Witness Name: Prof. Richard Knight
Statement No.: WITN5592001
Exhibits: WITN5592002-12
Dated: 18.04.22

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF PROFESSOR RICHARD KNIGHT ON BEHALF OF THE NATIONAL CJD RESEARCH AND SURVEILLANCE UNIT ("NCJDRSU")

I provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 16 December 2020 and a Supplementary Rule 9 dated 15th October 2021.

I, Professor Richard Knight, on behalf of the NCJDRSU, will say as follows: -

Section 1: Information

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

Address: GRO-C
Email: R.Knight GRO-C
Date of Birth GRO-C 50

Current Employment: Emeritus Professor of Clinical Neurology,
National CJD Research and Surveillance Unit, Centre of Clinical Brain Sciences
University of Edinburgh

Qualifications:
BA (Oxon) [PPE]
BM BCh (Oxon) [Medicine]
FRCP(E)
BSc (OU) [Open: Maths & Physics]

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.**

PRE-REG HS General and Vascular Surgery The Radcliffe Infirmary, Oxford 02.1977-08.1977

PRE-REG HP General Medicine Horton General Hospital, Banbury 08.1977-02.1978

SHO General Medicine/Geriatrics West Park Hospital, Macclesfield 02.1978-08.1979

SHO General Medicine/ Diabetes/Neurology Gloucestershire Royal Hospital 02.1979-02.1980

Registrar General Medicine/Gastroenterology Lister Hospital, Stevenage 02.1980-11.1980

Registrar Neurology Regional Department of Neurology, Derby 11.1980-02.1982

Research Registrar/Clinical lecturer Neurology/CJD Oxford 02.1982-10.1983

Registrar The Radcliffe Infirmary Oxford Neurology 10.1983-04.1986

Senior Registrar Neurology Northern General Hospital, Edinburgh 04.1986-09.1987

Consultant Neurologist/Hon Sen Lecturer Neurology Aberdeen RI 09.1987-12.1996

University of Edinburgh:
Honorary Senior Lecturer 1996-2004.
Honorary Reader 2004- April 2006
Reader May 2006-July 2008
Personal Chair Aug 2008-2017
Professorial Fellow 2017-2019

Emeritus Professor 2019-

NHS (Lothian University HT):
Consultant Neurologist 1996-April 2006
Honorary Consultant Neurologist May 2006-

NCJDSU/NCJDRSU Roles:

Clinical Neurologist	1996-2002
Deputy Director	2002-2005
Director	2005-2007
Deputy Director	2008-2009
Director	2009-2017
Clinical Neurologist	2017-
Epidemiology Lead	2021-

Provided Consultant NHS Neurology services at:
Aberdeen RI, Aberdeen
Raigmore Hospital, Inverness
Western Isles Hospital, Stornoway
Western General Hospital, Edinburgh
Dumfries & Galloway Royal Infirmary, Dumfries
Roodlands Hospital, Haddington
Newbattle GP Surgery, Newbattle,
Royal Infirmary of Edinburgh, Edinburgh

Comments:

a. 1982-83: Research post in the University of Oxford Department of Clinical Neurology, with Professor Bryan Matthews. Research in surveillance, clinical features and diagnosis of CJD in England and Wales.
b. From 1996 onwards, based in the NCJDSU (later called NCJDRSU), involved in surveillance and associated research, CJD, in the UK.
c. 1997 onwards Membership of International CJD surveillance/research collaborations.

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.**

a. **Presently Continuing Roles:**

i. Specialist Adviser to the vCJD Trust Committee 2002-

ii. Member of CJD Resource Centre Oversight Committee 2007-

iii. Chair of the UK CJD Support Network Management Committee 2011-

iv. Official Friend & Advisor to the CJD International Support Alliance 2009-

b. **Past Roles:**

i. Deputy Director & Director of NCJDRSU

ii. Member of the DH/MRC Research Advisory Group on TSEs

iii. Member of SEAC (Spongiform Encephalopathy Advisory Committee)

iv. Member of CSM Ad Hoc Expert Working Group on TSEs

v. Member of the Department of Health CJD Therapy Group

vi. Member of MRC Prion Disease Therapy Outcome Measures Group, CJD Therapy Group

vii. Member of MRC New Therapy Scrutiny Group

viii. Member of ACDP (Advisory Committee on Dangerous Pathogens)

ix. Member of ACDP TSE/Prion Sub-Group

x. Member of SaBTO Advisory Committee (safety of Blood, Tissues & Organs)

xi. Member (Observer) DH National Prion Monitoring Cohort Oversight Committee

xii. Member of STN Management Committee (Scottish TSE Network)

xiii. Medical Advisor Member of the Human BSE Foundation Committee

xiv. Member of MSP (Organophosphates & Human Health) Veterinary Products Subcommittee

xv. Member of SCENHIR EC Committee on the Safety of Human-derived Products with regard to vCJD.

xvi. Chair, NEUROCJD (EU-funded CJD Collaborative Surveillance & Research in 10 European countries + Israel. (1998-2005)

xvii. Co-Chair EuroCJD (EU-funded CJD Collaborative Surveillance & Research in 10 European countries) (1998-2007)

c. **Written & Oral Evidence to HCSTC [TSTC0000039, TSTC0000049].** I will confine my answer to those aspects for which I am directly responsible i.e. the written submission which was prepared as a consensus NCJDRSU document under my then Directorship and the (presumably faithful) recording of the evidence I submitted orally (but not the evidence others presented orally). My statements on these are:

i. They were, according to all I knew then, indeed accurate and true at the time of submission.

ii. There have been some developments since then that are additions to the evidence but they occurred since the time of those submissions. As these developments are dealt with elsewhere, I will not go into detail here but simply list the important ones:

1. The 'Appendix III' Study has been completed and published (RLIT0000725).

2. Further work relating to the Appendix samples is progressing [no results yet available].

3. There has been a definite MV vCJD case identified(WITN7034010).

4. There have been publications concerning blood tests for vCJD but the points made about the necessity for proper evaluation and the difficulties of this still stand (NHBT0033626, WITN5592003, WITN5592004).

5. The prepublication papers concerning vCJD and Blood mentioned in Q 191 has been published (WITN5592005).

6. The study of the elderly mentioned in Q179 was agreed, funded and started, essentially as a feasibility study as there were considerable methodological concerns about the ability to undertake a study of elderly dementia cases even within a single locality such as the Lothian region. This study is completed and a paper is in pre-submission form. No unsuspected cases of vCJD were found.

d. **Other Inquiries, Investigations, Criminal or Civil Litigations.**

I have been involved in WHO Consultations on CJD.

I have presented evidence to the FDA on CJD.

I have provided expert opinion legal reports in two cases:

i. In relation to the possible exposure of an individual to the risk of vCJD related to albumin

ii. In relation to the possible exposure of an individual to the risk of vCJD from a hospital error in the use of plasma.

I provided a report and attended Court as an expert witness in relation to a vCJD family requesting a Health Authority to give their son, who had vCJD, an unproven treatment (intra-cerebro-ventricular Pentosan Polysulphate).

Section 2: General Background:

4. **Please set out a brief introduction to the NCJDRSU including its establishment, objectives and primary functions.**

   a. **Establishment.**The NCJDRSU was established in 1990 (then the NCJDRSU), funded by the UK Department of Health in response to the BSE epidemic. The primary objective was to identify and investigate cases of CJD in the UK, in order to determine any changes in incidence or disease phenotype (that is, the clinical symptoms an individual may present with) that could indicate transmission of BSE to humans.

   b. **History & Name.** In terms of the history of the NCJDRSU's establishment, there had been a previous CJD surveillance project between 1980 and 1985, covering England and Wales. This project retrospectively collected CJD data for the period 1970 to 1979, and then did so in real-time for 1980 to 1984. When surveillance was restarted in 1990, covering the whole of the UK, data were collected retrospectively for the 1985-1990 period. Surveillance continues. The Unit was called the CJD Surveillance Unit from 1990, the National CJD Surveillance Unit from 1991, and has been called the National CJD Research and Surveillance Unit from 2011. The Unit's functions did not change but the name was altered to better reflect our activities.

   c. **The main functions of the NCJDRSU:**

      i. Investigating suspect cases of all forms of CJD to determine, as accurately as possible, the numbers of cases of each form of CJD.

      ii. To determine any changes in the numbers of cases and the disease phenotype that might indicate transmission of BSE to humans.

      iii. Having detected a change, to determine whether such a change was indeed due to BSE transmission.

      iv. Having detected cases thought to be due to BSE transmission, to characterise the clinical features of such cases and to formulate diagnostic criteria, if possible.

v. Alongside this, there is associated research concerning epidemiological, clinical, diagnostic, pathological and aetiological aspects of prion diseases.

5. The Inquiry is aware that vCJD is not included as a notifiable disease under Schedule 1 of The Health Protection (Notification) Regulations 2010. Do you know the reasons for this? How does this affect the Unit? If vCJD was a notifiable disease, would this assist the Unit? If so, how?

a. Variant CJD is not a notifiable disease under Schedule 1 of The Health Protection (Notification) Regulations 2010 (the same is true for other forms of CJD). The Unit does not know if there are specific official reasons for vCJD not being a formally notifiable disease (as defined in the way you state). However, the NCJDRSU has always been of the opinion that formal notification of CJD (including vCJD) would be difficult, would not add anything and, in fact, would probably hinder surveillance (especially the recognition of atypical cases). In any discussions, that has been our expressed view.

b. Notification requires two things: Clear notification criteria and a suitable body to which cases should be notified.

c. There are no clear notification criteria such as might be defined for some other conditions [such as a positive HIV test], aside from a positive neuropathological diagnosis on biopsy or autopsy material. The decision as to whether a case is indeed likely to be CJD requires clinical experience and judgement, taking into account variations in clinical phenotype and investigation results. Because CJD is rare, clinicians often have limited experience and access to experienced clinicians is an important step in diagnosis. In addition, the driving purpose behind the UK surveillance system was to detect new or atypical forms of CJD; defining notification criteria on the basis of established case descriptions would run the risk of having only typical cases notified with unusual variants being overlooked. So, having rather open criteria (generally expressed as: a clinician thinks that prion disease is a possibility) maximises the chances of picking up atypical cases. In addition, having referrals made to a set of experienced clinicians (rather than, say, public health bodies), allows for expert clinical input and case classification. Public Health notification still

occurs via separate reporting at the time of diagnosis. Clinicians might well hold off formal notification if they are very unsure about the diagnosis but might well be prepared to discuss a doubtful case with a fellow, but more experienced, clinician. The access to expert opinion is also an incentive for clinicians to refer suspect cases; they are getting active help not just being bound to notify to some sort of official body. Early case recognition is also important as it allows NCJDRSU staff to visit the patient (and examine them) in life, allows recommendations of further investigations, allows safety advice to be given, and helps data collection at a time when it is 'fresh'; notification only via neuropathological diagnosis would not identify all cases (autopsy may not be performed) and would lead to later case recognition.

d. We know of no adverse effect on the Unit. Indeed, we believe it has helped us. Firstly, we have been able to identify atypical cases at as early a clinical stage as possible. Secondly, we have been able to advise clinicians directly and thereby enhanced accurate diagnosis. Thirdly, we have been able to visit, and examine, patients promptly on suspicion of diagnosis. Finally, we have received referrals of cases that turn out to be CJD and cases which turn out to be other diseases (but which raised the suspicion of CJD in neurologists), this has allowed us to evaluate and refine diagnostic criteria and the diagnostic utility of proposed tests. as discussed elsewhere in this report.

6. What is the National Care Package and how does it work? What are its aims and objectives? How is the National Care Package funded? The Inquiry understands that it is based at the NCJDRSU. What is the reason for this?

The National Care Package (NCP) is the name given to a financial provision funded by NHS England. It is there to improve aspects of care for people with CJD (of all types). There are situations in which care could be provided but either the local health/care authority cannot provide it, cannot provide it in the most appropriate form or cannot provide it promptly enough (given the rapid progression of most CJD). In these situations, consideration can be given to providing funding for aspects of care that cannot otherwise be provided in whole

or in part. On diagnosis, an appropriate care plan is drawn up by local care teams, taking into account the patient's needs/wants, the family wishes and other particular circumstances (such as housing circumstances, nursing availability, appropriate care home availability etc). There is then the opportunity for the Nursing Care Team (NCT) (based at the NCJDRSU) to sanction any necessary funding from the NCP. It is provided on the basis of covering costs of improvements that cannot otherwise be met; it is not meant to replace ordinary funding. The cost of care, and the need for improved care for vCJD was identified in a report by Margaret Douglas and colleagues, undertaken by researchers based in the University of Edinburgh. Following this, the NCP was set up and, while the report concerned vCJD (WITN5592006), it was felt that the only reasonable way of administering it was to provide it for all cases of human prion disease. In the initial stages of diagnosis, there could be uncertainty as to the type of CJD at a time when extra care funding was needed. There were problems foreseen around a case requiring care with the possible diagnosis of vCJD, but who later was found to have sCJD (would care be then withdrawn?) or a case with uncertain vCJD that had to wait for care funding until the diagnosis then became firmer. In any case, the major funding requirements centred on vCJD, with its longer duration, typically in younger people, rather than the typically short duration sCJD, often occurring in the elderly, so most of the financial requirements would usually relate to vCJD. The NCP was set up following discussions with DH and it was to be administered via the NCJDSU/NCJDRSU since that Unit would be aware of the cases of CJD, as well as their classification and needs. The NCT was also funded by NHS England and the nurses in the NCT were based at the NCJDSU/NCJDRSU since they could then be involved in care advice, family support and NCP considerations at the earliest opportunity following referral to the Unit by local clinicians.

Section 3: General Background: Chronological Summary of the Emergence, Discovery & Scientific Developments of the Secondary Transmission of vCJD.

7. Identification of vCJD & Link to BSE

a. Between March 1995 and January 1996, 10 cases of CJD were identified that resulted in the recognition of a new form of CJD, then termed new variant CJD (nvCJD). The first case came to the attention of the Unit in March 1995; the other 9 between October 1995 and January 1996. Of these 10 cases, 8 had the onset of illness symptoms in 1994, the others in 1995.

b. These cases of CJD were identified in unusually young people, with some atypical clinical and neuropathological features. These were not immediately attributed to BSE infection for two broad reasons. Firstly, CJD had been reported previously in young people and clinico-pathological variations were recognised. Secondly, it was considered that intensive surveillance, in the light of significant publicity surrounding BSE and CJD, might well start to identify atypical cases that had been previously missed. However, as the number of such cases increased and the atypical pathological changes were recognised, there was increasing concern that they might represent instances of new human disease resulting from BSE infection.

c. In addition, there were established surveillance projects in other countries and discussion with these systems revealed that they were not identifying such cases at that time. This meant that these atypical cases were occurring in the country with the most significant BSE problem. A consensus was reached that these cases probably reflected BSE transmission to humans and the disease was named "new variant CJD" (nvCJD). The UK Government announced that there was a new form of CJD believed to be due to BSE in March 1996 and a paper describing the details was published in April 1996 (HSOC0010099). Subsequent transmission studies (using laboratory mice) produced experimental evidence, published in 1997, that nvCJD in man and BSE in cattle were caused by the same agent (DHSC0004125_011).

8. Subsequent vCJD developments

The main subsequent history in relation to vCJD (as nvCJD was renamed) may be summarised as:

a. Identification of further cases in the UK.

b. Identification of cases in other countries, especially France.
c. Development of diagnostic criteria for vCJD.
d. Recognition of diagnostic test results specifically helpful in vCJD-especially brain MRI and Tonsil Biopsy. Most recently, blood tests for vCJD have been developed but there has been opportunity to evaluate these in only small numbers of cases (due to the decline in vCJD numbers).
e. Better characterisation of the neuropathological features of vCJD.
f. Recognition of the involvement of lymphoreticular tissue in vCJD.
g. Further experimental and epidemiological evidence for the causative link between BSE and vCJD.

9. vCJD & Blood: Concern & Setting up the TMER Study.

a. The next significant point is the identification of vCJD transmission by blood. There was consideration given to the possibility of this, from the beginning of recognising vCJD. Firstly, iatrogenic transmission of other forms of CJD was already recognised (although not via blood). Secondly, it was thought that vCJD might behave differently from other forms of CJD. Thirdly, in particular, the involvement of the lymphoreticular system (including the spleen) in vCJD (not found in other forms of CJD) gave rise to particular consideration of possible blood infectivity in vCJD.

b. From its beginning in 1990, the Unit collected, routinely, information on blood transfusion and donation (as well as information on surgical procedures and other possible risk factors) in all cases of CJD and, following the identification of vCJD, the same information was gathered for variant cases. This continued with the vCJD cases, following their identification. Since it was known that sCJD was potentially transmissible and that sCJD was of unknown cause, a lot of research has been undertaken over many years to look at possible infective causes. Research undertaken in the early 1980s (prior to the identification of BSE, let alone vCJD), had considered possible risks such as occupation, diet, surgery and blood transfusion. The NCJDSU was continuing such research-not only looking for a possible change in CJD that might suggest BSE transmission to humans, but also to continue the research for possible causes of sCJD. However, the methodology of standard

surveillance at that time could address blood as a possible risk factor probably only through case-control methodology ie. comparing exposure to blood in cases with that in selected controls. A more detailed, more specific consideration of blood would require looking for possible links between identified donors and recipients (a 'look-back study'). In 1990, Professor Will of the NCJDSU had discussions with the Department of Health (DH) concerning setting up a system like that which is now used in the TMER study. At that time, such a study was judged to be impractical. To emphasise the historical context, at that time there was no evidence that blood was an actual risk for sCJD, and it predated the identification of vCJD.

c. In 1995, the Chair of SACTTI (The Blood Services Standing Advisory Committee on Transfusion Transmitted Infection) contacted the NCJDSU to discuss the possibility of a look-back study. The NCJDSU then discussed the possibility with the DH and the matter was discussed by the MSBT (Microbiological Safety of Blood and Tissues) committee which decided that such a study had no scientific justification and should not take place. Again, this was taking place prior to the identification of vCJD and the considerations of blood as a risk therefore related to forms of CJD other than vCJD.

d. Professor Will of the Unit contacted the MSBT Chair in April 1996 to raise again the possibility of some form of 'look-back' study; this being in the wake of the identification of vCJD and in the light of the fact that 1 out of the first 10 vCJD cases had acted as a blood donor. A meeting between NCJDSU and the UK Blood Services took place with an agreement to draft proposals for a CJD blood 'look-back' study. The MSBT now agreed that this research needed to be done. The first draft of the study proposal was prepared in May/June 1996 and the study was to be named TMER (Transfusion Medicine Epidemiology Review). MSBT considered this draft proposal which was then submitted to the relevant local Ethics Research Committee for the NCJDSU. Approval was granted in January 1997. The study concerned ALL types of CJD and not just vCJD. The NCJDSU/NCJDRSU is part of Edinburgh University and the principal investigators are employees of the University, with any clinical staff also

having contracts with the Lothian Health Services. If any research was/is to be undertaken by our staff then obtaining Ethics Committee approval would not simply be 'common' but obligatory and entirely normal practice.

e. There are other considerations and when the research has a widespread or national basis, it may be necessary to consult several Ethics Committees in different regions, as the NCJDRSU did for one research project.

f. [In relation to this specific history of events, it is my understanding that paralegals from the Inquiry spent time in the NCJDRSU and relevant documents were viewed by them at that time.]

10. The TMER Study Methodology

a. In the wake of vCJD, as noted above, a detailed blood 'look-back' study was considered more important than when the considerations related to sCJD, and the Transfusion Medicine Epidemiological Review (TMER) study was commenced in 1997. This is a collaborative study between the Unit and the National Blood Services (England, Scotland, Wales & Northern Ireland). In brief outline, the TMER entails the NCJDRSU passing on case details (with any recorded blood donation/transfusion history) to the Blood Services who then trace relevant donors and recipients. These details are passed back to the NCJDRSU to check whether any of these donors and recipients have been identified as CJD cases or are later referred as possible cases. These donors and recipients are also flagged with relevant death certificate providers and when these individuals die their cause(s) of death are notified to the NCJDRSU to check whether any of the cause(s) of death were related to vCJD/CJD. It should be emphasised that, at the point of establishing the TMER, blood transmission of prion disease had never been identified and, despite the considerations described above, generally, though not universally, expert opinion was that vCJD would probably not transmit by blood.

b. We now also send details of all cases of non-variant forms of CJD from English and Welsh patients notified to NCJDRSU to Blood Services

regardless as to whether they have a reported history of blood donations, and we are awaiting appropriate regulatory approval for Scottish and Northern Irish patients. This dataset extends from 2010 and captures all current cases.

11. The First case of vCJD blood transmission

a. The first case of vCJD transmission via blood was reported in 2004 (NHBT0008743_013). It was reported as a possible instance of blood transfusion transmission since it was, at that time a single instance and the link to a vCJD donor could possibly have been co-incidental; there was also no way of retrospectively proving the transmission- the attribution was made on the basis of association (the individual had received blood from a donor who had gone on to develop vCJD). This individual had been notified to the NCJDRSU as a case of CJD by a neuropathologist. At the same time, a death certificate copy had been received by the NCJDRSU (with respect to death certificates, see Section 8 paragraph 30 & 31). Because of the diagnosis listed on the death certificate, the individual's name was checked via the TMER study and it was found he had been notified to the NCJDRSU, via TMER, as a recipient of blood from a vCJD donor. A visit to the family was arranged for further data collection (with respect to visits after death, see Section 8 paragraph 29 & 30). The transfusion in question was of non-leucoreduced RBCs (red blood cells).

b. This case is an example of the 'multiple, overlapping, case ascertainment' system employed by the NCJDRSU (acting to ensure that cases are not missed, as far as possible). Suspected cases in life may be notified by clinicians; cases diagnosed by pathologists may be notified after death; death certificate copies sent to the NCJDRSU inform us of possible cases; in the instance of possible blood transmission, the TMER study flags individuals of possible concern.

12. The identification of further cases of blood transmission.

I. **If known by the Unit, please set out the dates of these contaminated transfusions.**

II. **Were any of the individuals who gave blood later found to be contaminated, known to the Unit before they donated blood?**

III. **Has the Unit been able to track down the infected donor/s of these transfusions?**

IV. **The Inquiry is aware that the TMER study commenced in 1997 and that leucodepletion was introduced in 1999. Could leuco-depletion have been introduced sooner? Please explain why/why not.**

a. Further cases were identified, including two cases who received blood from the same donor, which makes the connection between disease and transfusion one without any reasonable doubt. All the identified blood transmissions of infection (4 in total) relate to non-leucoreduced Red Blood Cell Transfusions (given before universal leuco-reduction was introduced). The 4 transmissions resulted in clinical vCJD in 3 cases and in asymptomatic infection in the other case (NCRU0000109_082). The dates of the transfusions of non-LR RBCs in the 4 known cases of RBC-related vCJD infection transmission were: Mar 1996, Sept 1997 and Dec 1997 in the 3 cases that resulted in clinical vCJD in the recipients, and April 1999 in the case who was asymptomatically infected. There is one further case of asymptomatic infection, this being considered to be related to blood product (Factor VIII), not blood (HCDO0000799). None of the donors of blood that was implicated in the 4 transmissions via RBCs or in the production of the implicated Factor VIII were known to the NCJDSU before they donated. This was clearly impossible as, at the time of donating, they were normal, healthy individuals and they became known to the Unit only later, when they developed symptoms of vCJD. We became aware of the donors through routine CJD surveillance, when they became ill. We obtained some information about their donor history during our routine data gathering from referred cases. Then, through the TMER mechanism, we notified their details to Blood Transfusion Services who extracted detailed donation information and traced recipients. Those recipient names were then provided to the Unit and we were thus able to determine that certain recipients had indeed developed vCJD or had

evidence of asymptomatic vCJD infection (as evidenced by abnormal vCJD-type prion protein in lympho-reticular tissue).

13. Leuco-reduction

As stated above, the RBC donations involved were all non-leuco-reduced. Universal leuco-reduction was introduced in 1999. As I understand it, Leuco-reduction (LR) has potential benefits other than those relating to potential vCJD infectivity. The question as to why LR was introduced in 1999 and not earlier would need to be addressed to the Blood Services. The decision to adopt universal LR was taken before any evidence that vCJD could indeed be transmitted by blood. There would be logistic and technical matters to solve in implementation which would, therefore, be completed a while after any decision to introduce it was taken. Some of these matters are discussed in a paper by Prowse in 2000 (WITN5592007). They are also discussed in the minutes of SEAC for July 1998: DHSC0042543_020) and in the minutes for SEAC October 1997: NCRU0000174). It should be stressed that the NCJDSU/NCJDRSU does not make policy decisions. It is a surveillance/research organisation that provides reliable data and expert opinion to bodies that make policy decisions.

14. TMER & Ethical considerations/approval.

The Inquiry is aware that in 2000, ethical consent for the TMER study was placed on hold), "The view is maintained that recipients from confirmed donors should not be informed, but this raises serious practical difficulties in the event that such recipients could in the future present as blood donors." To the best of your recollection, please set out what prompted the adjournment of the TMER study pending ethical review in 2000, when it had begun in 1997?

a. As described above, there were discussions of a possible blood 'look-back' study even in 1990. The actual TMER proposal was approved in January 1997 by the Lothian Research Ethics Committee (LREC). The TMER, as approved then, was a blood study involving all types of CJD (not restricted to vCJD) in which it was stated that neither identified donors or recipients would be

contacted, as after obtaining ethical advice, it was considered that such actions were not justified. If the TMER study was a research study undertaken by the NCJDSU/NCJDRSU, with staff employed by the University of Edinburgh and the Lothian University Hospitals Trust, then it would need approval by the appropriate Lothian Ethics Committee, as detailed in this statement at paragraph 15. In October 1999, MSBT considered the implications of the possibility that individuals who had received blood from donors who later developed vCJD might themselves become blood donors in future. MSBT asked the NBS to take action to ensure the blood supply was protected under such a circumstance. NBS decided the only way to do this-in the absence of notifying recipients-was to create a special blood donor panel and register such recipients (who had not been informed of their exposure) on to this panel so they would be recognised if they became a blood donor in future. This was an interim measure pending further advice from CJD Incidents Panel. However, this action raised concerns regarding the ethical approval in place and the issue was raised with the chair of LREC. He felt a national policy as described above and with approval of DH should be adhered to but felt further discussion with LREC was required and as a consequence, renewal of ethical approval was not granted and was withdrawn in January 2000.

b. In May 2000, Professor Will discussed two points with the LREC Chair, asking for ethical approval to be reconsidered in the light of these:

i. There was a view held by DH and NBA that it would be unethical not to do the TMER study; this being the only mechanism by which transmission of vCJD through blood or blood products could be identified (and as such a matter of great importance to public health and public health policy).

ii. The setting up of an Expert Group on the management of CJD Incidents to consider the issue of recipients of blood donations from patients who later develop vCJD (and individuals who were identified as being operated on using surgical instruments previously used on vCJD cases). Policy decisions regarding individual incidents, including recipients who themselves act as blood donors, will be considered by this separate DH Expert Group on a case-by-case basis. Following this, the Chair of LREC wrote to NCJDSU, reinstating ethical approval. The

TMER itself would still not notify recipients and donors - this issue would be dealt with by the Expert Committee (which was the CJD Incidents Panel) on a case-by-case basis. In 2004, after the identification of the first blood transmission case, the question over whether the TMER should in fact be covered by ethical approval was raised in the form of whether the TMER should be regarded as research or should it be a public health/surveillance programme which informed patients as a matter of course. Advice from the Health Research Authority was sought and the advice given was that the TMER should be considered a public health/surveillance programme rather than research and so, from then on, ethical approval was not required. It should be noted that this took place after blood transmission had been identified. At the times of previous discussions, no actual transmission had occurred and the risk was theoretical. [The Inquiry has documents (NHBT0004070 and NHBT0004096) that allude to, and indeed, generally describe, the ethical approval of the TMER study. The ethical concerns are also discussed in detail.]

15. Further Comments on TMER & Ethics.

On 16th December 1997, a Position Statement of the National Blood Service , (NHBT0004115), notes at point 4, "The Lothian Ethics Committee, which reviewed the ethical basis of decision making in respect of the follow-up study being undertaken by the National CJD Surveillance Unit, determined that no attempt should be made to trace recipients, or to tell them they had received CJD-implicated donations." What was your understanding of the reasons why the ethics committee had reached this view? Did the National CJD Surveillance Unit follow this advice?

a. The ethics considerations around, and the LREC approval of, the TMER have been raised as particular matters on which the Inquiry would like more detail, along with a request for me to relate my own understanding of them. The Inquiry provides a document (NHBT0004115) with a question as to my understanding of why the Lothian Ethics Committee

reached the decision it outlined in that document. In the provided document there is a paragraph as follows: "It is possible that the very act of advising recipients in these circumstances would itself be construed as an injury, given the mental suffering that would undoubtedly result and given the probable impact on the recipient's status with respect to life/ healthcare insurance." This does, I think, indicate the general ethical concerns that were discussed at that time. These discussions predated any identification of actual blood transmission of vCJD.

b. I can outline my personal understanding of the ethical concerns in more detail. A proposal to identify recipients of blood that had been donated by individuals who, while being healthy at the time of donation, later developed vCJD, does raise ethical questions, especially in the contemporary absence of evidence of blood transmission of vCJD. Firstly, identification of the recipient would mean holding information that they had been exposed to a theoretical risk of a serious infection. Holding that information about them, without informing them, is an ethical concern. On the other hand, informing them leads to other ethical concerns (as indicated in the quote above).

c. As another consideration, if individuals who had received a vCJD-implicated blood transfusion were to turn up at a donor centre to give blood, what should be the action? If the donation was accepted, could this be seen as exposing others to a theoretical risk? If the individual were to be rejected as a donor, then would they be told why? If so, they would then be informed of the exposure of which they may previously have been unaware. If they were allowed to donate, but the donation then secretly discarded, this poses clear ethical concerns. If this situation were to be avoided by telling recipients of the theoretical risk, it could be a very mixed message: 'you may have been exposed to a risk but its only theoretical and no transmission has ever been identified, so don't worry but, by the way, you are not allowed to donate blood as it might be a risk to others.' These concerns then have to be considered in the light of the potential public health considerations of possible risk to others.

d. In relation to the question as to whether the NCJDSU followed the advice of the Lothian Ethics Committee, I can only state that we would/could not

undertake research that requires Ethics Committee approval when that approval is not given.

e. However, there are two additional points.
    i. Firstly, with respect to notifying individuals at risk (say from a vCJD-implicated blood transfusion), this is not a matter for the NCJDRSU. We do not notify individuals; this is a matter for Blood Services and Public Health Bodies.
    ii. Secondly, the TMER study did take place and was re-started, after the resolution of the ethics committee problem, and, eventually, as a Public Health Surveillance activity, not as a 'research project'.

16. In 1997 the Inquiry understands that the Lothian Ethics Committee were asked to review the ethical basis of decision making of the follow up study being undertaken by the national CJD surveillance unit. Is this correct? If so, how did this come about? The document (DHSC00932337)

a. This document was provided by the Inquiry, described as about "the follow up study being undertaken by the national CJD surveillance unit" with questions about this. In response to questions raised about this, it is important to note that the document refers to a Case-Control Study proposal concerning risk factors (of all sorts) for sporadic and variant CJD. It was indeed submitted for approval to the Lothian Ethics Committee as it was a research project proposed by the NCJDSU/NCJDRSU. In case there is confusion (since, elsewhere, the Inquiry uses the term 'follow up study' to refer to the TMER study), this study was not specifically about blood or VCJD, but included both, was not the TMER study and it did not involve tracing of recipients or donors.

Section 4: General Background: Overview of the NCJDRSU's Relevant Relationships and How Information is Shared Between These Entities.

17. Key Government Relationships

The key relationships in governmental terms has been with the UK Department of Health, Public Health England, Public Health Scotland, the Scottish Health

Department, Public Health Wales and The Public Health Agency (Northern Ireland) (bodies that may have changed their names over time). [Note: various bodies have changed in name and structure over time; the precise nature of the relationships depends on the particular body and the relevant communication matter; the two joint funders of the Unit were England and Scotland].

18. Sharing of Information.

Information has been shared regularly and frequently both on an ad hoc basis and on a formal, regular basis. 'Ad hoc' contact has concerned particular developments (such as the identification of vCJD, the identification of transmission via blood etc). Regular data provision has been via formal review meetings, Annual Reports, monthly reporting on numbers of referrals of suspect cases and deaths from CJD, provision of copies of publications and presentations at meetings attended by government staff. In addition, the Unit has provided requested material to Government Departments in relation to Parliamentary Questions. Any information provided to Government bodies has been provided in line with rules of clinical governance and with appropriate confidentiality/consent.

19. The NCJDRSU, MRC Prion Unit & the NPC

The NCJDRSU has had a long-standing and collaborative relationship with the NPC (National Prion Clinic) and the MRC Prion Unit (in London). This has involved sharing of clinical data, pathological reports and pathological specimens (including brain and blood). We have joint publications based on this collaboration. Under the National Referral System (see Section 2, paragraph 5 and Section 7, paragraph 26), the NCJDRSU and the NPC have ensured that both Units are aware of notified suspect cases. The junior staff of both Units have frequent and regular contact by phone to ensure appropriate coordination of approaches to clinicians, patients and families. The National Referral System includes arrangements for sharing of blood samples between the two Units. There have been regular, monthly, meetings of the senior clinical staff of both Units, to review common data from referred cases. There have been many informal discussions between members of the NCJDRSU, NPU and NPC at national and international Prion Meetings.

Section 5: General Background: The NCJDRSU's Involvement or Membership of Any Committees, Groups, Associations, Working Parties or Societies.

20. The NCJDRSU, or individual members of its staff, have been involved in a very large number, and range, of committees, groups, working parties etc., with potential relevance to the Inquiry's Terms of Reference. It would be very difficult, and lengthy, to give a complete listing, especially since many bodies have given consideration to possible transmission through blood and blood products at different times and different staff members have been involved at different moments. Some major, important involvements (past & present) are listed below:

- Membership of SEAC (The Spongiform Encephalopathy Advisory Committee)
- Membership of ACDC (Advisory Committee on Dangerous Pathogens)
- Membership of ACDC TSE-SUBGROUP (Transmissible Spongiform Encephalopathy Subgroup)
- Membership of the Samples Oversight Committee (has been known under other names)
- Membership of SaBTO (Safety of Blood, Tissues & Organs Committee)
- Membership of the Paediatric Components Working Group of SaBTO European Medicines Agency
- European Commission Committees
- WHO (World Health Organisation) Meetings
- EUROCJD & NEUROCJD (2 international collaborative surveillance/research collaborations)
- PIND (The Progressive Intellectual and Neurological Deterioration Study Group) Attendance at the Joint Funders Meetings
- Expert Witness attendance at the Science & Technology Committee (UK blood & vCJD).

Section 6: General Background: Transfusion Medicine Epidemiology Review ("TMER"): Main Findings & Resulting Steps Recommended and Implemented to Protect Blood Supply.

21. The TMER study

The TMER study is a collaborative project between the NCJDRSU and UK Blood Services ("UKBS"). Its aim is to identify any possible transmissions of CJD through the UK blood supply-with arms dealing with vCJD and other forms of CJD (sporadic, iatrogenic & genetic) respectively. The study does not deal with blood products as part of its remit or design. Information about blood products may, however, come to light through the study.

22. The main specific findings of the TMER study:

a. The identification of the cases of red cell transfusion related infections/cases as detailed in Section 8 and at paragraphs 11 & 12.

b. There is a lot of accumulated data concerning individuals potentially exposed to infection via blood, but who have either died or who remain alive with no known evidence of vCJD infection/disease. The basic data is available on the TMER website (www.cjd.ed.ac.uk/projects/TMER).There are also a number of publications detailing TMER data and findings-listed on the website.

23. Steps taken to reduce blood transmission risk

a. There are a number of steps that have been taken by Government to limit the possibility of vCJD transmission by blood/blood products. It is presumed that the Inquiry is already familiar with these. They include:

- Withdrawal and recall of blood and associated products obtained from donors who develop vCJD (1997).
- Importation of plasma for UK plasma fractionation (1998/1999).
- Leucodepletion of all blood components (1998/1999)
- Deferral of blood donors meeting certain criteria
- The promotion of more appropriate blood/blood product use in the NHS.

b. The Unit played no direct role in risk reduction measures such as product recall, other than to provide data from our research and surveillance to bodies that makes decisions on such actions and then enacts them.

c. All of these policies were established and have been continually reviewed in the light of the findings from TMER. While it is not really possible to state whether all of these steps are simply and solely the result of TMER (certain steps were instituted early, before TMER results-such as the first above listed

measure), it is certainly the case that the continual review of these measures has relied heavily on TMER data.

24. Recent Plasma Policy Change.

The recent change in plasma policy (2019), where UK ministers withdrew an age-related restriction on the use of UK-sourced plasma and pooled platelets, was based on a number of considerations which included the data from TMER as a major component.

25. The MHRA 2021 Report

As far as I know, the NCJDRSU was not directly involved with the MHRA (Medicines and Healthcare products Regulatory Agency) April 2021 Critical risk assessment report, concerning the use of UK plasma for the manufacture of immunoglobulins, and the subsequent advice by the Commission on Human Medicines (CHM). However, the report clearly discusses data resulting from the NCJDRSU's surveillance. My personal view is that the decision reached on the policy to use UK plasma for immunoglobulin manufacture is a reasonable one. The report presents good evidence as to the low risk involved from vCJD and presents evidence as to the increasing need for immunoglobulin product.

Section 7: Reporting Process to both the NCJDRSU and the Prion Unit: When and Why the Reporting Process was Introduced.

26. When & why 'the reporting system' was introduced.

a. It depends on what is meant by 'the reporting process' in the question posed. The initial reporting process was established at the start of the Unit's surveillance i.e. 1990.

b. The reporting system was introduced in order to identify cases of CJD being seen in different clinical settings in different parts of the UK.

c. In the initial years, the reporting of suspect cases was to the NCJDRSU (then the NCJDSU). This was done by phone, letter or fax, with NCJDSU staff completing a referral form on the basis of information provided and then seeking further information.

d. Following the institution of the National Prion Clinic (NPC) in London and the possibility of a treatment trial, the NCJDSU and the NPC had discussions with the then UK CMO and an agreed National Referral System was established in 2004, with clinicians being asked to inform the NCJDSU and the NPC simultaneously using a standard form. In addition, each unit agreed to notify each other in any instance of a suspect case being notified to only one unit. This was felt necessary to ensure that both the NPC and NCJDRSU were aware of all suspect cases and to avoid any uncertainty or confusion amongst referring clinicians, especially in the context of the planned first UK clinical trial of potential therapy for CJD about to be undertaken by the NPC.

e. This system remains in place.

f. However, the system does not preclude clinicians contacting either or both Units for advice in an informal way. When this happens, both Units ensure that the other is aware of the situation. If a case is thought likely, then the clinicians are encouraged to make the approach a formal one with the usual referral protocol then being followed.

Section 8: The Reporting Process to both the NCJDRSU and the Prion Unit: When a Case or Suspect Case is Reported to the NCJDRSU.

27. The Reporting Process in practice.

a. The system is based on requesting clinicians and pathologists to notify via the national referral process (as detailed above) if they are seeing/have seen a case of suspected CJD (of any form). There is no precise definition of a 'suspect case' other than that the referrer is considering CJD as a possibility. This was a deliberate decision because the system wanted to identify any unusual or new disease phenotypes and not to just identify cases based on known, typical characteristics. Variant CJD, and other forms of CJD, are not notifiable diseases under Schedule 1 of The Health Protection (Notification) Regulations 2010. This point is discussed in detail in Section 2 paragraph 5.

b. In the event of a case being notified to the NCJDRSU, a case identification number is generated and a file created (both hard copy and digital). At this

point, the NCJDRSU and the NPC ensure that both units are in fact aware of the suspect case.

c. The next step taken by the NCJDRSU is to gather core clinical data from the referrer including the results of any key investigations. If necessary, certain investigations (such as brain MR imaging) are reviewed directly by the NCJDRSU (which may be done via national imaging data systems or by sending of digital files). The case is then classified in terms of probability as 1.0 (definite), 2.0 (Probable), 3.0 (Possible), 4.1, 4.2 or 4.3 (defined in Section 10 paragraph 41) and in terms of CJD type (sporadic:s, variant:v, genetic:g, iatrogenic:i). [The Diagnostic Criteria are provided as a separate document (WITN5592002)]. For example, a case may be classified as 1.0v, 3.0s etc. The classification criteria have been developed on the basis of accumulated experience and adapted according to the results of review in practice and the development of new diagnostic tests. They have been discussed regularly reviewed by international surveillance and research collaborative groups in order to maintain consistency between different countries. Further actions depend on the case classification and consent. We try to visit definite and probable cases in all such cases. Possible or 4.1 cases (see Section 10 paragraph 41) may be visited depending on the individual details. If not visited, Possible 4.1 or 4.2 cases are kept under review, according to developments.

28. Case Classification & Autopsy

a. The case classification, apart from 1.0, is a clinical classification, based on clinical features and clinical investigation results (such as MR imaging, CSF tests etc). A 1.0 classification requires neuropathological examination of the brain and so is possible only if a brain biopsy is undertaken in life or an autopsy examination performed after death. Brain biopsy is undertaken only rarely and, in general, would be considered if there a reasonable possibility of another, treatable, cause for the illness. If there is no consent for an autopsy, the classification remains as it was determined during life. Since autopsies are usually a matter of family consent, the failure to obtain such consent means that a final, neuropathological, diagnosis is not always made, The obvious effect on surveillance is that the number of 'definite' cases is lower than it otherwise would be and, correspondingly, the number of 'probable' cases is higher.

b. In my view, for the vast majority of cases, this has little overall effect. The clinical diagnosis of most cases of sCJD and vCJD is not only 'probable' (as defined) but actually highly probable and really beyond any reasonable doubt. I would fully support attempts to achieve a high autopsy rate, but there are logistic/service difficulties in obtaining autopsies at times and I, personally, would not like autopsies to become mandatory unless there were very good reasons for making them so.

29. Visiting referred Cases and Consent.

Visiting of cases can take place only if the local clinician in charge and the patient/family give consent. Before a visit, the possibility of CJD has to have been discussed with the patient/family, by the local clinician. Consent is nearly always given. Details of the consent process are given below:

i. In general, we do not obtain consent from a living patient as they are usually too neurologically impaired to give consent; it is obtained from a relative. There have been a few occasions where a patient has been able to give consent. The process is that a clinician contacts us about a case. We get verbal consent from this clinician to visit their case and the relatives. We ask the clinician to get verbal consent from the relatives. If it is obtained, then we visit and, at the visit, give information sheets to the relatives and ask them to sign a consent form. The information sheets and consent forms are those that were approved at the time Ethics Committee approval for the research was obtained.

ii. If the patient is deceased, we normally get verbal consent from the clinician who looked after the patient (hospital or GP) to contact the relatives. We contact the relatives by phone or letter and obtain informal consent to visit and interview them. When we visit for the interview, we give them information sheets and obtain a signed consent form as above.

iii. It is very rare for people not to give consent, over 30 odd years, I can recall only 2 instances; both gave consent initially and then later withdrew consent for us to obtain further data or to keep or use data. In one instance, the withdrawal of consent reflected the relative's (incorrect) view that the Unit was dishonestly distorting figures to protect

Government bodies. The other expressed great anxiety concerning confidentiality over the data. In general, everyone is reassured that the Unit will treat individually identifiable material in the same secure way as is practised in the Health Service. On occasions, the family does not wish for an immediate visit as their relative is extremely ill or has only just died; in those cases, we obtain consent to visit the family later. In reply to the specific further questions: it is not a significant problem for the Unit and it has not altered over time. There are a few reasons why the families give consent readily, including a wish to help research into the disease and getting the opportunity for discussing this rare disease with experts.

30. The Visit

a. In all cases, where possible, a member of the NCJDRSU visits the patient and family. The local clinical notes are viewed, along with any investigations (such as brain images, EEGs etc). The patient is interviewed (if their condition allows it), examined and the family are interviewed using a standard questionnaire. A blood sample may be taken (although usually this is taken by the NPC at the time of their visit). Following the visit, further information is collected by phone, email, fax or letter, concerning any further test results, the clinical course, date of death and whether any autopsy is performed.

b. The National Referral Protocol is that the NCJDRSU visits first and then the NPC. The NCJDRSU has 5 working days in which to make the visit, though there may be slight variations in particular circumstances, after discussion with the NPC. In recent times, visits have not been possible and the contact has been by phone, skype, zoom or other means (due to the Covid situation).

c. The above describes the commonest situation: a referral of a living suspect case by a local clinician. However, there are other situations that arise:

iii. The patient may be in a terminal condition at the point of referral and it is felt, by the referring clinician or family, that a visit should wait until after death. A 'late' visit is then arranged at an appropriate interval.

iv. The individual is notified to us after death, by a clinician or pathologist. We obtain information as to the most appropriate

family member to contact and the most appropriate methods of contact. Then, if possible, to arrange a 'late' visit.

v. The NCJDRSU obtains copies of Death Certificates that are coded as CJD or dementia related to CJD [A810 or F02.1, currently] on a regular basis. We check to see if these names are already known to us. If not, we try to obtain further information from local clinicians and then, if appropriate, try to arrange a 'late' visit.

vi. Clinicians may ring for advice on cases over which they feel very uncertain. They may ring the NCJDRSU or the NPC or both. Such cases are evaluated and further action depends on the exact situation.

vii. CSF tests (such as 14-3-3 and RT-QuIC) are now routinely used in the diagnosis of CJD. The national CSF laboratory for this purpose is situated in the NCJDRSU. We receive requests for these tests and, if they relate to individuals not referred to us as suspect CJD cases, we obtain further information and encourage referral if appropriate.

viii. Occasionally, our neuro-radiologist receives requests for an opinion on MRI scans or our neuropathologist is asked for an opinion on a neuropathological specimen. If this suggests a case we do not already know about, we try to obtain further detail.

ix. Very occasionally, the CJDSN (CJD Support Network, a support charity of CJD in the UK) gets an enquiry that suggests a case we have not heard about, or a member of the public contacts us. We would then try to follow this up although it may turn out not be a case of CJD.

31. Some Data on Initial Notification by Death Certificate or Relatives/Public

a. Over the 30 year period 1990-2020:

- Total number of cases *initially* notified to NCJDRSU by Death Certificate: 142
- Total number of cases *initially* notified to NCJDRSU by Relative/Public: 43 [see comment below, concerning 'initially']

b. Of the 142 Death Certificate Notifications:

- 37 finally classified as Definite/Probable CJD
- 15 finally classified as Possible CJD
- 69 finally classified as NOT CJD
- 21 unclassified

c. Of the 43 Public Notifications:

- 23 finally classified as Definite/Probable CJD
- 6 finally classified as Possible CJD
- 14 finally classified as NOT CJD

Note: The notifications referred to as being made by routes such as Death Certificate/Public/CJDSN are recorded as such as this was the *initial* way in which the NCJDRSU was notified. This does not exclude the fact that such cases may be notified a little later by a more usual mechanism. For example, contact by a relative with subsequent notification by a clinician or Death Certificate notification with subsequent notification by a clinician or pathologist.

Section 9: The Reporting Process to both the NCJDRSU and the Prion Unit: The Systems in Place to Ensure That no vCJD Cases are Missed.

In general, please see details given above at section 2 paragraph 5, section 8 paragraphs 27-30.

32. Autopsy Rate

We encourage as high an autopsy rate as possible, including trying to enable arrangements for experienced centres to undertake autopsies for other centres that feel unable to undertake them.

33. Overlapping Methods of ascertainment.

a. With any surveillance system an important concern is that not all cases may be identified. Our case ascertainment policy is based on the deliberate including of suspect cases without a limiting, self-fulfilling definition of 'suspect' i.e. encouraging clinicians to refer any case if they feel a prion disease is at least being considered, without requiring a high degree of suspicion. Another aspect of our policy is that of using multiple, over-lapping methods of case

ascertainment; the main elements of this being:

i. Referral of suspect cases by clinicians (whether neurologists, medicine for the elderly specialists, psychiatrists etc).

ii. Obtaining copies of death certificates from the Office of National Statistics (ONS) and National Records of Scotland (NRS) under rubrics A810 (Creutzfeldt-Jakob disease incl. subacute spongiform encephalopathy) and F02.1 (Dementia in Creutzfeldt-Jakob disease). Then, if CJD is a possibility and the person is not already known to us, attempting to find out the relevant clinical information retrospectively.

iii. Referral of cases by pathologists who identify prion disease at autopsy or on biopsy.

iv. Reviewing cases referred to the CSF (14-3-3 and RT-QuIC) laboratory which is embedded in the Unit and contacting clinicians if CSF is being sent from a patient we are not already aware of.

v. Frequent phone conversations with colleagues at the National Prion Clinic, with regular formal meetings with them, to compare records and to ensure bilateral awareness of all cases.

vi. Following up of possible cases that come to our awareness through families contacting the CJDSN (CJD Support Network) for advice or support, if we are not already aware of them.

b. We have made specific attempts to try to identify missed cases, to enhance surveillance and to try to ensure that we identify cases that are due to blood/blood products. These are discussed in separate paragraphs 34-39 below.

34. Misclassification of Deaths Study.

You co-authored a British Medical Journal study published on 15 January 2001 titled, 'Extent of misclassification of death from Creutzfeldt-Jakob disease in England 1976-96: retrospective examination of clinical records'. It stated, "the surveillance system is unlikely to have missed a significant number of cases among people aged 15-44 years. Hence, any rapid increase in the number of cases of variant Creutzfeldt-Jakob disease in this age group is likely to be real, not artefactual" (Please see NHBT0004373). As to this:

i). Why were patients outside the age range 15 - 44 excluded from this study?

ii). Are you able to draw any conclusions as to the under assignment of Creutzfeldt-Jakob disease in patients outside that age range between 1976 - 96 from this study? If so, what are they?

a. One study looked at the possible misclassification of deaths in England 1976-1996 (NHBT0004373). [The relevant study publication is known to the Inquiry: NHBT0004373]. This study selected the 15-44 age group (patients outside this age-band were excluded). As the study was limited to this age group, it is difficult to see how this study itself could provide data to make conclusions about under-ascertainment in other age groups. The paper discussion recognised this as a limitation to the study and stated the reasons for it. I provide two quotes from the study publication:

b. "A third limitation is that only patients aged 15 to 44 were included. This age group is suitable for detecting cases of variant Creutzfeldt-Jakob disease but less so for sporadic disease. A definitive diagnosis of Creutzfeldt-Jakob disease also requires histologic examination of brain tissue and the likelihood of a post mortem examination in patients dying from dementia decreases with age hence it is possible that cases of sporadic disease may be missed in elderly people. Finally any people with Creutzfeldt-Jakob disease who were certified as dying from non-neurological disorders such as bronchopneumonia would not have been included in the samples of deaths investigated."

c. "Furthermore, the implementation of a surveillance system may artifactually increase the incidence of a disease. Our findings suggest that the national surveillance system for Creutzfeldt-Jakob disease that started in 1990 and the earlier surveillance for possible cases are unlikely to have missed a significant number of cases among people aged 15 to 44 years. Under ascertainment of variant Creutzfeldt-Jakob disease in this age group is therefore unlikely during the early years of the bovine spongiform encephalopathy epidemic. Consequently, any rapid increase in the number of cases of variant Creutzfeldt-Jakob disease among people aged 15 to 44 years is likely to be real rather than an artefact due to better awareness and detection."

35. PIND (Progressive Intellectual & Neurological Deterioration) Study.

This is a joint study with UK paediatric neurologists, with regular meetings to review progressive neurological conditions in children, with NCJDRSU involvement to check that there were no unsuspected cases of vCJD in children. No unsuspected cases have been identified.

36. TMER (Transfusion Medicine Epidemiological Review).

This is the blood study that is discussed at paragraphs 10-15 & 21-22.

37. PID (Primary Immuno-Deficiency) Study.

This is a study with staff based in the NCJDRSU, looking at patients with Primary Immuno-Deficiency, who, as a result of their condition, receive plasma-derived products. Clinical information is collected and any pathological data reviewed.

38. UKHCDO (Haemophilia Centres Doctors Organisation) Study

a. A 5-year prevalence study of vCJD in 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. Professor Ironside was a named collaborator on this project and was responsible for the laboratory work that would be carried out in NCJDRSU on the tissue samples collected in this project.

b. On 7th September 2009 Professor Ironside 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. 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.

39. The Inquiry is aware of the report titled 'Critical risk assessment report: use of UK plasma for the manufacture of immunoglobulins and vCJD risk' published on 21st April 2021.

i. What role (if any) did the Unit play in this consultation?

ii. What's the Unit's view of reversing this vCJD precautionary measure in relation to the subclinical risk of asymptomatic blood donors?

iii. Please elaborate, on the point at page 10, that cases of vCJD are being misdiagnosed as sporadic CJD.

iv. How does familial consent to conduct a post-mortem affect the surveillance of vCJD cases?

The "Over 65 Study"

a. There are two noted observations relating to sporadic CJD (sCJD):

i. The annual mortality rate of sCJD has increased over the years, especially in the elderly.

ii. The annual mortality rate of sCJD rises rapidly with age up to around the age of 75 and then it falls sharply.

b. The first observation has sometimes led to questions as to whether this increase in sCJD cases could be due to 'hidden' vCJD cases amongst the elderly sCJD cases. Indeed, a specific request from the Inquiry asked for

comment on a statement on page 10 of the April 2021 MHRA report entitled "Critical risk assessment report: use of UK plasma for the manufacture of immunoglobulins and vCJD risk" (WITN5592008).The request asked for comment on the statement that "cases of vCJD are being misdiagnosed as sporadic CJD". To be precise, on page 10 of this report, it does not state 'that cases of vCJD are being misdiagnosed as sporadic CJD' but that "Several experts are concerned that some cases of vCJD are misdiagnosed as sporadic CJD, especially in the elderly". It is a little difficult to comment in detail as it is not stated who these "several experts" are, what is the basis for their concerns, where these concerns have been expressed, nor their suggestions of the magnitude of the possible mis-diagnosis. The Report -in the form I have seen - does not list the membership of the body that produced it. As far as I am aware, the Unit played no role in the production of this report.

c. I have, in various meetings, and in informal discussions, heard expressions of concern that cases of vCJD might be mistaken as cases of sCJD. There are several reasons that have been put forward which I will discuss below:

i. If the claim is based on the fact that there has been a rise in annual mortality rates over time (and, particularly in the elderly), there are good reasons for suggesting this concern is misplaced. Firstly, there are very good, adequate, explanations for the rise in sCJD cases (which has been noted over many years), including increased awareness of the condition, better understanding of atypical forms of sCJD and far better diagnostic tests. Secondly, and importantly, one can compare the UK sCJD annual mortality rates with those of other countries. There are non-BSE countries (such as Australia) that have sCJD rates as high, or even higher, that that of the UK. Moreover, in all countries (BSE risk or not), with established surveillance systems, similar rises in sCJD figures have been seen over the same time period.

ii. It is certainly the case that one main differential clinical diagnosis of vCJD is sCJD, with some overlap in clinical features and some investigation results (such as MR imaging findings). The absence of autopsy diagnosis in some cases, especially in the elderly, means that definite diagnosis is not always obtained. However, in the vast majority of cases, the conditions are clinically distinguishable and all suspect

cases of all forms of CJD are referred to, and evaluated by, the NCJDRSU which is familiar with the potential for diagnostic confusion. We also discuss referred cases with the National Prion Clinic and so a range of experts review diagnostic classification of all suspect cases. There are also investigations (such as CSF RT-QuIC) that reliably differentiate sCJD and vCJD in most cases.

iii. Elderly patients with a dementing illness may be thought, too readily, to have a cause common in their age group, such as Alzheimer's disease.

iv. Variant CJD in the elderly may be clinically different from vCJD in younger age groups and so may not be recognised. However, from the characteristics of the older cases of vCJD that have been identified, there is nothing to suggest that the clinical picture would be significantly different.

v. Elderly patients may not be as readily referred to neurology services as those in younger age groups.

vi. The autopsy rate in elderly dementia is very low.

d. It is, of course, true that, without neuropathological/molecular analysis, there could, conceivably, be an atypical variant case diagnosed as sporadic, but this error could also, conceivably, be one of diagnosing a sporadic case as a variant one. In any case, if this occurs, it must be a very rare event. As things stand, it is essentially a theoretical concern.

e. My own opinion is that it is very unlikely that cases of vCJD are being misdiagnosed as sCJD, either in general, or specifically in the elderly.

f. However, it was thought entirely reasonable to try to check on the possibility of missed vCJD cases in the elderly. In addition, even if cases of vCJD are not being missed in the elderly, the second observation listed at the start of this paragraph is of potential importance: why does the annual mortality rate for sCJD fall sharply after the age of 75? Is it because of under-ascertainment of sCJD in the very elderly or is it a real observation that might have implications for understanding the cause of sCJD?

g. Some sort of enhanced surveillance in the elderly had been considered by the Unit for several years-including in the period before vCJD was identified. It is important to stress that there are two driving forces behind such a consideration

(as outlined above): an 'older' interest in the causation of sCJD and a 'newer' concern that vCJD cases might be either missed or misdiagnosed in the elderly. However, there were significant conceptual and logistic problems. Because of the high incidence of dementing illnesses in the elderly, any manageable study would need to be limited both geographically and in terms of which patients were referred. Finally, additional funding was obtained for the "Over 65 Study" which was designed to investigate 'atypical' dementia presentations in the over 65s in the Lothian region of Scotland. It began recruiting in 2016, with staff based in the NCJDRSU. It was designated as a feasibility study since it was not clear how well the proposed methodology would work or be cost-effective enough to extend to other areas. At this point (2021), two statements can be made: Firstly, despite reasonable funding and dedicated staff, recruitment has fallen short of predictions and it is not likely that the methodology can be extended further in time or area; Secondly, no previously unsuspected cases of prion disease (including vCJD) have been found.

Section 10: The Reporting Process: The Diagnostic Criteria & Categorisation in Layperson's Terms of Cases of CJD.

40. Comments on Diagnostic Criteria.

a. Diagnostic criteria are potentially useful in trying to ensure consistency of diagnosis between different clinicians and over time. Additionally, they can act as guides to practical clinical diagnosis, especially for clinicians relatively inexperienced in a particular condition. They are important in research as they help to ensure that its results relate to a well-defined, homogenous group of patients. In vCJD, defined diagnostic criteria have been very helpful in comparing figures between different countries.

b. Diseases are often diagnosed on probability grounds- an absolutely definite diagnosis is not possible in many instances. Therefore, having grades of probability in the diagnosis is usual.

c. Definite diagnoses require a specific pathological finding or an entirely specific test result and these are not always available in all illnesses.

d. The design of diagnostic criteria is typically an iterative process. In other words, a disease may be described and data collected leading to suggested diagnostic criteria. Then, these criteria are applied in practice and assessed as to their accuracy. It is not unusual for the criteria to be adjusted in the light of further clinical data or the development of investigations. For example, diagnostic criteria for MS (multiple sclerosis) were adjusted to include brain imaging findings after the clinical use of MRI was established. Another example is the inclusion of loss of sense of smell and taste for a diagnosis of COVID, following the recognition of this as a common symptom.

41. Diagnostic Categories of CJD

a. CJD in general has been classified as Possible, Probable or Definite. "Definite CJD" requires a neuropathological examination of brain tissue, showing the characteristic pathology. "Probable CJD" is based on the exclusion of other possible illnesses, a collection of certain clinical features and the results of certain investigations. "Possible CJD" is based on the exclusion of other illnesses and a collection of certain clinical features. The precise set of clinical features and the particular investigation results varies according to the type of CJD-being different for genetic, sporadic, variant and iatrogenic forms.

b. On being referred a suspect case, the NCJDRSU classifies the diagnostic status as follows:

1.0 Definite

2.0 Probable

3.0 Possible

4.1 Does not meet the criteria for definite, probable or possible, but no other definite diagnosis and CJD cannot be excluded totally

4.2 No definite other diagnosis but not CJD as there are certain aspects that exclude CJD (for example, MR features that explain the symptoms but are not seen in CJD or inflammatory changes in the CSF (cerebro-spinal fluid) that are incompatible with CJD)

4.3 Not CJD and a clear/definite other diagnosis.

c. In the case of 4.1 CJD, the Unit follows the progress of the case, to see if CJD becomes more likely, comes to meet the diagnostic criteria, or becomes 4.2/4.3. As well as the primary probability numerical classification, the case is given an

alphabetical class (s,g,v,i) according to the considered type. For example 1.0g CJD= definite genetic CJD; 2.0v CJD= probable variant CJD; 3.0s= Possible sporadic CJD; 2.0i= Probable Iatrogenic CJD.

d. The initial case classification is reviewed constantly and altered in the light of further data. The date of any change, and the reason for the change, is recorded in the Unit's database. The reason may be change of clinical features, results of investigations or autopsy report.

e. In addition, the diagnostic criteria have changed slightly over the years, as accumulated knowledge and improved diagnostic tests have allowed their modification.

[*The current diagnostic criteria are provided as a separate document (WITN5592002).]

Section 11: The Reporting Process: Clinicians Informally Discussing 'Doubtful Cases' of vCJD with The NCJDRSU.

42. Firstly, please see the referral process discussion, Section 8, paragraphs 27-30.

In essence, a doubtful case is one in which the clinical profile and/or test results make it unlikely that the illness is CJD but there are no features that definitively exclude CJD. For example: a very long history (gradually increasing cognitive impairment over 5 years); the absence of characteristic features (such as purely cognitive impairment with no other neurological problems); the presence of clinical features that are unusual in CJD (such as frequent epileptic seizures in the early illness). Sometimes, it may be a combination of things that make a diagnosis of CJD unlikely: an atypical clinical profile, normal brain MRI and negative CSF tests. However, we do not dismiss 'doubtful' cases as we are wanting to identify atypical cases and to ensure surveillance is as complete as possible.

As already detailed, records are kept of all cases.

Details are obtained from relevant clinicians, follow-up contact is maintained, advice is given with respect to investigations that might help diagnosis. We have,

despite any doubt or uncertainty about the diagnosis, a relatively low threshold for trying to arrange a visit to the patient/family.

Section 12: The Reporting Process: Reporting to the NCJDRSU of a 'Suspect Case' Through Sources Other Than Clinicians.

43. Please see data detailed above at paragraphs 30, 31 & 33-38.

In essence, the action is not different: we try to assess the likely diagnosis on the basis of information given, try to obtain further detail, classify the case and decide on whether or not a visit should be made.

The details are necessarily different. For example, referrals from directly involved clinicians already provide the necessary clinical data, whereas a notification by a member of the public requires us to identify and approach a relevant clinician to obtain the necessary information. Notification by death Certificate also requires us to contact relevant clinicians to obtain medical records.

Section 13: The Reporting Process: Patient Support Through the CJD Support Network.

44. This is essentially a matter that should be addressed by the CJDSN itself, which is an independent registered charity. However, in outline the CJDSN offers:

(a) A phoneline service for support.

(b) A web-site with information on CJD.

(c) 'Social media' support (eg a closed Facebook Group for relatives and carers).

(d) Financial grants for hardship.

(e) On-line meetings on relevant topics (such as diagnosis and care).

(f) A family support meeting once a year.

Section 14: Annual Reports

45. NCJDRSU Annual Reports

The NCJDRSU has published an annual report every year since 1992, with the most recent being 2020. The requested figures are given below.

46. How many cases in the UK have been categorised as definite vCJD, contracted as a result of blood and blood products?

As a result of blood: Three. Definite vCJD related to RBC transfusions.

As a result of blood products: None.

47.How many cases in the UK have been categorised as probable vCJD, contracted as a result of blood and blood products?

As a result of blood: None

As a result of Blood Products: None.

48. How many cases in the UK have been categorised as possible vCJD, contracted as a result of blood and blood products?

As a result of blood: None

As a result of Blood Products: None

49. How many cases in the UK have been categorised as vCJD diagnosis unclear, contracted as a result of blood and blood products?

Depends on what the question means, but in terms of cases thought to possibly have vCJD but not to meet the criteria for Definite, Probable or Possible:

As a result of blood: None

As a result of Blood Products: None

50. Two Instances of asymptomatic infection.

There were two instances of blood/blood product transmission of infection but not resulting in clinical vCJD (and which would, therefore, not fit into the diagnostic categories listed above):

i. One case related to RBC transfusion who died of a non-CJD illness and, at autopsy, was found to have lymphoreticular abnormal prion protein deposition. This has been classified as asymptomatic infection with BSE/vCJD related to blood (NCRU0000109_082).

ii. Another case related to a blood product (Factor VIII) who died of a non-CJD illness and, at autopsy, was found to have lymphoreticular abnormal prion protein deposition. This has been classified as asymptomatic infection with BSE/vCJD related to a blood product (HCDO0000799).

51. How many individuals in the UK have been exposed to the higher risk of vCJD as a result of receiving blood or blood products?

Individuals designated as at higher risk of vCJD as a result of blood: 64

The information in relation to blood products should be sought from Public Health England.

52. How many of these individuals have been notified of this risk?

The NCJDRSU does not notify such individuals. This information should be requested from Public Health England.

53. If possible, please provide a breakdown of the geographical distribution with respect to the above-requested figures.

We do not usually provide detailed geographical breakdowns for confidentiality reasons. Data on those at-risk should be sought from Public Health England.

Section 15: vCJD Incidence Reports: Why the Current Data Does Not Extend Beyond 2011.

54. Data beyond 2011.

The current data *does* extend beyond 2011, right up to the present time. Monthly case figures are provided. The "Incidence Reports", to which the Inquiry may be referring, were quarterly trend analyses produced by Nick Andrews. These were not 'incidence' reports as such, but analyses of trends relating to dates at onset of symptoms, dates at diagnosis and dates at death for vCJD cases ie. Quarterly figures detailing how many people had a clinical illness beginning in a certain time period, how many diagnoses were made and

how many had died. These were required at a time when cases were being identified fairly frequently and there was interest and concern as to the trajectory of the outbreak. These particular analyses were no longer of particular use when case numbers started to fall-there have actually been only 2 further deaths due to vCJD since the last analysis in 2011. However, we update case numbers and publish the monthly figures on our website, with a copy being sent to UK DH and Dr Katy Sinka at PHE.

Section 16: vCJD Incidence Reports: The Current Incidence Rate.

55. The Current Incidence Rate

It depends on what is meant here. "Incidence rate" is a term that can have different meanings. The data that we provide are:

(a) Death figures i.e. how many people have died from vCJD in each selected time period.

(b) Diagnosis figures i.e. how many people have been diagnosed with vCJD in each selected time period.

(c) Onset of clinical illness i.e. how many people have had the onset of recognisable symptoms of vCJD in each selected time period. The current UK vCJD figures for each, over certain time periods are:

(a) No deaths over the last 5 years.

(b) No new diagnosis for the last 5 years.

(c) Last recorded onset of symptoms in a case was in 2014.

Section 17: vCJD Incidence Reports: The Likely Possibility of a 'Second Wave.'

56. The likely possibility of a 'second wave', if known:

a. It is not quite clear as the meaning of 'second wave'.

b. If the 'second wave' refers to a death numbers peak occurring at a later date than the presently recognised numbers death peak in 2000, related to variation in incubation period determined by *PRNP*-129 genotype, then it has always been considered likely that there would be a second peak (or second and third

peaks) relating to codon 129 MV and VV genotypes. The degree of this likelihood is unclear as is the case magnitude of any such further peak. However, there are reasonable theoretical grounds for thinking that any second or third wave would be likely to be no bigger, and probably smaller, than the first wave. Modelling of the vCJD epidemic was undertaken by Garski & Ghani in 2010 (WITN5592009). In this they estimated the following cumulative future numbers from 2010 to 2179:

Total vCJD cases: 390 [95% Credibility Interval: 83-3000]
Total MM: 200 [20-2200]
Total MV: 160 [4-980]
Total VV: 13 [0-85]

Identifiable blood cases:
Total:17 [1-220]
MM:12 [0-160]
MV: 4 [0-57]
VV: 0 [0-5]

Given the observed data since 2010 up to 2021, one might be inclined to think that the lower part of the 95% credibility interval is more likely than the upper part.

c. If the 'second wave' refers to cases that are secondary transmission cases, from person to person, it has always been considered a possibility that such cases would occur and at a later time than those due to primary dietary BSE transmission. The likelihood of this was uncertain, as was the number of such cases, if it were to occur. The recognition of blood-related cases (and asymptomatic infection) was proof that such cases could occur. However, detailed surveillance and associated research has not identified any cases due to other transmission means (such as general surgery or dentistry) (WITN5592010, WITN5592011).

d. Modelling of the vCJD epidemic has been performed with predicted numbers of blood- related secondary transmission cases as an output, based on various assumptions. The predictions have been compared to observed numbers and

then the model's inputs adjusted so as to best match the observed data, with recalibration of the predicted case numbers (RLIT0000939).

Section 18: vCJD Incidence Reports: How The Incidence Rate Affects Decisions Relating to The Mitigation of The Risk of transmission of vCJD via blood and blood products.

57. As discussed above, there is uncertainty as to the true magnitude of the risk of secondary blood/blood products transmission of vCJD. This is an inevitable consequence of the large number of uncertainties surrounding the factors that determine the risk-such as the number of subclinical infections in the population, the degree of infectivity in such affected individuals, the degree of that infectivity in blood, the constancy or variation of such infectivity over time, the precise factors that determine if blood transfusion transmits infection and so on. Modelling of the risk requires assumed inputs and then predicts the potential outcome. Modelling can then estimate the likely effect of protective measures. If, as has been the case, the observed case numbers are significantly lower than predicted, the modelling can be adjusted to produce outputs that reasonably fit the actual data and the possible benefits or adverse outcomes of changes in the protective measures can be modelled. For example, as detailed in the PCWG Report, observed case data informed the decision to relax certain restrictions (RLIT0000939).

Section 19: Research (Testing, Cure & Treatment): Research The NCJDRSU is or has been Involved in with Respect to Possible Cures or Treatment for vCJD.

58. The unit has been, and is, involved in various aspects of research with respect to CJD, including vCJD. This research has involved tests for CJD but this has not primarily involved treatment.

Section 20: Research (Testing, Cure & Treatment): Research The NCJDRSU are or Have Been Involved in with Respect to Diagnostic Tests for vCJD and development of tests.

59. The research the NCJDRSU has undertaken with respect to diagnostic tests, has been related to all forms of CJD, including sCJD and vCJD.

a. It is not quite clear as to what is meant specifically by "development" of tests. For example, the Unit has not undertaken any development of MRI techniques but we evaluated MRI findings as diagnostic tests. Our involvement has been with evaluating clinical diagnostic tests used in life and in neuropathological tests used on biopsies and autopsy material. In relation to the clinical tests, our main concerns have been with CSF 14-3-3 assays, CST RT-QuIC tests, EEG appearances and MR brain imaging findings. We are ideally placed to evaluate the sensitivity, specificity, positive predictive value and negative predictive value of such tests, since we have an ideal testing population. We can obtain the results of these tests in patients referred to us as being suspected of having CJD by practising clinicians, comparing the results in those that turn out not to have CJD with the results in those that do (as well as comparing results in different forms of CJD). In addition, we would expect referrals of the vast majority of, if not all, CJD cases in the UK without the potential for selection bias. Additionally, we attempt to see as many cases as possible in life, obtaining accurate information and copies of test results. Finally, because we take part in international collaborative research networks, we have the opportunity of extending evaluation of tests over a large number of cases.

In relation to test development, Alison Green, of the NCJDRSU, did not develop the RT-QuIC method but she did modify/adapt it for use.

The evaluation of clinical diagnostic tests undertaken by the Unit & the main relevance to forms of CJD is as follows:

EEG: sCJD

MRI: sCJD and vCJD

CSF 14-3-3: sCJD

CSF RT-QuIC: sCJD

b. In relation to blood and vCJD, we provided samples in a collaboration with others but we did not develop the test reported by Bougard et al.[5] We provided urine samples in a collaboration with others, but did not develop the relevant urine test reported by Moda et al (WITN5592012). The Neuropathology Laboratory in NCJDRSU did

not develop new "tests", but modified existing techniques such as immunohistochemistry for the detection of disease-associated prion protein in paraffin-embedded tissue sections and Western blot examination for the detection and biochemical characterisation of disease-associated prion protein in homogenates of brain and other tissues to obtain optimal results. The optimised techniques developed in the Neuropathology Laboratory in NCJDRSU for the detection of disease-associated prion protein in paraffin-embedded tissue sections were modified for use in the Appendix 1, 2 and 3 prevalence studies of asymptomatic vCJD infection in the UK.

Section 21: Research (Testing, Cure & Treatment): Research The NCJDRSU are or Have Been Involved in with Respect to Diagnostic Tests for Asymptomatic vCJD.

60. This question specifies research with respect to asymptomatic vCJD and the response is therefore limited to that area. As stated above, the optimised techniques developed in the Neuropathology Laboratory in NCJDRSU for the detection of disease-associated prion protein in paraffin-embedded tissue sections were modified for use in the Appendix 1, 2 and 3 prevalence studies of asymptomatic vCJD infection in the UK.

61. Terminology.

a. There may be some terminological confusion in this area and a preliminary statement concerning terminology could be helpful. Infection with vCJD may be symptomatic or asymptomatic. In the first situation, affected individuals are clinically ill with brain disease; in the second, they are infected with vCJD, with known or assumed infection in tissues such as the spleen, tonsil, lymph nodes or appendix but they have no clinical illness of any sort-they are 'silently' infected. If they are asymptomatically infected, they may be 'pre-clinically' infected or 'sub-clinically' infected. In the first case, it means they are silently infected but, after a period (that may be years), they become ill and it then becomes clear that the preceding time was one of pre-clinical infection. The

term 'subclinical' may also be used in this situation (and, until they develop actual disease, it cannot, logically, be known that the infection is 'pre-clinical'). However, in precise usage, the term 'subclinical' is reserved for those who become infected but never become ill. Naturally, this distinction may be a little arbitrary when diseases have a long incubation period-for example, if the time from infection to clinical disease is, say, 40 years, and infection takes place in a 75 year old, they may never develop disease simply because their life span exceeds the incubation period. In the following answers, the term 'asymptomatic' will be used to refer to any person who is infected but well; the term 'pre-clinical' vCJD will be used only when subsequent disease development justifies the use and the term 'subclinical' will be reserved for the possibility of being infected in such a way that the person infected would never become ill.

b. To be precise: The operational definition of asymptomatic infection with vCJD is: the presence of abnormal, disease-related, prion protein, of a type associated with BSE/vCJD, in non-brain tissues (spleen, tonsil, appendix, Peyer's patches, lymph nodes), in the absence of any vCJD neurological illness. In cases where the brain has been neuropathologically examined, there is no pathological evidence of vCJD in the brain. For definitions of 'pre-clinical' & 'subclinical', see paragraph 61(a).

62. Tests for clinical and asymptomatic vCJD

a. An important point of note is that the Unit's involvement in tests for vCJD has, primarily, been with tests for clinical vCJD. The reason for this is straightforward: it is possible to assess tests for clinical vCJD as it is known that any tested individual does indeed have vCJD and one can then compare the positivity of any test with the known fact of disease. However, tests for asymptomatic vCJD face a big methodological problem: if one tests a person without known vCJD, and obtains a negative result, perhaps that it is just because they are not infected. Conversely, if a positive result were found, is this a true or false positive test result? -since there is no straightforward method of separately confirming the subclinical infected status of the individual.

b. However, in one study, in collaboration with a French group, it was found that there were, in existence, some blood samples that had been taken from 2

French individuals who had, later, developed vCJD. This was an unprecedented opportunity to use the test under evaluation on pre-clinical blood samples. Positive results showed that this particular blood test could give positive results in pre-clinical vCJD. However, this was a result concerning only 2 individuals, and relating to pre-clinical vCJD (not necessarily to subclinical vCJD) (WITN5592004). The two individuals who had pre-clinical blood samples tested in the study reported by Bougard D et al (2016) were French nationals who donated blood to French Blood Services before they became ill with vCJD. Moreover, as cases of vCJD, they are included in the French, not UK, statistics. Any blood donated by them would have been for use in the French Health Services and subject to French policy/regulations. They donated blood on several occasions; the only definite information available to me is that these donations must have been made after 1999 and before 2015. They were not, in the final analysis subclinical cases as they both died of vCJD but, at the time of donating blood, they were pre-clinical cases of vCJD (ie asymptomatic infection cases with their pre-clinical status at the time of their donating being confirmed retrospectively, once they had become ill). There is no evidence that these two French individuals contracted vCJD from blood and it is assumed they were dietary-related French cases.

63. Asymptomatic infection linked to blood/blood products.

There are only 2 cases of proven asymptomatic vCJD infection that have been linked to blood or blood products, both in the UK. One related to blood (non-LR RBCs) and is one of the 4 known cases of RBC-related vCJD infection as discussed above at section 3 paragraph 12 (NCRU0000109_082). The other relates to the use of Factor VIII for haemophilia treatment (HCDO0000799). Both of these cases died for reasons other than vCJD and it cannot be known if they were truly subclinical infections or just people who died within the incubation period. In the case of the RBC-related case, the donation was transfused in April 1999 and the recipient died 5 years later. The donor was diagnosed with vCJD in March 2001. There was one other recipient of blood from the same donor who received leuco-reduced RBCs in May 2000 and who died of non-CJD causes in 2005.

Section 22: Actions such as Identification of 'at risk' individuals, Product Recall and Notification

64. Product Recall: In the cases of the identified blood-transmission of infection/disease, given the limited shelf-life of RBC units, I cannot conceive that there was any blood left to recall by the time the vCJD risk became known. However, if any implicated RBCs had been available, they would have been withdrawn from use. Under the TMER protocol, any other recipients of blood from the relevant donor would have been identified. There was one other recipient of blood from the same donor who received leuco-reduced RBCs in May 2000 and who died of non-CJD causes in 2005. In the case of the Factor VIII administration (administered in 1994 and 1996), anything from the implicated batch would have been withdrawn from use. The NCJDRSU does notidentify other recipients of such implicated plasma products nor notify them.

65. In relation to the identification of infected donors and recipients, this depends on routine CJD surveillance and the TMER study (its processes are detailed elsewhere in this statement at paragraphs 4, 9, 10, 11, 12, 21, 36, 37 & 38). In brief, the Unit notifies the Blood Services of vCJD cases, the services check to see what blood they donated and who received it and then notify us of the recipients. It is then a matter of determining if names are included, or come to be included, as cases of vCJD through surveillance and, in the case of asymptomatic infection, determining-in the event of death- if there is tissue available for analysis.

66. Genotype Data

The two cases of vCJD that donated blood when they were in a pre-clinical phase (in France), and which were reported in the Bougard et al paper (WITN5592004), were both of *PRNP*-129 MM genotype.

The two asymptomatically infected individuals identified in the UK after exposure to blood and Factor VIII, both were of PRNP-129 MV genotype.

67. Notification.

The Unit does not notify 'at risk' individuals that they are 'at risk'-this is a matter

for other bodies.

68. Possible Commercial Availability of tests.

It is not known whether there are any specific plans to make such a blood test, as that described in the Bougard D et al publication (WITN5592004),commercially available.

However, it is important to note that there are many complex considerations in such a move:

(a) A test to be used widely in a population such as healthy blood donors, would need more evaluation than has so far proved possible.

(b) A test that works in a small laboratory, on a limited number of samples, over a time frame appropriate to a research study is not necessarily easy to scale up to one that can process a large number of samples over a short time frame in a number of different localities (as might be required for blood transfusion units).

(c) The possibility of using such a commercial test would have to be evaluated in terms of its cost/opportunity cost.

(d) The use of such a test, in the context of a safe blood supply, would need consideration in the light of the actual magnitude of the risk of vCJD blood transmission, bearing in mind the very small number of identified transmissions to date.

Statement of Truth

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

Signed ____ GRO-C _____

Dated _____18/04/22_____

Table of exhibits:

Reference	Title	Exhibit no.	Relativity URN
*	A copy of the current CJD Diagnostic Criteria supplied as a separate document.	WITN5592002	
1	Gill O N et al. Prevalence in Britain of abnormal prion protein in human appendices before and after exposure to the cattle BSE epizootic. Acta Neuropathologica 2020; 139(6):965		RLIT0000725
2	Mok T et al. Variant Creutzfeldt–Jakob Disease in a Patient with Heterozygosity at *PRNP* Codon 129. NEJM 2017. DoI:10.1056/NEJMMc1610003.		WITN7034010
3	Edgeworth J A et al. Detection of prion infection in variant Creutzfeldt-Jakob disease: a blood-based assay. Lancet 2011; 377: 487–93		NHBT0033626
4	Concha-Marambio L et al. Detection of prions in blood from variant Creutzfeldt-Jakob disease. Sci Transl Med 2016; 8(370):370ra183.	WITN5592003	
5	Bougard D et al. Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease. Sci. Transl. Med 2016; 8, 370ra182	WITN5592004	
6	Davidson L et al. Variant CJD and blood transfusion: are there additional cases? Vox Sang 2014 107:220	WITN5592005	
7	Myles et al. Variant Creutzfeldt-Jakob disease: costs borne by families. Health Soc.Care Community. 2002 Mar;10(2):91-8. PMID: 12121267	WITN5592006	
8	Will RG et al. 'A new variant of Creutzfeldt-Jakob disease in the UK'. Lancet. 1996; 347:921-5		HSOC0010099

9	Bruce M.E et al, 'Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent'. Nature 1997; 389:498-501		DHSC0004125_011
10	Llewellyn C.A, et al. 'Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion' Lancet. 2004; 363:417-421		NHBT0008743_013
11	Urwin P J M et al. Creutzfeldt–Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. Vox Sanguinis 2016; 110, 310–316.		NCRU0000109_082
12	Peden A. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia (2010), 16, 296–304.		HCDO0000799
13	Prowse C. Universal Leucodepletion: experience of implementation in Scotland. La Trasfusione Del Sangue. 2000; 45(5):240-246.	WITN5592007	
14	www.cjd.ed.ac.uk/projects/TMER		
15	Majeed A et al. Extent of misclassification of death from Creutzfeldt-Jakob disease in England 1979-96: retrospective examination of clinical records. BMJ 2000 320: 145-147		NHBT0004373
16	MHRA 2021 Critical Risk Assessment report: Use of UK plasma for the manufacture of immunoglobulins and vCJD risk.	WITN5592008	
17	Garske T and Ghani AC. Uncertainty in the Tail of the Variant Creutzfeldt-Jakob Disease Epidemic in the UK. PLoSOne. 2010; 5(12):e15626	WITN5592009	
18	Ward H et al. Risk Factors for variant Creutzfeldt-Jakob disease: A Case-control, Study. Ann Neurol 2006;59:111–120.	WITN5592010	
19	Everington, D. and Smith, A.J. and Ward, H.J.T. and Letters, S. and Will, R.G. and Bagg, J. (2007) Dental treatment and risk of variant CJD - a case control study. British Dental Journal 202(8):pp. 470-471.	WITN5592011	
20	SaBTO: Guidance Reports, Risk Reduction Measures for variant CJD: Paediatric Components Working Group (PCWG) Report 2019 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829906/SaBTO_PC_report.pdf: SaBTO: Guidance Reports .		RLIT0000939

21	Moda F et al. Prions in the urine of patients with variant Creutzfeldt-Jakob disease. NEJM 2014 7;371(6):530-9	WITN5592012	

Schedule of Relativity Documents referred to into Statement

	Description	**Document Date**	**Relativity URN**
1.	Journal Article: BMJ 'Extent of misclassification of death from Creutzfeldt-Jakob disease in England 1979-96: retrospective examination of clinical records' by Azeem Majeed et al.	15/01/2000	NHBT0004373
2.	Position Statement, re: the nature of advice to be given to patients who have been treated with plasma products manufactured from a plasma pool which includes plasma from a donor suffering from nvCJD.	16/12/1997	NHBT0004115
3.	Notes of a meeting of the European Medicines Evaluation Agency's Expert Workshop on Human TSE's and Plasma-Derived Medical Products, 15 May 2000, by L. Williamson.	20/06/2000	NHBT0004096
4.	Proposal, re: project titled "Case- Control Study of Creutzfeldt-Jakob Disease".	25/03/2002	DHSC0032337_107
5.	House of Commons Science and Technology Committee Oral evidence regarding whether prions currently pose the most significant risk to the UK blood supply.	26/03/2014	TSTC0000049
6.	Written evidence submitted by the National CJD Research & Surveillance Unit in their capacity as a partner in the TMER study that identified the known cases of actual blood and blood product prion disease/infection transmission.	01/01/2014	TSTC0000039
7.	Minutes from the Secretariat of the Spongiform Encephalopathy Advisory Committee (SEAC) about the 51st Meeting held on 15 June 1998	July 1998	DHSC0042543_020
8.	SEAC minutes of 45th meeting held on 24 October 1997.	19/12/1997	NCRU0000174