Witness Name: Professor Robert Will

Statement No.: WITN7098001

Exhibits: WITN7098002; PHEN0000003

Dated: 9.5.2022

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF Professor Robert Will

I provide this statement in response to a request under Rule 9 Request of the Inquiry Rules 2006 dated 29 November 2021.

I, Robert Will, will say as follows: -

Section 1: Introduction

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

Professor Emeritus Robert Will

GRO-C

Edinburgh GRO-C

Date of birth: GRO-C 1950

MA MD MB BChir FRCP(E) FRCP FMedSci

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.**

Employment history:

July 1974 - Dec 1974- Pre-registration House Physician, North Middlesex Hospital

Jan 1975 - July 1975 - Pre-registration House Surgeon, The London Hospital

July 1975 - July 1976 - Senior House Officer, General Medicine, North Middlesex Hospital

Sept 1976 - Dec 1977- Registrar, General Medicine/Neurology, North Middlesex Hospital

Jan 1977 - Aug 1978 - Registrar, General Medicine/Neurology, North Middlesex Hospital

Sept 1978 - April -1979 Registrar, Gough Cooper Dept of Neurosurgery, National Hospitals, Queen Square

May 1979 - Oct 1979- Senior House Officer, National Hospital, Queen Square

Nov 1979 - Jan 1982- Honorary Registrar in Neurology, Department of Clinical Neurology, University of Oxford

Professor W B Matthews

During this appointment I was a research registrar on an MRC funded project on the Epidemiology of Creutzfeldt-Jakob disease. An MD thesis with this title was approved for a Degree by the University of Cambridge in 1985

Feb 1982 - Oct 1983 - Registrar in Neurology/Psychiatry, St Thomas' Hospital

Nov 1983 - July 1985 - Registrar in Neurology, National Hospital, Queen Square

Aug 1985 - Aug 1987 - Senior Registrar in Neurology, National Hospital, Maida/ Vale/Guy's Hospital

Oct 1987 – Oct 1996 - Consultant Neurologist/ Lothian Health Board, Department of Neuroscience, Western General Hospital

Oct 1996 – Mar 2012 - Half time: Consultant Neurologist Lothian Health Board/ Half time: Honorary Senior Lecturer, University of Edinburgh/ Professor of Clinical Neurology (from 1998)

Apr 2012 – Mar 2018- Part time Professor of Clinical Neurology, University of Edinburgh

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

Committee Membership potentially relevant to the Inquiry:

UK:

- Consultative Committee on Research into SEs (The Tyrrell Committee,1989-1990)
- Member of the Department of Health and MAFF Spongiform Encephalopathy Advisory Committee (1990 - 1998). Deputy Chairman 1994 – 1998
- Member of the SEAC Epidemiology Sub-Group (1997 - 2005)
- Co-opted member of the Allen Committee Medical Research Council Subcommittee on Spongiform Encephalopathies (1991 – 1995)
- Member of the Committee of Safety of Medicines Working Party on Spongiform Encephalopathies (1990 – 1998)
- Member of the Committee on Human Aspects of Spongiform Encephalopathies [COHASE] (1996)
- Member of the CJD Incidents Panel (2003-2016)
- Member of the UK CJD Resource Oversight Committee (2009-2018)

Non-UK:

- Delegate at WHO Consultation on Public Health Issues Related to Animal and Human Spongiform Encephalopathies (1991, 1993, 1995, 1996, 1999, 2000)
- Delegate at EMEA/EMA consultations (1998, 2004, 2007, 2010, 2013, 2016)
- Invited speaker at US Food and Drug Administration TSE Advisory Committee (1998, 2004, 2004, 2009, 2013, 2017)
- Invited speaker at Irish Blood Transfusion Service (2003, 2005)
- Invited Speaker at the Paul Ehrlich Institute (2003,2004, 2005, 2009)

- Member of the Scientific Advisory Board LFB (Laboratoire Francais Biotechnologie) (2003-2016)

CJD Support:

- National CJD Support Package (DH funded) 2001-2018 - Responsibility for managing the Support Package shared with Prof R Knight
- Committee member of the CJD Support Network (1994 - 2002)
- Member of "Friends and Advisory Group" of the CJD International Support Alliance (2009-2018)

Research:

- National CJD Research and Surveillance Unit: Co-principal Investigator 1990-2018
- Transfusion Medicine Epidemiology Review (the TMER study) 1996-2018 - Co-investigator
- The European CJD surveillance system (EuroCJD) 1993-2018 - Principal investigator
- Member of the Executive Committee of the EU NeuroPrion Research Group (2003-2010)
- Member of the Scientific Advisory Committee for PrioNet Canada (2006 - 2012)
- Member of the WHO International Health Regulations (2005) (IHR 2005) Roster of Experts (2009-2018)

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

I was a witness at the BSE Inquiry - Findings and Conclusions published in 2000

Section 2: Knowledge of Risk of vCJD transmission via blood transfusions and blood products.

The Inquiry seeks to gain an understanding as to how knowledge of risk of vCJD

developed over time within the UK Government, Blood Services, Haemophilia Centres and other NHS organisations and the adequacy of their response.
Please provide the following:

5. **A chronological summary list of journal articles that you contributed to which relates to addressing the emergence, discovery and scientific development over time of the risks of vCJD infection and the risk of secondary transmission via blood and blood products.**

TMER publications:

- Llewelyn CA, Hewitt PE, Knight RSG, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 2004; 363: 417-421.
- Hewitt PE, Llewelyn CA, Mackenzie J, Will RG. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiology Review study. Vox Sanguinis 2006; 91: 221-230.
- Gillies M, Chohan G, Llewelyn CA, Mackenzie J, Ward HJT, Hewitt PE, Will RG. A retrospective case note review of deceased recipients of vCJD-implicated blood transfusions. Vox Sanguinis 2009; 97: 211-218.
- Ward HJT, Mackenzie JM, Llewelyn CA, Knight RSG, Hewitt PE, Connor N, Molesworth A, Will RG. Variant Creutzfeldt-Jakob disease and exposure to fractionated products. Vox Sanguinis 2009; 97: 207-210
- Chohan G,Llewelyn C, Mackenzie J, Cousens S, Kennedy A, Will RG, Hewitt PE. Variant Creutzfeldt-Jakob disease in a transfusion recipient: coincidence or cause? Transfusion 2010; 50: 1003-1006.
- Davidson LRR, Llewelyn CA, Mackenzie JM, Hewitt, PE, Will RG. Variant CJD and blood transfusion: are there additional cases? Vox Sanguinis 2014; 107(3): 220-225.
- Urwin PJM, Mackenzie JM, Llewelyn CA, Will RG, Hewitt PE. Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. Vox Sanguinis 2016; 110: 310-316.
- Urwin P, Thanigaikumar K, Ironside JW, Molesworth A, Knight RS, Hewitt PE, Llewelyn C, Mackenzie J, Will RG. Sporadic Creutzfeldt-Jakob disease in 2 plasma product recipients, United Kingdom. Emerg Infect Dis 2017; 23(6): 893-897.

- Mackenzie JM, Turner M, Morris K, Field S, Molesworth AM, Pal S, Will RG, Llewelyn CA, Hewitt PE. Accuracy of a history of blood donation from surrogate witnesses: data from the UK TMER Study. Vox Sanguinis 2018; 113(5): 489-491.

Other publications relevant to the Inquiry:

Harries-Jones, R, R Knight, R G Will, S Cousens, P G Smith, W B Matthews, 1988, Creutzfeldt-Jakob disease in England and Wales, 1980-1984: a case-control study of potential risk factors: Journal of Neurology, Neurosurgery & Psychiatry, v. 51, p. 1113-1119

Esmonde, TFG, R G Will, J M Slattery, R Knight, R Harries-Jones, R de Silva, W B Matthews, 1993, Creutzfeldt-Jakob disease and blood transfusion: Lancet, v. 341, p. 205-207

Will RG, Kimberlin RH, 1998, Creutzfeldt-Jakob Disease and the Risk from Blood or Blood Products: Vox Sanguinis, v.75, p. 178-180

Chamberland, ME, J Epstein, R Y Dodd, D Persing, R G Will, A DeMaria, J C Emmanuel, B Pierce, R Khabbaz, 1998, Blood safety: Emerging Infectious Diseases, v. 4, p. 410-411.

van Duijn, CM, N Delasnerie-Lauprêtre, C Masullo, I Zerr, R de Silva, D P W M Wientjens, J P Brandel, T Weber, V Bonavita, M Zeidler, A Alpérovitch, S Poser, E Granieri, A Hofman, R G Will, 1998, Case control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95: Lancet, v. 351, p. 1081-1085.

Will RG, 1999, CJD and blood transfusion: CJD Support Network Information Sheet, p. 8-9.

Bishop MT, Baybutt H, Aitchison L, McConnell I, Head MW, Ironside JW, Will RG, Manson JC. Predicting susceptibility and incubation time of human to human transmission of vCJD. (2006) Lancet Neurology DOI:10.1016/S1474-4422(06) 70413-6, 393-8

HJT Ward, D Everington, S Cousens, B Smith-Bathgate, M Leitch, S Cooper, C Heath, RSG Knight, PG Smith, RG Will. Risk Factors for Variant Creutzfeldt-Jakob Disease: A Case-Control Study. Annals of Neurology, ISSN: 1531-8249, ISSN: 0364-5134, Volume 59, Issue 1, 2006, Pages: 111-120

Hewitt PE, Llewelyn CA, Mackenzie J, Will RG. Letter: Three reported cases of variant Creutzfeldt-Jakob disease transmission following transfusion of labile blood components. Vox Sanguinis, 2006; 91(4): 348.

Clarke P, Will RG, Ghani AC. Is there the potential for an epidemic of variant Creutzfeldt-Jakob disease via blood transfusion in the UK? J R Soc Interface 2007; 4: 675-684.

M Bishop, D Ritchie, R Will, J Ironside, M Head, V Thomson, M Bruce, J Manson. No major change in vCJD agent strain after secondary transmission via blood transfusion. PloS One, 2008; 3 (8): 1-6.

Appleford NE, Wilson K, Houston F, Bruce LJ, Morrison A, Bishop M, Chalmers K, Miele G, Masse E, Prose C, Manson J, Will RG, Clinton M, Macgregor I, Anstee DJ. alpha-Haemoglobin stabilising protein is not a suitable marker for a screening test for variant Creutzfeldt-Jakob disease. Transfusion 2008; 48: 1616-1626.

Ward HJT, Everington D, Cousens SN, Smith-Bathgate B, Gillies M, Murray K, Knight RSG, Smith PG, Will RG. Risk factors for sporadic Creutzfeldt-Jakob disease: Ann Neurol 63:347-354, 2008.

Molesworth AM, Mackenzie J, Everington D, Knight RS, Will RG. Letter: Sporadic Creutzfeldt-Jakob disease and risk of blood transfusion in the United Kingdom. Transfusion. 2011 Aug; 51(8): 1872-1873.

P Brown, J-P Brandel, T Sato, Y Nakamura, J MacKenzie, RG Will, A Ladogana, M Pacchiari, EW. Leschek, and LB. Schonberger. Iatrogenic Creutzfeldt-Jakob Disease, Final Assessment. Emerging Infectious Diseases: 2012; 18: 901-907

J de Pedro Cuesta, MR Tovar, H Ward, M Calero, A Smith, CA Verduras, M Pocchiari, ML Turner, F Dorland, D Palm, RG Will. Sensitivity to Biases of Case-Control Studies on Medical Procedures, Particularly Surgery and Blood Transfusion, and risk of Creutzfeldt-Jakob Disease. Neuroepidemiology 2012; 39:1-18.

M. Checchi, P.E Hewitt, P Bennett, H.J.T. Ward, R.G.Will, J.M. Mackenzie & K. Sinka. Ten-year follow-up of two cohorts with an increased risk of variant CJD: donors to individuals who later developed variant CJD and other recipients of these at-risk donors. Vox Sanguinis 2016; 111: 325-332

D Bougard, JP Brandel, M Bélondrade, V Béringue, C Segarra, H Fleury, JL Laplanche, C Mayran, S Nicot, A Green, A Welaratne, D Narbey, C Fournier-Wirth, R Knight, R Will, P Tiberghien, S Haïk, J Coste. Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease. Research Article, Prion Diseases, Science Translational Medicine. 8, 37000ra182 (2016) 21 December 2016.

A Diack, R Will, J Manson. Public health risks from subclinical variant CJD. PLOS Pathogens 2007; 13(11): e1006642.

P Urwin, K Thanigaikumar, JW Ironside, A Molesworth, RS Knight, PE Hewitt, C Llewelyn, J Mackenzie, R Will Sporadic CJD in 2 plasma product recipients, United Kingdom Emerging Infectious Diseases 23 893-897 2017

P Hewitt, R Will. 2018. vCJD Case Studies. Blood Safety. A Guide to Monitoring and Responding to Potential New Threats. Editors - Hua Shan, Roger Y. Dodd. Pg 143-155.

6. A summary of the steps which the committees and organisations you were a part of took, if any, to ensure that the government and NHS bodies were informed about the risks of vCJD transmission via blood and blood products.

I was a member of the SEAC Committee and after a meeting in 1997 the following statement was released by the Committee:

'SEAC - advice to Ministers

The Committee have recently concluded that the transmissible agent of nvCJD is indistinguishable from that of BSE but distinctly different from that of classical CJD. Recent research (some unpublished) suggests that the pathogenesis of nvCJD differs from that of classical CJD and the former may have more involvement of lymphoreticular tissues possibly involving circulating lymphocytes. Therefore, it is logical to seek to minimise any risk from blood or blood products by reducing the number of lymphocytes present.

SEAC recommends that the Government should consider as a precautionary policy of extending the use of leuco-depleted blood and blood products as far as is practicable. It will be for the National Blood Authority to devise a strategy to implement such a policy.'

It is hard to remember the details of the meetings attended and even more difficult to remember my opinions at various times because these have inevitably been influenced by subsequent scientific findings. However, my views on these risks are stated in the various publications related to blood including a paper published in 1998 after the identification of vCJD, but prior to the recognition of transfusion transmission of this condition (CJD and the risk from blood or blood products. RG Will, R H Kimberlin Vox Sanguinis 1998, 75, 178-180). The abstract of this article reads:

'The occurrence of iatrogenic cases of CJD and the isolation of infectivity in (blood) in some laboratory transmission studies of TSEs raises the possibility that CJD might be accidentally transmissible through blood or blood products, Epidemiological evidence, although not conclusive, does not suggest that classical CJD is transmissible through this route. However, new variant CJD might pose greater risks of accidental transmission of infection and mechanisms to reduce the theoretical risk are under consideration. The theoretical risks from CJD and nvCJD must be balanced against the established therapeutic benefits of blood and blood products.'

7. **The Inquiry is aware that a proposal for a vCJD Transfusion Medicine Prospective Support and Study was made while you were the coordinator at the Transfusion Medicine Epidemiology Review (TMER) and advisor for vCJD-related patient care and neurological assessment and classification [NCRU0000117_002]. The proposal stated that the programme was a, "prospective follow-up which aimed to facilitate provision of special resources to address [patients diagnosed with vCJD following blood component transfusion] concerns, to monitor their health status and to collect and archive blood and residual tissue samples for testing and further research. Please provide answers to the following:**

a. Was ethical approval granted by an ethical committee? If so, which one?

The protocol states that '*After review by the Department of Health and the CJD Incidents Panel...ethical approval would be sought from the London* MREC'.

This project was primarily the responsibility of the Health Protection Agency (HPA), which therefore took on the issue of ethical approval. I was not directly involved with this. I have no access to any documents regarding this and I cannot remember what

happened, but the study would not have proceeded unless the ethical issues had been resolved.

In an Update to the CJD Incidents Panel in 2012 there is the following footnote:
'2. Research Activities: Research Activities are those that do not fall under the remit of surveillance, but these are covered by the Enhanced Surveillance Research Project (REC reference 07H071879, approval received 25/2/2008).' (WITN7098002)

In my submission to the Inquiry, I referred to a paper by Checchi et al (PHEN0000003), which was based on data derived from this study. This includes the following statement:

'The surveillance was established under PHE's cover under section 251 of the National Health Services Act 2006 and Statutory Instrument 2002 No 1438, the Health Service (Control of Patient Information) Regulations 2002, to process patient identifiable information for surveillance purposes. Research Ethical Committee and Research Governance approval was therefore not required.'

b. Were blood and residual tissue samples taken for testing and further research? If yes, please detail the results of such testing/research;

I do not believe that any blood samples were obtained in the course of this project by the NCJDRSU. However, I believe blood samples were obtained by the National Prion Clinic (NPC). Some were tested for genetic analysis at codon 129 of PRNP (see response to Question 16 n.) If other investigations were carried out on these samples, I do not know the outcome.

I was not responsible for any tissue samples that were obtained in the course of this project.

c. The follow-up procedure was carried out primarily by the HPA as described in the protocol.

I was personally involved in supporting one recipient. The hospital records have been destroyed, but I believe I saw the recipient and family members at the request of the GP in the outpatient clinic at the Western General Hospital, Edinburgh. The recipient was clearly very anxious about the information he had received about blood

transfusion and vCJD. In 2009 the family contacted the Unit, because they believed that the individual's medical care had been compromised by his 'at risk' status for vCJD. This was discussed at the CJD Incidents Panel. In addition, a senior member of staff at the NCJDRSU telephoned a family member to discuss the situation and arranged for one of the nurses from the National CJD Care Package to be in contact with the individual and the family to provide continuing support.
In 2010 the individual received a letter asking about obtaining blood specimens. This was declined, but the contact caused the individual and family further distress and they asked that any future communication with the 'authorities' should be through the NCJDRSU.

I was not involved with the follow-up of any other individual identified through this study as far as I can remember.

d. How were the health of such patients monitored?;

See response to c.

e. What did the package of care consist of?;

See response to c.

f. Were the aims of the study met? Please provide details.

Following the formation of the CJD Incidents Panel, the study was expanded to take in other 'at risk' groups, including those potentially exposed through surgical instruments. My main overall role in the study was to determine whether individuals who died in the various 'at risk' groups had symptoms suggestive of vCJD before death. The HPA/PHE provided details from the death certificate of any deceased 'at risk' individual to the NCJDRSU. Hospital and GP records were requested in order to determine the cause of death and the presence of any clinical or investigative features to suggest vCJD prior to death.

By 2018 I had reviewed the records of 58 individuals and none had evidence of vCJD prior to death.

This included 3 blood recipients, 5 donors to vCJD cases, 3 highly transfused individuals, 2 implicated plasma recipients,10 other recipients of donors to vCJD cases, 1 platelet recipient and 34 surgical 'at risk' individuals.

A paper on the ten-year follow-up of two of these cohorts was published in 2016 (see Checci et al in the list of references).

Section 3: Actions and Decisions

The Inquiry seeks to understand what actions the Government and other organisations took in response to the risk of vCJD transmission via blood and blood products.

8. **The Inquiry is aware that you were the founder and clinical neurologist for the National CJD Surveillance Unit from 1990, throughout the key period in the development of knowledge of vCJD transmission.**

Please provide the following:

a. **A summary of the steps taken during your time at the National CJD Surveillance Unit to ensure that the (Government, Blood Services, NHS bodies, medical profession) and patients were informed and educated about the risks of vCJD transmission via blood and blood products.**

The issue of vCJD transmission via blood and blood products was likely to have been discussed at a number of the Committees listed above, for which I have no access to relevant minutes. These committees will have reported to the Department of Health. Since the start of CJD surveillance in May 1990 the NCDRSU has promptly reported any important developments or findings directly to the Department of Health, including the identification of the first suspected case of transfusion transmission of vCJD.

NHS Blood and Transplant were partners in the TMER study and the findings from this study were thereby also directly reported to the Blood services and thence to the Department of Health.

The medical profession was informed of new scientific findings related to blood transfusion via scientific publications, the on-line annual reports from the Unit and through talks and lectures. The international scientific community were informed by similar routes and in addition, through the regular meetings of the EuroCJD network

(which included the majority of Member States of the EU and regular attendance by representatives from other countries, including Argentina, Australia, Canada, China, Japan and the USA). It is of note that cases of vCJD who had previously acted as blood donors were identified in a number of other EU countries.

In 2008 I was involved in the production of an ECDC Threat Assessment entitled *'Two vCJD cases in a family in Spain:2008.'* This described the first reported cluster of cases of vCJD in the same family, which was attributed to regular sharing in the consumption of cattle brain.

The possibility that there might be an increased risk of vCJD in family members led to the suggestion that such relatives might be classified as at risk for public health purposes and should not act as blood donors. The last paragraph balanced this view by listing the large number of unaffected family members in the UK, including '450 family members of 166 cases (123 children and 327 siblings.)' The policy of classifying the relatives of those with vCJD as at increased risk of vCJD was not introduced in the UK or other EU countries.

Relatives of patients were informed about the risks via the CJD Support Network UK, the International CJD Support Alliance (at which I gave talks on the vCJD blood issue at a number of their annual meetings) and the Australian CJD Support Network. All the CJD support organisations produced booklets for the relatives of patients and these included sections on vCJD and blood transfusion.

Staff from the NCDRSU discussed a range of issues related to vCJD when they met the relatives of patients at the initial hospital assessment, including the risk of blood transfusion The Unit also provided an information booklet for families, which included a section on blood transfusion.

b. **An account of your understanding during your time at the NCDJSU of the relative risks of vCJD infection from the use of domestically sourced blood and blood products and the use of commercially supplied blood products.**

See response to question 6.

9. **On 29 March 2011, a TMER meeting was held. The attendees discussed your role in the Prion Unit's implementation of a diagnostic blood test [NCRU0000109_014].**

a. Please provide information on the test the Prion Clinic wanted to use?

The test was clearly a highly significant research development, raising the possibility of a diagnostic and/or screening test for vCJD.

b. What was your view of the test? You stated that you felt "very uneasy" about the test. Please detail your reasons for this view. Has your perspective on this since changed? If so, why?

My unease about the test was because it has not been independently validated, in concurrence with the minutes, in which Dr P Hewitt had stated that this was *'not yet a validated test'*. There were also uncertainties about how to interpret the test if it was to be used for diagnostic purposes. A positive test might indicate abnormal prion protein in blood, but not if this predicted whether this would lead to clinical disease, nor whether a positive test was associated with infectivity in blood. There was a possibility that there may be clearance of the abnormal protein with time – in some animal models of prion disease blood infectivity was transient. A negative test indicated the absence of abnormal prion protein in blood but could not exclude that infectivity in blood might develop after time in individuals exposed orally to infection with BSE.

A blood test with high sensitivity and specificity might be used for screening, but the volume of tests that would be necessary for testing individual blood donations would inevitably lead to a large number of false positive tests in addition to true positives. There was a pressing need for a gold standard blood test to allow distinction between false positives and false negative results.

My perspective on this issue has been influenced by the assessment of candidate blood tests carried out by NIBSC and discussed at the CJD Sample Oversight Committee. A small number of putative tests were evaluated and none proved sufficiently sensitive and specific. At least one of these tests had very promising preliminary data, but did not perform adequately on blinded testing, underlining the importance of independent evaluation of any candidate test.

c. Have any effective diagnostic pre-symptomatic blood tests been developed since?

The possibility of a diagnostic presymptomatic blood test for vCJD has been underlined by studies in animal models, for example Saa et al 'Presymptomatic detection of prions in blood' Science 2006 313, 92-93. The PMCA amplification technique used in this study was later adapted to vCJD and published in 2016 Concha-Marambio et al Detection of prions in blood from patients with vCJD Science Translational Medicine 8 1-7. Many of the vCJD samples used in this study were provided by the NCJDRSU as noted in the acknowledgements section of the paper.

This study examined samples from symptomatic vCJD cases, but another PMCA study demonstrated not only that prions were present in symptomatic cases, but also in samples from 2 blood donors with positive results 1.3 and 2,6 years before they developed vCJD (Bougard et al 2016 Detection of prions in the plasma of pre-symptomatic and symptomatic patients with vCJD Science Translational Medicine 8 1-9). The majority of vCJD samples from clinical cases in this study were provided by the NCJDRSU.

Further validation of this approach to developing a pre-symptomatic blood test for vCJD is very difficult, because of severe limitations in the availability of pre-symptomatic samples from known cases of vCJD.

d. Please set out the practical issues arising from the ownership/ custodianship of vCJD samples by different institutions and how this affects the research and development of such diagnostic tests.

vCJD samples were held by a number of institutions, notably the NCJDRSU and the NPC. I was not responsible for tissue samples held at the Unit.

Blood samples from vCJD cases were stored at the NCJDRSU, but these were restricted both in number and sample volume. There were a number of requests for vCJD blood samples from academic groups and commercial companies, but there were clearly insufficient samples to meet all these requests, a number of which were excluded because of the large volume of samples required.

The requests for samples were discussed by senior staff at the Unit and samples were provided to a small number of academic groups, including the NPC and other groups attempting to develop tests or to identify infectivity in vCJD blood. The results of these studies are referred to elsewhere in this document.

The NCJDRSU had no expertise in test evaluation and provided vCJD blood/plasma samples to the NIBSC, under the auspices of the CJD Sample Oversight Committee in order that formal evaluation of candidate vCJD blood tests could be carried out. After the formation of this Committee, senior staff at the NCJDRSU discussed other requests for vCJD blood samples with the Committee, including those from academic groups.

10. **In a letter to you from David Onions from the University of Glasgow regarding Baxter Healthcare's concerns over the transmission of vCJD in blood products [DHSC0004805_264] states that a draft protocol by Baxter and collaborated on by groups at the University of Alabama for a proposed study was provided to you. Please answer the following questions:**

a. Please provide details of the protocol proposed by Baxter Healthcare;

The results of the Baxter study, including details of the protocol, were published in 2016: Blood transfusion studies of prion infectivity in the squirrel monkey: the Baxter study Transfusion 2016 56 712-721, In brief, the vCJD component of this study did not detect infectivity in blood after a 7 year -period of observation.

b. Were you involved in the study proposed and in what capacity;

I was involved, I believe in the early 2000s, in discussions with the principal investigator, Dr Paul Brown of the National Institutes for Health (NIH), Bethesda, Maryland USA about the aims of the study and had an informal meeting with Dr Brown and a representative from Baxter regarding the supply of blood and tissues from vCJD cases for this study. I discussed the study with my colleagues at the NCJDRSU and it was decided to provide the required samples in order that the study could go ahead. I subsequently heard updates on the study directly from Dr Brown or from lectures he gave on the subject.

I was not involved in the writing of the paper described above as my input into this study was limited.

c. Were you contacted by any other healthcare organisations regarding any studies or look-back exercises?

As far as I am aware the NCJDRSU did not provide blood samples to any other healthcare organisation until 2015 when blood samples were provided to a research group under the auspices of the Etablissement Français du Sang (also see the response to Answer 9d). This collaboration resulted in the publication listed above (Bougard et al, Detection of prions in the plasma of pre-symptomatic and symptomatic patients with vCJD).

Blood samples were provided to the National Institute for Biological Standardisation and Control (NIBSC), via the CJD Sample Oversight Committee in order to establish panels of samples for the validation of candidate blood based diagnostic tests.

vCJD blood samples were provided to a number of academic groups (see Answer 9d).

Section 4: Look back and Notification exercise

The Inquiry has heard evidence of the experiences of a number of infected and affected individuals who were notified of their 'at risk' status of vCJD. The Inquiry seeks to gain an understanding of the rationale behind policy decisions made in relation to notifying at-risk individuals and how this changed over time.

11. Please summarise the steps which the committees and organisations you were a part of took, if any, to ensure that the medical profession and implicated patients were informed about the risks of vCJD transmission via blood and blood products.

See response to Question 8.

12. **In a letter to you from Dr F.A Ala, dated 23 February 1995 [DHSC0032368_057], Dr Ala discussed the drawbacks and actions of undertaking a "look-back" exercise aimed at tracing patients who received blood components from donors subsequently found to be suffering from CJD.**

a. What was your response to the concerns outlined in this letter?

I believe I must have talked on the phone to Dr Ala as indicated in the first paragraph of this letter, but I have no memory of this. The letter indicated that the UKBTS SAACTI Committee had proposed a look-back study in CJD. This letter (23.2.1995) predated the identification of the first case of vCJD.

The letter commented on the practical and ethical issues of such a study, but my initial response was supportive as I believed blood transfusion and CJD was an important issue for public health.

On 24.4.1995 I wrote to Dr Ala in strictest confidence with details of some CJD cases who had been blood donors *'after discussion with the DH.'* This was done to assess the feasibility of such a study. Dr Ala had written *'I suggest we pause after this first phase in order to share such information we have succeeded in gleaning. We can then decide upon the need for and nature of any further action.'*

b. What decisions were taken regarding the look-back exercise following these discussions?

A proposal for the study which was discussed at the MSBT (Microbiological Safety of Blood and Tissue) Committee. The response was that such a study should not be undertaken, in part because it could not provide an absolute negative result. It was also thought that the numbers of known cases of CJD were too small to provide a basis for a quantitative assessment.

I wrote to Dr Ala to request that the sCJD data sent by the Unit should be destroyed.
On May 5th 1995 I wrote a letter to the DH regarding the whole issue of sCJD and blood transfusion in order to provide a detailed scientific justification for such a study. This included the following statement *'The crucial question is whether the public health implications of a look-back study over-ride the important ethical considerations regarding confidentiality'* and *'I would be grateful if guidelines regarding the provision of such (patient) information were provided.'*

c. At the time, did you consider or make any suggestions as to how the look-back should be conducted?

The study was not carried out.

d. In your opinion, was the look-back successful? Please explain the reasoning for your answer.

The study was not carried out.

13. **The Inquiry understands that the TMER started in 1996 and saw collaboration between the National CJD Surveillance Unit and the National Blood Authority. In an email sent by you to Dr Peter Christie [NCRU0000298_011] you briefly discussed the progress of the Review and the ethical issues they faced related to informed consent.**
Please provide the following:

a. Details of the ethical issues the TMER faced;
b. Details of the structure and implementation of the TMER;
c. Details of any other issues the TMER faced, such as access to and management of information and records etc.,;
d. Your opinion on the success of the TMER.
e. Whether the issues about informed consent and the participation of Scotland were resolved, and if so, how.

Most of these issues are discussed elsewhere in this document and point e. regarding the participation of Scotland is discussed in the email correspondence between Dr Christie in the response to Question 15.

In April 1997 the LREC was asked to approve a change in the TMER protocol to include 'controls'. This was approved in October 1997.

In October 1999 MSBT considered recommending actions in response to the concern that recipients of blood from a vCJD donor may themselves donate blood. The MSBT recommendations and NBS implementation raised concerns about the ethical approval of the TMER study and this was discussed with the Chair of the LREC. His view was that a national policy to protect public health must be adhered to, but that further discussions with the LREC were necessary. Ethical approval was suspended pending these discussions and ethical approval was reinstated in May 2000.

In 2001 some recipients of fractionated plasma products were informed of the potential exposure to vCJD. This policy ultimately depended on information provided by the TMER and the NCJDRSU became concerned that this might affect the ethical basis of the study. This was discussed at a meeting of the CJDIP and the view of the committee was that the decisions made by the CJDIP and others on public health matters (eg notification of exposed recipients) should be clearly separated from the ethics of the TMER study.

14. **In 1998, Jack Gillon, Patricia Hewitt and yourself drafted a proposal regarding a limited look-back programme to be conducted by the UK Transfusion Services and the CJD Surveillance Unit [NHBT0016056_002]. At pages 9 and 10 of the proposal it was considered unethical to notify individuals who had received blood from a donor who had subsequently developed CJD. Additionally, it was decided that hospital records would not include reasons for the look-back on documentation. Please answer the following:**

a. Please detail the reasons behind this decision, including details of the individuals and organisations involved;

In May 1996 I wrote to Dr J Metters to suggest that a study of CJD and blood transfusion should be undertaken and he replied that this research needed to be carried out. 'MSBT agreed that this research should be carried out *'but without any contact being made with recipients of blood from donors who subsequently developed CJD.'* In a letter of 23 May 1996, I wrote *'I well understand the importance of the ethical issues and the research protocol will of course be submitted to a research ethics committee.'*

Dr Hewitt and Dr Gillon discussed the study with NBS legal advisors and other blood services and it was decided to include a reverse study investigating the donors who had given blood to individuals who later developed CJD.

A draft proposal was written by Dr Hewitt and Dr Gillon and the study was entitled 'Transfusion Epidemiology Review (TMER).' MSBT considered the proposal and asked for it to be submitted to the Local Research Ethics Committee by the NCDRSU. This was done in October 1996 and approval was given in January 1997.

The proposal stated that *'the limited look-back would take place without notification of the recipients. The reasons are as follows:*

1. *There is no screening test available which can detect the possibility of an individual being susceptible to the development of vCJD in the future.*
2. *There is no diagnostic test available to detect whether an individual has been infected with the agent which causes CJD.*
3. *The diagnosis of CJD can only be made with certainty on examination of pathology specimens post-mortem.*
4. *There is no intervention which can be offered to individuals detected to be at increased risk of the disease, or to those who have already developed symptomatic disease.'*

'For all the above reasons. It is considered unethical to notify any individual who has received blood from a donor who subsequently developed CJD.'

A look-back study of CJD in the USA started in 1995 and reached a similar conclusion on this ethical issue ie that identified recipients should not be informed. I believe this study continues to the present.

The TMER protocol also included the following statement *'It should be noted that, should there be any change in the capacity to diagnose the disease, or if any intervention becomes available in the future, then the transfusion services should have in place a mechanism for contacting the identified recipients.'*

The issue of flagging donors known to have received blood from people subsequently shown to have developed vCJD was discussed in a letter of 12.1.2000 from the Health Services Directorate. This included the following statement *'the view of the lawyers was that the flagging procedure described by the NBA is not out of line with current requirements of the Data Protection Act 1984 or the new 1998 Act. It was also considered that there was probably no requirement under either the old or the new DPA on national blood services to inform people who have received implicated blood components that they were being or had been flagged to avoid their blood getting into national supplies.'*

b. How long did the look-back programme last, including any extensions?;

The TMER study continues to the present.

c. **What regions did the look-back programme cover, including names of hospitals?;**

The TMER study covered the whole UK.

d. **What discussions were had regarding the information which would be obtained from patients to identify whether they had donated blood?;**

Questions on blood transfusion and donation have been included in the questionnaire used by the UK CJD surveillance system since 1980. The relatives of patients are asked if the affected individual had donated blood and, if so, the details of frequency of donation and site of donation. The relatives are also asked if the affected individual have ever received a blood transfusion and, if so, the details of the location and timing of transfusions.

In order to ensure that blood donations were not missed, all cases of vCJD were reported to the National Blood Services to check for a history of blood donation, even in cases reported not to have been donors by their family. The quality of the information gained by this methodology is discussed in TMER reference 13 ' Accuracy of a history of blood donation from surrogate witnesses.'

e. **How was the look-back programme received by organisations impacted, such as the NHS and blood services?;**

I do not know.

f. **Please provide details on the findings of this look-back programme;**

Please see the list of TMER references.

g. **What decisions were taken following the conclusion of the look-back programme?**

The TMER study has not ended.

h. **The proposal states that the CJD Surveillance Unit in Edinburgh had clinical information in relation to reported cases of CJD in the UK. Please outline what this information was.**

The NCJDRSU obtained clinical information on the history and evolution of symptoms, the results of investigations, past medical history, family history and occupational history,

15. **The Inquiry is aware of some of the issues regarding information sharing faced by TMER. In a letter received by you from Dr Ian Franklin [NCRU0000111_054], he expressed reservations about providing donor information without consent. He further stated he was also unable to obtain donor consent as there was a lack of guidance available regarding the information they could provide as to why their data was required.**

Please answer the following:

a. **What was your response to the reservations Dr Franklin submitted;**
b. **What actions were taken following this letter;**
c. **What considerations were given to the lack of consent from individual donors?;**
d. **What discussions/meetings were had in response to this letter;**
e. **What revisions, if any, were made to the standard operating procedures;**
f. **What discussions were had with the Scottish authorities (or any other departments) regarding the TMER procedure;**

Dr Franklin expressed his ethical concerns regarding the reverse component of the TMER study in a message in March 2001. He felt unable to provide data on a small number of cases because of these concerns.

There was subsequently an interchange of messages between Dr Franklin and I regarding the TMER study, but there was no resolution and the missing data was not provided. In December 2001 I contacted Dr Christie, Scottish Office to explain the situation and in January I wrote to Dr Franklin to try and arrange a meeting to discuss the issue. A meeting was held at the St Andrews House, Edinburgh in March 2002, chaired by Dr Aileen Keel, Deputy Chief Medical Officer and a compromise was reached as described in Dr Keel's letter following the meeting.

g. Did TMER receive any other criticisms?

The family of the first transfusion transmitted case of vCJD case contacted my colleague Professor R Knight in February 2004 as they were concerned about aspects of the TMER study. Arrangements were made for the family to come to the NCJDRSU on February 23rd 2004 for a meeting with Professor Knight and I, which lasted for several hours. We discussed the origin and methodology of the TMER study and the ethical decision not to inform recipients of the exposure to blood derived from vCJD cases. We were grateful to receive a letter of thanks from the family after the visit.

However, the family made the point that the diagnosis and care of their relative may have been adversely affected by the decision not to inform recipients. The diagnosis of vCJD in this case was only made at post-mortem, at least in part because the individual was significantly older than previous cases. If it had been known that the patient was at increased risk of developing vCJD, it is likely that the correct diagnosis would have been made in life and this would have greatly eased the distress to the patient and the family who would have been able to make informed decisions.

After the first case of transfusion transmitted vCJD the decision was made to inform the other recipients of the risk of vCJD, indicating that this unforeseen effect of the ethical decisions on the TMER would not be repeated. In 1996 when the TMER protocol was developed there was limited experience of vCJD, but this was a disease of younger individuals with a relatively stereotyped clinical characteristics, allowing prompt identification of cases. There was great uncertainty that transfusion transmission of vCJD would occur, nor that a different age group would be affected.

I believe that the criticisms of the TMER made by the family of this case were correct and I have apologised to them.

16. **The TMER was set up in Edinburgh to investigate whether there was evidence that CJD or vCJD may have been transmitted via the blood supply. With regards to the formation and success of the TMER reviews, please answer the following. You may wish to read [NCRU0000109_045] and [NCRU0000109_092] to answer the questions.**

a. Who was involved in the creation of TMER and the initial look-back exercise;

The TMER was (and is) a collaborative study between the UK National Blood Services and the NCJDRSU. I had been in discussion with the DH about a look-back study of blood transfusion in CJD for some years (see response to Question 12 and the letter I wrote to DH on 5.5.1995). Following the identification of vCJD in 1996, the need for a look-back study was reconsidered by the DH and a number of committees, including, I believe, SEAC, MCA and MSBT. The decision was made to go ahead with a look-back study of blood transfusion and CJD, including vCJD.

The original protocol was written by Dr P Hewitt and Dr J Gillon and I contributed some amendments to the draft protocol.

b. What discussions were had and between whom regarding its creation;

See response to a.

c. What was the procedure of the initial look back exercise;

See TMER papers for details of the protocol: A summary of the TMER methodology is described in NCRU000109_045.

In brief: a group of patients with CJD and matched controls who were known to have donated blood were identified by the NCJDSU and details passed on the UK BTS. The donations were traced and the fate of the donations identified through blood bank records. The details of recipients of cases and controls were provided to the Unit to determine whether any of the named individuals subsequently developed CJD or vCJD.

In the reverse process details of individuals reported to have received a blood transfusion in the past were provided by the Unit to UKBTS. Blood bank records were checked to identify the blood donors and their details were provided to the Unit to determine if any of the donors subsequently developed CJD or vCJD.

d. What were the results of the initial look back exercise, specifically, how many people were identified;

Data for the TMER as of 2006 are provided in NCRU0001_092.

Updated information from the TMER up to 2016 is as follows:

- 168/178 vCJD cases in the UK were eligible to donate (ie aged>17 years)
- Number of vCJD cases from which blood components issued: 18
- Number of recipients identified from these 18 cases: 67
- Years during which vCJD blood was donated: 1996-2007
- Components transfused: red cells 27, leuco-depleted red cells 25, fresh frozen plasma 3, buffy-coat reduced red cells 2, fresh frozen plasma (leuco-depleted) 2, whole blood 2, cryo-depleted plasma 1, cryoprecipitate 1, platelets(pooled) 1, platelets (pooled, leuco-depleted) 1.
- Plasma fractionation (from 11 vCJD donors); 25
- Years during which vCJD plasma sent for fractionation 1986-1998
- Number of recipients transfused 1980-1999: 40
- Number of recipients transfused 2000-2004: 27 (all components leuco-depleted)

By 2016 53 recipients of vCJD components had died and 14 were alive, between 12 and 23 years post-transfusion. 8/14 had received leuco-depleted red cells.

Three clinical cases of vCJD were identified in component recipients and one pre-or sub-clinically infected individual.

The four vCJD infections were identified in the 32/67 individuals who survived at least 5 years after the blood transfusion. All had received a non-leuco-depleted blood component.

The last death of a vCJD case linked to prior blood transfusion was in 2007.

The last primary vCJD case identified in the UK died in 2016.

15/178 cases of vCJD were reported to have received a blood transfusion.

There was no record of transfusion in 1 case, the transfusions predated available records in 4 and transfusion records were found in 10 cases.

There were 192 donors identified who gave blood to vCJD patients.

e. Did the identified people include donors, as well as, recipients;

See above.

f. How many other look-back exercises were conducted;

To my knowledge this was the only look-back study of blood transfusion and CJD in the UK.

g. Why were further look-back exercises conducted;

To my knowledge this was the only look-back study of blood transfusion and CJD in the UK.

h. Who was involved in the exercises;

See above.

i. What was done with the results of the various exercises;

The results of the TMER study were published in a series of scientific papers and were presented at scientific, regulatory and CJD family support meetings eg FDA TSEAC , EMEA, WHO etc..

j. Did you have input in the notification of the people identified;

I had no direct involvement in this.

k. What was the procedure of such notification;

I do not know

l. How did this procedure develop over time and why;

I do not know.

m. In your opinion, were the look-back exercises successful? Please explain the

reasoning for your answer;

To quote NCR000112_069:

'*The TMER study has provided compelling evidence that vCJD is transmissible through blood transfusion'. The reason for this statement is that four vCJD infections have been identified in a relatively small cohort of individuals who received blood transfusion from individuals who themselves later developed vCJD. To quote from NCR00012-069: 'In view of the small size of the recipient population (n=66) and the background mortality rate for vCJD in the general UK population (0.24/million/annum), these observations provide strong evidence that vCJD can be transmitted from person to person through blood transfusion.'*

n. How have these look-back exercises informed future risk?

There are a number of factors that may inform future risk.

4/67 individuals who received a blood component transfusion from a 'vCJD' donor have been infected with vCJD
The period elapsed between the blood transfusion and the development of vCJD in the three recipients who developed clinical disease was between 6.5 and 8.3 years.

As of January 2022, the 13 living recipients of blood from a 'vCJD' donor have been unaffected by vCJD for 17-29 years since the transfusion.

All four infections followed transfusion with non-leucodepleted blood components.
The majority of living recipients received leuco-depleted blood components, including three Methionine Methionine (MM) homozygotes.

There is some evidence that the codon 129 genotype may influence susceptibility to transfusion transmitted vCJD. All three clinical cases of transfusion transmitted vCJD were MM homozygotes (as are all but one of the primary cases of vCJD and 40% of the general UK population).

This issue of codon 129 genotype is discussed in TMER publication 11. Urwin et al. This includes the description of a surviving recipient who received a blood transfusion from the same donor involved in 2/3 of the known transfusion transmitted cases. This

individual was a Methionine Valine (MV) heterozygote and had a negative tonsil biopsy some years after the transfusion.

There have been no new cases of transfusion transmitted vCJD since 2007.

None of the clinical CJD cases are judged to have been caused by exposure to plasma derived products.

17. **The Inquiry understands that you sought further ethical approval for another look back exercise in 1999/2000. Please outline the aims of this look back, why it was designed in the way that it was, and the outcome. Please also indicate what if any steps you took to ensure that patients identified as being at risk of CJD through the look back programme were appropriately notified by The Expert Group on the Management of CJD Incidents. You may find NCRU0000112_068 and NCRU0000112_069, of assistance.**

The two letters refer to the TMER study, which is discussed in the responses to other questions from the Inquiry.

18. **In an email from Dr Patricia Hewitt [NHBT0097077_017] dated 20 July 2005, she outlined precautionary measures to reduce the risk of vCJD transmission. She proposed a notification exercise of donors who had donated in the last five years following a risk assessment by the Department of Health. Please answer the following:**

NHBT0097077_017 relates to the decision in 2005 to inform 110 donors, whose blood had been transfused to three people who later developed vCJD, that they should be 'considered at risk of vCJD for wider public health purposes.'

a. **What was your involvement, if any, with this notification exercise?**

No direct involvement. I believe I may have offered to be contacted by anyone concerned by this action.

b. **What did the risk assessment consist of?**

I do not have access to the risk assessment, although I presume it must have been discussed at the CJD Incidents Panel.

c. **Of the 156 cases identified, 4 were confirmed as having had blood transfusions that experts believe could be linked with vCJD. Does this remain true today?**

Yes

d. **What information was shared during the notification exercise?**

I do not know

19. **The Inquiry is aware that you received instructions from the Department of Health and the MCA on how and when to notify the blood services for suspect nvCJD cases. In a letter between Professor Ian Franklin and Patricia E Hewitt, your role in the notification process was discussed and it was recommended by Ms Angela Robinson that Ms Hewitt, Professor Ian Franklin and yourself liaise to organise the meeting with the blood services.**
Please see NHBT0008875 and provide answers for the following:

a. **Please provide details of the instructions you received from the DoH and the MCA, including names of the individuals who you were in contact with and if possible, supporting documentation;**
b. **The letter states that the blood services were not consulted when issuing these instructions. Is this correct in so far as you are aware? Do you have any understanding as to why this was? Please provide any details of the discussions which were had in respect of this issue, the individuals and organisations involved in such discussions and if possible, supporting documentation;**
c. **The letter initiates plans for the organisation of a meeting between the National Blood Authority, Scottish National Blood Transfusion Services and you. Did this meeting take place? If so, what was the outcome?**
d. **Please provide details of when this meeting was held, who attended, what was discussed and the results. Please provide supporting documentation.**

I have limited access to relevant documents to respond to this question
a, b, c, d.

On 5th Nov 1997 I received a letter from Dr Metters stating that SEAC, CPMP and MSBT all agree that the paucity of information on the pathogenesis of nvCJD and lack of data on the risk of transmission by blood and blood products require that a precautionary approach must be taken. It cannot be assumed that the risk will be similar to sporadic CJD. The CPMP recommended that unused blood products… should be quarantined. The same precautionary principle would apply equally to any labile blood components that had not been used.

To reduce the possibility of implicated blood products (and labile components) being used, it is clearly important for all relevant information about any donor who is suspected of having nvCJD to be passed to the Transfusion Service as soon as possible. In this way the blood products to which the donor has contributed can be traced and re-call arrangements put in place.

I sent a memorandum to clinical staff at the Unit on that day stating

1. If we identify any suspect case of nvCJD in England and Wales with a history of blood donation or reception the details should be forwarded immediately to Angela Robinson of the National Blood Authority.
2. We should also inform Dr Metters at the DH in London but this should include only our reference number and general information. It should not include the patient's name, dob or address.
3. Dr Metters is writing to me with the addresses of the contact blood transfusion centres in Scotland and Northern Ireland.

In a letter to Professor Franklin on 18.11.1997 I wrote:

'I have received a letter from the DH suggesting that any relevant information on suspected cases of nvCJD should be passed on as soon as possible to the relevant Blood Transfusion Service.'
In a letter to me from Dr Franklin in March 1998 he stated that the 'CPMP and the CSM had advised that UK blood services should be recalling and tracing recipients of blood products containing a donation from someone in the strongly suspected as well as proven category of nvCJD.'

The letter also comments on my intention to obtain approval from the Lothian REC for a consent form for the relatives of vCJD cases giving permission to inform the blood

services of the diagnosis in their relative. Professor Franklin raised the issue of cases in which the relatives might refuse such consent and the concern that this might prevent the statutory requirement for Blood Services to withdraw such products.

In a letter from Dr Angela Robinson on 24th November the importance of prompt notification of vCJD cases was underlined by the following statement.: *'My understanding from BPL is that products made from plasma sent for fractionation might still be in date if donated from 1992 onwards, so I would be grateful if you could let me know the moment you have or have not confirmed this case so if any recall action is necessary it can be expedited as soon as possible.'*

A meeting was held on May 5th 1998 at SNBTS Headquarters in Edinburgh to discuss the notification of cases of vCJD. I have the agenda for this meeting, but not the minutes. I believe Professor Franklin and Dr Metters were among those who attended the meeting. An SOP for the SNBTS was written, I think, after this meeting in which there is the following statement *'The DH has instructed the CJDSU to notify the UK Blood Transfusion Services suspected of or diagnosed as having vCJD'.*

I believe the issue of obtaining consent from the relatives of vCJD cases to inform the Blood Services was discussed and it was decided that it was essential to let the Blood Services to be informed of new cases of vCJD as it was imperative for public health that any extant blood or blood products be withdrawn. Thereafter the policy of the NCJDRSU was to inform families of vCJD cases that we had an obligation to provide the National Blood Service with their relative's details because of the potential need to withdraw any extant blood or blood products.

In this context it may be relevant to consider that of the total of 24 donors in whom records were traced, 4 had donated blood shortly after the onset of clinical symptoms and 3 shortly before clinical onset.

It is important to stress that the notification of cases of vCJD was not carried out under the auspices of the TMER study, The instruction from Dr Metters (to notify cases of vCJD to the Blood Services) was necessary for compliance with regulatory authorities in relation to medicinal products. This notification was not part of the TMER study and was not required for the study protocol.

In January 1998 I received a letter from Dr Metters confirming the notification process for incident cases of vCJD.

In May 1998 I received a letter from Dr P Hewitt with a notification form for the NCJDRSU to use when notifying the Blood Services of new cases of vCJD.

In 2005 it was decided that details of all cases of vCJD should be provided to all four National Blood Services to check that blood had not been donated in one country by a resident of another country. Professor Franklin wrote on 20 Jan 2005 *'On reflection, we have come to the view that should such a case slip through the existing arrangements that this would be hard, if not impossible to justify to the public and to Ministers on the basis of confidentiality, where an overriding duty of protecting the blood supply (and hence the Public Health) exists. You may be assured that this data sharing will be conducted in as secure a way as possible and will use advice from Caldicott Guardians and Data Protection Officers to minimise any DPA concerns.'*

Section 5: Impact and assistance

20. **The Inquiry seeks to understand the impact of testing and notification on patients and donors. How did the care and assistance provided by the NC assistance was provided to patients or family members who had participated in the various look-back exercises, notification procedures and testing as well as, those who were impacted by CJD and vCJD. You may wish to look at NHBT0004374_002, HCDO0000243_076 and CABO0000266 to assist your answer.**

In Dr Hewitt's letter of 25.11.1999 it states that the NCJDRSU 'has offered help in both counselling and ongoing support' to donors informed that they are at increased risk of developing vCJD.

As far as I can remember I had no contact with any of these donors as this was primarily dealt with by the Blood Services. I did have contact with the families of two recipients of blood transfusions derived from donors who later developed vCJD, as described above in the responses to sections 7c and 15g.

The two other documents refer to a paper describing the clinical features of a series of vCJD cases and a report on the impact of vCJD on the relatives of vCJD patients.

The first paper was aimed at providing a detailed description of the clinical features of vCJD to aid in the future diagnosis of vCJD.

The second document was a study aimed at identifying the care and information needs of patients with vCJD and their families. This was thought to be a priority as vCJD was a new disease, there was the possibility of a large epidemic and we were aware from contact with the families of early vCJD cases that the diagnostic process had often been distressing and that the care of patients had often been poor. The aim was to identify specific problems in order to try and improve care in the future. As I had no expertise in this type of research, I was fortunate that Dr Douglas, Dr Campbell and colleagues at the Department of Public Health, University of Edinburgh agreed to lead the study.

Another paper from this study describing the economic costs borne by the families of vCJD cases was published in 2002 (S Myles et al Variant CJD; costs borne by families Health and Social Care in the Community, 2002 ;10: 91-98).

Section 6: Scale of Exposure

The Inquiry seeks to gain an understanding as to the number of people who have been exposed to vCJD and the extent to which this can be assessed and quantified.

Please provide the following:

21. What is the prevalence of vCJD in the general population today? Please attach a summary of any research studies or papers, reports, recommendations, look back exercises and databases that you contributed to, which have addressed the prevalence of the transmission of vCJD in blood and blood products.

The prevalence of vCJD infection in the general population is unknown but is of critical importance for risk assessment.

Estimates have been based on the results of the Appendix I and Appendix II studies, which suggest that a proportion of the general population have abnormal prion protein in the appendix and may be infected with vCJD. The estimated prevalence of abnormal appendix prion protein ranged from 239/million (CI 49-692) in the Appendix I

study and 493/million (CI 282-801) in the Appendix II study. The implication that there was a significant number of people in the UK who were sub- or pre-clinically infected with vCJD was clearly of importance for public health because of the potential for case-to-case transmission via blood, blood products or contaminated surgical instruments. The Appendix I and Appendix II studies were of fundamental importance to public health policy, including the considerations of the CJD Incidents Panel.

No formal control data were available for the two appendix studies and the Appendix III study was carried out in order to study appendices from pre-1980, before the identification of BSE, and in those born after 1996 after which it was judged that population exposure to BSE was believed to be minimal ie *'in groups thought to be unexposed to BSE'*.

Unexpectedly 7/29,516 appendices were found to be positive, 2/7 in the pre-1980 cohort and 5/7 in those born after 1996. The prevalence of positives was estimated to be similar in all three appendix studies and the morphological appearances in the appendices was also similar in all 3 studies. These results are difficult to interpret. The Appendix II study showed no geographical difference in prevalence of positives, whereas mortality rates for vCJD have been consistently about double in the north of north of the UK as compared to the south. The codon 129 genotype distribution in the positive samples was distinct from that of vCJD. To date no case of vCJD in the UK has been born after 1989, when the Specified Bovine Offals (SBO) ban was introduced, whereas there have been 4 cases born after 2000 in continental Europe in which similar measures to the SBO ban were not introduced until some years after being introduced in the UK. In this context it is surprising that 5 positive appendices were found in those born after 1996.
One of two interpretations raised by the authors of the Appendix III study is that 'this background prevalence is unrelated to the intensity and extent of dietary exposure to BSE'.

As the authors also indicate it is possible that further evidence of the nature of the positive prion protein staining in appendices may be informed by further laboratory investigations, including those funded by the Department of Health Policy Research Programme,

22. **Your view on the effectiveness of any look back studies, in particular TMER, to trace recipients of vCJD infected blood and blood products.**

The aim of the TMER study was to identify whether vCJD could be transmitted via blood transfusion. The identification of three clinical cases of vCJD and one pre- or subclinical infection in individuals who had previously received a blood transfusion from donors who later developed vCJD provides strong evidence that vCJD is transmissible through blood transfusion.

23. In an email exchange with you and Dr Chris Verity, you stated there may be 4,000 people who were infected with sub-clinical vCJD.

a. Were there any reported changes to this number? You may wish to review **NCRU0000292_003** and your findings in **TSTC0000049** when answering this question. There is a typographical error in the email to Dr Chris Verity. This should read 1:4000 rather than 4000. The Appendix II study stated *'the estimated prevalence range largely overlapped that from the first survey but was narrower with a higher central estimate (1:2000 v 1:4000).'*

b. Please provide a current estimate of the prevalence of those infected with sub-clinical vCJD.

See response to Question 21.

Section 7: Other issues

Please exhibit all documents relevant to this request to the written statement.
Please include any other information which has not been specifically requested above, if it may assist the Inquiry and is relevant to the Terms of Reference.
To assist you in addressing the questions and requests set out below I attach to this letter a number of documents which are listed below.

If, in order to provide your statement, you require copies of other documents which may be held by the Inquiry, please let me know as soon as possible.

If any questions relate to matters outside of your knowledge or experience, please say so.

As stated above, a number of prion protein amplification studies have identified abnormal prion protein in vCJD blood, which might be associated with infectivity in blood. The level of infectivity in vCJD blood is of critical importance to risk assessment, but studies using amplification techniques cannot provide an accurate measure of the level of infectivity in blood because the starting seed may be at a very low level, which may be insufficient to result in transmission in a real-life setting.

In a paper published in 2014 'Detection of Infectivity in Blood of persons with Variant and Sporadic CJD (Douet et al Emerging Infectious Diseases 2014 10 114-117)' the authors used a highly sensitive transgenic mouse model to demonstrate infectivity levels of 2.12 ID/ml in the plasma of a single patient with vCJD (with an estimated level of infectivity in whole blood of 4.45 ID/ml). The study also found infectivity at a level of 2.12 – 3.70 ID/ml in 2/4 plasma samples from cases of sporadic CJD. It is of note that epidemiological studies in sporadic CJD, including those in the UK and USA, have not identified evidence that this condition is transmissible through blood transfusion.

In 2015 the NCDRSU provided vCJD blood samples to this research group and the results are unpublished. However, with permission of the lead scientist, the preliminary results have shown that 5/10 of the vCJD cases had no evidence of infectivity in blood (n=1) or buffy coat (n=4) and the levels of infectivity in the other 5 cases were low, ranging from 1.3 - 4.4 ID/ml. Infectivity was found in plasma in 3 cases, in whole blood in 1 and in buffy coat in 1.

These results suggest that the levels of infectivity in vCJD blood or plasma are low and that not all vCJD cases have detectable infectivity in blood even in the clinical phase of disease.

Statement of Professor Robert Will

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

Signed ____Robert Will_____

Dated _____9.5.2022_____

Table of exhibits:

Date	Notes/ Description Exhibit number
26/05/2016	PHEN0000003
[undated]	WITN7098002