplification of the true dose-response interaction and does not account for the interactions between the agent and the host in the infection process, which may affect the final outcome" (WITN7034018).

9. Please provide an explanation of the terms clinical and subclinical vCJD.

a. Infection with vCJD may be symptomatic (clinical) or asymptomatic. The terminology for vCJD infection in the absence of clinical signs and symptoms is confusing and includes terms such as asymptomatic infection, pre-clinical infection and sub-clinical infection. "Asymptomatic infection" covers both the terms of pre-clinical and sub-clinical infection. In my opinion, the term "pre-clinical" vCJD should be used only when the subsequent onset of disease (i.e. clinical signs and symptoms) justifies its use; it is perhaps most appropriately used in retrospect to refer to the incubation period prior to the onset of signs and symptoms of disease in an individual with clinical vCJD. The term "subclinical" should be restricted to refer to individuals who are infected with vCJD but would never become ill.

10. Please provide a description of the signs and symptoms a person may experience when first infected with vCJD.

a. HSOC0010099 describes the early clinical signs and symptoms of vCJD that allowed its identification as a distinct form of human prion disease. The onset of these signs and symptoms will occur after an incubation period (estimated at around 13 years (DHSC0004210_030, DHSC0004526_058)) following infection with BSE. I am not aware of any information on clinical signs and symptoms that may occur around the time of infection with BSE. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who may be able to provide additional information in response to this question.

11. Please provide a description of the period that may elapse between first being infected with vCJD and symptoms first emerging (a "latency period") and what is known about any factors which may affect the length of this latency period either by shortening or prolonging it.

a. The average incubation period for vCJD following infection with BSE has been estimated for individuals with the PRNP codon 129 MM genotype at around 13 years on the basis of mathematical modelling and statistical analysis (DHSC0004210_030, DHSC0004526_058). In other acquired human prion diseases (iatrogenic CJD and kuru), the PRNP codon 129

genotype can influence the disease incubation period, which can last up to several decades (WITN7034019). It therefore seems reasonable to assume that cases of vCJD in individuals with a PRNP codon 129 MV or VV genotype would have an incubation period that is likely to be longer than that for the PRNP codon 129 genotype. A single case of definite vCJD in an individual with the PRNP codon 129 MV genotype has been reported in the UK (WITN7034010); I am unaware of any similar cases outside the UK. On the basis of experimental models of prion diseases it is likely that other genes may act as susceptibility factors or influence the disease incubation period. This is not an area of my expertise, but Professor Mead is a clinical Neurologist with extensive expertise in genetics and will be able to provide further information on this topic.

b. In addition to genetic influences, incubation periods in prion diseases can be influenced by different routes of infection and by disease transmission across species (WITN7034017, WITN7034020). The incubation periods between the date of transfusion and the onset of vCJD symptoms in the 3 PRNP codon 129 MM UK patients who developed vCJD following blood transfusion from vCJD-infected donors are known (see the response to Question 8 above). These incubation periods are shorter than the estimated incubation period for BSE in PRNP codon 129 genotype individuals, as would be expected in the absence of a "species barrier" to transmission and a different route of infection (intravenous as opposed to oral) at 6 years and 6 months; 7 years and 10 months; and 8 years and 4 months.

12. **Please provide a description of the symptoms – physical, mental, and cognitive – a person may experience as vCJD progresses.** HSOC0010099 describes the early signs and symptoms of vCJD that allowed its identification as a distinct form of human prion disease. As a non-clinician, I did not interact with patients and therefore this question is beyond my area of professional experience and expertise. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

13. **Has vCJD changed or mutated since its emergence, and if so, how and with what consequences to resultant disease?** As far as I am aware, the prion strain responsible for vCJD has not altered since it was described and is maintained in individuals with both the PRNP codon 129 MM and MV genotypes (WITN7034021). In a recent review of vCJD, my former colleague Professor Robert Will and I described the clinical and neuropathological features of vCJD, including the signs and symptoms of the disease and the frequency with which they had occurred (WITN7034022). The key neuropathological features have not changed over the years and were preserved in the case of vCJD in a UK patient with the PRNP codon 129 MV genotype (WITN7034010). As a non-clinician, I did not interact with patients and therefore the question of altered clinical disease is beyond my area of professional experience and expertise. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

14. **Please provide a description of any treatments that have been provided to people infected with vCJD over the years up to the present day. Please set out the requirements of each treatment regime, any contra-indications to the treatments and the known side effects.** As a non-clinician, I did not interact with patients or prescribe treatments and therefore this question is beyond my area of professional experience and expertise. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question. Professor John Collinge was the lead clinician on the MRC PRION-1 partially randomised clinical trial on the safety and efficacy of quinacrine in human prion disease.[6]

15. **Please consider and address the prognosis and life expectancy of people infected with vCJD and how this has changed over the years. Please also identify any predictive factors as to life expectancy and prognosis. When considering this issue please consider in particular:**
    a. **Whether early diagnosis and/or treatment makes a difference to prognosis and/or life expectancy? If so, is there an optimum period**

[6] https://www.ctu.mrc.ac.uk/studies/all-studies/p/prion-1

of time within which a person should receive treatment? Has this differed over time? As a non-clinician, I did not interact with patients and therefore this question is beyond my area of professional experience and expertise. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

b. **Whether the prognosis or life expectancy is different for a person who is co-infected with HIV, HCV and/or HBV compared to a person infected solely with vCJD?** I am unaware of any vCJD patients who were co-infected with HIV, HCV and/or HBV. However, as a non-clinician, I did not interact with patients and therefore this question is beyond my area of professional experience and expertise. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

16. **Is it possible for a person with vCJD to spontaneously clear the disease and/or can vCJD ever be cured? If so, what is the likelihood of either of these occurring?** I am unaware of any patient with vCJD spontaneously recovering or being cured of the disease. However, as a non-clinician, I did not interact with patients and therefore this question is beyond my area of professional experience and expertise. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

17. **What is known about how vCJD affects people with:**
    a. **haemophilia,**
    b. **von Willebrand disease**
    c. **thalassaemia,**
    d. **sickle cell anaemia,**

    differently from those who do not have a bleeding or blood disorder?

I am unaware of any cases of vCJD in individual with any of the 4 disorders listed above. However, as a non-clinician, I did not interact with patients and therefore this question is beyond my area of professional experience and expertise. Professors

Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

18. **What advice and information would you expect a person now to be given about vCJD, including advice and information about the risks of transmission, prognosis and treatment options?**

    a. The information and advice given to a person would depend on their individual circumstances, e.g. as a member of the public, as a relative or carer of a patient with vCJD, as a person who has been identified as being at increased risk of vCJD, or as a healthcare professional who interacts with patients who are suspected of suffering from vCJD or have been identified as being at increased risk of vCJD. For the latter group, I would expect the information and advice to be provided in person by a healthcare professional or an expert in patient communication familiar with the complexities of CJD. The explanation should be given using clear language and include details on the nature of prion disease, the origins of vCJD and how vCJD may be transmitted from person to person, along with examples of circumstances in which vCJD is not known to be transmitted from person to person (e.g. within members of a family). The uncertainties around vCJD prevalence and the overall population risk of vCJD in the UK should be addressed, along with the difficulties of estimating the magnitude of increased vCJD risk on an individual basis and the current lack of a test to detect asymptomatic infection. The healthcare precautions required for individuals at risk of vCJD should also be addressed and advice provided on how an "at risk" individual can help stop potential vCJD spread to other people in a healthcare setting. This interaction should be accompanied by written information sheets in clear language, including FAQ and details of how to access sources of further information and personal support. The issue of insurance for individuals at risk of CJD has been raised in the past and can be addressed by reference to the relevant document from the Association of British Insurers (WITN7034040). All this information and advice should be updated regularly and reviewed in the light of relevant

new scientific and medical advances, e.g. in testing for prion infections, or effective treatments or prophylaxis.

b. As a non-clinician, I did not interact with patients and therefore the topics of prognosis and treatment are beyond my area of professional experience and expertise. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

19. **Are there any guidelines or protocols or any guidance in place currently for those treating people diagnosed with vCJD or at risk of having contracted vCJD as to when to provide information to family members, or recommend testing family members or previous sexual partners? What is good clinical practice in this regard?** As a non-clinician, I did not interact with patients and therefore this question is beyond my area of professional experience and expertise. I am not aware of any reports of person-to person transmission of vCJD within families or between sexual partners. No evidence of vertical (mother-to child) vCJD transmission has been identified (WITN7034023). Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

20. **What are the current clinical guidelines for infection control when treating a person with vCJD or who has been exposed to vCJD infected products?** The Advisory Committee on Dangerous Pathogens' Transmissible Spongiform Encephalopathy (ACDPTSE) Subgroup has published guidance "Minimise transmission risk of CJD and vCJD in Healthcare Settings" (WITN7034047). This guidance covers patients with, or at risk of, CJD and vCJD.

21. **Is there any work being undertaken to find a cure for vCJD? If so, please explain what that is.** As a non-clinician, I did not interact with patients or prescribe drugs and therefore this question is beyond my area of professional experience and expertise. I am aware that research into drug development for neurodegenerative diseases including CJD is being carried out, but since I

retired from work in 2017 my knowledge of this field is not up to date. Professors Richard Knight, Simon Mead and John Collinge are all clinical Neurologists who will be able to provide a response to this question.

Section 3: Knowledge of Risk

22. **The Inquiry is investigating how knowledge of the risk of vCJD developed over time within the UK Government, Blood Services, Haemophilia Centres and other NHS organisations. The Inquiry is aware of your involvement in the initial discovery of vCJD (HSOC0010099); the development of screening and diagnostic tests (DHSC0004747_040); and the identification of vCJD infections where blood has been implicated (NHBT0008743_013; HCDO0000799). With this in mind please give a history of the emergence and discovery of vCJD in the UK and around the world and in broad terms what has been understood about vCJD over the years.**

    a. **Initial discovery of vCJD and its acceptance as a new disease entity.**

        i. Surveillance of Creutzfeldt-Jakob disease (CJD) was reinstituted in the United Kingdom in May 1990 in order to identify any changes which might occur as a consequence of potential human exposure to the bovine spongiform encephalopathy (BSE) agent. My colleague Professor Robert Will was the Director of the NCJDRSU at the Western General Hospital, Edinburgh and had previous experience of conducting surveillance for CJD in England and Wales in a project led by Professor Bryan Matthews in Oxford in the 1980s. CJD case ascertainment was mostly by direct referral from Neurologists and Neuropathologists, but also by reviewing death certificates. Professor Will and I used our professional networks in the UK (The Association of British Neurologists and the British Neuropathological Society) to raise awareness of the Surveillance Project and encourage referral of suspected cases across the UK.

ii. Cases were subject to detailed clinical, neuropathological and epidemiological analysis in order to detect any changes in the referred cases that might represent the consequences of exposure to BSE. Current cases in the UK were compared to those identified in the previous CJD surveillance project in Oxford and were also compared with the results from contemporary CJD surveillance projects using comparable methodology in other European countries (including France, Germany and Italy). This allowed a detailed characterisation of the range of neuropathological phenotypes occurring in current cases of CJD in the UK. In addition to meticulous observer-based microscopic analysis (otherwise known as "classical neuropathology"), I had obtained research funding from the Biotechnology and Biological Sciences Research Council (BBSRC) to develop automated computer-based image analysis techniques to quantify the microscopic features of CJD, in order to provide an objective assessment of the severity and distribution of various neuropathological features in different brain regions.

iii. Of the 207 cases of CJD (sporadic, iatrogenic and genetic) examined since May 1990 in NCJDRSU I identified 10 cases with closely similar neuropathological findings that clearly distinguished them from other current UK CJD cases, with numerous florid amyloid plaques composed of prion protein in the cerebrum and cerebellum, posterior thalamic gliosis and widespread accumulation of abnormal prion protein in the brain (HSOC0010099). This observer-based assessment was confirmed by the results of automated image analysis of the nature, severity and distribution of the key neuropathological features observed (WITN7034024). These cases had come to the attention of NCJDRSU in 1995-96. The patients were relatively young compared to sporadic CJD (median age 29 years compared to 65 years) and had a lengthy duration of illness (median 12 months compared to 4 months). Their clinical features were also distinct from sporadic CJD, with early behavioural

changes, sensory changes followed by ataxia and other movement disorders, with progressive dementia in the later stages of the disease. In contrast, sporadic CJD characteristically present with rapidly progressive dementia accompanied by focal neurological signs. All vCJD cases were methionine homozygotes at codon 129 in the PRNP gene (codon 129 MM), while cases of sporadic CJD can occur in all three possible codon 129 genotypes (MM, MV and VV). DH were kept closely informed of these findings as new cases emerged and more data became available. I discussed and presented the neuropathological findings in strict confidence to senior colleagues in the UK, who agreed with my description and interpretation.

iv. Professor Will and I were invited to describe our finding in this series of 10 patients to the Spongiform Encephalopathy Advisory Committee (SEAC) on 8th March 1996, when I presented both descriptive and quantitative neuropathological data to help justify our interpretation that these cases represented a new variant form of CJD in the UK that had not been identified previously. SEAC accepted this interpretation. Our findings were announced in the House of Commons on 20th March 1996, by which time we were preparing a manuscript describing our findings for publication. The announcement was immediately followed by a Press Conference in London that Professor Will and I attended to answer questions on our work. This was followed by intense local, national and international media interest in our work, which was overwhelming at times. Our manuscript was submitted to the Lancet and underwent rapid peer review, after which it was revised following consideration of the reviewers' comments and was accepted for fast-track publication, which occurred in the Lancet on 6th April 1996 (HSOC0010099).

v. In May 1996 Professor Will and I were invited to a meeting of the World Health Organisation (WHO) to present our findings on vCJD and to justify its recognition as a new form of CJD to a large international panel of experts in CJD and related disorders. Our

conclusion that vCJD was a new disease entity was accepted by the panel and by the WHO, leading to a series of meetings over the next 10 years in the WHO on vCJD and other forms of CJD in terms of diagnosis, surveillance, infection control and reference materials for diagnostic test development.

b. The first case of vCJD outside the UK

i. On 4th April 1996 I was visited by a French Neuropathologist from Lyon, Dr Nicolas Kopp, who was aware of our findings from articles in the Press and asked me to review the neuropathological features of an unusual case of CJD in a 26 year old male that he had recently encountered. I confirmed that the findings in his case were identical to those in our series of 10 patients. This was the first case of vCJD identified outside the UK, the details of which were soon published in a letter to the Lancet on 27th April 1996 (DHSC0045235). On 24th April 1996 I attended the European Congress of Neuropathology in Paris and presented our findings to the attendees, who included Neuropathologists from across Europe, the USA and Australia. I also gave a practical diagnostic seminar on vCJD to the French Neuropathologists, who were aware of the case of vCJD in Lyon and were preparing for the possibility of further cases in France. I also agreed to review any cases of suspected vCJD in other countries and to allow other Neuropathologists to visit NCJDRSU to study the UK cases.

c. Relationship of vCJD with BSE

i. In our paper describing vCJD, the possibility of a relationship with BSE was raised: "These cases appear to represent a new variant of CJD, which may be unique to the UK. This raises the possibility that they are causally linked to BSE. Although this may be the most plausible explanation for this cluster of cases, a link with BSE cannot be confirmed on the basis of this evidence alone" (HSOC0010099).

ii. Additional evidence of a possible link to BSE first came from the identification of a close similarity between the neuropathological

features in the UK vCJD cases with the neuropathology of experimental BSE transmission to macaques following intracerebral inoculation in France, the results of which were published in collaboration with Dr Corinne Lasmezas and colleagues in Nature on 27th June 1996 (RLIT0000728).

iii. Additional evidence came from a detailed molecular analysis of the disease associated prion protein (PrP^{Sc}) in the brain in vCJD, sporadic and iatrogenic CJD and natural and experimentally transmitted BSE in collaboration with Professor John Collinge. This study found that the molecular characteristics of PrP^{Sc} in the brain in vCJD were distinct from sporadic and iatrogenic CJD, but closely similar to natural and experimentally transmitted BSE. These results were published in Nature on 24th October 1996 (MHRA0021347).

iv. Formal proof that the prion strain in vCJD has close similarities to the BSE strain in cattle and other BSE infected species (domestic cats, greater kudu and nyala), but is clearly distinct from the strains identified in sporadic CJD and scrapie came from experimental strain typing studies in wild-type mice in collaboration with Dr Moira Bruce and colleagues in the Institute for Animal Health BBSRC/MRC Neuropathogenesis Unit in Edinburgh. This work was planned at an early stage in our identification of vCJD, as the experimental strain typing involved is a complex and lengthy process (with incubation periods in mice of more than one year) that represents the "gold standard" for defining the biological properties of prion strains. The results were published in Nature on 2nd October 1997 (WITN7034015). This important finding has been replicated in several different laboratories across the world in a range of other model systems (reviewed in (WITN7034025)).

d. Development of diagnostic and screening tests.

i. The accumulated evidence summarised in (c) above supports the hypothesis that vCJD is an acquired human prion disease resulting from transmission of the BSE agent to humans, most

likely via the food chain. A case-control study of risk factors for vCJD in the UK found evidence that dietary exposure to BSE-contaminated beef products was the main route of infection of vCJD. There was no convincing evidence of increased risk through medical, surgical, or occupational exposure or exposure to animals (WITN7034026). This implies that the BSE agent must spread from the gut to the brain, where prion replication causes brain damage resulting in neurological signs and symptoms. Evidence from early experimental transmission studies of scrapie in animal models suggested that prion replication can occur in lymphoid tissues such as the spleen prior to invasion of the central nervous system (WITN7034016).

ii. Accordingly, my colleague Professor Jeanne Bell and I had developed a protocol for autopsies on cases of suspected CJD and other "high risk" autopsies (e.g. in HIV or Hepatitis B) that pose a risk of infection in the autopsy room, which was published in 1997 (DHSC0041081_006). In addition to sampling tissue from the brain and spinal cord, this included sampling of a wide range of other tissues of potential interest (including the lymphoid tissues of the intestines, appendix, lymph nodes, spleen, tonsil and thymus) when appropriate consent had been obtained. These tissue samples were stored in both fixed and frozen formats to allow a wide range of laboratory investigations (including biochemical analysis and experimental transmission studies) where appropriate.

iii. It was therefore possible at an early stage in our investigations into vCJD to study a range of lymphoid tissues and other non-nervous system tissues for the detection of disease-associated prion protein by established methods such as immunohistochemistry for prion protein on paraffin-embedded tissue sections. If positive, the corresponding frozen samples from these tissues were then available for biochemical and molecular analysis of PrP^{Sc}, which cannot be performed on fixed or paraffin-embedded tissues.

iv. DHSC0004747_040 is a research letter I published in collaboration with Professor John Collinge and colleagues in the Lancet on 11th January 1997 describing the use of immunohistochemistry to detect abnormal prion protein in paraffin-embedded sections of tonsil from a vCJD patient (the first case of vCJD in which a range of lymphoid tissues were available for analysis). These results were accompanied by the results of biochemical and molecular analysis of PrP^{Sc} in the corresponding frozen tissue sample and in a frozen brain tissue sample. Normal brain and tonsil tissues were used as controls. The results showed that most of the abnormal prion protein accumulate in the germinal centres of the lymphoid follicles in the tonsil and that the biochemical profile of PrP^{Sc} in the tonsil was closely similar to the PrP^{Sc} in the brain. This initial report supported the hypothesis that prions can accumulate in lymphoid tissues in vCJD and may therefore also be present in blood. It also offered the possibility of using tonsillar biopsy as a diagnostic test for vCJD in living patients. Further studies on lymphoid tissue from additional cases of vCJD showed widespread accumulation of abnormal prion protein in follicular dendritic cells and macrophages of the germinal centres in the intestine, appendix, lymph nodes, spleen, tonsil and thymus (reviewed in (WITN7034012)). A subsequent larger joint study, including both autopsy tissues and tonsil biopsy tissues from patients with suspected vCJD confirmed the earlier findings and reinforced the potential value of tonsil biopsy in vCJD, particularly in reducing the need for a brain biopsy to make a diagnosis (NHBT0004118_005).

v. On 29th August 1998, in collaboration with Dr David Hilton and colleagues in Plymouth, I published a research letter in the Lancet describing the detection of abnormal prion protein using immunohistochemistry in germinal centres in paraffin-embedded sections of an appendix that was surgically removed from a patient 8 months before the onset of the signs and symptoms of vCJD (DHSC0038548_050). Involvement of the tonsillar tissue

before onset of neurological disease had been shown in 1996 from the age of 10 months in sheep infected with scrapie (SBTS0004144_175); however, our findings were the first demonstration of PrP in lymphoid tissue in human beings during the incubation period of vCJD. Involvement of gut-associated lymphoid tissue before the clinical onset of disease is in keeping with an enteric route of entry for prion agents (WITN7034016).

vi. An implication of the presence of PrP in the appendix during the incubation period of variant CJD is that it offered the opportunity for large scale screening of appendectomy and, presumably, tonsillectomy, specimens removed since the onset of the BSE epidemic. Such a study would provide new data on the proportion of the population at risk of developing variant CJD, although it is not known at what stage during the incubation period of variant CJD that lymphoid tissue becomes involved or whether this involvement will inevitably lead to the development of neurological disease.

vii. Further discussions with Dr Hilton on a potential project of this type were taken forward by DH through the Medical Research Council (MRC), who established the MRC Steering Group on the Prevalence of Detectable PrP in Lymphoid Tissues in 1998. This group provided advice and guidance to DH on the study design and inclusion criteria, tissue selection, methodology for prion protein detection, ethics, size, scope and approach to the interpretation of results from a vCJD prevalence study base on the detection of abnormal prion protein in lymphoid tissues. Once these and various other issue had been agreed and Ethics Approval had been granted, the study was funded by DH via MRC and commenced in Edinburgh and Plymouth. Preliminary results on the first 3000 samples, all of which were negative, were published in 2000 (DHSC0038568_037). A parallel specificity study found no evidence of prion protein positivity in human lymphoid tissues involved in other pathological processes, including infections, inflammation and neoplasia (WITN7034027).

The final results were published in 2004 (NHBT0063957_002) and reported 3 positive cases out of the 12,674 assessable samples studied, giving an estimated prevalence of vCJD infection of 237 per million in the UK. The result of two subsequent larger vCJD prevalence studies were reported in 2013 (PRIU0000069) and 2020 (WITN7034009). The first of these found a prevalence of 493 per million in the UK population exposed to BSE and the result of PRNP codon 129 genetic analysis found a high proportion of positive cases were valine homozygotes (codon 129 VV) compared with the frequency in the normal population, and in contrast with the findings in vCJD patients, which at that time were all methionine homozygotes (codon 129 MM). The 2020 study analysed over 29,000 samples from 2 populations thought to have been unexposed to BSE: individuals born between 1891 and 1965 who underwent appendectomy between 1962 and 1979 (pre-BSE); and individuals born after 1996 who underwent appendectomy between 2000-2014 (post-BSE) (WITN7034009). Seven appendix samples were positive for abnormal prion protein, of which two were from the pre-BSE exposure era and five from the post-BSE period. None of the positive samples were from appendices removed before 1977, or from patients born after 2000.

viii. The overall results of the three Appendix studies indicate a prevalence of vCJD infection of around 240-500 per million UK population. All three possible PRNP codon 129 genotypes (MM, MV and VV) are represented in the positive cases. This finding is consistent with experimental evidence that all 3 PRNP codon 129 genotypes are susceptible to infection with vCJD (NHBT0008745_002). None of the positive samples in the three Appendix studies came from individuals later diagnosed with vCJD.

ix. Two possible interpretations of these results are suggested (WITN7034009): either there is a low background prevalence of

abnormal PrP in human lymphoid tissues that may not progress to clinical vCJD; alternatively, all positive specimens are attributable to BSE exposure, requiring dietary exposure to BSE to have begun in the late 1970s and continued through the late 1990s. The authors state "whichever interpretation is preferred, the contrast between the prevalence of abnormal PrP and the number of clinical vCJD cases seen to date (mid-2020) strongly suggests that possibly none of those in whom abnormal PrP is detected through an ante-mortem lymphoid tissue survey will develop any symptoms of prion disease".

e. The identification of vCJD infections where blood has been implicated

i. The TMER study was established in 1997 as a collaborative project between NCJDRSU and the UK Blood Services to investigate whether there is any evidence that vCJD or other forms of CJD may have been transmitted via the blood supply. My clinical colleague Professor Robert Will was the principal investigator for NCJDRSU in this study. I have provided further information on the TMER study in my response to Question 8.

ii. Four instances of probable transfusion transmitted vCJD infection have been identified by the TMER. These findings strongly suggest that vCJD may be transmitted via blood transfusion. The clinical diagnosis of vCJD in Cases 1, 3 and 4 were confirmed by neuropathological and biochemical examination in NCJDRSU of the brain and other tissues following autopsy. Experimental transmission studies of tissue samples from Case 2, who died of an unrelated cause with no signs and symptoms of vCJD (DHSC0004215_039), confirmed the presence of vCJD infectivity in the spleen, but not in the brain (NHBT0033619). These results support the concept that asymptomatic individuals infected with vCJD harbour infectivity in their lymphoid tissues, and presumably also in blood. vCJD prions have been detected by highly sensitive biochemical assays in blood samples from vCJD

patients and from individuals infected with vCJD before their onset of clinical signs and symptoms (i.e. during an asymptomatic or pre-clinical infection) (WITN7034013, WITN7034014).

23. Please provide a chronological overview of the scientific developments of the risks of vCJD infection and of secondary transmission via blood and blood products. As part of this, please include:

a. What was understood about the infectivity and transmissibility of other forms of CJD in blood in the period from 1985 onwards. Please comment upon what research was conducted and how it informed the knowledge of risk of vCJD transmission in blood.

i. In 1985 the first case of iatrogenic CJD in a recipient of human pituitary growth hormone produced in the UK was reported **(RLIT0000729)**. Prior to this, the possibility of person-to-person transmission of CJD by blood transfusion had been raised in view of the high transmission rate of natural scrapie in sheep, the widespread occurrence of kuru in certain tribes in Papua New Guinea and experimental transmissions of kuru and CJD to non-human primates; this was reinforced by the identification of iatrogenic transmission of CJD via injections with human pituitary growth hormone (reviewed in WITN7034019, WITN7034028).

ii. As far as I am aware, the previous case control study in the 1980s directed by Professor Bryan Matthews to identify risk factors for CJD in England and Wales did not find any evidence of transmission by blood transfusion. The actual risk of transmission of sporadic CJD via blood transfusion has not been quantified and as far as I am aware there has been no definitive report of such a transmission. Furthermore, case control studies and lookback evaluations of recipients of blood donors who subsequently developed sporadic CJD have found no conclusive evidence for transmission via blood transfusion over many years (see WITN7034028 for review).

iii. Paul Brown has reviewed a series of experiments in various experimental models of prion disease and in naturally occurring scrapie in sheep and goats (NHBT0098003). The first of these

were conducted in the early 1960s. Thereafter, the experimental approach was inconsistent, using various inocula (whole blood, serum, blood clot, buffy coat etc.) and a range of transmission routes (intracerebral, intraperitoneal, subcutaneous). Perhaps unsurprisingly the results were comparably diverse, but instances of successful transmission of infectivity were recorded (NHBT0098003). These data were considered in the DNV risk assessment of 1999 (NHBT0008380).

iv. Subsequent studies by Paul Brown and colleagues identified that in an experimental model of Gerstmann-Straussler-Scheinker syndrome (GSS, an inherited human prion disease) infectivity in blood appeared to be associated particularly with the cellular components in the buffy coat and in plasma. In the buffy coat, infectivity levels varied from 10-20 infectious doses (ID)/ml during the preclinical stage of the infection to 50-110 ID/ml at the terminal stage of the illness. For plasma, infectivity levels varied from undetectable to 5 ID/ml during the preclinical stage of infection to 20-30 ID/ml) at the terminal phase of the illness (reviewed in NHBT0098003). These data were considered in the DNV risk assessment of 2003 (MHRA0007248).

v. Most of the infectivity assays in these experiments were based on intracerebral inoculation of the buffy coat or plasma. These reported infectivity levels are much lower than those found in the brain (around 10^6 ID_{50}/g) and in lymphoid tissues (around 10^3 ID_{50}/g) in vCJD in humans, reported in 2001 from a collaborative study between NCJDRSU and the Institute for Animal Health Neuropathogenesis Unit in Edinburgh (DHSC0004472_043).

vi. Since 2000, modelling studies in BSE-infected sheep have demonstrated the efficient transmission of BSE by intravenous transfusion of all clinically relevant labile blood components including red blood cells, platelets and plasma. Infectivity can be transmitted in blood components from sheep in a preclinical stage of BSE infection and a recent study has found that variations in

the donor prion protein genotype may influence transfusion transmission rates (WITN7034017).

b. How the disease mechanism of vCJD and its involvement with the lymphoreticular tissues was established. Please comment upon how this research informed the knowledge of risk of vCJD transmission in blood.

i. Evidence from early experimental transmission studies of scrapie in animal models suggested that prion replication can occur in lymphoid tissues such as the spleen prior to invasion of the central nervous system (see WITN7034016 for review). Preclinical detection of infectivity was achieved in lymphoid tissues following experimental transmission by the intraperitoneal, intragastric and subcutaneous routes (WITN7034016).

ii. vCJD is an acquired human prion disease resulting from transmission of the BSE agent to humans, most likely via the food chain. This implies that the BSE agent spreads from the gut to the brain, where prion replication causes nerve cell death and brain damage, resulting in neurological signs and symptoms. Evidence from experimental transmission of prions in animal models suggests that prion replication can occur in lymphoid tissues such as the spleen prior to invasion of the central nervous system (WITN7034016). Since the spleen is involved in the filtration of blood, the possibility that prions could also be present in blood was further studied experimentally. Since 2000, modelling studies in sheep have demonstrated the efficient transmission of BSE by transfusion of labile blood components including red blood cells, platelets and plasma. Infectivity can be transmitted in blood components from sheep in a preclinical stage of BSE infection and a recent study has found that variations in the donor prion protein genotype may influence transfusion transmission rates (WITN7034017).

iii. My colleague Professor Jeanne Bell and I developed a protocol for autopsies on cases of suspected CJD and other “high risk”

autopsies (e.g. in HIV or Hepatitis B) that pose a risk of infection in the autopsy room (NHBT0004118_005), sampling a wide range of both fixed and unfixed tissues. It was therefore possible at an early stage in our investigations into vCJD to study a range of lymphoid tissues and other non-nervous system tissues for the detection of disease-associated prion protein by established methods such as immunohistochemistry for prion protein on paraffin-embedded tissue sections. If positive, the corresponding frozen samples from these tissues were then available for biochemical and molecular analysis of PrP^{Sc}, which cannot be performed on fixed or paraffin-embedded tissues.

iv. DHSC0004747_040 is a research letter I published in collaboration with Professor John Collinge and colleagues in the Lancet on 11th January 1997 describing the use of immunohistochemistry to detect abnormal prion protein in paraffin-embedded sections of tonsil from a vCJD patient. This was accompanied by the result of biochemical and molecular analysis of PrP^{Sc} in the corresponding frozen tissue sample and in a frozen brain tissue sample. Normal brain and tonsil tissues were used as controls. The results showed that most of the abnormal prion protein accumulate in the germinal centres of the lymphoid follicles in the tonsil and that the biochemical profile of PrP^{Sc} in the tonsil was closely similar to the PrP^{Sc} in the brain. This initial report supported the hypothesis that prions can accumulate in lymphoid tissues in vCJD and may therefore also be present in blood. It also offered the possibility of using tonsillar biopsy as a diagnostic test for vCJD in living patients. Further studies on lymphoid tissue from additional cases of vCJD showed widespread accumulation of abnormal prion protein in follicular dendritic cells and macrophages of the germinal centres in the intestine, appendix, lymph nodes, spleen, tonsil and thymus (reviewed in WITN7034012). A subsequent larger joint study, including both autopsy tissues and tonsil biopsy tissues from patients with suspected vCJD confirmed the earlier findings and

reinforced the potential value of tonsil biopsy in vCJD, particularly in reducing the need for a brain biopsy to make a diagnosis (NHBT0004118_005).

v. The presence of infectivity in lymphoid tissues in vCJD was confirmed in a collaborative study between NCJDRSU and the Institute for Animal Health Neuropathogenesis Unit in Edinburgh, which reported significantly lower levels of infectivity in lymphoid tissues (around 10^3 ID_{50}/g) than in the brain (around 10^6 ID_{50}/g) (DHSC0004472_043).

vi. The TMER study has identified four cases of transmission of vCJD infectivity via blood transfusion from donors who subsequently died from vCJD. Three of the four recipients also died from vCJD (confirmed following post mortem examinations) while the fourth recipient died from an unrelated cause. Following a post mortem examination, evidence of an asymptomatic vCJD infection was found in the spleen and a lymph node of this recipient, but not in the brain or any other tissues examined. This recipient had the PRNP codon 129 MV genotype, while the three recipients who died from vCJD all had the PRNP codon 129 MM, as had all previous vCJD patients. The presence of infectivity in the spleen was subsequently confirmed in experimental transmission studies, which also confirmed the absence of infectivity in the brain, in keeping with our initial neuropathological and biochemical findings. This is the first recorded case of autopsy detection of an asymptomatic vCJD infection (DHSC0004215_039). These findings support the hypothesis that immunohistochemical deposition of abnormal prion protein in paraffin sections of lymphoid tissues from asymptomatic individuals is a marker of vCJD infectivity (NHBT0033619). This hypothesis is the basis of the methodology of the three Appendix studies.

c. **The risk assessments that were carried out within the scientific community and by external bodies such as Det Norske Veritas, quantifying the risk of vCJD transmission in blood (NHBT0008380;**

MHRA0007248). Please include an outline of your understanding of the findings. You may wish to refer to your previous comments on the first Det Norske Veritas report (DHSC0003998_006, see page 10), and, a discussion of the reports by the CJD Incidents Panel (HCDO0000254_119); SEAC (DHSC0004424_052) and the SACTTI Working Group on vCJD (JPAC0000114_018).

i. An independent assessment of the risk to patients of exposure to vCJD infectivity in blood products was carried out on behalf of the Department of Health (DH) by Det Norske Veritas Consulting (DNV) and reported in 1999 (NHBT0008380). DNV had previously carried out a series of BSE risk assessments for DEFRA over 1997-99 (NCRU0000158_065). The report concluded "it is not possible to make any firm predictions about the level of risk from any vCJD infectivity that may be present in the blood of people incubating the disease. With our current level of knowledge....it has not been possible to estimate the absolute level of risk and the results have been presented in terms of the risks per infected donation". "If it is assumed that blood from a person infected with vCJD can carry infectivity,... the infectivity level in a full unit of red blood cells, platelets or plasma may be sufficient to cause infection."

ii. The Report also states that the estimates of infectivity in plasma derivatives were based on experiments in an animal model "together with an assumption that the infectivity in the products is proportional to its protein content and that there is no reduction in infectivity from further processing steps, such a fractionation, filtration and chromatography. This is considered very pessimistic, so that the estimated infectivities in plasma derivatives are likely to be over estimated". This combination of input estimates of infectivity from animal models and pessimistic assumptions about the effect of further processing steps was questioned during the review process prior to publication (DHSC0003998_006).

iii. This Report (NHBT0008380) considered the available data from different experimental models on the dose-response relationship in prion infections and concluded with the assumption that the dose-response function for vCJD is linear without any threshold. This assumption was described subsequently as "likely to be a simplification of the true dose-response interaction and does not account for the interactions between the agent and the host in the infection process, which may affect the final outcome" (WITN7034018). Other criticisms of the data used in the Report centred on its use of results from experimentally infected animal models, some with very high levels of infectivity in many tissues, with less emphasis on data from naturally occurring animal prion diseases. The model assumptions and risk assessment methodology have also been questioned in a review of transmissible spongiform encephalopathy risk assessments in the UK (NCRU0000158_065).

iv. On the basis of the assumptions made in this report, an infected donation was estimated to result in up to 2.6 new infections, around half of which were predicted to be due to plasma derivatives. 80% of those infected were predicted to live long enough to develop vCJD. Subsequent data from a dose response model of CJD infectivity in a non-human primate model estimated a mean infection rate of 76% among human recipients who receive one unit of whole blood collected from an infected donor near the end of the incubation period (WITN7034018).

v. The initial DNV Risk Assessment of 1999 was subsequently revised by DNV in 2003 (MHRA0007248), in order to "update the earlier document by analysing research papers published since 1998; to extend the original study to include any plasma derivatives not included before; to adapt the 1999 report to provide a tool that the CJD Incidents Panel can use to estimate possible risks and determine advice given to patients known to have received potentially contaminated blood products".

vi. Concerning the estimates of infectivity levels in plasma derivatives, the revised Report now recognised that the risk of infection "varies significantly with the assumptions made about the level of infectivity and its distribution across plasma fractions. As the size of dose, number of doses and the size of the plasma pool all affect the potential risk, a calculator has been included in this Report". In contrast to the 1999 Report, the estimates of infectivity in plasma derivatives in the Revised Report "have been estimated based on two alternative approaches using the blood components and plasma fractions results".

d. How different patterns of prion distribution throughout body tissues were used to hypothesise exposure to vCJD through blood, rather than food (see DHSC0038559_048, point 6).

i. Detailed studies by Kimberlin and Walker in the 1960s analysed the spread of the sheep prion disease scrapie from the gut to the brain following experimental infection of mice via the alimentary tract. Uptake of the prion agent from the gut was followed by the spread of infectivity to the spleen and lymph nodes (see WITN7034016 for review). Subsequent experimental infection of mice with the scrapie and BSE showed initial accumulation of abnormal prion protein in the lymphoid tissues of the gut (Peyer's patches) and the mesenteric lymph nodes adjacent to the gut prior to the infection of other lymphoid tissues, including the spleen. This pattern of infectivity was also found in sheep experimentally infected with BSE via the oral route (WITN7034016). A similar pattern of lymphoid tissue infectivity could therefore be expected in vCJD according to the hypothesis that vCJD results from an orally acquired infection with BSE through the consumption of contaminated beef products.

ii. Our studies of lymphoid tissues in vCJD did indeed find a similar distribution of abnormal prion protein in gut-associated lymphoid tissues including the appendix, lymph nodes, tonsils, the thymus in younger patients (the thymus atrophies with age and can be difficult to identify in older patients) and in the spleen in patients

with the PRNP codon 129 MM genotype (WITN7034012). However, our investigations showed a different distribution of abnormal prion protein in the lymphoid tissues from the patient with the codon 129 MV genotype who died after receiving a blood transfusion from a donor who later died from vCJD, but did not develop signs and symptoms of vCJD prion to death (DHSC0004215_039). In this patient, abnormal prion protein was demonstrated in the spleen and in a cervical lymph node, but not in the appendix, tonsil or the gut-associated lymphoid tissues of the large intestine (DHSC0004215_039). This distribution of abnormal prion protein in the lymphoid tissues suggests that a route other than the oral route may have been responsible for the vCJD infection: in this case, presumably the intravenous route. The presence of vCJD infectivity in the spleen, but not in the brain, was subsequently confirmed following experimental transmission of these tissues (NHBT0033619).

24. **The Inquiry understands that prior to the first confirmed case of blood transmissible vCJD in 2003, the risk of vCJD infectivity and transmissibility in blood was estimated by other means. The inquiry is aware that part of your role in the Creutzfeldt-Jakob Disease Incidents Panel (CJDIP), Spongiform Encephalopathy Advisory Committee (SEAC) and the Standing Advisory Committee on Transfusion Transmitted Infections (SACTTI) working party on vCJD involved advising on the infectivity of Transmissible Spongiform Encephalopathy (TSEs). How was the theoretical risk of vCJD gauged?**

    a. The CJDIP used the DNV Report of 1999 as the basis of the section on the Infectivity of Blood Components in the Consultation Framework Document "Management of possible exposure to CJD through medical procedures" published in 2001 (NCRU0000158_065). This included estimates of infectivity levels in whole blood, plasma, white cells and platelets, red cell, and cryoprecipitate based on the DNV Report. For plasma derivatives, the Framework Document concluded: "While the pool size and processing details will need to be assessed for each

incident, it seems clear that albumin, Factor IX, and high purity Factor VIII are all likely to have low infectivity levels. Crude factor VIII and immunoglobulin may, however, be of concern. The management of incidents involving these, and other plasma derivatives is discussed in section 6. These risks will be reassessed once a revised estimate of infectivity has been completed".

b. CJDIP agreed that individuals should be classified as being 'at increased risk' of CJD if they are considered to have 1% risk of CJD in addition to the background risk in the UK population following specific iatrogenic exposures, or if they are at risk of genetic forms of CJD. The 1% threshold level is used as a cut-off for implementing public health precautions and is not intended to be a precise measure of an individual patient's risk (WITN7034030).

c. Following the 2003 revision of the DNV Risk Assessment, a vCJD Risk Calculator for plasma derivatives was created by Dr Philippa Edwards of the DH CJD Policy Unit. This was verified by the Economics and Operations Research Group in DH and accepted by the CJDIP in April 2003 (HCDO0000840). The Risk Calculator produces an estimate of the infectivity per gram/iu and per vial of each plasma derivative manufactured from a plasma pool containing a donation from an individual later found to have vCJD. It also calculates the dose that is estimated to contain an ID50 of 0.02. This represents a 1% increased risk of infection in the recipient, which is the level of risk that the CJDIP considered sufficient to warrant recipient notification.

d. On this basis, the CJDIP advised that surviving recipients of implicated red cell concentrates identified by the TMER study should be informed and public health precautions implemented to minimize the risk of secondary vCJD transmission. Together with batch-specific manufacturing data, the Risk Calculator was used by CJDIP to estimate the potential vCJD infectivity in each batch of implicated plasma product. For each of the major assumptions underlying the risk assessment, the most precautionary option was chosen. The implicated plasma products were divided into three groups based on the assessed risk. Amongst those considered to pose a high risk were FVIII, FIX and antithrombin

concentrates, of which as little as one vial of treatment led to an exposure in excess of the defined risk threshold (HSOC0016641). Products in the medium risk group included those in which exposure to substantial quantities was required to reach the risk threshold such as immunoglobulins, and the low-risk group comprised products with such low levels of potential infectivity as could effectively be ignored as causing any additional vCJD risk. The low-risk group also included some FVIII products that had been manufactured using implicated albumin as an excipient (HSOC0016641). To reduce the possibility of onward transmission of vCJD, CJDIP advised in 2004 that public health precautions should be taken in recipients of 'high risk', and 'medium risk' implicated plasma products who had exceeded the 1% additional risk threshold. As stated above, a 'population' or 'umbrella' approach was implemented in patients with inherited bleeding disorders who had received UK plasma sourced products between 1980 and 2001. This policy was advised by UKHCDO and endorsed by CJDIP, DH and the Haemophilia Society, the UK charity representing patients with inherited bleeding disorders (HSOC0016641).

Section 4: Response to Risk

25. **What were the structures in place to enable you and your colleagues to disseminate the information you had about the risk of vCJD from blood and blood products to the medical, and patient communities?**
    a. **Medical Community**
        i. **Presentations at local, national and international medical and scientific conferences.** Examples are listed in WITN7034002.
        ii. **Publications in medical and scientific journals.** Examples are listed in WITN7034003.
        iii. **Professional networks** such as the UK Blood Services via the TMER Study, UKHCDO via the collaborative surveillance project for evidence of vCJD infection in tissues from haemophilia patients, Neurologists via the Association of British Neurologists,

Neuropathologists via the British Neuropathology Society, Paediatric Neurologists via the PIND study and Immunologists via the PID study, Pathologists, Haematologists and Researchers via the Royal College of Pathology and the Human Tissue Authority.

iv. **Research collaborators** such as UKHCDO, UK Blood Services, The MRC Prion Unit, NIBSC and the Institute for Animal Health BBSRC/MRC Neuropathogenesis Unit.

v. **Regular contacts at relevant Committees** such as SEAC, ACDP TSE subgroup, CJD Incidents Panel, the Advisory Committee on Transfusion Transmitted Infection Working Group on vCJD and the Microbiological Safety of Blood and Tissue for Transplantation vCJD Subgroup.

vi. **Regular contacts at various Committees relevant to research**, particularly the MRC Allen Sub-Committee on Human Spongiform Encephalopathies and the MRC Steering Group on the Prevalence of Detectable PrP in Lymphoid Tissue.

vii. **Interviews** in the published media, radio and television.

b. **Patient Community**

i. As a non-clinician I had no regular interaction with patients or their relatives. I did meet some patients and relatives at occasional conferences at which I had given presentations. I answered questions from individual patients both after my presentations and at informal meetings at other times during the conferences.

ii. I also interacted with a range of patients and their relatives during my work as a Member of the HTA at presentations, consultation events and open days.

iii. It is also possible that patients and relatives attended one of the public lectures that I gave on vCJD and related matters, and these individuals may have been aware of our work on vCJD through interviews I gave in the press, radio and television.

26. What role did you have in advising on risk reduction measures? What measures have you advised should be put in place over the years? You may wish to comment on the following measures:

a. **Donor selection and exclusion policies:** I had no role in donor selection and exclusion policies.
b. **Importation of plasma from the USA and elsewhere:**I had no role in the importation of plasma from the USA and elsewhere.
c. **Leucodepletion and prion filtration:** I had no role in leucodepletion. The assessment of the efficacy of prion filters and the results of validation studies on prion filters were discussed in the committees and subgroups that I attended, including the ACDP TSE subgroup and its working groups. I had no role in decisions over the use of prion filters in the UK.
d. **Product withdrawal, quarantine and recall:** I had no role in product withdrawal, quarantine and recall.
e. **Recombinant blood products:**I had no role in recombinant blood products
f. **Promotion of blood alternatives:**I had no role in the promotion of blood alternatives.
g. **Surveillance infrastructure:** My role in surveillance infrastructure is described in my responses to Questions 4 and 22 above.
h. **Development of Screening and Diagnostic Tests:** My role in the development of screening and diagnostics tests is described in my response to Question 22, section (c) above.

27. **Please set out what steps (in so far as you are aware) the Blood services and Government took to mitigate the risk of secondary transmission of vCJD in blood and blood products in line with the risk indicated by emerging scientific research and risk assessments. In particular did the Blood Services and/or the Government accept the advice that the CJDIP, SEAC and SACTTI gave about the risk of vCJD and any risk reduction measures?**
    a. In 1996 I was invited to attend a meeting of the UK Blood Services in Edinburgh to give a presentation of vCJD and answer questions from the attendees. The minutes of this meeting record that "an active collaboration with the CJD Surveillance Unit" in relation to the transfusion history of vCJD patients and the development of case control studies

and lookback studies should be established (NHBT0007197). The issue of leucodepletion was also raised in the discussion at this meeting.

b. As far as I am aware, the UK Blood Services took the following steps to mitigate the risk of secondary transmission of vCJD in blood and blood products:

From 1997: Committee for Proprietary Medicinal Products recommends withdrawal of implicated batches of plasma products where a donor subsequently diagnosed with vCJD had contributed to the plasma pool.
1998-99: Introduction of Universal Leucodepletion
1998: DH announcement that fractionation of UK plasma would cease, and plasma supplies would be obtained from areas with a low prevalence of BSE.
2003-2006: Funding for treatment with recombinant factor concentrates became available for children with Haemophilia
2003 - 2007: DH Health Service Circulars HSC 2002/009 "Better Blood Transfusion - Appropriate Use of Blood" and 2007/001 "Better Blood Transfusion - Safe and Appropriate Use of Blood" gave guidance to "further improve the safety and effectiveness of transfusion", "avoid the unnecessary use of blood and blood components in medical and surgical practice" and "avoid unnecessary blood transfusion in obstetric practice".
2003: Imported fresh frozen plasma introduced for the treatment of children born after the adoption of food safety measures in 1996. The imported material would be subject to methylene blue treatment to reduce the risk of transmission of blood-borne viruses.
2003-2006: Funding became available for recombinant factor concentrates for all adult patients with haemophilia.
2004. Individuals who had received a blood transfusion since 1980 were excluded from blood transfusion.
2005. Blood donors whose blood had been transfused into individuals who subsequently developed vCJD were excluded from future donation.

These mitigation steps were reviewed in 2012 by Millar and Makris (WITN7034031) and by Seed et al. (WITN7034028) in 2018.

28. Were these steps sufficient and timely in your view? If not, what more could or should have been done?

a. I am not an expert in Transfusion Medicine. The UK Blood Services could provide further expert information on the practicalities of introducing the mitigation steps listed above. I am therefore not in a position to suggest what, if any, further mitigation steps might have been possible in view of the need to maintain the supply of blood in the UK.

b. It may have been possible to introduce universal leucodepletion at an earlier date. Leucodepletion had been used in other countries for reasons unrelated to vCJD, including reduction in the incidence of febrile transfusion reactions and a reduced risk of Cytomegalovirus transmission.

c. Seed et al. (WITN7034028) commented on the DH announcement in 1998 to cease fractionation of UK plasma: "This decision pre-dated any decision by the regulators and was in part precipitated by the complexity of the requirement to withdraw batches of product containing plasma from individuals who were subsequently diagnosed with probable or definite vCJD."

d. Millar and Makris (WITN7034031) commented on the recall of Factor VIII and Factor IX concentrates in 1998, 2000 and 2001: "No public health precautions were advised at the time of any of these recalls. The consensus given by the DH at the time was that patients would 'not benefit from this knowledge, and that uncertainty created by informing patients could cause unjustified worry and create a permanent blight on their lives'. In spite of this, and given the experience of the public health responses to HIV and HCV, and the resultant impact in the lives of affected patients and relatives, haemophilia physicians advocated for the right of recipients of implicated batches to be informed, even in the absence of known risk".

Section 5. Screening Tests

29. **How is vCJD currently tested for and diagnosed? Please include descriptions of the tests and procedures used to effect diagnoses and also provide an analysis of how reliable the various diagnostic tests currently are.**
    a. There is no single test for a diagnosis of vCJD. vCJD is diagnosed using a set of internationally accepted criteria that include the results of clinical, genetic, radiological and laboratory investigations and allow a diagnosis of possible, probable and definite vCJD (WITN7034041). These criteria have been validated and shown to be highly sensitive and specific (WITN7034032).
    b. Only definite and probable cases are included in the NCJDRSU reports on vCJD cases in the UK. The investigations that I was involved in comprise the neuropathological diagnosis following examination of the brain after autopsy, or occasionally following a brain biopsy procedure, and includes the biochemical analysis of PrP^{Sc} in the brain. Neuropathological examination is necessary for a diagnosis of definite vCJD.

30. **Please provide a chronological summary of the development of diagnostic and screening tests for clinical and subclinical vCJD. Please explain how reliable these tests have been over the years. Please describe the extent of your involvement with any of these studies and developments.**
    a. I have addressed these issues in my response to Question 22, section d "Development of diagnostic and screening tests."
    b. In addition, in 2016 vCJD prions were also detected by highly sensitive biochemical assays in blood samples from vCJD patients and from samples taken from individuals infected with vCJD before their onset of clinical signs and symptoms (i.e. during an asymptomatic or pre-clinical infection) (WITN7034013, WITN7034014). In the first of these studies (WITN7034013), a request to provide a sample of vCJD tissue as a positive control for the biochemical assay was approved by the MRC Edinburgh Brain and Tissue Bank. I have collaborated for several years

with Dr Claudio Soto, the senior author in this study. I had no role in the second study (WITN7034014).

31. Do you consider there is a need to introduce blood donor screening for vCJD? Please explain your answer.

a. A validated sensitive and specific blood test for vCJD infection in the absence of clinical signs and symptoms of vCJD could potentially answer the question as to the number of asymptomatically infected people in the UK with a greater degree of accuracy than the retrospective vCJD prevalence studies using archival appendix tissues. The challenges of developing such a test should not be underestimated (WITN7034028, WITN7034031). Were such a test available, I think that it should be used initially in an unlinked anonymous population study, as has been done for HIV and other infections. This would require Ethics approval and input from relevant experts in epidemiology and other fields beyond my expertise.

b. However, routine screening of blood donors would require not only a validated rapid screening test that could deal with large numbers of samples in multiple laboratories, but potentially also a second confirmatory test to ensure a high sensitivity and specificity of results. The routine testing of blood donors would require additional important considerations, including the ethics of using such a test, analysis of the likely rates of false negative and false positive results, practical consideration of the consequences to an individual of a positive result, the consequences of a false positive or negative result, the potential impact on the UK blood supply and the NHS and its patients more widely. These matters were considered in a DH report in 2009: "Mapping out the consequences of screening blood donations for PrP^{Sc}" (WITN7034042). A decision on whether or not to introduce blood donor screening for vCJD would require detailed consideration of these and other related topics, many of which are beyond my expertise.

c. Set out whether your position has changed since your evidence given to the Parliamentary Inquiry. My position on the need for and utility of sensitive blood assays to determine the prevalence of

asymptomatic vCJD infection in the UK has not changed. My comment on the need for more widespread screening of lymphoreticular tissues was addressed by the Appendix 3 study, the results of which were published in 2020 (WITN7034009).

d. **Explain why in your evidence given to the Parliamentary Inquiry and in your 2006 article, "Variant Creutzfeldt–Jakob disease: risk of transmission by blood transfusion and blood therapies" (RLIT0000668), you indicated there was an urgent need for more widespread screening of lymphoreticular tissues and the development of sensitive blood assays in order to assess the prevalence of subclinical vCJD in the general population?**

   i. Three major retrospective prevalence studies, based on the analysis of anonymized appendix samples for the presence of abnormal prion protein, estimate that the number of asymptomatic vCJD carriers in the United Kingdom may be around 240-500 per million UK population (WITN7034009), which differs significantly from the number of reported cases of vCJD from NCJDRSU. These findings indicate a potential for secondary transmission of vCJD from these asymptomatic carriers by blood transfusion, organ and tissue donation or certain surgical procedures and highlights the need for a sensitive, reliable, and fast diagnostic test with a high specificity and sensitivity for vCJD infection, particularly in those who display no clinical signs or symptoms.

   ii. Published comments on this topic from members of UKHCDO (HSOC0016641, WITN7034031) and UK Blood services (WITN7034028) in peer-reviewed scientific articles indicate a general support for these possible applications for such a test. Although two differing technologies have been used to detect vCJD prions in blood, including prion amplification methods (WITN7034013, WITN7034014) and a solid-state capture assay (NHBT0033626), neither to my knowledge has yet been employed in the UK for the purposes mentioned above. An investigation to determine the diagnostic accuracy of the solid-

state capture assay for vCJD (and hence its suitability for clinical use and for screening prion-exposed populations) included large numbers of blood samples from healthy blood donors in the USA and UK in addition to samples from patients with vCJD, other forms of human prion diseases and non-prion neurodegenerative disorders found a sensitivity of 71.4% and a specificity of at least 98.1% for vCJD (NHBT0034206). Subsequent discussion of these results questioned the suitability of this assay for screening blood donations, but the authors proposed that it should be used first in an unlinked anonymised prevalence study of asymptomatic vCJD infection in the UK population (PRIU0000231). I do not know if this proposal has been acted upon.

Section 6: Surveillance and Tissue Sampling

32. **What is the prevalence of vCJD in the general population? In responding to this question, please provide a summary of any notable research studies or papers, reports, recommendations, look back exercises and databases which have addressed this issue. Please describe the extent of your involvement, if any, with these studies and developments.**
    a. The prevalence of asymptomatic vCJD infection in the UK was investigated in three major retrospective prevalence studies in which I participated, based on the analysis of anonymised appendix samples for the presence of abnormal prion protein (WITN7034009, WITN7034027, PRIU0000069). Together, the results estimate that the number of asymptomatic vCJD-infected individuals in the United Kingdom may be around 240-500 per million UK population (WITN7034009, WITN7034027, PRIU0000069). All three possible PRNP codon 129 genotypes (MM, MV and VV) are represented in the positive cases.
    b. As stated above, two possible interpretations of these results are suggested (WITN7034009): either there is a low background prevalence of abnormal PrP in human lymphoid tissues that may not progress to clinical vCJD; alternatively, all positive specimens are attributable to BSE exposure, requiring dietary exposure to BSE to have begun in the late

1970s and continued through the late 1990s. The authors state "whichever interpretation is preferred, the contrast between the prevalence of abnormal PrP and the number of clinical vCJD cases seen to date (mid-2020) strongly suggests that possibly none of those in whom abnormal PrP is detected through an ante-mortem lymphoid tissue survey will develop any symptoms of prion disease".

c. **The Inquiry is aware that the NCJDSU is responsible for surveillance of new cases of vCJD, and that it has conducted prospective and look-back studies in collaboration with the Blood Services and UKHCDO. Please give a description of your role at the NCJDSU and in any of the surveillance studies conducted with the Blood Services and UKHCDO. These documents may be of assistance to you: (HCDO0000133_024; ICHT0000007; DHSC0033372; HCDO0000109_013; HCDO0000131_056; HCDO0000464; HCDO0000718).**

d. **TMER study.** The purpose of the TMER study is to investigate whether there is any evidence that Creutzfeldt-Jakob disease (CJD) or vCJD may have been transmitted via the blood supply. This is a collaborative study between the UK Blood Services and NCJDRSU. My clinical colleague Professor Robert Will was the principal investigator for NCJDRSU in this study. I had no involvement in the study design, application for funding or Ethics approval. My role in this project was to provide a neuropathological diagnosis on the cases in the study and to study their pathological and biochemical features in relation to vCJD cases unrelated to blood transfusion. This information was then reported to Professor Will, who in turn shared it with his TMER collaborators in the UK Blood Services. I continued to support the TMER study in this way until my retirement in 2017.

e. **Haemophilia Surveillance Study.**

   i. The first meeting I had with a member of the UK Haemophilia Centre Director's Organisation (UKHCDO) was in 1997, when Dr Christopher Ludlam, Consultant Haematologist in the Royal Infirmary of Edinburgh and Chair of the UKHCDO met Professor Will and myself to discuss the potential implications of our recent

findings in vCJD for haemophilia patients and services. During this meeting we discussed the possibility of a prospective study to collect blood and tissue samples taken with consent for research from haemophilia patients during life and at autopsy to help determine the extent to which the haemophilia patient population might have been infected by vCJD by testing for the presence of abnormal prion protein in lymphoid tissue. Such samples could potentially be retested by new and more sensitive methods, particularly if a blood-based assay became available. This suggestion raised complex considerations over issues of patient consent and study ethics, which Dr Ludlam agreed to discuss with UKHCDO members. Dr Ludlam subsequently published a letter "New-variant Creutzfeldt-Jakob disease and treatment of haemophilia" in the Lancet in 1997 (WITN7034006) and discussed the suggested study on tissue samples from haemophilia patients at the meeting of the UKHCDO Executive on 6th February 1998 (HCDO 0000464).

ii. In 1998 my fellow Neuropathologists Professor Jeanne Bell (Edinburgh), Professor Margaret Esiri (Oxford), Dr James McLaughlin (London) and I published a paper with Professor Christine Lee, Director of the Haemophilia and Haemostasis Unit, Royal Free Hospital, London and Dr Ludlam "Retrospective neuropathological review of prion disease in UK haemophilia patients. This study was based on a pre-existing collection of brain tissue samples from Edinburgh, Oxford and London that had been collected with consent for research as part of a MRC-funded study on HIV disease in the brain in haemophilia patients. These samples were re-examined microscopically using a technique to detect the abnormal form of prion protein that accumulates in the brain in CJD and vCJD. No evidence of prion disease or early prion infection was identified in the 33 cases examined (HCDO0000133_024).

iii. I had subsequent discussions on the project suggested to Dr Ludlam with Professor Christine Lee, who was the Chair of the

Transfusion Transmitted Infections Working Party of the Advisory Committee of the UKHCDO. Professor Lee discussed possible funding for the suggested project with Dr John Stephenson in DH and wrote to NCJDRSU on 22nd December 1999 requesting confirmation of the Unit's participation in this project (provided by Professor Will, the Unit's Director) and details of the laboratory activities involved at NCJDRSU and the financial requirements to support this work, which I provided in a letter dated 5th January 2000.

iv. A 5-year prevalence study of patients with haemophilia was commissioned and funded by the DH in 2000 and coordinated by the UKHCDO following ethical approval from the London Multi-Centre Research Ethics Committee (MREC/01/2/11) to an application in 2001 by Professor Christine Lee on behalf of UKHCDO (HCDO0000718). The aims of this study were to determine the extent of exposure of individual patients with inherited bleeding disorders to implicated batches of clotting factor concentrate, to request consent to analyse tissue biopsies and autopsy material for the abnormal prion protein found in vCJD in NCJDRSU and to notify possible and confirmed clinical cases of vCJD in the UK haemophilia population (WITN7034031).

v. I was a named collaborator for this project and was responsible for the laboratory work that would be carried out in NCJDRSU on the tissue samples collected in this project, but was not involved in the Ethics application.

vi. On 9th October 2001 I gave a presentation "Overview of vCJD prion disease" to the Joint Annual General Meeting of the British Society for Thrombosis and Haemostasis and the UKHCDO in Bath. Unfortunately, I no longer possess a copy of this presentation.

vii. In February 2003 Professor Frank Hill, Chairman of UKHCDO, wrote to members of the Organisation to confirm that DH had agreed to fund the UKHCDO vCJD prevalence study and encouraged members to participate (HCDO0000109_013). In

2004 I gave a presentation on the Blood Product Associated Risk of vCJD and progress on the DH-funded prevalence project to the UKHCDO Annual General Meeting in Edinburgh (HCDO0000254_835).

viii. On 7th September 2009 I reported to the HCDO the first positive result detecting the abnormal prion protein found in vCJD in a spleen sample from a patient included in this DH-funded study (HCDO0000131_056). This positive result came from one region of the spleen of a haemophilia patient who had no signs or symptoms of vCJD prior to death and was heterozygous (MV) at PRNP codon 129. No abnormal prion protein was detected in the other tissue samples from this patient, including the brain. His lengthy treatment history included receipt of over 9000 units of Factor VIII concentrate prepared from plasma pools known to include donations from a vCJD-infected donor. The findings were published in Haemophilia in 2010 (HCDO0000799). The finding of a single positive result from a single tissue sample was difficult to interpret and the possibility of accidental cross-contamination was investigated. Clinical, epidemiological and statistical analyses suggested that the most likely route of vCJD infection in this case was the receipt of UK plasma products, but this could not be proven conclusively. No further positive cases in the DH-funded prevalence study have subsequently been identified to my knowledge.

f. PID study

i. In 2006, under the leadership of Dr Matthew Helbert, Consultant Immunologist in Manchester, I helped establish the Primary Immunodeficiency Surveillance (PID) study, a DH-funded project that aims to find out whether any evidence of abnormal prion protein can be found in antibody deficient patients (including children) who received certain UK-sourced immunoglobulin products between 1996 and 2000. The products were made from plasma from UK donors and patients treated with these products may have been exposed to vCJD. I was involved in the study

design, but was not involved in the Ethics application for this study. The study involves immunology teams and patients throughout the UK. Participants are followed over several years, testing any available tissue (from surgical biopsies) and blood (for when a suitable test becomes available) for the abnormal prion protein that causes vCJD. Participants and their relatives can also consent to donate tissues obtained from a post-mortem examination. All tissues are examined in NCJDRSU and the results are provided to Dr Helbert and his team in Manchester using a study reporting form. Following Dr Helbert's retirement in 2015, management of the study transferred from Manchester to Edinburgh, and is now led by Professor Richard Knight and a team at NCJDRSU. To date, no primary immunodeficient patients have shown symptoms of prion disease, nor is there any evidence of prion infection in the tissues tested (WITN7034033).

g. Appendix studies

i. DHSC0004747_040 is a research letter I published in collaboration with Professor John Collinge and colleagues in the Lancet on 11th January 1997 describing the use of optimised immunohistochemistry to detect abnormal prion protein in paraffin-embedded sections of tonsil from a vCJD patient in the Neuropathology Laboratory in NCJDRSU. This was accompanied by the result of biochemical and molecular analysis of PrP^{Sc} in the corresponding frozen tissue sample and in a frozen brain tissue sample in the MRC Prion Unit, London. Normal brain and tonsil tissues were used as controls. The results showed that most of the abnormal prion protein accumulate in the germinal centres of the lymphoid follicles in the tonsil and that the biochemical profile of PrP^{Sc} in the tonsil was closely similar to the PrP^{Sc} in the brain. This initial report supported the hypothesis that prions can accumulate in lymphoid tissues in vCJD and may therefore also be present in blood. It also offered the possibility of using tonsillar biopsy as a diagnostic test for vCJD in living patients. Further studies on lymphoid tissue from additional cases of vCJD showed

widespread accumulation of abnormal prion protein in follicular dendritic cells and macrophages of the germinal centres in the intestine, appendix, lymph nodes, spleen, tonsil and thymus (reviewed in (WITN7034012)). A subsequent larger joint study, including both autopsy tissues and tonsil biopsy tissues from patients with suspected vCJD confirmed the earlier findings and reinforced the potential value of tonsil biopsy in vCJD, particularly in reducing the need for a brain biopsy to make a diagnosis (NHBT0004118_005).

ii. On 29th August 1998, in collaboration with Dr David Hilton and colleagues in Plymouth, I published a research letter in the Lancet describing the detection of abnormal prion protein using immunohistochemistry in germinal centres in paraffin-embedded sections of an appendix that was surgically removed from a patient 8 months before the onset of the signs and symptoms of vCJD (DHSC0038548_050). Involvement of the tonsillar tissue before onset of neurological disease had been shown in 1996 from the age of 10 months in sheep infected with scrapie (SBTS0004144_175); however, our findings were the first demonstration of PrP in tissue in human beings during the incubation period of CJD. Involvement of gut-associated lymphoid tissue before the clinical onset of disease is in keeping with an enteric route of entry for the vCJD agent.

iii. An implication of the presence of PrP in the appendix during the incubation period of variant CJD is that it offered the opportunity for large scale screening of appendectomy and, presumably, tonsillectomy, specimens removed since the onset of the BSE epidemic. Such a study would provide new data on the proportion of the population at risk of developing variant CJD, although it is not known at what stage during the incubation period of variant CJD that lymphoid tissue becomes involved or whether this involvement will inevitably lead to the development of neurological disease.

iv. Further discussions with Dr Hilton on a potential project of this type were taken forward by DH through the Medical Research Council (MRC), who established the MRC Steering Group on the Prevalence of Detectable PrP in Lymphoid Tissues in 1998. This group provided advice and guidance to DH on the study design and inclusion criteria, tissue selection, methodology for prion protein detection, ethics, size, scope and approach to the interpretation of results from a vCJD prevalence study base on the detection of abnormal prion protein in lymphoid tissues. Once these and various other issue had been agreed and Ethics Approval had been granted, the study was funded by DH via MRC and commenced in Edinburgh and Plymouth. Preliminary results on the first 3000 samples, all of which were negative, were published in 2000 (DHSC0038568_037). A parallel specificity study found no evidence of prion protein positivity in human lymphoid tissues involved in other pathological processes, including infections, inflammation and neoplasia (WITN7034027). The final results were published in 2004 (NHBT0063957_002) and reported 3 positive cases out of the 12,674 assessable samples studied, giving an estimated prevalence of vCJD infection of 237 per million in the UK.

v. The results of two subsequent larger vCJD prevalence studies were reported in 2013 (PRIU0000069) and 2020 (WITN7034009). The first of these found a prevalence of 493 per million in the UK population exposed to BSE and the result of PRNP codon 129 genetic analysis found a high proportion of positive cases were valine homozygotes (codon 129 VV) compared with the frequency in the normal population, and in contrast with the findings in vCJD patients, which at that time were all methionine homozygotes (codon 129 MM). The 2020 study analysed over 29,000 samples from 2 populations thought to have been unexposed to BSE: individuals born between 1891 and 1965 who underwent appendectomy between 1962 and 1979 (pre-BSE); and individuals born after 1996 who underwent appendectomy

between 2000-2014 (post-BSE) (WITN7034009). Seven appendix samples were positive for abnormal prion protein, of which two were from the pre-BSE exposure era and five from the post-BSE period. None of the positive samples were from appendices removed before 1977, or from patients born after 2000.

vi. I was involved as a co-author in the Appendix 1 study and NCJDRSU received funding from DH to support this participation. I was also a co-author on the Appendix 2 and 3 studies and played an active role in the assessment of borderline or suspected positive cases.

h. Conclusions and impact

i. The results of the TMER study have had a major impact in confirming the transmission of vCJD infectivity to four recipients of non-leucodepleted red cell concentrate from donors who later died from vCJD. No comparable instances of transmission of vCJD infectivity have been identified to date in recipients of leucodepleted red cell concentrates, thus justifying the decision to introduce universal leucodepletion in the UK in 1998-99.

ii. Three of the four recipients died from vCJD, while the fourth recipient was found to have an asymptomatic infection in the lymphoid tissues. This recipient differed from the others in terms of the PRNP codon 129 genotype, which was MV, while the three recipients who died from vCJD were all PRNP codon 129 MM. The presence of infectivity in the spleen was subsequently confirmed in experimental transmission studies, which also demonstrated the absence of infectivity in the brain, in keeping with our initial neuropathological and biochemical findings. This is the first recorded case in the UK of autopsy detection of presumed pre- or sub-clinical vCJD infection (DHSC0004215_039). These results support the hypothesis that immunohistochemical deposition of abnormal prion protein in paraffin sections of lymphoid tissues from asymptomatic individuals is a marker of

vCJD infectivity (NHBT0033619). This hypothesis is the basis of the methodology of the three Appendix studies.

iii. The overall results of the three Appendix studies indicate a prevalence of vCJD infection of around 240-500 per million UK population (WITN7034009). All three possible PRNP codon 129 genotypes (MM, MV and VV) were represented in the positive cases in these studies. This finding is consistent with experimental evidence that all 3 PRNP codon 129 genotypes are susceptible to infection with vCJD (NHBT0008745_002). None of the positive samples in the three Appendix studies came from individuals later diagnosed with vCJD.

iv. The data from the 3 Appendix studies has contributed to discussions on potential risks of secondary transmission of vCJD in several DH committees, including the ACDP TSE Subgroup and the CJD Incidents Panel. These data have also contributed to risk assessments on vCJD transmission by blood and blood components, the most recent of which are the 2019 DHSC Technical Report "Risk assessment of the transmission of vCJD by blood components" (WITN7034043) and the 2021 MHRA Research and Analysis report "Critical risk assessment report: use of UK plasma for the manufacture of immunoglobulins and vCJD risk" (WITN7034044).

33. **Please provide a description of how tissue samples were obtained, assessed and stored in surveillance studies investigating blood and blood products.** I can provide information on the surgical tissue samples and the autopsy tissues from the brain and other organs that I examined in my role as a Neuropathologist in NCJDRSU. Other types of samples taken from patients in life, specifically cerebrospinal fluid (CSF) and blood, were the responsibility of my clinical colleagues Professor Robert Will and Professor Richard Knight.

a. Tissue samples from the TMER study

i. The way in which brain and other autopsy tissues from patients identified in the TMER were obtained, sampled and stored were

similar to the tissues from other patients referred to NCJDRSU for a diagnosis for CJD Surveillance purposes.

ii. The brain and other tissue samples were obtained following autopsy in Edinburgh or other Neuropathological centres in the UK. In some cases the relatives gave consent for the autopsy and for the retention of the brain or parts of the brain for diagnosis and research. Consent was also obtained for the retention of tissue samples for other organs including lymphoid tissues (spleen, lymph nodes, tonsil, appendix etc.) peripheral nerves, muscle, pituitary, kidney, heart and liver. Some autopsies were performed under the auspices of HM Coroner in England, Wales and Northern Ireland, and the Procurator Fiscal in Scotland. Under such circumstances, the relevant Coroner or Fiscal Office was contacted in order to ask the relatives for consent for retention of the organs and tissue samples retained for the purposes of diagnosis in the medicolegal autopsy for research. On these occasions I was happy to speak to the relatives about the reasons for requesting consent and to answer any questions raised. The relatives were informed that they had the right to withdraw their consent at any subsequent time, and that such requests would be fulfilled. Information on how to withdraw consent was provided.

iii. Autopsy tissues were sent from the autopsy suite of the hospital or medicolegal mortuary in which the autopsy had been performed. NCJDRSU provided a guidance document to the Pathologist performing the autopsy for tissue sampling, to include fixed and frozen tissue samples when possible. NCJDRSU arranged an approved courier with containers to facilitate the collection of these samples from the autopsy suite concerned and transport them rapidly to our Unit. Once fixation was completed, the fixed tissues were sampled for neuropathological examination and processed into paraffin blocks. The frozen tissues were samples for biochemical analysis of PrP^{res}. The results of these investigations were provided in a report to Professor Robert Will,

who shared the information with his TMER collaborators in the UK Blood Services.

iv. The fixed and frozen tissue samples were retained for research purposes in NCJDRSU under the Ethics Approval for the MRC Edinburgh Brain and Tissue Bank, unless the relatives had requested that they should be returned to an Undertaker for cremation or burial. If so, the frozen tissues concerned were thawed and then fixed in formalin (for Health and Safety reasons) prior to being transported by an authorised courier to the Undertaker concerned.

b. Tissue samples from the Haemophilia Surveillance Study and the PID Study.

i. The Haemophilia surveillance study and PID study samples from living patients were paraffin-embedded lymphoid tissues (appendix, spleen lymph node etc.) that had been removed as part of the surgical treatment of the individual concerned. These individuals had given consent for these samples to be examined in NCJDRSU for the detection of abnormal prion protein by immunohistochemistry. The paraffin-embedded tissue blocks were sent to NCJDRSU according to current guidance for the transport of fixed human tissues from the study co-ordinating centres, who obtained the samples from the Histopathology Departments in the hospital where the surgical procedures had been performed. Once the sections had been cut and stained for abnormal prion protein by immunohistochemistry, the sections were examined microscopically by myself and other members of the Neuropathology team and assessed for prion protein positivity. Once we had reached a consensus opinion, the paraffin tissue blocks were returned either to the study co-ordinating centre or to the Histopathology Department from which they originated. We did not store any of these surgically obtained blocks in NCJDRSU as they formed part of the clinical record of the individuals concerned.

ii. Consent was obtained from relatives of the patient for the examination of autopsy tissues following either a hospital or Coroner's autopsy. Autopsy tissues were sent from the autopsy suite of the hospital in which the autopsy had been performed. NCJDRSU provided a guidance document to the Pathologist performing the autopsy for tissue sampling, to include fixed and frozen tissue samples when possible. NCJDRSU arranged an approved courier with containers to collect these samples from the hospital concerned and transport them rapidly to our Unit. Once fixation was completed, the fixed tissues were sampled for neuropathological examination and processed into paraffin blocks. The frozen tissues were samples for biochemical analysis of Pr^{Pres}. The results of these investigations were provided to the study co-ordinating centre using a study report form provided for this purpose. The fixed and frozen tissue samples were retained for research purposes in NCJDRSU under the Ethics Approval for the Brain and Tissue bank, unless the relatives had requested that they should be returned to an Undertaker for cremation or burial. If so, the frozen tissues concerned were thawed and then fixed in formalin (for Health and Safety reasons) prior to being transported by an authorised courier to the Undertaker concerned.

iii. Details of the Haemophilia surveillance programme, along with the various Ethics approvals and protocols, are included in HCDO0000799. Details of the PID surveillance programme including the Ethics approval are included in the publication by Helbert et al. 2016 (WITN7034033).

34. Please provide an explanation of how ethics and patient's consent was considered when conducting vCJD sampling, surveillance and research. Please also specify the ethical approval process to distribute patient material to third parties for these purposes, including commercial research. You may wish to refer to these documents: (DHSC0004526_050; DHSC0004074_035; MHRA0011461).

a. Ethics approval was obtained by NCJDRSU for the surveillance of CJD in the UK. The TMER has Ethics approval (NHBT0008743_013) and the PIND study has Ethics approval. The Haemophilia surveillance study has ethics approval (HCDO0000799) and the PID surveillance study also has Ethics approval (WITN7034033).

b. The "patient material" I refer to in this response is the fixed and frozen tissue samples that were taken for storage in the Brain and Tissue Bank in NCJDRSU. This does not include blood and CSF samples taken from living patients.

c. The Brain and Tissue Bank in NCJDRSU is part of the MRC Edinburgh Brain and Tissue Bank (EBTB).[7] This bank has Ethics approval from the East of Scotland Research Ethics Service REC1 to function as a research tissue bank.

d. The storage and use of the fixed and frozen tissue samples requires the consent of the relatives of the patient. Any qualification of the consent from the relatives, e.g. not to be used for industry research, is recorded and respected when tissue samples are selected for provision to researchers. Tissue samples from the EBTB can be made available to researchers, subject to appropriate application and subsequent approval by the EBTB Local Management Group.

e. The Director of the EBTB is Professor Colin Smith. The work of EBTB is overseen by the Local Management Group, comprising the Director, staff employed in the bank and two lay members. Strategic oversight of EBTB is carried out by a Steering Group comprising an independent Chairperson, independent experts who have expertise or special interests in the activities and ethics of brain banking, at least two lay members, a representative of NHS Lothian Research & Development and a representative from the UK Medical Research Council.

f. EBTB is part of the MRC's UK Brain Banks Network.[8] The UK Brain Banks Network supplies tissue samples to academic and industry

[7] https://www.ed.ac.uk/clinical-brain-sciences/research/edinburgh-brain-and-tissue-bank
[8] https://webarchive.nationalarchives.gov.uk/ukgwa/20210831000000/http://mrc.ukri.org/research/facilities-and-resources-for-researchers/brain-banks/

researchers in the UK and internationally. All brain banks in the Network have approval to provide tissue samples to research projects and pilot studies. Approval is based on scientific merit and also takes into account ethical issues (if peer review and ethics approval has not already been obtained). All of the brain banks in the Network have generic ethics committee approval to function as research tissue banks, which means that they can provide tissue samples to UK-based researchers for a broad range of studies without the need for the researchers to obtain their own ethics approval.

35. **How effective have the vCJD surveillance and the prospective and look-back studies been with regards to blood and blood products? Could more have been done? If so, what? You may find MHRA0011461 of assistance in answering this question.**

    a. The surveillance of all forms of CJD in the UK is dependent on the cooperation of Neurologists, Neuropathologists, other health care professionals across the UK, and the relatives of patients with all forms of CJD, which is acknowledged in the Annual Reports, peer-reviewed publications, presentations and other output from NCJDRSU. This effective co-operation allowed the early identification of vCJD as a distinct entity from other forms of CJD in the UK and has been maintained subsequently. However, it is not possible to state with certainty that all cases of CJD in the UK have been identified by NCJDRSU since the surveillance project began in 1990, particularly in the population of elderly individuals where the incidence of other forms of dementia is high, as I stated in my oral evidence to the Parliamentary Science and Technology Committee on 27th November 2013 (TSTC0000051).

    b. The prospective and look-back exercises regarding blood and blood products are conducted as part of the TMER study. I was never directly involved in these exercises, but participated in the neuropathological examinations to confirm the cause of death in the recipients of transfusions from vCJD donors identified in the TMER study. This mechanism was effective and allowed the diagnosis of vCJD to be

confirmed in the 3 transfusion-related cases of vCJD. It also allowed the identification of a fourth recipient of a blood transfusion from a vCJD donor as being infected with vCJD despite the absence of clinical signs and symptoms of the disease at the time of death. No vCJD-related neuropathology and PrP^{Sc} was found in the brain, but abnormal prion protein was identified in the spleen and in a cervical lymph node (DHSC0004215_039). This case was the first example of a vCJD infection in the PRNP codon 129 MV genotype (all previous cases of vCJD had occurred in the individuals with the PRNP codon 129 MM genotype). The presence of infectivity in the spleen was subsequently confirmed in experimental transmission studies, which also demonstrated the absence of infectivity in the brain, in keeping with the initial neuropathological and biochemical findings (NHBT0033619). These results support the hypothesis that immunohistochemical deposition of abnormal prion protein in paraffin sections of lymphoid tissues from asymptomatic individuals is a marker of vCJD infectivity. This hypothesis is the basis of the methodology of the three Appendix studies.

c. The DH-funded prevalence study of vCJD infection in haemophilia (HCDO0000131_056) has also been effective in that it allowed the detection of the abnormal prion protein found in vCJD in a spleen sample from an asymptomatic PRNP codon 129 MV patient who had received over 9000 units of Factor VIII concentrate prepared from plasma pools known to include donations from a vCJD-infected donor. This positive result came from one region of the spleen; all other tissues tested were negative, including the brain. Our findings were published in Haemophilia in 2010 (HCDO0000799). The finding of a single positive result from a single tissue sample was difficult to interpret and the possibility of accidental cross-contamination was investigated. Clinical, epidemiological and statistical analyses suggested that the most likely route of vCJD infection in this case was the receipt of UK plasma products, but this could not be proven conclusively. I am not aware of any further positive cases being detected in this study. I was not involved

in communications with Haemophilia patients concerning this study, but feel the study could have benefitted from more patients being recruited.

d. Results from the PID study were published in 2016, showing no evidence of abnormal prion protein in the 23 tissue samples examined from 15 of the 75 PID patients exposed to UK-sourced immunoglobulin, including batches derived from donors who went on to develop vCJD. The PID study is still active and I anticipate the further patients will be or have already been recruited and more tissue samples examined.

e. The autopsy rate for patients with all forms of CJD in the UK has declined since 2015(See figure 2- WITN7034045), but is still higher than the autopsy rate in the general UK population. Nevertheless, it is possible that the autopsy rate in CJD patients could be improved upon. As a non-clinician I am not involved in requesting consent for autopsy and retention of tissues for diagnosis and research. I am aware of the issues around these topics raised at the time of the BSE Inquiry (MHRA001146) and have always tried to ensure that communication of the results of the examinations I performed on these tissues and the diagnosis based on these findings are provided as soon as possible to my clinical colleagues in NCJDRSU and to the Pathologist who performed the autopsy.

f. I am also aware of the issues raised in MHRA0011461 around providing support to the relatives of vCJD patients and have tried to ensure that all enquiries for further information or clarification of the complex terminology in my Autopsy Reports are dealt with as soon as possible. I have also assisted the CJD Support Network (CJDSN) by providing information for relatives and undertakers, articles for their website, responding to requests from the CJDSN Co-ordinator for advice and information on all forms of CJD, and by attending CJDSN Family Support Days when invited.

Section 7: Notification

36. The Inquiry is aware that a number of notification exercises were carried out to inform recipients of blood and blood products that they may have been exposed to vCJD. Please provide an overview of these vCJD notification exercises and what prompted them. In particular:

a. How were decisions made and by whom?

i. Blood transfusions.

1. A notification exercise may be required after an individual diagnosed with clinical vCJD is found to have previously donated or received blood components. This is identified by the NHS Blood Services and NCJDRSU as part of the TMER study (NHBT0008743_013), which was established in 1997, prior to the establishment of the CJDIP in 2000. The methodology for the TMER study has been described in detail (WITN7034034). Three patient groups are considered to have an increased vCJD risk following blood incidents and should be notified (WITN7034030): recipients of blood from donors who later develop vCJD; blood donors to vCJD cases, and recipients of blood from donors to vCJD cases. The latter two groups are considered 'at increased risk' as the donor to a vCJD case is considered to be a potential source of the recipient case's infection, and, if so, would be incubating the infection themselves and could have infected other blood recipients.
2. I was not involved in the identification of individuals considered "at increased risk" in the TMER study and was not involved in the notification process.

ii. Plasma derivatives.

1. The revised DNV Risk Assessment of 2003 (MHRA0007248) allowed the creation of a Risk Calculator to be used by the CJDIP for plasma derivatives manufactured from a plasma pool containing a donation from an individual who later developed vCJD (HCDO0000840). The Risk Calculator was used to calculate for each batch the dose estimated to contain an ID_{50} of 0.02, which represents a 1% increased risk of vCJD infection that the CJD IP considered sufficient to warrant patient notification.
2. The events leading to the 2004 plasma product patient notification exercise are clearly described by Millar et al. 2010 (HSOC0016641): "By the time of the 2004 CJDIP recommendations, the fate of products manufactured from 23 plasma donations derived from nine UK plasma donors who later developed vCJD had been established. These

donations had undergone fractionation to produce albumin, immunoglobulin and clotting factor concentrates, including 16 batches of FVIII and eight batches of FIX that were distributed in the UK. TMER surveillance identified that these donations included plasma from at least one donor who, it is likely, had already transmitted vCJD via red cell concentrates (NHBT0008743_013). At this time, it was considered likely that further batches of UK-sourced plasma products would become implicated as future vCJD cases arose. Therefore, to prevent secondary spread to other patients a 'population' or 'umbrella' approach was implemented in patients with inherited bleeding disorders who had received UK plasma sourced products between 1980 and 2001. This policy was advised by UKHCDO and endorsed by CJDIP, DH and the Haemophilia Society, the UK charity representing patients with inherited bleeding disorders."

3. "As a result, all patients with bleeding disorders who had been treated with UK-sourced pooled factor concentrates between 1980 and 2001 were considered to be 'at-risk' of vCJD for public health purposes and precautions were required to minimize the potential risk of secondary transmission. The start date of 1980 was when BSE was believed to have entered the human food chain and the end date of 2001 was the last possible expiry date of any product manufactured by UK fractionators and sourced from UK donors. This approach was based on the assumption that many further vCJD implicated batches of clotting factor concentrate would subsequently be identified and that only small volumes of implicated FVIII or FIX treatment were required for the recipient to be deemed 'at-risk' of vCJD. It was anticipated at that time that extending the 'at-risk' group of patients with inherited bleeding disorders and anti-thrombin deficiency in this way would significantly reduce the risk of secondary vCJD transmission".
4. "Such an approach differed from that taken in patients with primary immunodeficiency disorders in whom immunoglobulin forms the mainstay of treatment. As much larger quantities of this product are required to reach the 'at-risk' threshold, individual risk assessments were undertaken in these patients".

5. As a member of CJDIP I was involved in the early stages of this sequence of events, but was not involved in the notification process.

iii. How were the thresholds set by the CJDIP to determine who should be notified of exposure (HCDO0000254_119, points 18-20; JPAC0000114_018, point 8; HCDO0000840), set?

1. The CJDIP defined categories of individuals who can become 'at increased risk' of CJD following a recognised iatrogenic exposure, taking into account a number of factors including the level of prion infectivity in the tissue or fluid to which the patient had been exposed, the volume of the tissue or fluid that the patient had been exposed to, and the date and route of exposure (e.g. intravenous, intracerebral etc.). The level of prion infectivity in the tissue or fluid concerned was based on the recommendations in the DNV risk assessments of 1999 and 2003, the data from the experimental transmissions of vCJD tissues in the UK (DHSC0004472_043), and the classification of the level of infectivity in the "Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies" published by the WHO. The data reported in the WHO tables were originally assembled by an expert group (in which I participated) appointed during a WHO Consultation held in 2003 and subsequently updated in 2005 and 2010. The 2010 revision was considered to "reflect the current status of knowledge about infectivity in body tissues, secretions, and excretions of humans with sporadic or variant Creutzfeldt-Jakob disease (CJD); cattle with typical or atypical bovine spongiform encephalopathy (BSE); sheep with scrapie; and (for the first time), deer or elk with Chronic Wasting Disease (CWD)" (WITN7034046).
2. If patients had been exposed to a 'threshold' of 1% or greater potential risk of vCJD over and above the general risk to the UK population believed to have resulted from dietary exposure to the BSE agent, CJDIP advised that they should be considered 'at increased risk', notified of this status and requested to take public health precautions. This 1% additional risk equates to an exposure of 0.02 ID_{50}, which is the equivalent level of infection at which public health precautions are implemented for patients exposed to vCJD via surgical instruments

(HCDO0000254_119). The 1% threshold level is used as a cut-off for implementing public health precautions and is not intended to be a precise measure of an individual patient's risk (WITN7034030).

3. On this basis, the CJDIP advised that surviving recipients of implicated red cell concentrates identified by the TMER study should be informed and public health precautions implemented to minimize the risk of secondary vCJD transmission. Together with batch-specific manufacturing data, the Risk Calculator was used by CJDIP to estimate the potential vCJD infectivity in each batch of implicated plasma product. For each of the major assumptions underlying the risk assessment, the most precautionary option was chosen. The implicated plasma products were divided into three groups based on the assessed risk. Amongst those considered to pose a high risk were FVIII, FIX and antithrombin concentrates, of which as little as one vial of treatment led to an exposure in excess of the defined risk threshold (HSOC0016641). Products in the medium risk group included those in which exposure to substantial quantities was required to reach the risk threshold such as immunoglobulins, and the low-risk group comprised products with such low levels of potential infectivity as could effectively be ignored as causing any additional vCJD risk. The low-risk group also included some FVIII products that had been manufactured using implicated albumin as an excipient (HSOC0016641). To reduce the possibility of onward transmission of vCJD, CJDIP advised in 2004 that public health precautions should be taken in recipients of 'high risk', and 'medium risk' implicated plasma products who had exceeded the 1% additional risk threshold. As stated above, a 'population' or 'umbrella' approach was implemented in patients with inherited bleeding disorders who had received UK plasma sourced products between 1980 and 2001. This policy was advised by UKHCDO and endorsed by CJDIP, DH and the Haemophilia Society, the UK charity representing patients with inherited bleeding disorders (HSOC0016641).

   iv. **What other role did the CJDIP play in these exercises?** At the meeting on 10th April 2003 (HCDO0000254_119) the CJDIP

members present (including myself) offered to support the notification exercises with the provision of information on vCJD to "the central group of individuals with a core brief capable of counselling". I was not approached afterwards for support in this regard. I am not aware of any other role the CJDIP played in these exercises.

v. **Were these notification exercises effective in your view? If not, what could and should have been done differently?** I was not involved in these notification exercises or the monitoring of the outcomes of these exercises, but at the meeting on 10th April 2003 I was concerned by an apparent lack of advance planning for such a large and complex exercise.

vi. **Were these notification exercises carried out at the right time and in the right way? If not, why not, what could and should have been done differently?** I was not involved in the notification exercises or the monitoring of the outcomes of these exercises. In view of the numbers of patients from whom notification was required, rather than attempt a mass notification it might have been possible to use a phased approach beginning with those who had been exposed to the highest levels of potential vCJD infectivity and then progressing to those with lower potential exposures. This approach may have been considered, but I am not aware if it was implemented.

Section 8: Other issues

I have no further issues to raise.

Statement of Truth

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

Signed:

GRO-C

James Ironside

Dated: 28th April 2022

Table of exhibits:

Notes/ Description Exhibit number	EXHIBIT NO.	Added to Pdf
Exhibit 1. Professor James W Ironside. List of Presentations to UK Blood Services, UKHCDO and UK Medical Professionals.	WITN7034002	Y
Exhibit 2. Professor James W Ironside. List of Publications with UK Blood Services and UKHCDO.	WITN7034003	Y
Exhibit 3. Professor James W Ironside. Published references cited in Witness Statement text (numbered in order of citation).	WITN7034004	Y
Exhibit 4. Professor James W Ironside. Academic, UK Government and other related website addresses referred to in the Witness Statement text (listed in order of citation).	WITN7034005	Y

Table of References

Reference	Title	Exhibit no.	Found on Relativity
1	New variant CJD and treatment of haemophilia. Lancet 1997.	WITN7034006	
2	Estimation of numbers of people incubating vCJD cases in UK. Lancet 1998.	WITN7034007	
3	Uncertainty in the tail of the vCJD epidemic 2010	WITN7034008	
4	Prevalence of abnormal PrP in human appendices in UK. Acta Neuropathol 2020	WITN7034009	
5	Variant Creutzfeldt–Jakob Disease in a Patient with Heterozygosity at PRNP Codon 129. New Engl J Med 2017.	WITN7034010	
6	sCJD in 2 UK fractionated plasma product recipients	WITN7034011	
7	Pathological diagnosis of vCJD. APIMS 2002.	WITN7034012	
8	Detection of prions in blood from patients with vCJD. Sci Transl Med. 2016.	WITN7034013	
9	Detection of prions in the plasma of presymptomatic and symptomatic	WITN7034014	

	patients with vCJD. Sci Transl Med. 2016.		
10	Transmissions to mice indicate that vCJD is caused by the BSE agent. Nature 1997.	WITN7034015	
11	The spread of prions through the body in naturally acquired transmissible spongiform encephalopathies. FEBS 2007	WITN7034016	
12	Preclinical transmission of prions by blood transfusion is influenced by donor genotype and route of infection. PLOSPAT 2021	WITN7034017	
13	Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet 2004		DHSC0004215_039
14	Prion Infectivity in the spleen of a PRNP heterozygous patient with subclinical vCJD. Brain 2013.		NHBT0033619.
15	Risk reduction strategies for vCJD transmission by UK plasma products and their impact on patients with inherited bleeding disorders. Haemophilia 2010.		HSOC0016641
16	Development of Dose-Response Models of Creutzfeldt-Jakob Disease Infection in Nonhuman Primates for	WITN7034018	

	Assessing the Risk of Transfusion-Transmitted vCJD. J Virol 2014.		
17	Epidemiological evidence of higher susceptibility to vCJD in the young. BMC 2004.		DHSC0004210_030
18	Updated projections of future vCJD deaths in the UK. BMC Infect Dis 2003		DHSC0004526_058
19	Creutzfeldt-Jakob disease- a systematic review of global incidence, prevalence, infectivity, and incubation. Lancet Inf Dis 2020.	WITN7034019	
20	Prion agent diversity and species barrier. Vet Res 2008	WITN7034020	
21	Variant Creutzfeldt-Jakob disease strain is identical in individuals of two PRNP codon 129 genotypes. Brain 2019.	WITN7034021	
22	Sporadic and Infectious Human Prion Diseases. Cold Spring Harb Perspect Med. 2017	WITN7034022	
23	Is there evidence of vertical transmission of vCJD? J Neurol Neurosurg Psych 2009	WITN7034023	
24	A New Variant of Creutzfeldt-Jakob Disease- Neuropathological and Clinical Features. Cold Spring Harb Symp Quant Biol 1996.	WITN7034024	

25	New variant of Creutzfeldt-Jakob disease in a 26-year-old French man. Lancet 1996.		DHSC0045235
26	BSE transmission to macaques. Nature 1996.		RLIT0000728
27	Molecular analysis of prion strain variation and the aetiology of new variant CJD. Nature 1996.		MHRA0021347
28	Variant CJD. 18 years of research and surveillance. Prion, 2014.	WITN7034025	
29	Risk factors for variant Creutzfeldt-Jakob disease. A case control study. Ann Neurol 2006	WITN7034026	
30	Principles and practice of high risk brain banking. Neuropathol Appl Neurobiol 1997.		DHSC0041081_006
31	Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. Lancet 1999.		NHBT0004118_005
32	Prion immunoreactivity in appendix before clinical onset of variant Creutzfeldt-Jakob disease. Lancet 1998.		DHSC0038548_050
33	Preclinical test for prion diseases. Nature 1996.		SBTS0004144_175

34	Retrospective study of prion-protein accumulation in tonsil and appendix tissues. Lancet 2000.		DHSC0038568_037
35	Specificity of lymphoreticular accumulation of prion protein for variant Creutzfeldt–Jakob disease. J Clin Pathol 2004.	WITN7034027	
36	Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. J Pathol 2004.		NHBT0063957_002
37	Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic- large scale survey. BMJ 2013.		PRIU0000069
38	Predicting Susceptibility and incubation time of human-to-human transmission of vCJD. Lancet Neurol 2006.		NHBT0008745_002
39	Creutzfeldt-Jakob disease after administration of human growth hormone. Lancet 1985.		RLIT0000729
40	CJD and blood transfusion Safety. Vox Sang 2018.	WITN7034028	
41	Blood infectivity, processing and screening tests in transmissible spongiform encephalopathy. Vox Sang 2005.		NHBT0098003

42	Detection of variant Creutzfeldt-Jakob disease infectivity in extraneural tissues. Lancet 2001.		DHSC0004472_043
43	Transmissible spongiform encephalopathy risk assessment. The UK experience. Risk Analysis 2005.		NCRU0000158_065
44	Management of possible exposure to CJD through medical procedures. CJDIP 2001.	WITN7034029	
45	Managing the risk of iatrogenic transmission of Creutzfeldt Jakob disease in the UK. J Hosp Infect 2014.	WITN7034030	
46	Dealing with the uncertain risk of vCJD transmission by coagulation replacement products. BJH 2012.	WITN7034031	
47	Validation of diagnostic criteria for variant Creutzfeldt–Jakob disease. Ann Neurol 2010.	WITN7034032	
48	Detection of prion infection in variant Creutzfeldt-Jakob disease. A blood-based assay. Lancet 2011.		NHBT0033626
49	Population Screening for Variant Creutzfeldt-Jakob Disease Using a Novel Blood Test. Diagnostic accuracy and feasibility study. JAMA Neurol 2014.		NHBT0034206

50	Blood Test for Variant Creutzfeldt-Jakob Disease. Letter and Reply. JAMA Neurol 2014.		PRIU0000231
51	No evidence of vCJD infection in immunodeficiency patients treated with UK -sourced immunoglobulin.Vox Sang 2016.	WITN7034033	
52	CJD and blood transfusion. updated results of the UK Transfusion Medicine Epidemiology Review Study. Vox Sang 2016.	WITN7034034	

Table of Website Links

Website Link	**Title**	**Exhibit No.**
https://content.hta.gov.uk/sites/default/files/2020-11/Code%20A.pdf	Human Tissue Authority, 'Code A: Guiding Principles and the Fundamental Principle of Consent'	WITN7034035
https://cdn.who.int/media/docs/default-source/biologicals/transmissible-spongiform-encephalopathies/tse-04-02.pdf?sfvrsn=b1a19f62_3&download=true http://www.cjd.ed.ac.uk/sites/default/files/figs.pdf	World Health Organisation, Report, Working Group on International Reference Materials for Diagnosis and Study of Transmissible Spongiform Encephalopathies, 2002	WITN7034036
http://www.cjd.ed.ac.uk/sites/default/f	NCJDRSU, Creutzfeldt-Jakob	WITN7034

iles/worldfigs.pdf	Disease in the UK (By Calendar Year), 2022.	037
http://www.cjd.ed.ac.uk/sites/default/files/worldfigs.pdf	CJD, Edinburgh, Variant CJD Cases Worldwide, 2022.	WITN7034038
https://webarchive.nationalarchives.gov.uk/ukgwa/20130123200045/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_100357	Department of Health, vCJD Risk Assessment Calculations for a Patient with Multiple Routes of Exposure, 2009.	WITN7034039
http://www.sibf.org.uk/wp-content/uploads/2017/11/abi-statement-on-insurance-and-cjd.pdf	Association of British Insurers, Information about Insurance for People at Risk of CJD, 2009.	WITN7034040
http://www.cjd.ed.ac.uk/sites/default/files/criteria.pdf	CJD, Edinburgh, Criteria of CJD cases.	WITN7034041
https://webarchive.nationalarchives.gov.uk/ukgwa/20130123195706/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_094804	Department of Health, Mapping out the consequences of screening blood donations for PrPsc, 2009.	WITN7034042
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/843533/risk-assessment-of-the-transmission-of-vcjd-by-blood-components.pdf	Department of Health & Social Care, Risk Assessment of the transmission of vCJD by Blood components, 2019.	WITN7034043
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/978993/Use_of_UK_plasma_for_the_manufacture	Medicines & Healthcare Products Regulatory Agency, Use of UK Plasma for the manufacture of immunoglobulins and vCJD risk,	WITN7034044

_of_immunoglobulins_and_vCJD_risk.pdf	Critical Risk Assessment Report.	
http://www.cjd.ed.ac.uk/sites/default/files/report29.pdf	The National CJD Research & Surveillance Unit, 29th Annual Report 2020, Creutzfeldt-Jakob Disease Surveillance in the UK	WITN7034045
https://www.who.int/bloodproducts/tablestissueinfectivity.pdf	World Health Organisation, WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies, 2010.	WITN7034046
https://www.gov.uk/government/publications/guidance-from-the-acdp-tse-risk-management-subgroup-formerly-tse-working-group	TSE Agents: Safe Working & Prevention of Infection, Infection, Prevention & Control of CJD and Variant CJD in Healthcare and Community Settings, updated 2015.	WITN7034047

Table of Documents

URN	Date	Description
TSTC0000051	27/11/2013	Transcript of the "Oral Evidence: variant Creutzfeldt-Jakob Disease (vCJD), HC 846" from witnesses Professor James Ironside, Dr Roland Salmon and Professor John Collinge.
TSTC0000050	01/11/2013	Written Evidence submitted by Professor James W Ironside to the Parliamentary Inquiry on Blood, Tissue and Organ Screening.

RLIT0000668	01/01/2006	Article titled "Variant Creutzfeldt–Jakob disease: risk of transmission by blood transfusion and blood therapies" published in Haemophilia, by J.W. Ironside.
NHBT0007197	09/04/1996	Notes of a meeting held at the Royal College of Physicians of Edinburgh on 9th April 1996 to Discuss the Possible Implications of a Likely New Variant of Creutzfeldt- Jacob Disease for UK Transfusion Services.
HSOC0010099	06/04/1996	Article, from the Lancet, entitled 'A new variant of Creutzfeldt-Jakob disease in the UK.'
DHSC0004747_040	11/01/1997	The Lancet, "Diagnosis Of New Variant Creutzfeldt-jakob Disease By Tonsil Biopsy", by Andrew F. Hill, 1997
DHSC0038559_048	29/06/2004	Minutes of the Advisory Committee on the Microbiological Safety of Blood and Tissues for Transplantation 33rd meeting, 29 June 2004.
NHBT0008743_013	07/02/2004	The Lancet (Vol 363), 'Possible Transmission Of Variant Creutzfeldt-jakob Disease By Blood Transfusion', by C A Llewelyn, et al., 2004.
HCDO0000799	25/02/2010	Journal of Haemophilia, "Variant CJD Infection In The Spleen Of A Neurologically Asymptomatic Uk Adult Patient With Haemophilia", by A. Peden, et al. 2010.
NHBT0008380	01/02/1999	Det Norske Veritas (Feb 1999) Report 'Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products', for the Spongiform Encephalopathy Advisory Committee and the Department of Health. Contains four appendices: 'Extraction and Use of Human Blood Products', 'Infectivity of Blood', 'Comparisons with Other Sources of Risk', 'Summary of Assumptions'.
MHRA0007248	01/02/2003	Det Norske Veritas (Feb 2003) Report 'Risk Assessment Of Exposure To vCJD Infectivity In Blood And Blood Products For Department Of Health.

DHSC0003998_006	01/01/1997	Expert comments on the Det Norske Veritas (DNV) revised report on vCJD Blood Risk Assessment. Comments from: Bob Perry SNBTS; Peter Foster, SNBTS; Paul Harrison, BPL; J. Ironside, Edinburgh University; Chris Prowse; NBS; and John Stephenson, Department of Health.
HCDO0000254_119	21/05/2003	Email from Sarah Johnston of the Blood and Healthcare Associated Infections Unit at the Department of Health to members of the CJB Incidents Panel Sub-Committee which includes Minutes of the CJD Incidents Panel Sub-Committee on the management of risks from blood products and plasma derivatives potentially contaminated with vCJD. The meeting was held on Thursday 10 April 2003.
DHSC0004424_052	13/06/2002	Minutes of the Spongiform Encephalopathy Advisory Committee (SEAC) 74th meeting, 13 June 2002.
HCDO0000133_024	undated	Report of a study titled 'Retrospective Neuropathological Review of Prion Disease in UK Haemophiliac Patients'.
ICHT0000007	25/02/2003	Surveillance of vCJD-DOH funded UKHCDO study, by Professor Frank Hill .
DHSC0033372	05/01/2000	Letter from Dr. James W. Ironside, Neuropathology Laboratory to Professor Christine Lee, Royal Free Hospital, re: Surveillance of new variant CJD UKHCDO, discusses recipient 109 participation; budgetary requirements for laboratory activities and other related matters.
HCDO0000109_013	01/02/2003	Letter from Professor Frank Hill (Chairman, UKHCDO) to unspecified colleagues providing details of a UKHCDO vCJD surveillance study of haemophilia (and other bleeding disorder) patients. The letter provides a breakdown of the components of the study and advises

		on how data will be stored.
HCDO0000131_056	28/11/2008	UK Haemophilia Centre Directors Organisation and Department of Health Surveillance on notification of biopsy/post mortem results in UK National Haemophilia Database. Confirmation of receiving samples from Bristol, Cardiff, Edinburgh, London, Grimsby and Newcastle Upon Tyne. Signed by Professor Ironside.
HCDO0000464	06/02/1998	Minutes of the Ninth Meeting of the UK Haemophilia Centre Directors' Organisation Executive Committee. The minutes discuss new variant CJD, surveillance of vCJD, funding of UKHCDO activities, meetings with the Department of Health and therapeutic guidelines.
HCDO0000718	03/01/2001	Letter from C. Lee Professor of Haemophilia to Louise Cox (London MREC) re the MREC application entitled "Prevalence Studies in Haemophiliacs". Prof Lee states that careful surveillance is needed of those who may be at increased risk of CJD because of blood product exposure.
DHSC0004526_050	16/05/2003	Minutes of the Microbiological Safety of Blood and Tissues for Transplantation (MSBT) vCJD Subgroup, Skipton House.
DHSC0004074_035	18/03/2003	Email chain between Professor James W. Ironside, National CJD Surveillance Unit, Rowena Jecock, Department of Health, and Charles Lister, re: HIV, HEPC, vCJD, Haemophiliacs: Testing for infectious diseases and study ethics.
MHRA0011461	01/10/1998	Statement from the CJDSU to the BSE inquiry, by Prof. R. G. Will and Dr. J. W. Ironside, CJD Surveillance Unit.

JPAC0000114_018	30/04/2003	Draft minutes of SACTTI Working Group on vCJD meeting [number unknown], 30th April 2003 by videoconference.
HCDO0000840	16/01/2004	Draft Guide to the Plasma Derivatives vCJD Risk Calculator.
DHSC0004072_006	15/12/2003	Note of an ad hoc meeting to discuss vCJD and blood at the Skipton House on 15 December 2003.
JPAC0000029_108	01/02/2002	Notes of the SACTTI Working Group on vCJD meeting on 1 February 2002.
HCDO0000254_835	14/10/2004	Email from Frank Hill to James Ironside, re: UKHCDO AGM session on blood product associated risk of vCJD.