Joint UKBTS Professional Advisory Committee ([1])

Position Statement

Variant Creutzfeldt-Jakob disease

September 2021

Approved by: Standing Advisory Committee on Transfusion Transmitted Infections.

September 2021 - The contents of this document are believed to be current. Please continue to refer to the website for in-date versions.

Background

Creutzfeldt-Jakob disease (CJD) is one of a group of diseases called Transmissible Spongiform Encephalopathies (TSE) or Prion Diseases. These diseases, in general, have long incubation periods and are characterised by severe and irreversible damage to the central nervous system resulting in death. They are caused by prions, abnormal accumulations of protein, which differ from conventional microorganisms such as bacteria and viruses. So far there are no clinically effective treatments for any TSE including CJD.

Sporadic, iatrogenic and familial Creutzfeldt-Jakob disease

Sporadic or classical CJD, which was first described in the early 1920s, occurs worldwide and affects around one to two persons per million per year with a median age of onset of 65 years. Patients experience a rapidly progressive dementia with death typically occurring within six months of their first symptoms. Other forms of human prion disease have since been described, including Kuru which was endemic in the Fore people of Papua New Guinea in the 1950s and transmitted through cannibalistic funeral rites. There are also rare familial forms of human prion disease due to inherited genetic abnormalities. In addition, transmission of sporadic CJD has occurred in the past during medical care through neurosurgical instruments, corneal and dura mater grafts and cadaveric pituitary derived human growth hormone and gonadotrophins. A series of epidemiological case control, look back and surveillance studies over the last 35 years have not revealed any confirmed cases of transmission of sporadic CJD by blood components, plasma products, or peripheral tissues (such as bone, skin and heart valves). However, as a precautionary measure, UK Blood Services apply agreed UK and European exclusion criteria (in line with WHO recommendations) to exclude anyone who could have an increased risk of iatrogenic or familial CJD from donating blood, tissues or haematopoietic stem cells.

UK Blood Transfusion Services criteria for excluding blood and tissue donors who have, or who could have, an increased risk of human prion diseases:

Obligatory: ***Must not donate if:***

- *Diagnosed with any form of CJD, or other human prion disease.*
- *Identified at increased risk of developing CJD or another form of human prion disease. This includes:*
    - *Individuals at familial risk of CJD or another form of human prion disease (have had two or more blood relatives develop CJD or*

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another form of human prion disease or have been informed following genetic counselling that they are at risk)

- *Individuals who have been told that they have been put at increased risk from surgery, transfusion or transplant of tissues or organs.*
- *Individuals who have been told that they may be at increased risk because a recipient of blood or tissues that they have donated has developed a human prion disease.*
- *Recipients of dura mater grafts.*
- *Recipients of corneal, scleral or other ocular tissue grafts.*
- *Recipients of human pituitary derived extracts.*

Exceptions: *If the donor has had two or more blood relatives develop CJD or another form of human prion disease and, following genetic counselling, they have been informed that they are not at risk, accept.*

This requires confirmation by a ***Designated Medical Officer****.*

Variant Creutzfeldt-Jakob Disease

A different form of Creutzfeldt-Jakob disease – variant CJD - was first reported in 1996. Unlike sporadic CJD, this disease affects younger people (a median age at death of 28, range 14-75 years old). Clinical presentation is also different. Variant CJD patients show signs of behavioural disorder, depression and anxiety followed by problems with sensation and co-ordination leading to progressive dementia and death over a period of on average 14 months (range 6-114 months). The clinical, epidemiological, neuropathological and experimental data all point to variant CJD being caused by the same strain of prion as Bovine Spongiform Encephalopathy (BSE). This is a different strain of prion from those seen in sporadic CJD.

To date there have been 178 definite and probable cases of variant CJD in the UK, 28 cases in France, and 26 cases elsewhere in the world. Some of these latter cases are thought to have acquired the disease in the UK. The other patients are thought to have been infected in their country of origin, but possibly through eating beef of UK origin. In 2020, a case of variant CJD was reported in a technician who had previously worked in a French prion research laboratory. The infection is plausibly related to accidental occupational exposure to BSE adapted murine brain samples 7.5 years earlier (NEJM 2020; 383: 83-85). Details on the number of UK and world-wide cases of variant CJD can be found on the National Creutzfeldt-Jakob Disease Research and Surveillance Unit (NCJDRSU) website (www.cjd.ed.ac.uk). The eventual number of individuals within the UK population likely to develop variant CJD remains uncertain, though the number of new cases is diminishing within the past 5 years (in 2016) and it is similarly uncertain how many current or past blood or tissue donors could be incubating the disease. All cases of clinical variant CJD, except three from the UK, are believed to be primary cases resulting from eating BSE contaminated meat products. In December 2003, the first presumed transmission of variant CJD by blood transfusion was described. The transfusion occurred in 1996; the blood donor was well at the time but went on to develop symptoms of variant CJD in 1999. The recipient was diagnosed with variant CJD in 2003. A probable transmission of variant CJD prions, not leading to clinical disease, was reported in July 2004. On this occasion the patient received blood in 1999 from a donor who went on to develop symptoms of variant CJD 18 months later. The recipient died of unrelated causes 5 years after the transfusion with no evidence of neurological disease but at

post-mortem was found to have evidence of abnormal prion accumulation in the spleen and a lymph node. The second presumed blood-associated transmission leading to clinical disease was reported in February 2006. The patient developed symptoms about 8 years after receiving a blood transfusion from a donor who developed symptoms of variant CJD about 20 months after donating blood. A third presumed blood-associated transmission leading to clinical disease was reported in January 2007 in a patient who developed symptoms just over 8 years after receiving a blood transfusion from a donor whose symptoms of variant CJD appeared about 17 months after donating this blood. This donor was also associated with one of the earlier transmissions.

A further presumed transmission of prions was described in February 2009. The patient suffered from haemophilia and had received batches of Factor VIII to which a donor who subsequently developed vCJD had contributed plasma. The patient died of other causes but was found at post-mortem to have evidence of prion accumulation in his spleen. Further details are published in Peden *et al*. (Haemophilia 2010; 16: 296-304).

The UK Blood Services have taken a number of measures to try to reduce the risk of transmission of variant CJD by blood, plasma and tissue products:

These include:

- Withdrawal and recall of any blood components, plasma derivatives, cells or tissues obtained from any individual who later develops variant CJD (announced December 1997).
- Importation of plasma from countries other than the UK for fractionation to manufacture plasma derivatives (announced May 1998, fully implemented October 1999, partially rescinded February 2021).
- Leucodepletion of all blood components (decision announced July 1998, fully implemented Autumn 1999).
- Importation of clinical Fresh Frozen Plasma (FFP) for patients born on or after 1st January 1996, announced on 16 August 2003 and implemented by the end of June 2004. This was extended to all patients under the age of 16 by July 2005. As those born on or after 1st January 1996 began to turn 16 from 1 January 2012, this rule reverted to its original wording to ensure that these individuals continued to receive imported plasma past their 16th birthday. This measure was rescinded in September 2019.
- Exclusion of whole blood donors who state that they have received a blood component transfusion in the UK since 1st January 1980, (April 2004). Extended to whole blood and apheresis donors who may have received a blood component transfusion in the UK since 1st January 1980 in August 2004 and to any donors who have been treated with UK plasma derived intravenous immunoglobulin or have undergone plasma exchange. This was further extended in November 2005 to transfusions anywhere in the world.
- Exclusion of live bone donors who have been transfused since 1st January 1980 (July 2005).
- Exclusion of blood donors whose blood has been transfused to recipients who later developed variant CJD, where blood transfusion cannot be excluded as a source of the vCJD infection and where no infected donor has been identified (July 2005).
- Promotion of appropriate use of blood and tissue products and alternatives throughout the NHS.

Questions and Answers

- *How many people are currently incubating variant CJD in the UK?*

Estimates of the number of people likely to develop variant CJD (and therefore currently incubating the disease) continue to vary. It is also possible that some people could be "infected" with this agent but never progress to clinical disease. Data collected by the National

CJD Research and Surveillance Unit show that variant CJD mortality in the UK peaked in 2000 and has since fallen with the last patient described in 2016. The observation is encouraging; however, some caution should be exercised. There is a continuing discrepancy between the likely number of cases projected from the current clinical evidence of variant CJD and the number of infected people projected from retrospective studies of appendix samples which suggests that around 1/2,000 (range 1/1,250 to 1/3,500) healthy people in the general population could be sub-clinically infected: http://www.cjd.ed.ac.uk/projects/transfusion-medicine-epidemiology-review-tmer
Recent studies showing prion accumulation also in appendices removed before 1980 and from people born after 1996 raise questions around the specificity of these findings.

To date the majority of probable and definite cases of clinical variant CJD have been in people who are methionine homozygous at codon 129 of the prion protein gene. A single UK case of probable variant CJD in a patient who was heterozygous at this genetic locus has been described. In addition, the second of the transfusion recipients and the patient with haemophilia referred to above, both of whom had evidence of abnormal prion protein but not clinical vCJD, were heterozygous at this locus and two of the patients positive for abnormal prion accumulation in the retrospective study of tonsils and appendices were homozygous for valine. These observations suggest that other genotypes may also be susceptible to infection with variant CJD prions, possibly with a lower frequency of clinical disease and/or longer incubation periods (as has been seen in some cases of Kuru and peripherally transmitted iatrogenic CJD). In addition, further cases could arise due to secondary human to human transmission via medical or surgical instruments or blood, plasma, cell or tissue products, though no known such cases have been seen so far.

- *How many UK patients have been exposed to blood components or plasma products from donors who went on to develop variant CJD and have they been informed?*

Eighteen people who later developed variant CJD were traced as blood donors and gave blood donations that were transfused to recipients. Sixty-seven recipients of blood components from these donors were identified of whom 14 were still alive, all of whom survived for at least 10 years since the blood transfusion. Their doctors were informed of their exposure to these products (http://www.cjd.ed.ac.uk/TMER/TMER.htm).

Eleven blood donors who later developed variant CJD contributed to 25 plasma pools from which 191 plasma product batches were manufactured. The CJD Incidents Panel (since disbanded) requested a model to help assess the level of risk of exposure to variant CJD for recipients of plasma products. This model was developed by the Health Protection Agency and is now maintained by its successor body, Public Health England (PHE). The model allows one to calculate a dose of each product (in implicated or non-implicated batches) beyond which it is likely that an infection-control threshold will be surpassed. It has been kept under regular review, and has informed patient notification (and de-notification) exercises. Patients recognized to be at increased risk of exposure have, where possible, been informed of their exposure to these products and precautionary steps taken to minimize the risk of any further transmission through blood, tissue or organ donation, or by medical or surgical instrumentation. Further information can be obtained from the PHE website: https://www.gov.uk/government/collections/creutzfeldt-jakob-disease-cjd-guidance-data-and-analysis.

- *How many* UK *patients are exposed to blood components each year and have not developed variant CJD?*

Estimates of numbers of transfusion recipients in hospitals supplied by NHSBT were made from data collected from representative hospitals in 2001/2002 and published in 2009. The figures for the 12-month period were: red cells: 433,000 recipients, FFP: 57,500, and platelet components 41,500. Since NHSBT accounts for the majority of issued blood components in

the UK, the approximate figures for total number of UK recipients can be estimated by uplifting these figures by ~~20~~ 15% though it should also be noted that demand for red cells has fallen significantly since this study was carried out.

The EASTR study reported that the median age of recipients of red cells, FFP and platelets was 69 years, 64 years and 59 years respectively. This study followed the survival of recipients for post-transfusion to determine the long-term survival of the cohort. The 10-year survival was highest for adult recipients of red cells (36%) compared with 30% for both FFP and platelets (Morley et al., 2016). A proportion of recipients in any one year may be transfused in following years, so it is not possible to give an accurate figure for the total number of people who have been transfused in the UK since the appearance of variant CJD (1996) but the total will be many millions of people. Ten of these many millions have developed clinical variant CJD, including the three (referred to above) who have been linked to a donor who also later developed variant CJD. In one case the transfusion was given close to disease onset, and in two cases the donations could not be linked to identified blood donors. In the remaining four cases all, or most of, the blood donors could be identified, and none of the donors has developed variant CJD.

- *Are additional donor selection criteria being applied?*

Countries out with the UK, including the USA, Canada, New Zealand, Australia, Hong Kong and several European countries including Germany, Switzerland, Austria and Eire have taken the precautionary step of excluding blood donors who have spent more than a defined period living in the UK between 1980 and 1996. Eire withdrew this donor exclusion criterion in October 2019. From 5th April 2004, whole blood donors who know that they have received blood component transfusions in the UK on or after 1st January 1980 have been excluded from blood donation. This measure generally resulted in the deferral of 3-5% of potential blood donors. From August 2004 this deferral criterion was extended to blood donors unsure whether they had received a transfusion and to platelet apheresis donors. From July 2005 live bone donors were also included in this deferral criterion. Tissue donation from deceased donors transfused or possibly transfused since 1980, except in the last week of life, is not normally accepted. Because of shortages in supply, this exclusion does not currently apply to the donation of heart valves, ocular tissue and skin provided the donor's total transfusion exposure is limited to less than 80 units of blood or blood components. In addition, any history of transfusion after 1980 must be recorded and remains part of the documentation associated with the donation. Anyone who has received UK derived coagulation factors, intravenous normal immunoglobulin or underwent plasma exchange between 1980 and 2001 is also deferred from blood donation.

- *Will the UK blood services continue to use non- transfused UK donors?*

At present, the majority of blood components (*i.e.* red cells, platelet and clinical plasma) and peripheral tissue (bone, skin, tendon, heart valves and cells) are derived from UK donors. It is unlikely that large quantities of blood or tissues could be sourced from non-remunerated donors out with the UK. Even if this were possible, it could increase the risk of exposure to other infectious agents, would be very difficult to implement for components with short shelf lives and could precipitate critical shortages. The issue is therefore one of a balance of risks and benefits.

- *Is there a blood test available for* variant *CJD?*

Not at present. The types of tests that are used to screen blood and tissue donations for viruses cannot be applied to variant CJD because of the different type of infectious agent (abnormal prion protein rather than bacteria or virus). Researchers from the MRC Prion Unit have developed a blood test which has been demonstrated to be sensitive enough to detect abnormal prion in the blood of some patients with clinical variant CJD. Similarly, two

international groups have developed assays which can detect prions in the blood of experimentally infected animals. However, considerable work is required to bring a test from the research laboratory through to the clinic and it is currently uncertain whether these tests will prove accurate enough to reliably detect infection in the asymptomatic incubation period of infection in humans.

- *Can donors contract* variant *CJD from giving blood or tissues?*

No. Blood donations are taken through sterile, non-reusable, disposable needles and equipment so it is not possible for anyone to contract variant CJD by blood donation. The UK Blood Services have a duty to supply hospitals with the blood components needed for patient care. This can only be achieved with the help of blood donors and their continued support is vital.

For live tissue donation, no excess risk is involved in the operation that would not otherwise be incurred as part of the operation itself, to treat the patient's underlying condition. In the context of cadaveric tissue donations this risk is not applicable.

- *Does universal leucodepletion reduce the risk of transmission of* variant *CJD?*

Universal leucodepletion was introduced in the UK in 1999. In animal models where infectivity has been found in the peripheral blood, a large proportion has been associated with the white blood cells. Recently published animal data show that leucodepletion removes a proportion (about 50%) of prion infectivity, but is unlikely, by itself, to remove all infectivity. However, no instances of transfusion-transmission of variant CJD are known to have occurred since leucodepletion was introduced in the UK (1999).

- *Are there any other component processing steps which could reduce the risk of transmission of variant CJD by blood or tissues?*

The UK Blood Services supply platelets either by apheresis (*i.e*. from a single donor) or from pools of 4 donors. Pooled platelets are being suspended in platelet additive solution to remove most of the plasma, which is considered to reduce variant CJD risk. No other component processing steps have currently been demonstrated conclusively to reduce the risk of transmission of variant CJD.

For tissues, the donations are not pooled to reduced donor exposure. Steps to eliminate cross contamination during retrieval and processing are followed to minimise risk of transmission. More information is given below.

- *Are plasma derivatives likely to be infectious?*

Since October 1999, all plasma products including Factor VIII and Factor IX, immunoglobulins and albumin have been derived from non-UK donors. The majority of clotting factors now used in the UK are recombinant products which pose no risk of variant CJD infection. Therefore, there should be minimal risk to patients now receiving plasma products provided donors are from countries with a known low risk for BSE. The risk to patients who received plasma products before October 1999 is uncertain. One case of subclinical infection in a patient with haemophilia has been described, though the patient himself did not develop clinical disease. The UK Blood Services engaged in research on the ability of the plasma fractionation processes to remove prions. These studies involved the experimental addition of prion-infected material to blood and showed that there are steps during each manufacturing process which remove prions, though it remains unclear how closely these reflect the way in which the natural infective agent behaves. Similar studies have been performed by other organisations with similar results. The starting level of infection in plasma from UK donors remains unknown.

The risk from most UK derived plasma products is likely therefore to have been low. In February 2021 the Medicines and Healthcare Products Regulatory Agency and Commission on Human Medicines reviewed the cumulative information and concluded that the residual risk of transmission of vCJD by plasma products is now very low and that UK plasma can be used for the manufacture of immunoglobulins.

- *Are cell or tissue products likely to be infectious?*

The Standing Advisory Committee on Tissues and Cellular Therapy Products undertook a formal review together with the Health Protection Analytical Team to consider the risks of transmission of variant CJD by cells and tissues including new safety issues raised through *in vitro* propagation of cells.

Some specific initiatives have also been considered and / or implemented for improvement in the safety of tissues within the UK Blood Services to try to reduce the risk of transmission of variant CJD by bone and tissue transplantation. These include:

- Improved washing and blood removal techniques for processed sterilised bone grafts.
- The use of disposable instruments for some types of tissue retrieval and processing.
- Improvement in decontamination procedures prior to sterilisation of instruments.
- Batching of retrieval and processing of instruments to allow for the tracking of their use.
- Dura mater grafts are not provided

- *Should UK patients continue to accept blood and tissue products?*

Blood, plasma, cell and tissue products should only be given when they are essential to the quality of life, health or survival of the patient, and where there is patient consent. In these circumstances the benefits are carefully weighed against other transmission risks including variant CJD. In some circumstances alternatives are available which could reduce the exposure to blood or tissue products. UK Blood Services' clinicians continue to work with colleagues throughout the National Health Service in establishing and implementing guidelines for the appropriate use of blood and tissues. It is a priority for the UK Chief Medical Officers and the medical community in the UK to ensure that patients are treated with blood or tissue products only when there is real clinical benefit. SaBTO recommends that patients be offered the opportunity to give informed consent to blood transfusion whenever practicable and a series of information leaflets are available explaining the potential benefits and risks including those relating to variant CJD.

- *What is being done to ensure that blood and tissues are used only when there is a good clinical indication?*

On the advice of the UK Chief Medical Officers, national programmes for good transfusion practice have been established, supporting the work of local Hospital Transfusion Committees. Transfusion practitioners in hospitals carry out a role which includes training staff in safe blood administration (including detailed documentation), assisting with clinical audit, the development and implementation of evidence based clinical guidelines for the use of blood, and assisting with the investigation and reporting of adverse events to the Serious Hazards of Transfusion reporting scheme (SHOT). There is increasing use in the NHS of techniques that can, for some patients, reduce the need for transfusion of donor blood or avoid it all together. Among these are: the use of regional and hypotensive anaesthetic techniques, good temperature control in the perioperative period, salvage and reinfusion of red blood cells lost during surgery and the use of antifibrinolytic agents. However, transfusion may be unavoidable and life saving for patients who suffer massive blood loss and, for those undergoing chemotherapy for leukaemia or being treated for cancer, there may be no alternative to the use of donor blood components during periods when the bone marrow is not

functioning normally.

Tissue usage is much more restricted than that of blood and in most instances tissues are used when there is no better alternative. Notwithstanding, there are initiatives on auditing usage of particular tissues in specific circumstances to encourage and facilitate best practice