SaBTO

Advisory Committee on the
Safety of Blood, Tissues and Organs

Paediatric Components Working Group - Report

Importation of plasma and use of apheresis platelets as risk reduction measures for variant Creutzfeldt-Jakob Disease

March 2019

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1. Executive Summary

Following a discussion by the advisory committee on the Safety of Blood, Tissues and Organs (SaBTO) in January 2017, a working group of SaBTO was established to advise whether the risk reduction measures for transfusion transmission of variant Creutzfeldt-Jakob disease (vCJD) of importing plasma and using apheresis platelets for individuals born on or after 1st January 1996 and for patients with thrombotic thrombocytopenic purpura (TTP), should be maintained, withdrawn for some individuals, or withdrawn altogether.

The review considered numerous factors including the revised risk assessment, the equity of the current measures, the operational difficulties of maintaining the measures, and their cost-effectiveness. In considering the ethical aspects of both the current policy and the possible changes, the working group considered the duty to protect the vulnerable from harm, the need to treat all patients fairly, the need for trust and transparency and what level of risk is acceptable to wider society.

Based on evaluation of the risk of transmission of vCJD, SaBTO recommends that the current risk reduction measures of the provision of imported plasma and apheresis platelets for individuals born on or after 1st January 1996 or with TTP be withdrawn. Other risk reduction measures for vCJD should remain in place.

Key Points

a. Following recognition that blood, blood components, tissues and organs donated by infected donors could transmit the agent that leads to vCJD, several measures were introduced in the UK to reduce the risk of vCJD transmission.
b. Measures included deferral of high-risk donors, leucodepletion (removal of most of the white cells from blood and plasma) and, for those born after 1995, use of plasma imported from those countries where the risk is lower, and for some indications, the use of platelets from a single donor ('apheresis platelets').
c. In the UK, four people have been known to acquire vCJD infection from blood transfusions with three having died from vCJD (the other died of unrelated causes without any symptoms); the last known case was in 2006. All four had received non-leucodepleted blood before leucodepletion was introduced in 1999. There are no known cases of vCJD infection from transfusion of plasma or platelets.
d. A review from the ACDP (Advisory Committee on Dangerous Pathogens) showed the estimated number of future cases of vCJD to be considerably lower than previously forecast. As a consequence, as part of its regular review of guidance, SaBTO, in January 2017, established a working group to review the risk measures in place to reduce the risk of vCJD transmission from blood and blood components.
e. The working party noted the operational issues that had arisen as a result of implementing the guidance: these included the challenges of ensuring a robust supply of plasma that meets current UK quality standards and the challenges and risks that hospitals and blood establishments face in maintaining dual stocks of plasma. Hospital stakeholders were keen to emphasise the potential benefits to patients of lifting the current restrictions, which can lead to delays in the provision of care and the use of less suitable or effective plasma components.

f. In 2017, 110,000 units of imported plasma were issued in the UK. The working group estimated that stopping importation of plasma from abroad would slightly increase the risk to recipients of plasma: on average for every 5.2 million units of UK-plasma given, one additional death due to vCJD may occur (approximately 45 years' worth of transfusions).
g. Implementation of these recommendations for plasma would reduce the operational challenges for hospitals and would allow the NHS to re-invest the savings in other services. By 2020, the additional cost of importation is estimated to be approximately £5 million per annum, and this is expected to increase in coming years, adding up to a total additional cost of £814 million (undiscounted) over a 50-year period.
h. Other risk reduction measures (such as leucodepletion) will remain in place at this time.
i. Clinicians will still be able to prescribe commercial imported plasma products such as OctaplasLG for patients according to local and national guidelines.
j. Clinicians will be able to prescribe apheresis platelets donated by UK donors as clinically indicated.
k. It is important to note that the conclusions from the analysis on plasma cannot be extrapolated to the manufacture of plasma derived medicinal products from fractionation of plasma sourced in the UK. Further work would be required to determine the risks and benefits of using UK plasma for fractionation.

2. Summary

Background

SaBTO (the advisory committee on the Safety of Blood, Tissues and Organs) is an independent committee that is hosted by the Department of Health and Social Care; members are selected by interview after public advertisement. Members advise health ministers of the four UK nations on safety of blood, cells, tissues and organs. Policies are published on its website (https://www.gov.uk/government/groups/advisory-committee-on-the-safety-of-blood-tissues-and-organs) and are reviewed on a regular basis.

The UK has one of the safest blood supplies in the world, and decisions regarding safety initiatives are taken based on evidence of risk, ethical considerations and operational sustainability; cost is also considered. Where the evidence and/or the risk is not known, SaBTO makes recommendations on a precautionary basis. SaBTO reviews its guidance on a regular basis and also when new information becomes available.

The UK also has one of the world-leading haemovigilance organisations[1] which is responsible for collection of reports of adverse reactions related to transfusion so that the impact of policy decisions can be monitored.

Around two million units of blood components (red cells, platelets or plasma) are transfused in the UK every year. These may be given as a life-saving emergency treatment, to enable another treatment such as surgery or chemotherapy for cancer, or as the primary treatment for a long-term condition that affects the blood.

Variant Creutzfeldt-Jakob disease & transfusion

Variant Creutzfeldt-Jakob disease, or vCJD, is a neurodegenerative disease arising from the consumption of meat from cows with bovine spongiform encephalopathy (BSE, colloquially known as 'mad-cow disease'), which mainly occurred in the 1980s to early 1990s. vCJD may have an incubation period of years to decades and when the first cases of vCJD were seen in the late 1990s there was considerable concern that large numbers of people had been infected and that this could result in many deaths; vCJD is currently untreatable and, when symptoms arise, leads to death within 18 months. By 1996, stringent risk reduction measures were in place to prevent cows with BSE reaching the human food supply, so any individual born after 1995 should not have been exposed to BSE through food. vCJD has remained a rare disease with 178 cases diagnosed in the UK between 1995 and 2017.

When the first cases of vCJD appeared, there was concern that the disease could be transmitted from one individual to another by the transfusion of blood, blood products or blood components such as plasma and platelets. Although cases of transmission of vCJD from blood transfusion have occurred, there have been far fewer cases than originally forecast. Three people died following transmission of vCJD from two blood donors, who later developed vCJD. Another person who was known to have received a transfusion from a different blood donor (who later developed vCJD) was found to have evidence of vCJD in their spleen and appendix after they died (of another cause); this was presumed to be because of the transfusion. A fifth individual, who had haemophilia and received many doses

[1] www.shotuk.org

of Factor VIII concentrate (a medicinal blood product, not a blood transfusion), including some from a batch where one of the donors was known to have subsequently developed vCJD, was also found to have evidence of vCJD in their spleen when they died (also from another cause). Neither of the latter two cases had symptoms nor evidence of brain disease but the evidence of vCJD in their spleen could represent a pre-clinical form of the disease (before any symptoms became apparent). It should be noted that, although the last known case of transfusion-related vCJD was diagnosed in 2006, all the recipients infected by blood transfusion had received red cells that had not been filtered to remove white blood cells (leucodepletion or leucoreduction); this protective measure was introduced in 1999, after their transfusions. There have been no reports of vCJD transmission from plasma or platelet transfusion. There have been no cases of transfusion-related transmission anywhere else in the world even though some countries, such as France, have had cases of vCJD.

Transfusion transmission risk reduction measures for vCJD

The UK Departments of Health and UK blood services have introduced several vCJD risk reduction measures for blood, blood products and blood components. These include:

- Since December 1997, all blood components, blood products or tissues obtained from any individual who later develops clinical vCJD have been withdrawn/recalled to prevent their use.
- Since October 1999, white blood cells (which are thought to contain most of the infectious agent that causes vCJD) have been reduced in all blood components used for transfusion, by a process known as leucodepletion or leucoreduction.
- In 2004, all individuals who had themselves received a transfusion of blood components (anywhere in the world) since January 1980 were excluded from donating blood.
- Since 1999, plasma for the manufacture of fractionated plasma products, such as clotting factors and immunoglobulins, has been obtained from non-UK sources.
- Since 1998, synthetic (recombinant) clotting factor for the treatment of haemophilia has been provided to those aged under 16 years, and since 2005 this measure has been extended to all patients for whom it is clinically appropriate.
- Since 2004, plasma for transfusion to those born on or after 1st January 1996 has been obtained from outside the UK.
- Since 2005, provision of platelets collected from a single donor by apheresis for transfusion to children under 16; extended in 2013 to include those born on or after 1st January 1996
- In 2009, a minimum of 80% of platelets to be collected from single donors by apheresis, for transfusion to all recipients. This measure was reassessed and rescinded in 2013.

The UK also has an active surveillance programme for transfusion transmission of vCJD, the Transfusion Medicine Epidemiology Review (TMER). TMER is a collaboration between the UK Blood Services and the National CJD Research & Surveillance Unit. Any individual diagnosed with vCJD is investigated to see if they had donated blood or blood components or if they had ever received blood or blood components. The respective recipients or donors are traced and deferred from donating blood.

Importation of plasma and provision of apheresis platelets

The importation of plasma and provision of apheresis platelets for certain groups, were introduced as specific measures for individuals born on or after 1st January 1996 as they were considered not to have been exposed to BSE through their diet. Platelets and red cells have short shelf-lives (days and weeks, respectively) so it was considered to be impractical to source these components from non-UK countries with no, or very few cases of BSE. Plasma has a much longer shelf-life (years) as it can be frozen and can therefore be imported from suitable countries. Apheresis is a way of collecting platelets so that a single donor can provide enough for a therapeutic dose; this is in contrast with platelets collected from whole blood donations as platelets from four donations have to be pooled together to provide a therapeutic dose. Therefore, a patient receiving a dose of platelets sourced by apheresis will be exposed to the infection risk from fewer donors. Some individuals with thrombotic thrombocytopenic purpura (TTP) can receive multiple transfusions with plasma to treat their condition and, therefore, have an enhanced risk of exposure to plasma-borne pathogens including vCJD; these individuals also receive non-UK, pathogen reduced plasma. Since the first appearance of vCJD, the Department of Health and Social Care (DHSC) England has periodically carried out a risk assessment on the predicted number of future infections and associated deaths due to vCJD that could occur from the transfusion of blood components. This risk assessment uses highly precautionary assumptions and is likely to overestimate the number of future number of vCJD cases.

The risk assessment combines assumptions based on the latest understanding of the disease, experimental data, including studies to determine the number of individuals who may have the disease but have not developed clinical symptoms and the results of animal experiments, with the number of deaths due to vCJD that have actually occurred. Since 2006, as more time has elapsed without any further cases due to transfusion, the projected number of future deaths estimated by the risk assessment has been revised downwards. In addition, there is now a better understanding of the disease and studies on animals have shown that white cells carry most of the infectivity. This suggests that there is less infectivity in platelets and plasma than first thought and that leucodepletion is an important risk reduction measure, perhaps the most important, for all blood components.

Review of current practice

Following a discussion by SaBTO in January 2017, a working group of SaBTO, chaired by Dr Stephen Thomas, was established to advise whether the vCJD risk reduction measures in place for individuals born on or after 1st January 1996 and for patients with TTP, of importing plasma and using apheresis platelets, should be maintained, withdrawn for some individuals, or withdrawn altogether. No other risk reduction measures for vCJD transmission were considered.

The review considered numerous factors including the revised risk assessment, the equity of the current measures, the operational difficulties of maintaining the measures, and their cost-effectiveness. In considering the ethical aspects of both the current policy and the possible changes, the working group considered the duty to protect the vulnerable from harm, the need to treat all patients fairly, the need for trust and transparency and what level of risk is acceptable to wider society.

The review did not consider changing any of the other vCJD risk reduction measures and, indeed, assumed that they will remain in place.

There are practical difficulties for hospital departments having to maintain dual stocks of imported and UK plasma and of pooled and apheresis platelets to treat each patient group. This increases complexity, risk, cost and wastage of valuable resources. Hospital stakeholders were keen to emphasise the potential benefits to patients of lifting the current restrictions, which can lead to delays in the provision of care and the use of less suitable or effective plasma components.

In addition, the number of individuals in this group is growing year on year which will compound these difficulties and will also require significant quantities of these components to be stocked in all hospitals, trauma centres and, maternity units etc rather than primarily in children's' hospitals. The demand for plasma has been rising throughout the developed world to make immunoglobulin preparations used to treat a variety of other diseases. This means that non-UK blood services have little spare plasma to export to the UK, at the same time that UK blood services require increasing amounts of plasma to support the risk reduction measures.

The latest UK vCJD blood safety risk assessment was carried out in 2018 under the supervision of the Advisory Committee for Dangerous Pathogens Transmissible Spongiform Encephalopathy (ACDP TSE) subgroup. This expert subgroup and the full ACDP committee are hosted by, but independent of, DHSC England. ACDP TSE gave its support to the risk assessment as providing a highly precautionary estimate of the number of future cases and infections with specific figures for these numbers, while uncertain and subject to revision in the light of further data, considered to be of the right order of magnitude. This position was later agreed by the full ACDP committee in November 2018.

This risk assessment predicts that under current practice the best estimate is that eight deaths from vCJD could occur over the next 50 years due to plasma transfusions, with five of those being due to transmissions that have already occurred (the potential worst-case scenario would have 73 deaths over the next 65 years with 48 of those due to transfusions that have already occurred; the best-case scenario would be no future cases). For platelets, the best estimate is that there could be eleven deaths from vCJD over the next 55 years as a result of platelet transfusions with five of the transmissions having already occurred (the worst-case scenario estimates 137 cases over 75 years with 67 having already occurred; the best-case scenario predicts no future cases).

The SaBTO working group used predictions from the risk assessment to establish if the risk reduction measures of plasma importation and provision of apheresis platelets are still appropriate. The modelling showed that the impact of these measures was small. If these risk reduction measures were not in place, a further one to two clinical cases may occur due to plasma transfusions that take place over the next 50 years; and for individuals receiving pooled platelets rather than apheresis platelets, an additional three to four cases may occur due to transfusions that take place over the next 60 years (the worst-case scenarios estimated by the model would give an extra 15 cases for plasma and 45 cases for platelets due to transfusions over the same time period. The best-case scenario would be no

additional cases). This means that the additional risk of death from transfusion acquired vCJD would on average be 1 in every 5.2 million units of UK-plasma transfused and 3.1 million units of pooled rather than apheresis platelets transfused. To put these risks in context, the increased risk of death due to an accident while driving from London to Bristol and back (approximately 250 miles) is 1 in 1 million[2].

The working group then looked at the balance of cost and benefit of these measures to patients and the wider NHS. This was done, for each option, by calculating the overall costs, in terms of the blood components purchased, and patient impact, in terms of premature deaths due to vCJD, measured in Quality Adjusted Life Years (QALYs). QALYs are used to compare the impact of medical treatments using both the length and quality of life that are gained from different procedures. One QALY is the equivalent of one year of life spent in perfect health. In this case, the change in QALYs from using the different blood components was calculated using the number of years of life that would be lost by a patient if they died due to vCJD.

Maintaining importation of plasma for individuals born after 1995 and for individuals with TTP was estimated to cost £30 million per QALY (discounted) more than using UK-sourced plasma (the range from worst- to best-case in terms of clinical cases was £3 million to £2,100 million per QALY).

For the maintenance of a supply of apheresis platelets to individuals born after 1995, the cost was estimated to be £7 million per QALY (discounted) more than using pooled platelets (the range from worst- to best-case in terms of clinical cases was £1 million to £490 million per QALY).

For context, the National Institute for Health and Care Excellence (NICE) recommends that the NHS funds medicines and other procedures if they cost less than £20,000-£30,000 per QALY.

Recommendations of the paediatric components working group

The recommendations are that, based only on vCJD risk, the current risk reduction measures for individuals born on or after 1st January 1996 or with TTP be withdrawn. This is due to the revised risk assessment showing that the predicted number of deaths due to vCJD transmitted by plasma or platelets is lower than previously estimated and these risk reduction measures would only prevent a small number of additional deaths. Removing the current risk reduction measures (importation of plasma and provision of apheresis platelets) will allow more equal provision of components, less operational complexity and risk, and will allow more resources to be deployed to save lives elsewhere in the NHS. Clinicians will still be expected to follow local and national guidelines on managing individual conditions (such as the British Society for Haematology Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies).

[2] *Micromorts*, Understanding Uncertainty, Winton programme for the public understanding of risk. University of Cambridge. https://understandinguncertainty.org/micromorts

3. Introduction

Variant Creutzfeldt-Jakob disease (vCJD) is an incurable neurodegenerative disease first described in 1996. When symptoms occur, vCJD is invariably fatal. The disease is linked to the consumption of meat or meat derived products from cattle with Bovine Spongiform Encephalopathy (BSE). BSE was first identified as a new disease in cattle in 1986 but it is likely that BSE had been present in herds for some years before the disease was formally recognised. Cases of BSE in the UK peaked in 1993 and declined rapidly once effective control measure to limit transmission were implemented. By the start of 1996, stringent controls were in place to stop meat from BSE-infected cows reaching the human food supply. Consequently, individuals born in the UK after 1995 were considered to have no exposure to BSE from eating meat.

Of note, the most significant measure to stop the spread of BSE between cows was the prohibition of feeding of cows with ruminant derived meat and bone meal in 1988. There have been no cases of vCJD in anyone born in the UK after 1989.

To date, vCJD has remained a rare disease with 178 definite or probable vCJD cases in the UK. However, the agent which causes the vCJD is widespread in the lymphoreticular system of clinically affected individuals and for some time before these individuals develop symptoms. As vCJD has a long incubation period and infected individuals may be asymptomatic for years, the UK blood services have introduced risk reduction measures to reduce the risk of transmission by transfusion of blood or blood components. These included:

- Since December 1997, all blood components, blood products or tissues obtained from any individual who later develops clinical vCJD have been withdrawn/recalled to prevent their use.
- Since October 1999, white blood cells (which are thought to contain most of the infectious agent that causes vCJD) have been reduced in all blood components used for transfusion, by a process known as leucodepletion or leucoreduction.
- In 2004, all individuals who had themselves received a transfusion of blood components (anywhere in the world) since January 1980 were excluded from donating blood.
- Since 1999, plasma for the manufacture of fractionated plasma products, such as clotting factors and immunoglobulins, has been obtained from non-UK sources.
- Since 1998, synthetic (recombinant) clotting factor for the treatment of haemophilia has been provided to those aged under 16 years and, since 2005, this measure has been extended to all patients for whom it is clinically appropriate.
- Since 2004, plasma for transfusion to those born on or after 1st January 1996 has been obtained from outside the UK.
- Since 2005, provision of platelets collected from a single donor by apheresis for transfusion to children under 16; extended in 2013, to those born on or after 1st January 1996.
- In 2009, a minimum of 80% of platelets to be collected from single donors by apheresis, for transfusion to all recipients. This measure was reassessed and rescinded in 2013.

The UK also has an active surveillance programme for transfusion transmission of vCJD, the Transfusion Medicine Epidemiology Review (TMER). TMER is a collaboration between the UK Blood Services and the National CJD Research & Surveillance Unit.[3] Any individual diagnosed with vCJD is investigated to see if they had donated blood or blood components or if they had ever received blood or blood components. The respective recipients or donors are traced and barred from donating blood.

Of the 178 cases of vCJD, three cases are likely to have resulted from transmission of red blood cells from donors who later developed vCJD. Preclinical vCJD has also been observed in two individuals who died of other causes: Another individual who was known to have received a transfusion from a different blood donor (who later developed vCJD) was found to have evidence of vCJD in their spleen and appendix after they died (of an unrelated cause); this was presumed to be because of the transfusion. A fifth individual, who had haemophilia and received many doses of Factor VIII concentrate, including some from a batch where one of the donors was known to have subsequently developed vCJD, was also found to have evidence of vCJD in their spleen when they died (also from an unrelated cause). Neither of the latter two cases had symptoms nor evidence of brain disease but the evidence of vCJD in their spleen could represent a pre-clinical form of the disease). It should be noted that, although the last known case of transfusion-related vCJD was diagnosed in 2006, all the recipients infected by blood transfusion had received red cells that had not been filtered to remove white blood cells (leucodepletion or leucoreduction); this protective measure was introduced in 1999, after their transfusions. There have been no reports of vCJD transmission from plasma or platelet transfusion. There have been no cases of transfusion-related transmission anywhere else in the world even though some countries, such as France, have had cases of vCJD.

While the risk reduction measures taken by UK Departments of Health and UK blood services are believed to have reduced the risk of transmission of vCJD risk, two of these measures impose sizeable operational and economic burdens on the health services, introduce new risks associated with sufficiency of supply, and present operational difficulties at the point of use. These two measures, importation of plasma for provision of fresh frozen plasma (FFP) and cryoprecipitate and provision of apheresis platelets. were introduced specifically to protect individuals born after 1995 as these individuals were considered not to have been exposed to BSE through their diet and should be afforded protection to prevent exposure from transfusion. Also included were individuals with thrombotic thrombocytopenic purpura (TTP) as individuals with acquired TTP may require many doses of FFP as part of their treatment.

Platelets and red cells have short shelf-lives (days and weeks, respectively) so it was considered to be impractical to source these components from non-UK countries with no, or very few cases of BSE. Plasma has a much longer shelf-life (years) as it can be frozen and can therefore be imported from suitable countries. Apheresis platelets from a single donor can provide enough for a therapeutic dose; this is in contrast with platelets collected from whole blood donations as platelets from four donations have to be pooled together to provide a therapeutic dose. Therefore, a patient receiving a dose of platelets sourced by apheresis will be exposed to the infection risk from fewer donors. Some individuals with

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

thrombotic thrombocytopenic purpura (TTP) can receive multiple transfusions with plasma to treat their condition and, therefore, have an enhanced risk of exposure to plasma-borne pathogens including vCJD; these individuals also receive non-UK, pathogen reduced plasma.

Since the 2002 implementation of risk reduction measures to protect individuals born after 1995, these measures have been discussed and refined by SaBTO, its predecessor, the Advisory Committee on the Microbiological Safety of Blood, Tissues (and Organs) for transplantation (MSBT, later MSBTO) and the UK blood services as follows.

Plasma

In October 2002 MSBTO:

> *"…agreed with the recommendation that the most vulnerable group of FFP recipients (neonates and children born since 1996) should receive virally inactivated (Methylene Blue (MB)-treated)[4], US-sourced, single-unit FFP, ideally from untransfused male donors".*

In June 2004:

> *"MSBT advised that importation of single-unit (MB-treated Fresh Frozen Plasma (MB-FFP) from the US should be extended to supply all children up to age 16 as a vCJD risk reduction measure.*
>
> *MSBT noted that the British Committee for Standards in Haematology guidance already recommends solvent detergent treated FFP (SD-FFP) for the treatment of adults dependent on large volumes of FFP and recommended that this guidance be followed universally for the designated patient groups. Although not specifically aimed at reducing vCJD risk, the current guidance should have this additional benefit."*

These decisions were reviewed by SaBTO in March 2012 and it was decided *"that the importation of FFP3 should continue for those currently receiving it"* as a vCJD risk reduction measure but should not be extended to all recipients. Consequently, all plasma (FFP and cryoprecipitate) components for recipients born on or after 1st January 1996 and recipients undergoing plasma exchange for thrombotic thrombocytopenic purpura (TTP) are imported from countries with a significantly lower risk of vCJD.

Platelets

In 2005, the National Blood Service advised hospitals:

> *"that children [up to the age of 16] should whenever possible be given platelets derived from apheresis rather than pooled platelets" following a risk assessment by the DH Economics, Statistics Operational Research Department suggesting that the "risk is likely to be less for apheresis platelets compared to pooled because apheresis platelets are sourced from a single donor"*

[4] Methylene Blue (MB) is a phenothiazine dye which, on exposure to visible light, generates reactive oxygen species which can inactivate pathogens. MB is particularly effective on enveloped viruses such as HBV, HCV & HIV

Following SaBTO's 2013 removal of the requirement to collect 80% of platelets by apheresis, NHSBT and other UK Blood Services took an operational decision to continue to supply apheresis platelets to patients born after 1st January 1996 (an extension to the under-16 category). This practice was incorporated into the BCSH paediatric guidelines published in 2016).

SaBTO, in December 2014, acknowledged that it was:

"although not mandated, usual practice to provide apheresis platelets for paediatric patients".

It was suggested that SaBTO might in the future review the scope of apheresis platelet use.

The Advisory Committee on Dangerous Pathogens (ACDP) Transmissible Spongiform Encephalopathy (TSE) subgroup conducts periodic risk assessments on transmission of vCJD from blood and blood components. When the previous review was carried out in 2013 the assessment had predicted that, over the next 60 years, the number of vCJD cases arising from red cell transfusion would be in the range of 70 to 930 and, for plasma, in the range of 20 to 220. Estimates for the number of these clinical cases arising from future transfusions were roughly 160 (460 upper limit) and 45 (120 upper limit) from red cells and plasma, respectively. Since this assessment, there have been no reported transmissions of vCJD. In 2017, the ACDP TSE subgroup agreed to revise the blood safety risk assessment with inputs that reflected the latest scientific knowledge from animal models and studies on vCJD population prevalence and with outputs that more closely matched the actual number of vCJD transmissions observed to date. Also, in 2017, SaBTO agreed to establish a paediatric component working group to re-examine the feasibility of maintaining vCJD risk reduction measures for plasma and apheresis platelets. The SaBTO working group agreed to use the revised ACDP TSE subgroup blood safety risk assessment in the review, along with consideration of the ethics, operational impact and cost-effectiveness of maintaining these measures for individuals born on or after 1st January 1996 and for those with TTP.

The options considered by the SaBTO paediatric components working group were:

Option	Recipients of non-UK sourced plasma
U16 + TTP	Patients under 16 years of age All patients with TTP
U1 + TTP	Patients under 1 year of age All patients with TTP
None + TTP	All patients with TTP only
U16	Patients under 16 years of age only
U1	Patients under 1 year of age only
None	None

Option	Recipients of apheresis platelets
U16	Patients under 16 years of age
U1	Patients under 1 year of age
None	None

The paediatric components working group used the Alliance of Blood Operators risk-based decision-making framework[5] to conduct the review and determine the risk assessments required to complete the review process. Key to this process was consultation with key stakeholders, in particular, patients and patient advocates who may be most affected by changes to the current safety measures for vCJD transmission.

4. Ethical considerations

As part of the ABO risk-based decision-making framework process the working group prepared an ethical risk assessment to consider if the current risk reduction measures were fair and equitable.

Acceptable risk sufficient to justify change in policy

A change in policy may be associated with an increased risk to recipients, but the level of increased risk may be seen as acceptable when weighed with other risks and benefits. Interpretation of risk at a population level must take account of the fact that individuals and groups will have different perceptions of, and tolerance for, risk. Risks are perceived as less acceptable if they are involuntary, inequitably distributed and damage identifiable victims[6]. Risks of transfusion transmitted infections including vCJD can be seen as fulfilling these criteria. A potential additional factor relating to vCJD may be association of the origin of the risk with a perceived failure of the government's duty to protect public health and the resulting lack of public trust. Risk tolerance will depend on how individuals perceive a specific risk and how they weigh competing risks. For example, it is possible that people requiring multiple transfusions might accept a higher risk in order to ensure that sufficient plasma is available for their needs; or they may have less tolerance of a risk because they need to take that risk more often.

Treating different groups fairly

The principle of justice requires that people are treated fairly and not differently because of differences that are not morally relevant. The existing policy was based on a distinction between people born before or after 1st January 1996 and the assumption that those born after this date would not have been at risk of oral transmission of the infective agent. In retrospect this does not seem to be the only distinction that could have been made to identify people who had not been exposed to vCJD, for example vegans would not have been exposed. In addition, current epidemiological evidence now suggests that the number of people born before 1st January 1996 who may have been infected by oral transmission is very low. This raises the question of whether the current policy unfairly discriminates against members of the wider population who are also not currently likely to be carriers of vCJD. The review of policy provides an opportunity to ensure that all potential recipients of blood components are treated fairly in relation to bearing risks associated with transfusion. This does not necessarily mean that potential recipients will be treated equally. There may be morally relevant reasons for providing extra precautions in obtaining blood components for

[5] https://allianceofbloodoperators.org/abo-resources/risk-based-decision-making/rbdm-framework.aspx
[6] Sjoberg L: Factors in risk perception; Risk Anal 2000 20:1-11

some groups of patients because of an increased susceptibility to specific risks. However, any differences in approach for different groups needs to be justified in these terms.

Fairness to all patients

A further moral consideration for policy makers is the obligation to use limited resources to provide health benefit to the whole population. The importing of plasma and plasma components is associated with a cost which will increase as the relevant population for whom this is provided increases. This will have implications for health care funding in other areas. The NHS has a moral obligation to provide high quality care and to minimise risks of harm for all patients and so must balance risks and benefits across all areas of patient treatment and care.

Thus, in considering a change in policy over the use of imported plasma it will be necessary to take into account:

- Evidence of the level of risk of transmission of vCJD if imported plasma and plasma components are no longer used.
- Evidence of any additional risks from imported plasma and plasma components.
- The likelihood of maintaining an adequate and safe supply of imported components.
- The financial cost of continuing with the current policy of importing.
- Whether there are ethically justifiable reasons for treating specific groups differently.
- The psychological impact of a change in policy on recipients of plasma components.

The ethical importance of trust

The delivery of effective health care, including provision of blood and blood components, requires a high level of trust in the service from recipients and the public. Loss of trust or failure to trust can have negative consequences. The introduction of the current policy took place in relation to an episode where there was loss of public trust in the government to protect public health. The policy could be seen as a step to rebuild trust as well as an implied promise to protect future generations from harm. A change of policy could be seen by the public as a breach of the implied promise.

Engendering and maintaining trust is more likely if those affected by the decisions have a voice in the process and if changes to policy are transparent and based on available evidence and publicly accepted values. Clear and effective communication will be important both in engagement with stakeholders and the decision-making process for the final recommendations.

5. Operational risk assessment

Operational issues for the continued provision by UK blood services of imported plasma and apheresis platelets for patients born on or after 1st January 1996 were considered.

Plasma

Each UK blood services' offering is detailed in Table 1. Most of the UK and Irish blood services rely on the supply of some plasma components (FFP and cryoprecipitate) manufactured from imported plasma by NHSBT, in some cases alongside a supply of

commercial plasma product, for which they act as wholesalers. The commercial plasma product is manufactured by Octapharma, a large plasma fractionation company. The plasma is called OctaplasLG and is manufactured from large pools of around 2,000 donations, subjected to a solvent detergent pathogen inactivation process and packed in standardised 200 mL units. OctaplasLG is classed as a medicinal product, is not supplied in neonatal sized units, and is not suitable for manufacture into cryoprecipitate, hence the need to purchase imported cryoprecipitate components from NHSBT. An alternative to cryoprecipitate is fibrinogen concentrate, but this is only licenced for congenital (not acquired) hypofibrinogenaemia and so its use to treat active bleeding in other individuals is 'off-label'.

Importation of plasma from non-UK blood establishments

NHSBT imports plasma from outside the UK in order to manufacture certain components for the treatment of patients born on or after 1st January 1996, as a vCJD risk reduction measure in accordance with SaBTO recommendations. Whilst undertaking a procurement exercise for the supply of imported plasma and managing the resultant contract would seem to be a routine activity for a blood service, there are considerable complexities in this particular process. As detailed below there have been numerous challenges with contracts that have made the supply of imported plasma an extremely time-consuming process for a significant number of staff.

The first importation contract was established between NHSBT and a US blood service in 2003. This ran until 2009 when significant regulatory/jurisdictional challenges led to this arrangement ceasing to be viable. Since 2010, NHSBT has contracted with a UK-based intermediary for the import of untreated, single unit, unpooled plasma which is collected at two Austrian Blood Establishments (BEs) in Linz and Vienna. The contract is between the NHSBT and the supplier, who is responsible for managing sub-contracts with the Austrian BEs and transportation of the plasma. Whilst is has been possible for BEs to respond directly to the invitations to tender it is usual for intermediaries or brokers to bid as this reduces the challenges and demands on BEs to work with international customers, regulators, logistics etc. However, it can also complicate the process, as described below.

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Table 1: Current practice in UK and Irish blood services

	Paediatric plasma components	**Apheresis platelets**
NHSBT	Import 24,000 units of plasma from Austria per year, methylene blue (MB) treat, issue some as MB-fresh frozen plasma (FFP) (60 mL split or 250 mL bag) the majority is manufactured into MB-cryoprecipitate (cryo) (single or pool of 6). New contract to import 32,000 units of MB-FFP from Poland. In 2018 supply was very challenging - Group A pooled MB-cryo below national stock target of 10 days of stock ~50% of the time.	50% apheresis 50% pooled Provide as splits (four small units made from one large one) or adult therapeutic dose (ATD) for paediatrics and HLA-matched adults.
WBS	Wholesale for OctaplasLG and fibrinogen concentrate; also import a small amount of MB-cryo from NHSBT	40% apheresis 60% pooled
NIBTS	Import MB-FFP and MB-cryo from NHSBT Supply OctaplasLG for renal transplant patients	80% apheresis 20% pooled
SNBTS	Import 60 mL MB-FFP from NHSBT and single MB-cryo (not pools). Supply OctaplasLG for adults (clinicians reluctant to move to Octaplas for paediatrics due to safety/efficacy concerns i.e. lack of evidence cited in summary of product characteristics	80% apheresis 20% pooled Plan to reduce to 60:40 in 2018 Apheresis provided as splits or ATD for paediatrics and HLA-matched adults
IBTS	Supply fibrinogen, manufacture very small amounts of cryoprecipitate *(for paediatrics)* Wholesale for OctaplasLG and fibrinogen concentrate	70% apheresis 30% pooled, under review

The specification for the plasma requires that the pre-donation donor health check and the screening (microbiology testing) of blood samples meet the same requirements as for UK blood donations. This adds complexity for the potential suppliers as the UK has some requirements that go beyond those in the EU Directive, such as the screening of all donations for hepatitis E virus. After importation, NHSBT treats the plasma with a Pathogen Inactivation (PI) system (currently Methylene Blue; MB) to further reduce the risk of any transfusion transmitted viral infections and further processes the plasma into four finished components: paediatric FFP, neonatal FFP, single cryoprecipitate, and pooled cryoprecipitate. The importation contract was due to expire on 30th November 2017 but was extended following delays to the SaBTO review of its recommendations around vCJD risk reduction, and to allow for implementation of a new contract. The contract has now been extended to 31st August 2019, to run in parallel with the implementation of the new contract in order to mitigate the continued risks of short supplies (see below).

There are limitations to the Austrian contract in that it does not specify the requirement to supply a specific blood group mix as the supplier predicted that this would be an issue due to competition from the BEs' own internal customers and would not commit to a contractual obligation. As a result, the amount of non-Group O plasma received is not sufficient to meet increasing demands. NHSBT has taken operational steps to reprioritise production so that sufficient components are available to meet clinical guidelines, but stock targets for these components have had to be significantly reduced.

An OJEU tender exercise was undertaken in 2017/18, seeking a supplier of pathogen-reduced plasma for an initial period of two years with the option to extend for a further two years. The specification for the plasma was very complicated for a number of reasons, including:

- the source country must appear on a DHSC-approved list of nine countries with sufficiently low risk of vCJD[7];
- the source must comply with the EU Directive 2002/98/EC (effectively reducing this list to four European countries);
- the supplier must be of a sufficient size to have spare capacity to meet its domestic needs as well as the volume required for export;
- the required mix of blood groups was strictly defined;
- the collection and supply services must conform to UK regulatory standards and national guidelines such as screening for HEV;
- the electronic data file that accompanies each shipment needs to be compatible with NHSBT's IT system, and different BEs may have different software systems and different barcode systems in use for blood donation labelling.

Only one bid was received in response to the invitation to tender, and the incumbent supplier did not bid. It is likely that other potential suppliers felt that the terms of the specification were too onerous to meet, given that there are many alternative buyers for plasma – these

[7]https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/192586/Plasma_sourcing_paper_final_version.pdf

are mostly plasma fractionation companies based in the same jurisdiction and having less demanding specifications. It is expected that obtaining a supply from suitable European countries will become increasingly difficult as countries move to become self-sufficient in the supply of plasma[8].

A new contract was awarded in January 2018 to a new supplier for the supply of MB-treated plasma, which will be sourced and treated at a BE in Poland. Due to a number of contractual, regulatory, operational and quality challenges, it took nearly 12 months to establish the new supply.

In addition, there are other elements that require ongoing mitigation:

- Since the invitation to tender was issued, the demand for imported plasma has increased significantly. A previous increase in the number of units required has been agreed but demand has since risen by a further 10%. The original request was for 24,000 units pa but is now 32,000 units. The contract allows for an increase in volume, but this will take time to arrange as additional volume needs to be agreed by the Department of Health in Poland.
- To meet the increased demand, the supplier proposes to supply 20% of the plasma from female donors. This is allowed in the specification but is subject to screening of the female donors for antibodies against Human Leucocyte Antigens (HLA) and Human Neutrophil Antigens (HNA). The proportion of women who have such antibodies increases with their parity (the number of times they have been pregnant) as they are formed against HLA or HNA antigens in the foetus or placenta. Antibodies can also form via other routes such as transfusion or transplantation. HLA and HNA antibodies in donor plasma are associated with a severe reaction in recipients known as Transfusion Related Acute Lung Injury (TRALI) which was the commonest cause of death and severe morbidity as a result of transfusion prior to 2004 in the UK (and in other countries). NHSBT screens its female donors of platelets for these antibodies and requires the supplier to demonstrate that the screening is performed to the same standard. This may be demonstrated by accreditation by the European Federation for Immunogenetics, which is expected to take four to six months to complete. There is, therefore, a risk that the larger number of units expected in deliveries in 2019 may be 20% short.
- In addition, NHSBT has been instructed by the Department for Exiting the European Union (DExEU) to mitigate the supply chain continuity risk associated with Brexit through creation of an additional six-week stock-holding before March 2019.

NHSBT has therefore extended the current contract for the provision of Austrian plasma to August 2019. This will lead to a dual supply for many months, with the associated challenge of logistics, segregation, PI treatment etc. However, this will mitigate the risk of stock outage and will replenish the depleted stocks of components made from imported plasma.

[8]Plasma Supply Project of the Council of Europe https://www.edqm.eu/en/blood-transfusion-projects-1449.html

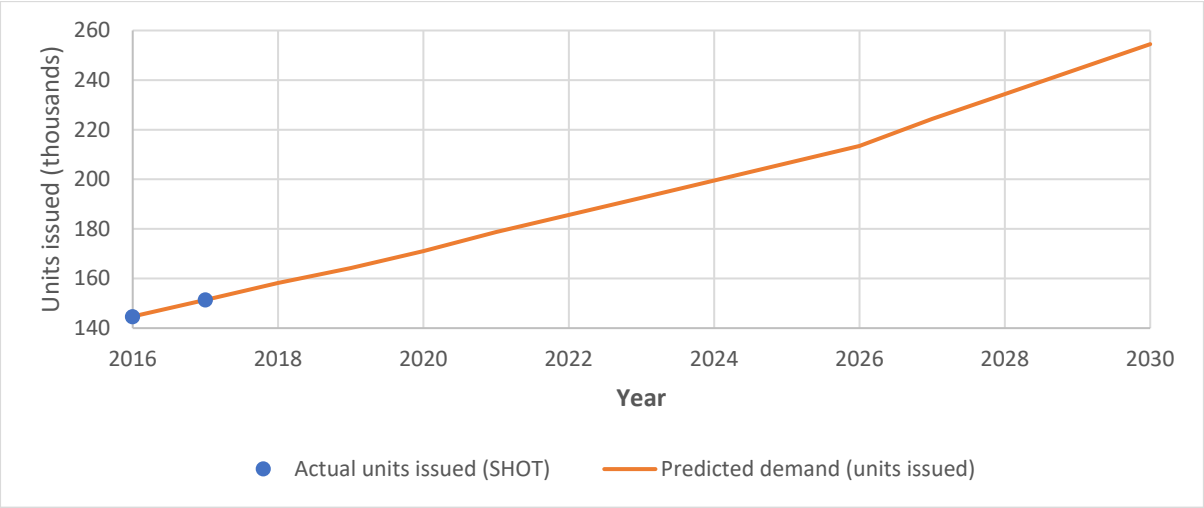
Plasma demand management and future strategy

Throughout the Summer of 2018 there was a significant risk of stock outage and mitigation plans were put in place but had any one of a number of scenarios materialised then active demand management or rationing would have been required. These scenarios included an increase in demand (>10%), a shortfall in supplied units (>10%), any production delays (>2 weeks), a delay in validation (>2 days), or increased waste/discard (>3%).

The main risk is demand for non-Group A plasma increasing by more than 10%. This has happened previously, for example when a new hospital customer begins ordering this component. Demand can be variable and as the numbers are small there is limited resilience. A number of steps had to be taken to mitigate these risks, these included: discussions with a clinical trial team to understand and reduce the additional orders resulting from hospitals participating in the trial; with other UK blood services to restrict their supply of non-Group A components; and with some hospitals that routinely use high volumes of non-Group A to see if their use could be managed differently.

If there is no change to the existing recommendations and the demand for plasma continues to grow as shown in Figure 1 whilst the supply becomes more challenging, it is likely that UK blood services will need to revise their strategy. In OctaplasLG there is a commercially available alternative product that hospitals could purchase for the treatment of patients born after 1995 that require FFP. There is no equivalent commercial product to replace non-UK cryoprecipitate (apart from off-label use of fibrinogen concentrate) and it would therefore be logical to use the imported plasma to manufacture cryoprecipitate. This presents two risks: i) commercial suppliers have no obligation to maintain their supply of FFP and could withdraw from the market at any point and nor do they have any obligation to keep prices low so without competition there is a risk of an increase in price from a monopoly supplier; and ii) the fibrinogen content of MB-cryo is considerably lower than in untreated cryoprecipitate (see Table 2) and close to that of untreated FFP so whether this is the optimal component could be questioned.

Figure 1 – Actual and predicted number of imported plasma units issued by the UK blood services each year.



Year	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Predicted issues (thousand plasma units)	171	179	186	193	199	206	213	224	234	244	254
Year-on-year increase	4%	5%	4%	4%	4%	3%	3%	5%	4%	4%	4%

Actual values are sourced from the annual SHOT report while predicted values are calculated by scaling 2017 issues by the change in population size (based on ONS 2016 projections) and usage by individuals born on or after 1st of January 1996 and with TTP (see analysis below). Key points to consider are: Usage patterns change and currently demand for FFP is declining but this is offset by an increase in demand for pooled cryoprecipitate; demand for cryoprecipitate may reduce over the long term due to the availability of alternative commercial fibrinogen products; and Road accidents (a major use of plasma products) are expected to decrease by 50% from 2012 levels by 2030 which will reduce the demand for plasma products.

Conclusions on practicalities of importing plasma

It is clear that arranging the importation of plasma to comply with the current SaBTO recommendation presents very significant operational challenges to UK blood services. Although this is manageable, it will become even more demanding in the coming years as the demand continues to increase, the supply becomes ever more challenging, regulatory requirements diverge, and jurisdictional boundaries change. In turn, this may result in increasing reliance of hospitals on commercial suppliers of FFP who have no mandate to maintain supply or prices. Furthermore, to meet increased demand, children and young adults are likely to receive plasma from screened female donors. All UK plasma is sourced from male donors to reduce the risk of TRALI (see page 20 for an explanation of TRALI risk from female donors).

Hospital operations - plasma

The current guidance and recommendations for different blood component provision for different recipient groups brings challenges to hospital practice in the blood bank, the

emergency department, in surgical and in medical care. The main challenges are around the maintenance of additional lines of inventory and the determination of a patient's age when prescribing a plasma component – this is obviously easier in some settings than others such as trauma.

Surveys of current practice – plasma component use

Two surveys were conducted in order to gather hard data on the challenges presented and on the prevalence of deviations from current guidance.

Fourteen of eighteen paediatric cardiac or high-use non-cardiac hospitals responded to the first survey, of which three reported being non-compliant with current recommendations by using UK sourced cryoprecipitate (or off-label fibrinogen concentrate) when imported plasma components should have been used according to guidelines. Five hospitals cited the higher cost of imported components as a challenge, and five cited supply issues as a challenge. Only three of the 14 hospitals reported being fully compliant with no complaints regarding the challenges this presented.

Eighteen of the 23 major trauma centres and all four children's trauma centres responded to the second survey. Only four major trauma centres use UK sourced FFP (UK-FFP) in the pre-hospital setting, with two of them using only UK-FFP, while the other two also reported using SD-FFP (OctaplasLG). The other centres reported using a mix of components – SD-FFP, UK FFP, MB-FFP and a commercially-available freeze-dried plasma. For the initial stage of resuscitation, 60% of users said that they use UK FFP, and later on they move to non-UK plasma if the patient's age required it.

In the comments received, most trauma centres indicated that rapid provision of plasma is considered more important than providing imported plasma, and therefore, in these situations UK plasma is released, usually under a pre-approved concessionary release for all patients. As soon as the age of patient is established, non-UK plasma is released where available. A recent change to the specification for UK-FFP and SD-FFP means that it may be stored, refrigerated, for up to five days after thawing so hospitals may have ready-to-use plasma on standby. This is not the case for imported MB-FFP as it has been through a pathogen inactivation process that affects the clotting factors and it is not acceptable for use more than 24 hours post thaw. The higher cost of this material and the increased chance of wastage means that hospitals do not hold any thawed units of imported MB-FFP but use UK-FFP as described above.

Anecdotal reports received from hospital transfusion laboratory managers included comments regarding the provision of a service to patients that was felt to be inferior in terms of the range and availability of components (including the use of not fully group-matched components), the lower coagulation factor content of the imported material, inappropriate stock holding levels of imported components and some examples of delays to patient treatment whilst components are sourced, thawed and prepared for administration.

Cryoprecipitate

If the current recommendations do not change, with the continual increase in demand due to the ever-expanding cohort of recipients, NHSBT has indicated that the majority of imported plasma would be used to prepare cryoprecipitate, as an alternative source of imported

plasma is available (SD-FFP, OctaplasLG). There is limited clinical evidence regarding the use of cryoprecipitate. The CRYOSTAT-2 clinical trial is underway and will assess early administration of cryoprecipitate in trauma, but it will be some time before the trial is complete. There is also a view held by some clinicians that cryoprecipitate prepared from imported and MB-treated plasma (MB-Cryo) is inferior to untreated FFP due to the reduced concentration of fibrinogen and other clotting factors, which are lost during the MB treatment process (see Table 2).

Table 2: Fibrinogen concentration of FFP, pooled and single cryoprecipitate[9]

Component	UK FFP	SD-FFP	MB-FFP	UK cryo pool	MB-cryo pool	UK single cryo	MB single cryo
Volume (mL)	267	200	229	237	291	49	46
Fibrinogen concentration (mg/ml)	2.57	2.31	1.7	7.05	4.05	8.78	5.43
Fibrinogen per unit (g)	0.69	0.46	0.39	1.67	1.18	0.43	0.25

Other considerations

It is a current SaBTO recommendation that neonates should not receive plasma components from first-time donors unless it has been pathogen reduced, and this is referenced in BSH guidelines[10]. The implications of any change to the recommendations needs to be carefully considered and included in discussions with stakeholders prior to making final recommendations.

Platelets

All UK blood services provide both apheresis and pooled platelet components, although the ratio differs between services. All services are moving away from the provision of 80% of platelets by apheresis since SaBTO rescinded its 2005 recommendation in 2013 and are using platelet additive solution (PAS) to resuspend pooled platelets in accordance with the 2013 recommendation. Pooled platelets are less expensive to manufacture as they are derived from the 'buffy coat' fraction of a proportion of the whole blood collections that are primarily used for red cell component manufacture. In comparison, apheresis platelet collections require specialist equipment with expensive consumables and are usually performed in fixed donor centres rather than on mobile sessions. Apheresis platelets are collected from a single donor and are thus of a defined HLA phenotype which may be matched to patients with specific needs. A proportion of platelet collections should therefore continue to be made using apheresis. Although there is no SaBTO recommendation to supply single donor (apheresis) platelets to younger patients, blood services made an operational decision to provide apheresis platelets, where possible, to patients who were 16 or under, and subsequently extended this to those born after 1995. The rationale was to allow alignment of provision of these components with the provision of imported FFP, so that

[9] Green L *et al;* BSH guidelines. *Br J Haematol* 2018, 181:54-67

[10] New HV *et al;* Guidelines on transfusion for fetuses, neonates and older children. *Br J Haematol*. 2016; 175:784-828

hospital IT systems could be set with consistent flags for the provision of 'paediatric components'. These requirements have since become incorporated in British Society for Haematology (BSH) guidelines. As the cohort of individuals born after 1995 grows, the demand for apheresis platelets will grow by around 1 % per annum, so it is appropriate to review this practice.

Stock management issues – platelets

Currently, hospitals can order 128 types of adult platelets given the number of options available:

- Blood group ABO and RhD (8 types)
- Apheresis or pooled (2 types)
- CMV negative or unscreened (2 types)
- High titre (HT) anti-A and anti-B neg or unscreened (2 types)
- Irradiated or not (2 types)

Each blood service, in theory, has to ensure that all 128 adult platelet options are available at each Stock Holding Unit (SHU) at all times or that appropriate substitution can be made if the precise order cannot be fulfilled. However, in practice services do not undertake proactive stock management of all 128 options for reasons of practicality and because forecasting usage and stock levels with a reasonable level of accuracy would be extremely challenging. For example, NHSBT has 15 SHUs and manages adult platelet stock only by ABO, apheresis or pooled and CMV neg or not (32 options). This is somewhat simpler for neonatal platelets, which only have 16 options (all apheresis, all CMV negative, all HT negative).

Apheresis platelets are more challenging to manage as they need to be specifically collected rather than manufactured from the numerous whole blood donations also being used for red cell and plasma manufacture. NHSBT is significantly overstocking apheresis platelets at all SHUs – around 50% of total platelets are apheresis versus demand of approximately 28%. This is due to two main reasons:

1) Apheresis platelets are used to meet demand for HLA matched platelets. A sufficiently large pool of apheresis platelet donors is needed in order to screen and select the genotypes that maintain the current level of A+B1 matching for HLA matched platelets. It is very difficult to predict demand for HLA matched platelets given the high level of matching required when a patient needs the platelets and therefore a selected individual platelet component may have to be moved to the relevant SHU to match the requirement of that patient; incurring additional transport costs to the blood service, potential delays in provision to the patient, and potential impact on the quality of the platelets during transportation[11]. If the patient age related recommendations for apheresis platelets were to change, blood services could choose to not reduce the proportion of platelets collected by apheresis, which would make operations much simpler and reduce transport costs and risks by having more HLA-typed stock available at each SHU for all patients that need matched units.

[11] Thomas S. Platelets: Handle with care; Transfus Med 2016 26:330-338

2) To optimize the costs of CMV testing, NHSBT tests all apheresis donations (one test yields two doses) but also tests around 30% of pooled platelets (four tests required for one dose). Similarly, over 90% of apheresis units are screen-negative for high titre antibodies to A and B antigens (HT neg), whilst only 70% of pooled platelets are labelled as HT neg (as a result of containing four screen-negative donations). This means that if a pooled platelet is ordered and requested as CMV neg and/or HT neg, the unit issued is more likely to be supplied from apheresis stock, which adds to the challenge of managing stock levels of this component. If the demand for apheresis platelets declines due to a change in the recipient cohort but the proportion of apheresis collections does not fall to the same degree, then these needs may be more easily met, providing a further operational benefit to the HLA stock issue mentioned above.

Hospital operations – platelets

Hospitals find it less challenging to observe the current guidelines on the use of apheresis platelet components. This is predominantly because when issuing platelets for younger patients the laboratory IT system should have controls that check the patient's date of birth and prevent component issue that is not consistent with BSH guidelines (although this may be overridden by an appropriately senior member of staff). However, some hospitals use the age of 16 as a cut-off for provision of apheresis platelets, which is not consistent with the BSH guidance that refers to those born on or after 1st January 1996.

In terms of inventory management, the need to maintain a stock of apheresis platelets in case a younger patient needs a platelet transfusion can lead to unnecessary expenditure by hospitals (in England apheresis platelets cost hospitals more than pooled platelets), the use of older platelets when the decision is made to refresh the stock, and increased wastage when the components do not get used before expiry. Data from the Account for Blood scheme in Scotland show that in hospitals the expiry rate of apheresis platelets exceeds that of pooled platelets (8 and 7 % respectively in 2017/18).

There is no qualitative difference in the function of platelets derived by apheresis or pooling buffy coats from whole blood (summarised in a paper from NHSBT[12]). The original aim of the recommendation to provide apheresis platelets to those born after 1995 was to reduce exposure to multiple donors and, therefore, exposure to vCJD. The revised vCJD risk assessment has taken this into account with regards to vCJD but an increase in the use of pooled platelets would lead to a potential increased exposure to other infectious agents – this is outside the scope of the vCJD risk assessment. If the current recommendations on provision of platelets to individuals born after 1995 to minimise exposure to vCJD was to change, clinicians would be free to use the most clinically appropriate component.

There have been a small number of incidents of 'special requirements not met' reported by the haemovigilance scheme SHOT[13]. In the 10 years 2008-2017 there were five reports

[12] http://hospital.blood.co.uk/media/28624/platelet-changes.pdf
Heddle NM *et al;* (systematic review). Comparison of corrected count increment (CCI) shows no differences between apheresis and buffy coat derived platelets; Transfusion 2008 July; 48(7):1447-1458
Slichter SJ *et al;* Type of platelet component had no relation to intertransfusion interval. Blood 2005 May15:105(10):4106-4114
TRAP study – N.England J. Med. 1997 dec 25;337(26):1861-9

[13] https://www.shotuk.org/

where pooled platelets were given instead of apheresis, but it is likely that is under reported as hospitals might not report this as an error if it was not considered possible to provide apheresis platelets. For example, in the acute transfusion reaction section of the paediatric chapter, although most allergic reactions to platelets in children are reported following transfusion of apheresis platelets, there are a number where they were following pooled platelets but the transfusions of the pooled platelets were not reported as having been given in error.

Conclusions on use of apheresis platelets

There is considerable complexity in the platelet supply chain, and this is compounded by the current recommendations regarding the age of the recipients. Collection of apheresis platelets is important for those patients that require HLA matched platelets and the ability to select from the entire inventory of apheresis platelets increases the possibility of finding a good match in a nearby SHU thus reducing the operational burden on blood services. Hospital practice would also be simplified by removing the need to retain apheresis platelets in stock just in case a younger patient should need them, thus reducing complexity and wastage.

Concluding thoughts on blood service and hospital operations

The current recommendations require blood services and hospitals to undertake significant additional work in the maintenance of numerous supply chains for plasma and platelets. The provision of imported plasma components is particularly challenging for blood services due to commercial and regulatory challenges, and the practicalities of clinical practice mean that hospitals are not always compliant with the recommendations. Management of the platelet supply chain is also complicated by the need to provide apheresis platelets for an expanding cohort, potentially impacting on provision of HLA-matched platelets for specific patients.

6. Analysis of vCJD risk reduction measures for plasma and platelets

Background

There are currently several vCJD risk reduction measures in place: leucodepletion of blood components (1999); importation of fractionated plasma derivatives (1998); excluding recipients of blood components and products from donating (2004); and the use of apheresis platelets[14] and imported non-UK sourced plasma for recipients in specific groups[15].

This analysis considers changes to only two of these measures: the importation of plasma, for the manufacture of Fresh Frozen Plasma (FFP) and cryoprecipitate (single and pooled), and the use of apheresis platelets as vCJD risk reduction measures. All other risk reduction measures are assumed to remain in place.

This work is an update on previous analysis presented to SaBTO (importation of plasma in 2012 and use of apheresis platelets in 2013). The following areas are outside the scope of this report:

- Changes to the use of leucodepletion, due to the many other benefits it brings in reducing adverse transfusion reactions and transmissions of infections such as Cytomegalovirus (CMV);
- importation of fractionated plasma derivatives, as this is outside the remit of SaBTO; and
- the exclusion of recipients of blood (after 1980) from donating, as this prevents the onward transmission of infections while having negligible impact on supply.

While the importation of plasma and use of apheresis platelets are believed to reduce vCJD risk they impose sizeable operational and economic burdens on the health services, introduce new risks associated with sufficiency of supply, and present operational difficulties at the point of use. As there have been no documented transmissions of vCJD via blood components since universal leucodepletion was introduced in 1999[16] and no documented transmissions via plasma[17] or platelets, it is appropriate to conduct a review of these measures.

This analysis assesses the impact to the health service of replacing imported non-UK sourced plasma with components sourced from the UK and replacing apheresis platelets with pooled platelets. To do this the direct costs of purchasing the relevant components are compared with the estimated number of clinical cases of vCJD. It deals with uncertainty by

[14] Following SaBTO's 2013 removal of the requirement to collect 80% of platelets by apheresis, NHSBT and other UK Blood Services took an operational decision to continue to supply apheresis platelets to patients born after 1st January 1996 (an extension to the under-16 category). This practice was incorporated into the BCSH paediatric guidelines published in 2016

[15] Recipients born on or after 1st January 1996 (2002) and those suffering from thrombotic thrombocytopenic purpura (2006)

[16] The last documented case of vCJD due to transmission via blood components died in 2006 and, like the other 2 cases, was infected by a transfusion of non-leucodepleted red blood cells

[17] The term plasma is used throughout this report to refer to both Fresh Frozen Plasma (FFP) and Cryoprecipitate (either single or pooled)

implementing logic taking precautionary assumptions which are more likely to overstate than understate the number of future cases.

The analysis does not include:

- vCJD infections that do not progress to clinical cases and so death as subclinical infections are assumed to result in no loss in health;
- any difference in risks due to infections other than vCJD or other clinical factors such as different component efficacies;
- further costs or savings that could occur due to operational changes to implement any proposed changes; or
- any reputational damage or litigation costs associated with vCJD infections (either symptomatic or asymptomatic).

Scenarios modelled

The options being considered in this report for both plasma and platelets are listed below. In each case it is assumed that the modelled option will be implemented by the start of calendar year 2020 and costs and benefits are discounted at the standard 1.5% rate. As the modelling assumes that dietary exposure to vCJD in the general population has been negligible since the year 2000 and that the maximum age of whole blood and apheresis donors are 70 and 80 years respectively, time horizons of 2070 and 2080 are used for calculating the costs associated with the different plasma and platelet options respectively.

UK data has been used for the total number of annual issues while SNBTS data on transfusion recipients has been combined with NHSBT data and current practice to calculate the proportions of each component type as NHSBT are the UK's largest blood service. Post transfusion survival rates have been fitted to the 10-year aggregated results of the EASTR study as a breakdown by the recipient type and number of components received was not available.

Plasma

Six options are considered compared to the current practice of providing importing non-UK sourced FFP and cryoprecipitate to all patients born on or after 1st January 1996 and those with thrombotic thrombocytopenic purpura (TTP):

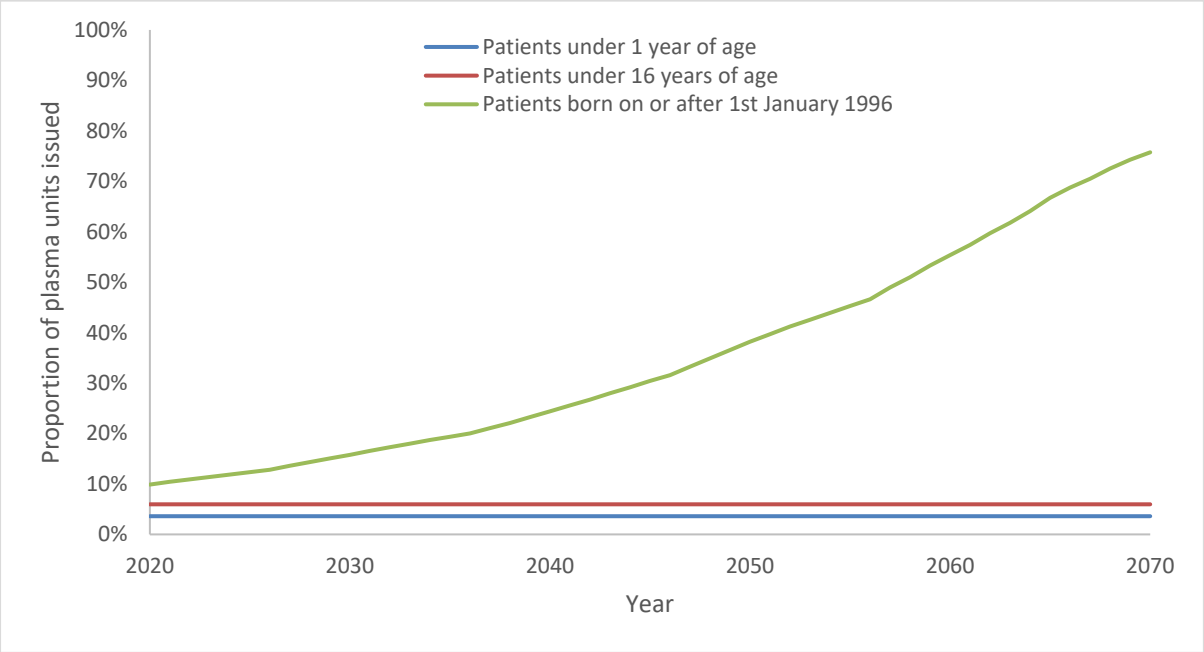
Option	Recipients of non-UK sourced FFP and cryoprecipitate
U16 + TTP	Patients under 16 years of age All patients with TTP
U1 + TTP	Patients under 1 year of age All patients with TTP
None + TTP	All patients with TTP only
U16	Patients under 16 years of age only
U1	Patients under 1 year of age only
None	None

The modelling makes the following key assumptions:

1. The total number of issues[18] are assumed to remain constant at 2017 levels[19] with 315k units of adult FFP, 6k units of neonatal FFP, 23k units of cryoprecipitate (pooled), and 12k units of cryoprecipitate (single) issued by the UK blood services annually[20];
2. There is no vCJD risk from all imported non-UK sourced plasma;
3. UK and non-UK sourced components can be used interchangeably (including for TTP recipients);
4. TTP recipients are modelled as receiving 3.3% of the total FFP issued per year (around 12k units)[21].

While overall demand is assumed to be constant, the proportion of the recipient population that belong to the group of patients born on or after 1st January 1996 is modelled as increasing each year and can be seen in Figure 2. In addition to the six-options being modelled, the cost implications of the different potential suppliers of imported FFP will be considered: Methylene Blue treated FFP (MB-FFP) supplied by NHSBT; and Solvent Detergent treated FFP (SD-FFP) a commercially available alternative product. Currently, cryoprecipitate is only supplied by NHSBT.

Figure 2 Proportion of plasma units issued by recipient group over modelled time horizon.



A break-down of the total annual UK plasma units issued by recipient group used in the modelling can be seen in Table 3.

[18] The modelling assumes that all issued units will be transfused to patients which is a precautionary assumption

[19] PHB Bolton-Maggs (Ed) D Poles et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2017 Annual SHOT Report (2018).

[20] The cost-effectiveness calculation will not be affected by any change in demand, assuming the relative proportion of each unit issued remains the same, as any increase in issues will lead to a corresponding increase in clinical cases

[21] Derived from data provided by University College London Hospitals (UCLH)

Table 3: Annual issues of both UK and imported non-UK sourced plasma units broken down by type and recipient group used in the modelling.

Plasma Units (k)	U1	U16 (excl. U1)	Remaining	Total
Neonatal FFP	5.6	-	-	5.6
FFP	0.9	3.8	310.6	315.4
- TTP Recipients	-	0.2	11.4	11.7
- Other Recipients	0.9	3.6	299.2	303.7
Cryoprecipitate (single)	6.3	4.5	1.5	12.3
Cryoprecipitate (pooled)	-	0.1	23.3	23.3
Total	12.9	8.4	335.4	356.6

Platelets

For platelets, three options are considered compared to the current practice of providing 50% apheresis platelets:

Option	Recipients of apheresis platelets
U16	Patients under 16 years of age
U1	Patients under 1 year of age
None	None

The modelling makes the following key assumptions:

- The total number of issues are assumed to remain constant at 2017 levels[22] with 314k units of platelets issued by the UK blood services annually of which 157k units are apheresis platelets (8k neonatal and 149k adult) and 157k are pooled platelets in platelet additive solution (PAS)[23];
- Apheresis and pooled platelets can be used interchangeably;
- Apheresis platelets are preferentially transfused to younger patients, this will maximise the impact of any change; and
- The modelling does not include the impact of HLA matched apheresis platelets (around 6% of all issues).

A break-down of the total annual UK platelet units issued by recipient group used in the modelling can be seen in Table 4.

[22] PHB Bolton-Maggs (Ed) D Poles et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2017 Annual SHOT Report (2018).

[23] The cost-effectiveness calculation will not be affected by any change in demand, assuming the relative proportion of each unit issued remains the same, as any increase in issues will lead to a corresponding increase in clinical cases

Table 4: Annual issues of platelet units broken down by type and recipient group used in the modelling.

Platelet Units (k)	U1	U16 (excl. U1)	Remaining	Total
Apheresis (neo)	7.8	-	-	7.8
Apheresis (adult)	3.6	24.1	121.3	149.0
Pooled in PAS	-	-	156.8	156.8
Total	11.4	24.1	278.1	313.6

Estimated future vCJD cases and infections associated with transfusion

The Department of Health and Social Care has previously developed a risk assessment model to estimate the future number of blood-borne vCJD cases and infections that might be prevented by stopping new transmissions. The model takes account of a range of evidence on relevant inputs (e.g. potential infectivity of components, annual number of units transfused, post transfusion survival), while also using calibration to take into account uncertainty around under-ascertainment and the continued absence of new clinical cases attributable to transfusion – and the lack of any known cases attributable to plasma or platelet components.

The underlying methodology used in the model was originally published in 2013[24]. This is a highly precautionary model as it deals with uncertainty by implementing logic that would potentially increase the number of future cases: it assumes the existence of a subclinical vCJD carrier state and includes a scenario in which the observed clinical cases are due to a small "rapid onset" recipient group with a greater number of future cases yet to occur; it assumes all recipients of *infective* units will be infected (though may not go on to develop clinical symptoms); the calibration allows for a high number of clinical cases to have already occurred but been missed due to under-ascertainment; and it uses ranges for its input parameters that include "worst case" values such as a population prevalence of subclinical carriers as high as 1 in 1,000.

The 2013 model has since been revised: to update the calibration parameters to account for the lack of any further known cases attributable to transfusion and the possibility of greater under-ascertainment in the elderly; to incorporate ACDP TSE's more precautionary interpretation of the Appendix III prevalence study[25]; to include additional types of component not previously explicitly modelled, specifically cryoprecipitate and pooled platelets in PAS; and to reflect results from ovine experiments about the relative infectivity of

[24] Bennett PG and Daraktchiev M. (2013) "vCJD and transfusion of blood components: an updated risk assessment" https://www.gov.uk/government/publications/vcjd-and-transfusion-of-blood-components-updated-risk-assessment

[25] ACDP TSE. (2016) "Updated position statement on occurrence of vCJD and prevalence of infection in the UK" https://app.box.com/s/hhhhg857fjpu2bnxhv6e

platelets and the impact of leucodepletion on the transmission probability of plasma and platelet components.[26]

In previous work when modelling platelets, it was assumed that the majority of infectivity is associated with any residual plasma volume in the unit as this was supported by rodent experiments. Recently there has been a growing body of literature that suggests that determining the infectious titre of blood components by intracranial inoculation of rodents does not accurately predict their ability to transmit when administered intravenously. Results from ovine experiments suggest that the majority of infectivity is instead associated with platelets themselves[27] and so the model has been updated to account for this effect.

The revised model was considered by the ACDP TSE Sub Group at its meetings of 8th February 2018 and, following further specific correspondence between the author and committee members who recommended changes, was re-circulated by email to members in August 2018. The committee were happy to support it as providing both a highly precautionary estimate of the number of future cases and infections and also the only practicable way of assessing the benefit of further interventions until more empirical evidence is available. Specific figures for the number of cases and infections, while uncertain and subject to revision in the light of further data, are considered to be of the right order of magnitude.

To account for the uncertainty in why there has only been a small number of clinical cases seen to date associated with all blood transfusions, for each component option being modelled (six plasma and three platelet - see above) two scenarios[28] are used. Under each scenario, initially the different input parameters are randomly sampled from their possible ranges. The model is then run using these inputs and the output kept only if it produces estimates for the number of clinical cases that agrees with the calibration. This process is repeated until 60,000 calibrated outputs (30,000 under each scenario) for each component option have been produced. The 95% Credible Interval (CI) is then calculated by selecting those runs for which there are 1,500 other runs that produce either greater or lower output giving the upper and lower bound respectively.

This gives the following range of estimates for the number of total infections and the number of clinical vCJD cases that might result from transfusions taking place from 2020 onwards in plasma and platelets under the current practice:

[26] Details of ovine model can be found in McCutcheon S et al. (2011) "All Clinically-Relevant Blood Components Transmit Prion Disease following a Single Blood Transfusion: A Sheep Model of vCJD." PLOS ONE 6(8): e23169. https://doi.org/10.1371/journal.pone.0023169

[27] See above

[28] Rapid onset MM subgroup and variable clinical attack rate

Table 5: Number of future infections and clinical cases of vCJD estimated by the DHSC risk assessment model for plasma (FFP and cryoprecipitate) and platelet (apheresis and pooled) components under the current practice.

Component	Future infections	Future cases[29]		
		Infected before 2020	Infected from 2020 onwards	Total
Plasma	57 (1 - 309)	4.9 (0.1 - 48.4)	2.8 (<0.05 - 27.1)	7.9 (0.2 - 72.8)
Platelet	124 (2 - 989)	5.3 (0.1 - 67.3)	5.7 (0.1 - 69.9)	11.2 (0.2 - 136.9)

Only cases infected from 2020 onwards can potentially be averted if all vCJD risk is mitigated. Values are medians and numbers in brackets are 95% credible intervals. Note values may not sum as they are taken over distributions.

The estimated number of clinical cases each year for plasma and platelets can be seen in Figure 3 and Figure 4 respectively and show that the annual number of clinical cases estimated remains low, albeit with high uncertainty, and spread over several decades.

For plasma, the annual number of cases remains small with a peak value of between <0.05 and 2.1 clinical cases per year (median value 0.2). The median distribution has a single peak centred at 2029. The upper 95% CI distribution also has a single peak of 2.1 clinical cases per year centred at 2042. Both the median and upper 95% CI exhibit long tails with future cases going out to around 2080 and 2090 respectively.

For platelets, the pattern in the annual number of cases is similar to that in plasma but exhibiting a higher potential maximum with a peak value of between <0.05 and 3.5 clinical cases per year (median value 0.3). The distributions are also wider than for plasma leading to a greater number of total cases spread across a greater time. The median has a peak value of 0.3 centred at 2035 while the upper 95% CI has a single peak of 3.5 centred 2047. Again, both median and 95% CI distributions exhibit long tails with future cases going out to around 2090 and 2100 respectively.

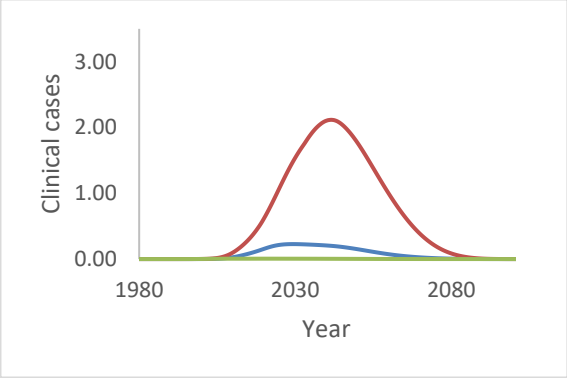


Figure 3: Estimated number of clinical cases due to plasma transfusions: median (blue); upper 95% CI (red); and lower 95% CI (green)

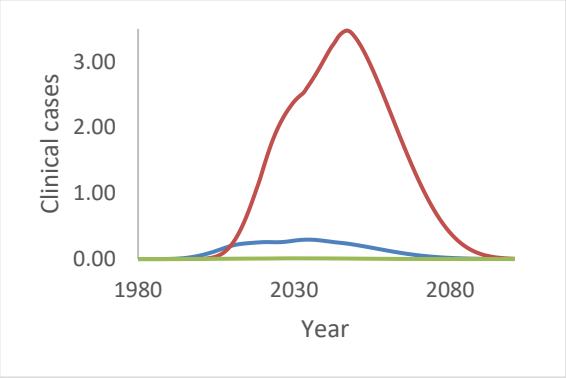


Figure 4: Estimated number of clinical cases due to platelet transfusions: median (blue); upper 95% CI (red); and lower 95% CI (green)

[29] All figures are probabilistically weighted averages over the population so can be fractional

The estimated number of clinical cases by year of infection for plasma and platelet can be seen in Figure 5 and Figure 6respectively. The shape of all the distributions is broadly similar with the future number of clinical cases tailing off from its current maximum such that 95% of future infections have occurred by 2039 and 2045 for plasma and platelets respectively.

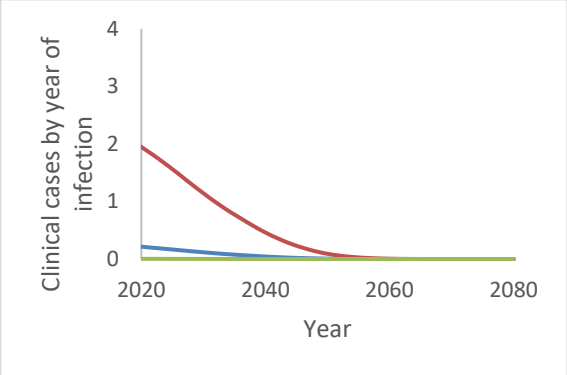


Figure 5: Estimated number of clinical cases due to plasma transfusions by year of infection: median (blue); upper 95% CI (red); and lower 95% CI (green)

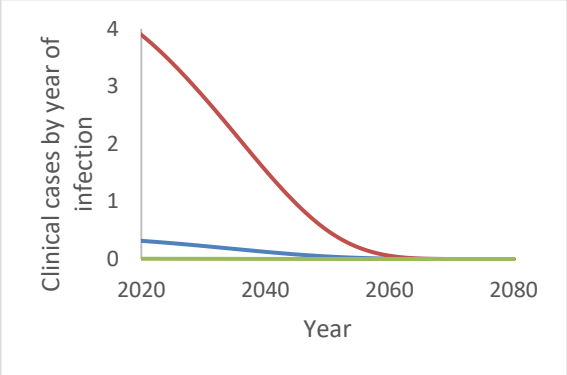


Figure 6: Estimated number of clinical cases due to platelet transfusions by year of infection: median (blue); upper 95% CI (red); and lower 95% CI (green)

Modelled options

The following additional infections and cases are estimated for each option being considered compared to the estimated future number under the current practice:

Table 6: Number of infections and clinical cases of vCJD estimated by the DHSC risk assessment model for plasma (FFP and cryoprecipitate) and platelet (apheresis and pooled) components under the different options being considered due to infections from 2020 onwards. Values are medians and numbers in brackets are 95% credible intervals.

Component	Option	Infections (from 2020 onwards)		Clinical cases (Infected from 2020 onwards)	
		Total	Additional	Total	Additional
Plasma	Current practice	57 (1 - 309)	-	2.8 (<0.05 - 27.1)	-
	U16 + TTP	65 (1 - 353)	8 (0 - 44)	3.6 (0.1 - 36.9)	0.8 (<0.05 - 9.8)
	U1 + TTP	66 (1 - 359)	9 (0 - 50)	3.8 (0.1 - 38.7)	1.0 (<0.05 - 11.6)
	None + TTP	68 (1 - 370)	11 (0 - 61)	4.0 (0.1 - 41.2)	1.2 (<0.05 - 14.2)
	U16	68 (1 - 368)	11 (0 - 59)	3.7 (0.1 - 37.7)	0.9 (<0.05 - 10.6)
	U1	69 (1 - 375)	12 (0 - 66)	3.9 (0.1 - 39.6)	1.1 (<0.05 - 12.4)
	None	71 (1 - 387)	14 (0 - 78)	4.1 (0.1 - 42.2)	1.3 (<0.05 - 15.0)
Platelet	Current practice	124 (2 - 989)	-	5.7 (0.1 - 69.9)	
	U16	164 (2 - 1309)	40 (1 - 319)	8.1 (0.1 - 103.6)	2.4 (<0.05 - 34.0)
	U1	173 (2 - 1382)	49 (1 - 393)	8.6 (0.1 - 110.7)	2.9 (<0.05 - 41.1)
	None	176 (2 - 1409)	52 (1 - 419)	8.8 (0.1 - 114.6)	3.1 (<0.05 - 44.9)

While the relative increase in clinical cases infected from 2020 onwards is high the absolute number of cases remains low under all options. The risk of a clinical case of vCJD per million units transfused broken down by proposed option can be seen in Table 7 and Table 8 for plasma, and platelets respectively. In all cases, the median additional risk is less than 1 per one million units transfused (less than 1 per two hundred thousand units transfused for the upper 95% CI). Generally, the risk decreases with increasing recipient group age as older patients tend to die before clinical symptoms occur due to the long incubation times of vCJD.

Table 7: Number of additional UK units transfused, clinical cases and risk by proposed option for plasma over the 50 years modelled. Values are medians and numbers in brackets are 95% credible intervals.

Option	Additional UK units (m)	Additional clinical cases (Infected from 2020 onwards)	Average units per additional clinical case (m)
U16 + TTP	4.99	0.8 (<0.05 - 9.8)	6.2 (0.5 - 461.4)
U1 + TTP	5.41	1.0 (<0.05 - 11.6)	5.7 (0.5 - 426.2)
None + TTP	6.06	1.2 (<0.05 - 14.2)	5.2 (0.4 - 391.6)
U16	5.59	0.9 (<0.05 - 10.6)	6.1 (0.5 - 450.8)
U1	6.00	1.1 (<0.05 - 12.4)	5.7 (0.5 - 417.7)
None	6.66	1.3 (<0.05 - 15.0)	5.2 (0.4 - 387.8)

Table 8: Number of additional pooled platelet units transfused, clinical cases and risk by proposed option for platelets over the 60 years modelled. Values are medians and numbers in brackets are 95% credible intervals.

Option	Additional pooled platelet units (m)	Additional clinical cases (Infected from 2020 onwards)	Average units per additional clinical case (m)
U16	7.40	2.4 (<0.05 - 34.0)	3.1 (0.2 - 240.9)
U1	8.87	2.9 (<0.05 - 41.1)	3.1 (0.2 - 237.2)
None	9.56	3.1 (<0.05 - 44.9)	3.1 (0.2 - 236.5)

Table 9 shows the risk for red blood cells determined by the model. This risk is lower than that for any recipient group for both plasma and platelets despite the fact that three clinical cases of vCJD have been documented due to transmissions by red blood cell transfusions and none due to plasma or platelets. The higher risk of plasma and platelets is, in part, because of the greater uncertainty in these components due to the lack of clinical cases of vCJD and the smaller number of units transfused to date.

Table 9: Number of units transfused, clinical cases and risk by recipient group for red blood cells over the 50 years modelled. Values are medians and numbers in brackets are 95% credible intervals.

Units transfused (m)	Clinical cases (Infected from 2020 onwards)	Average units per additional clinical case (m)
90.4	8.2 (0.4 - 49.6)	11.0 (1.8 - 252.2)

Cost and benefits

Quality-Adjusted life years (QALYs) lost

To estimate the number of QALYs lost per modelled clinical vCJD case, the model makes the following assumptions:

- Transfused patients have a lower life expectancy than the general population;
- The average QALY value of a year of life by age of an infected patient is the same as that in the general population (this will over-estimate the cost-effectiveness of the current risk reduction measure due to transfused patients being in less-than-perfect health);
- The QALY value of a year of life is zero once clinical symptoms of vCJD emerge, and that there will be no cure or effective treatment that will substantially mitigate the effect of this disease (this will over-estimate the cost-effectiveness of the current risk reduction measure due to patients with vCJD symptoms having a non-zero quality of life); and
- There is no QALY loss in patients who are infected but do not show clinical symptoms.

The average discounted QALY loss per clinical case by age is as shown in Table 10.

Table 10: Average lifetime QALYs of the general population and QALY loss per clinical case of vCJD (both discounted at 1.5%) and distribution of recipients by age for plasma and platelets. Values of average QALY loss per clinical case are medians and numbers in brackets are 95% credible intervals.

Age group	Proportion of recipients[30]		Average lifetime QALYs of the general population (discounted)[31]	Average QALY loss per clinical case at onset of clinical symptoms* (discounted)
	Plasma	Platelets		
<1	4%	4%	42	25 (18 - 33)
1 – 15	2%	8%	39	22 (16 - 31)
16 – 30	7%	10%	33	17 (11 - 25)
31 – 40	7%	9%	28	13 (7 - 20)
41 – 50	12%	14%	22	9 (5 - 16)
51 – 60	15%	19%	18	6 (3 - 12)
61 – 74	29%	22%	12	4 (2 - 8)
75+	24%	15%	6	2 (2 - 5)

*Note that values for plasma and platelets are broadly similar

As can be seen, the average QALY loss per clinical case is lower than that due to the death of an individual of the same age in the general population. This is due in part to the reduced life-expectancy of transfused patients but also the delay in the onset of clinical symptoms following infection meaning that infected patients are older. While the average QALY loss for younger recipients is higher the majority of plasma and platelets are transfused to the older population.

The estimated number of additional QALYs lost under each option is then calculated by applying these values to the number of additional clinical cases by age (Table 6). The standard discount rate of 1.5% per year is then applied to the QALYs lost.

Costs

Two scenarios are modelled for the cost and cost-effectiveness of plasma: MB-FFP / SD-FFP, in which the current proportion of imported non-UK sourced MB-FFP and SD-FFP units (91% SD-FFP and 9% MB-FFP imported non-UK units) remains constant; and SD-FFP only, in which imported non-UK sourced SD-FFP units are used exclusively for both adult and neonatal transfusions.

The unit costs used can be seen in Table 11 and Table 12, NHSBT 2018/2019 prices have been used for units sourced from the UK and imported non-UK sourced MB treated units

[30] Distributions derived from usage data supplied by Scottish National Blood Transfusion Service (SNBTS)

[31] Derived from ONS national life tables 2014-2016 and Szende, A., Janssen, B., & Cabases, J. (Eds.). (2014). Self-reported population health: an international perspective based on EQ-5D. Dordrecht (The Netherlands): Springer Netherlands.

while an indicative unit price of £75[32] has been used for imported non-UK sourced SD-FFP units.

Table 11: Unit costs of different plasma units based on source

Unit	Unit cost (£)		
	UK	MB	SD
FFP	28.46	183.53	75.00
Neonatal FFP	15.00*	51.40	75.00**
Cryoprecipitate (pooled)	177.55	1,113.45	NA
Cryoprecipitate (single)	31.63	192.99	NA

* These units are not currently produced and so estimated costs have been provided by NHSBT
** There is no commercially available alternative to neonatal FFP units so an adult unit must be used instead.

Table 12: Unit costs of different platelet units

Unit	Unit cost (£)
Platelets pooled in platelet additive solution (PAS)	185.86
Platelets apheresis	231.50
Neonatal platelets apheresis	91.04
Neonatal platelets pooled in PAS*	70.00

* These units are not currently produced and so estimated costs have been provided by NHSBT

The unit costs are then combined with the annual number of units issued (Table and Table) under each option across the modelled time horizon to give the total savings seen in Table 13 and Table 14. For plasma, if all hospitals were to move to using SD-FFP instead of MB-FFP there would be an additional discounted saving of £30m across the 50 years modelled.

All costs are discounted at the standard health benefit rate of 1.5% per year.

[32] Indicative price provided by NHSBT and based on the price differential validated by hospitals as part of NHSBT's outline consultation to understand any potential shift in demand to UK FFP.

Table 13: Undiscounted savings from using UK plasma instead of imported plasma under each proposed option in year 1, year 1 to 10, and over the 50 years modelled assuming imported non-UK sourced plasma remains in current proportion of MB-FFP / SD-FFP or moves to SD-FFP only.

Option	Year 1 savings (£m)		Year 1 to 10 savings (£m)		Total savings (£m)	
	MB-FFP / SD-FFP	SD-FFP only	MB-FFP / SD-FFP	SD-FFP only	MB-FFP / SD-FFP	SD-FFP only
U16 + TTP	2.1	2.2	33.1	34.5	686.7	693.9
U1 + TTP	3.1	3.2	43.0	44.1	737.0	742.5
None + TTP	4.5	4.6	56.9	58.0	808.0	813.6
U16	2.7	2.8	39.5	39.9	719.3	721.0
U1	3.7	3.7	49.5	49.5	770.3	770.2
None	5.1		63.4		841.3	

Table 14: Undiscounted savings from using pooled platelets instead of apheresis platelets under each proposed option in year 1, year 1 to 10, and over the 60 years modelled.

Option	Year 1 savings (£m)	Year 1 to 10 savings (£m)	Total savings (£m)
U16	5.5	55.4	337.8
U1	6.6	66.4	404.9
None	7.0	69.6	424.8

Cost-effectiveness

All options being considered in this analysis result in the *loss* of QALYs for greater *savings* to the UK health system. As this effectively represents selling a QALY, if an option has an incremental cost-effectiveness ratio (ICER)[33] greater than the standard threshold of £15k per QALY[34] it represents good value for money and should be adopted (as QALYs can be purchased more efficiently elsewhere by the health system).

Plasma

Looking at the ICER of all the proposed options (see Table 15), even in the very precautionary case of the upper 95% CI, moving to any of the proposed options from the current practice represents value for money for the UK health system as they are all significantly above the £15k per QALY threshold. Moving to using only UK plasma for all recipients would maximise the potential savings of £520m (discounted) over the next 50 years, at the risk of 1.3 (<0.05 – 15.0 95% CI) additional clinical cases of vCJD.

As the British Society for Haematology (BSH) Guidelines on the diagnosis and management of TTP recommend the use of SD-FFP these patients should continue to receive SD-FFP.

[33] The incremental cost-effectiveness ratio is defined as the difference in cost between the current practice and proposed options divided by the difference in their health effect (change in QALYs)
[34] The opportunity cost used in DHSC impact assessments

As the additional cost of SD-FFP for TTP patients is only £540k per year, under this option the potential savings would be £501m (discounted) over the next 50 years, at the risk of 1.2 (<0.05 - 14.2 95% CI) additional clinical cases of vCJD.

Table 15: Additional (discounted) QALYs loss, savings, and ICER of each option being considered assuming imported non-UK sourced plasma remains in current proportion of MB-FFP / SD-FFP or moves to SD-FFP only. QALY and ICER values medians and numbers in brackets are 95% credible intervals.

Option	Additional QALY loss	Savings (£m)		ICER (£m per QALY)	
		MB-FFP / SD-FFP	SD-FFP only	MB-FFP / SD-FFP	SD-FFP only
U16 + TTP	8.9 (0.1 - 87.6)	413	418	46 (5 - 3,183)	47 (5 - 3,222)
U1 + TTP	11.5 (0.2 - 115.3)	448	452	39 (4 - 2,705)	39 (4 - 2,728)
None + TTP	15.7 (0.2 - 159.7)	497	501	32 (3 - 2,201)	32 (3 - 2,218)
U16	9.9 (0.1 - 94.1)	435	437	44 (5 - 3,010)	44 (5 - 3,018)
U1	12.5 (0.2 - 121.9)	471	471	38 (4 - 2,585)	38 (4 - 2,584)
None	16.8 (0.2 - 166.4)	520	520	31 (3 - 2,143)	31 (3 - 2,143)

Platelets

The situation for platelets is similar to that with plasma (Table 16), with all options even under the upper 95% CI representing good value for money to the UK health system. Moving to using only pooled platelets in PAS for all recipients would maximise the potential savings of £277m (discounted) over the next 60 years, at the risk of 3.1 (<0.05 – 44.9 95% CI) additional clinical cases of vCJD.

Table 16: Additional (discounted) QALYs loss, savings, and ICER of each option being considered for apheresis platelet use. QALY and ICER values medians and numbers in brackets are 95% credible intervals.

Option	Additional QALY loss	Savings (£m)	ICER (£m per QALY)
U16	24.2 (0.4 - 254.2)	220	9.1 (0.9 - 628.0)
U1	34.1 (0.5 - 365.9)	264	7.8 (0.7 - 537.8)
None	39.2 (0.6 - 431.4)	277	7.1 (0.6 - 493.9)

It is interesting to note that moving from the current strategy in platelets to any of the proposed options is less cost-effective than it is for plasma (i.e. it saves less per QALY). This is due to two reasons: there is a greater vCJD risk posed by pooled platelets, increasing the number of QALYs lost, due to the greater donor exposure[35]; and there is a smaller difference in unit price between pooled and apheresis units compared with imported non-UK and UK sourced plasma, reducing the savings. In 2013 SaBTO removed the requirement to produce 80% of platelets by apheresis as a vCJD risk reduction measure.

Other issues and considerations

Uncertainty

The vCJD estimates have a high degree of uncertainty represented by the large range in the estimated number of future infections and clinical cases. For each additional year that passes without an observed clinical case this will decrease the estimated number of future clinical cases making the proposed options even more cost-effective.

If clinical cases of vCJD do start to appear then this will also impose further constraints on the calibration of the model, or may require the model to be redeveloped entirely, and so it is recommended that this analysis be revisited as some options might become less cost-effective.

vCJD infections

The risk assessment model only considers the QALY loss of vCJD infections that develop into clinical cases. At present there is no test to determine if an individual is currently an asymptomatic carrier of vCJD but if one were to be licensed the QALY loss due to infection associated with blood transfusions might need to be considered. In addition to the QALY loss, this may also pose a further reputational risk to the UK Blood Services and open them up to litigation.

The model also assumes that imported non-UK sourced plasma has no vCJD risk. If this were to change then it would make the proposed options even more cost-effective.

Clinical considerations

This report only considers the QALY loss associated with additional clinical cases of vCJD and does not consider other infections. As imported non-UK sourced plasma is chemically treated as a pathogen reduction step there may be additional benefits associated with a potential reduction in bacterial and viral transfusion transmitted infections (TTIs). This needs to be weighed against the fact that pathogen reduction has a negative impact on the coagulation factor content of plasma, potentially reducing its clinical efficacy.

The use of single donor units for both plasma and platelets will also reduce the risk of other TTIs due to the decrease in exposure (especially compared to very large pools such as those used for the manufacture of SD-FFP) but there may be additional benefits to pooling such as more consistent properties and fewer reactions.

[35] While cryoprecipitate (pooled) has an even greater donor exposure far fewer units are issued annually than platelets pooled in PAS

Matched platelets

No consideration has been made to the supply of HLA matched platelets. Currently, a high proportion of apheresis platelets are collected so that matched apheresis units can, in general, be supplied off-the-shelf. This may make the proposed decrease in apheresis platelets under any of the proposed options unfeasible or may necessitate a move to a call-up model of matched platelets. The costing impact of this change is outside the scope of this report.

Operational

UK sourced plasma that is surplus to requirements or not suitable for issue must be disposed of by the UK Blood Services at an additional cost. If the requirement for non-UK sourced plasma were to be removed then less of this plasma would need to be disposed of representing an additional saving.

The modelling makes no assumptions about sufficiency of supply (especially for less common blood groups) or how a change in demand under the proposed options for imported non-UK sourced MB plasma might impact the unit price. It is further assumed that the price of SD-FFP will remain the same once the MB-FFP alternative has been removed.

It has been assumed that if the UK Blood Services move to only using UK sourced plasma and pooled platelets in PAS, the increase in demand for whole blood donations could be met without additional cost.

7. Stakeholder Engagement

A stakeholder engagement plan was prepared by the review group and agreed with the full SaBTO committee on the 17th January 2019. Stakeholder information and FAQ sheets were prepared and sent with a covering letter to stakeholders after the SaBTO meeting. The information sheet contained provisional recommendations made by the working group and asked for feedback in time for the next SaBTO meeting. Feedback could be provided in writing and/or by representation at engagement meetings held in March 2019. A list of stakeholders and stakeholder documentation is provided in appendix 1.

Initial engagement meetings with the Haemophilia Society and Haemophilia Scotland recommended changes to the information sheet and FAQs and revised versions of these documents were sent to stakeholders in March.

Formal stakeholder meetings were held on the 12th & 13th March and included Haemophilia Society, Haemophilia Scotland, Haemophilia Wales, CJD Support Network, Bristol Royal Infirmary, Great Ormond Street Hospital, Birmingham Woman & Children's Hospital, Octapharma and Macopharma. Representatives of SaBTO & the working group also attended a forum meeting of the TTP Network on the 7th March.

Written responses were received from the Sickle Cell Society, Bristol Royal Infirmary, Haemophilia Scotland and the CJD Support Network.

Overall, the responses fell into three broad categories

Patient groups, including charities and clinical networks representing patients

- These groups had many suggestions to improvements in the way SaBTO was seeking to communicate the recommendations, these were noted and reflected in the changes to the stakeholder documentation and the final report to SaBTO.
- There was a general appreciation that SaBTO had sought to engage with them and provided an opportunity to listen to their views.
- Groups representing patients were aware of and generally understood the reasons for recommending the proposed changes. However, they thought it was not appropriate to be considering changes while the Infected Blood Inquiry was underway, particularly as vCJD transmission risk was within its remit. *It should be noted the Working Group was established before the IBI was announced*
- Some groups representing patients reported that they could not support any changes that could result in an increase in risk to patients, as this would be a failure in the duty of care to the individuals they represent. This view was not always held by affected individuals or their relatives, some of whom were reported to be in support of the proposals.
- Individuals with haemophilia are classified as having an enhanced risk of vCJD from exposure to blood components and products. This has a significant impact on access to healthcare services and can also have an emotional impact. If the risk of exposure to vCJD was now considered to be lower, then could the risk status of

these individuals be revised? *It was noted that this issue was not a matter for SaBTO but the Chair would ask Ministers to look at this issue.*

- It was not clear in the Report whether the risk assessment took into account cases of vCJD that were predicted to occur later in infected individuals with the MV or VV codon 129 genotypes. *The model took account of the current evidence on vCJD prevalence and the potential for additional cases with MV and VV genotypes*.

- Any ethical concerns over maintaining these measures could be overcome if the measures were extended to everyone. *SaBTO had considered and rejected universal provision of imported plasma in 2008*.

- The use of QALYs was difficult to accept for the infected blood community and haemophilia community as it felt like a 'figure on the value of life'

Clinicians treating individuals affected by the proposals

- There was concern that the clinicians would have to prescribe UK sourced plasma even if the available component or product was not clinically appropriate or against treatment guidelines. SaBTO members made it clear that this was not the intention of the review group and the final report would emphasise this.

Hospital transfusion laboratories

- These groups were strongly supportive of the proposals, highlighting the operational difficulties of the current requirements. It was not always possible to follow existing guidelines for post 1995 individuals as the components needed were not always in stock or ready to transfuse and delays in supply could compromise patient care.

- Paediatric hospitals can only use MB-cryoprecipitate which is an inferior product to non-pathogen-inactivated cryoprecipitate for some clinical treatments.

- Some hospitals overstock MB cryoprecipitate to be able to deal with emergencies, and this impacts the availability of stock for other hospitals.

- An example was given where it had been considered to be ethically unacceptable to use the entire national stock of MB-cryoprecipitate for one patient on one day knowing that there would then be no stock available the next day and the patient would receive UK plasma.

- In another example, terminally ill children had to wait up to four hours for delivery of apheresis platelets when being treated as an out-patient. This can occur on a daily basis.

- The general view was that the current situation was not sustainable.

Written responses from the Sickle Cell Society and The Platelet Society were supportive of the proposals

Some stakeholders informed SaBTO that they did not wish to participate in the review process as they did not hold a view on the proposals.

8. Conclusions

Review of current practice

A working group of SaBTO was established to advise whether the vCJD risk reduction measures in place for individuals born on or after 1st January 1996 and for patients with TTP, of importing plasma and using apheresis platelets, should be maintained, withdrawn for some individuals, or withdrawn altogether. The working group, chaired by Dr Stephen Thomas, was set up by SaBTO in 2017 as part of its regular programme of reviewing previous advice.

The review considered numerous factors including the revised risk assessment, the equity of the current measures, the operational difficulties of maintaining the measures, and their cost-effectiveness. In considering the ethical aspects of both the current policy and the possible changes, the working group considered the duty to protect the vulnerable from harm, the need to treat all patients fairly, the need for trust and transparency and what level of risk is acceptable to wider society.

There are practical difficulties for hospital departments having to maintain a dual stock of imported and UK plasma and pooled and apheresis platelets to treat each patient group. This increases complexity, risk, cost and wastage of valuable resources. In addition, the number of individuals in this group is growing year on year which compounds these difficulties. The demand for plasma has been rising throughout the developed world to make immunoglobulin preparations used to treat a variety of other diseases. This means that non-UK blood services have little spare plasma to export to the UK, at the same time that UK blood services require increasing amounts of plasma to support the risk reduction measures. The working group did not consider changing any of the other vCJD risk reduction measures and, indeed, assumed that they will remain in place.

The latest UK vCJD blood safety risk assessment was carried out in 2018 under the supervision of the Advisory Committee for Dangerous Pathogens Transmissible Spongiform Encephalopathy (ACDP TSE) subgroup. This expert subgroup and the full ACDP committee are hosted by, but independent of, DHSC England. ACDP TSE gave its support to the risk assessment as providing a highly precautionary estimate of the number of future cases and infections with specific figures for these numbers which, while uncertain and subject to revision in the light of further data, were considered to be of the right order of magnitude. This position was later agreed by the full ACDP committee in November 2018.

This risk assessment predicts that under current practice the best estimate is that around eight deaths from vCJD could occur over the next 50 years due to plasma transfusions, with around five of those being due to transmissions that have already occurred (the potential worst-case scenario would have around 73 deaths over the next 65 years with 48 of those due to transfusions that have already occurred; the best-case scenario would be no future cases). For platelets, the best estimate is that there could be around eleven deaths from vCJD over the next 55 years as a result of platelet transfusions with five of the transmissions having already occurred (the worst-case scenario estimates around 137 cases over 75 years with 67 having already occurred; the best-case scenario predicts no future cases).

The SaBTO working group used this risk assessment to establish if the risk reduction measures of plasma importation and provision of apheresis platelets are still appropriate. The modelling showed that the impact of these measures was small. If these risk reduction measures were not in place, a further one to two clinical cases may occur due to plasma transfusions that take place over the next 50 years; and for individuals receiving pooled platelets rather than apheresis platelets, an additional three to four cases may occur due to transfusions that take place over the next 60 years (the worst-case scenarios estimated by the model would give around an extra 15 cases for plasma and 45 cases for platelets due to transfusions over the same time period. The best-case scenario would be no additional cases). This means that the additional risk of death from transfusion acquired vCJD would on average be 1 in every 5.2 million units of UK-plasma transfused and 3.1 million units of pooled rather than apheresis platelets transfused. To put these risks in context, the increased risk of death due to an accident while driving from London to Bristol and back (approximately 250 miles) is 1 in 1 million[36].

The working group then looked at the balance of cost and benefit of these measures to patients and the wider NHS. This was done, for each option, by calculating the overall costs, in terms of the blood components purchased, and patient impact, in terms of premature deaths due to vCJD, measured in Quality Adjusted Life Years (QALYs). QALYs are used to compare the impact of medical treatments using both the length and quality of life that are gained from different procedures. One QALY is the equivalent of one year of life spent in perfect health. In this case, the change in QALYs from using the different blood components was calculated using the number of years of life that would be lost by a patient if they died due to vCJD.

Maintaining importation of plasma for individuals born after 1995 and for individuals with TTP was estimated to cost £30 million per QALY (discounted) more than using UK-sourced plasma (the range from worst- to best-case in terms of clinical cases was £3 million to £2,100 million per QALY).

For the maintenance of a supply of apheresis platelets to individuals born after 1995, the cost was estimated to be £7 million per QALY (discounted) more than using pooled platelets (the range from worst- to best-case in terms of clinical cases was £1 million to £490 million per QALY).

For context, the National Institute for Health and Care Excellence (NICE) recommends that the NHS funds medicines and other procedures if they cost less than £20,000-£30,000 per QALY.

[36] *Micromorts,* Understanding Uncertainty, Winton programme for the public understanding of risk. University of Cambridge. https://understandinguncertainty.org/micromorts

9. Recommendations of the paediatric components working group

The recommendations are that, based only on vCJD risk, the current risk reduction measures on importation of plasma and provision of apheresis platelets for individuals born on or after 1st January 1996 or with TTP be withdrawn. This is due to the revised risk assessment showing that the total number of deaths due to vCJD transmitted by plasma or platelets is predicted to be low and these risk reduction measures would only prevent a small number of additional deaths. Removing the current risk reduction measures on importation of plasma and provision of apheresis platelets will allow more equal provision of components, less operational complexity and risk, and will allow more resources to be deployed to save lives elsewhere in the NHS. None of the other risk reduction steps were included in this review. Clinicians will still be expected to follow local and national guidelines on managing individual conditions (such as the British Society of Haematology Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies).

It is important to note that the conclusions from the analysis on plasma cannot be extrapolated to the manufacture of plasma derived medicinal products from fractionation of plasma sourced in the UK. Further work would be required to determine the risks and benefits of using UK plasma for fractionation.

10. Members of Working Group

Chair

Dr Stephen Thomas	Member of SaBTO; Blood Service Manager, NHSBT

Working Group

Dr Susan Brailsford	Member of SaBTO; Consultant in Epidemiology & Heath Protection NHSBT/PHE
Prof Richard Knight	Member of SaBTO; Consultant Neurologist, National CJD Research & Surveillance Unit, University of Edinburgh
Dr Lynn Manson	Member of SaBTO; Consultant Haematologist, SNBTS
Dr Gail Miflin	Member of SaBTO; Medical & Research Director, NHSBT
Dr Helen New	Consultant in Paediatric Haematology & Transfusion Medicine, University College Hospital NHS Trust & NHSBT
Prof James Mason	Health Economist, University of Warwick
Dr Anne-Marie Slowther	Medical Ethicist, University of Warwick
Dr Jonathan Wallis	Consultant Haematologist, Newcastle upon Tyne Hospitals NHS Trust, and Chair of the National Blood Transfusion Committee
Gillian Hollis	Member of SaBTO; Lay representative
Matthew Katz	Analyst, DHSC

Secretariat:

Dr Gary Mallinson	SaBTO Secretariat/JPAC
Emily Coelho	SaBTO secretariat; DHSC

Observers:

Dr Stephen Field	Medical & Scientific Director, IBTS

Appendix 1

List of organisations included in stakeholder engagement

Addenbrooke's Hospital
Alder Hey Children's Hospital
All Party Parliamentary Group on Haemophilia & Contaminated Blood
Birmingham Children's Hospital
Birmingham Women's Hospital
Bristol Royal Infirmary
British Association for Perinatal Medicine
British Society for Haematology
Central Manchester Foundation trust
Children & Young People's Heath Support Group / Child Health Commissioners Group
Children with Cancer
Children's Cancer & Leukaemia Group
CJD Support Network
Glenfield General Hospital
Great Ormand Street Hospital for Children
Haemophilia Northern Ireland
Haemophilia Scotland
Haemophilia Wales
Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
Leeds general Infirmary
Macopharma
Octapharma
Royal College of Paediatrics and Child Health
Royal Cornwall Hospital
Scottish Infected Blood Forum
Sickle Cell Society
St Mary's Hospital
St Thomas' Hospital
The Haemophilia Society
The Platelet Society
TTP Network
UK Doctors' Haemophilia Organisation
UK Thalassaemia Society
Wexham Park Hospital

Appendix 2

Cover letter sent to stakeholders over the period 1 February 2019 to 6 March 2019

Dear XXX

The Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) advises UK ministers and health departments on the most appropriate ways to ensure the safety of blood, cells, tissues and organs for transfusion or transplantation. SaBTO has recently established a working group that has been examining two specific risk reduction measures for the transmission of variant Creutzfeldt-Jakob disease (vCJD) from blood components. The measures are:

- Importation of plasma for provision to persons born on or after 1st January 1996 and persons with Thrombotic Thrombocytopenic Purpura (TTP); and
- Provision of platelets collected by apheresis from single donors for provision to persons born on or after 1st January 1996.

These measures were introduced in 2002 for plasma and 2006 for platelets to reduce the risk of exposure to vCJD of individuals born after strict measures had been introduced to prevent meat from cows with Bovine Spongiform Encephalopathy (BSE) entering the human food supply, and those that receive a large number of transfusions.

Clinical cases of vCJD have fortunately remained rare. There have only been four known transmissions of vCJD, resulting in three deaths, from transfusions of red cells and the last of these cases was in 2006. All these cases were from red cells which had not been filtered to remove white cells (this safety measure was introduced in 1999) and there have been no known transmissions of vCJD from platelet or plasma transfusion.

The Advisory Committee on Dangerous Pathogens (ACDP) has recently completed a blood transmission risk assessment, based on what we now understand about vCJD, to estimate the number of future deaths from vCJD from transfusion of red cells, plasma and platelets. The review has shown that the risk of transmission of vCJD from blood is much lower than first anticipated in the 2000s when we understood much less about the disease. These two specific risk reduction measures are estimated to have a very small impact on this risk; we estimate that removing them would add an additional one or two clinical cases over the next 50 years for plasma and two to three cases over the next 60 years for platelet transfusions.

Maintaining patient safety has been the highest priority for the SaBTO working group. The revised model indicates that the risk is very low and that the current measures deliver a minimal safety benefit to patients. The group also considered the operational difficulties faced by the blood services and hospitals in continuing to maintain these measures and the ethical issues of providing a risk reduction measure for some individuals and not everyone, against the potential impact to some groups of withdrawing a protection that is currently applied.

Taking account all these considerations, the SaBTO working group has concluded that withdrawal of these risk reduction measures is appropriate. However, before the proposed recommendations are reviewed, the main SaBTO committee would like to have views of persons who currently receive these components or groups who may be directly or indirectly affected by the potential withdrawal of these measures.

If you wish to contribute to this process, we would be grateful if you could engage your colleagues and provide feedback to the SaBTO secretariat by 22nd March 2019. If you require further information we will be happy to answer enquiries or send representatives from the working group to meet with you. We are holding an open stakeholder meeting in London in mid-March to which you are welcome to attend or send representatives to share views with the working group. We will be in touch in due course with more detail. However, if you would like to attend, could you please register your interest with the SaBTO secretariat by 1 March 2019.

The feedback from all stakeholders will be included in a report to the main SaBTO committee later in the year. There will be a further opportunity to send a representative to attend this meeting as an observer.

We have attached an information sheet which explains in more detail the background of vCJD and blood transfusion and the issues considered by the working group as well as an informative FAQ document.

We look forward to hearing your views on this issue.

James Neuberger

SaBTO Chair

Statement on SaBTO's website can be found here.

Appendix 3

Follow up email sent to stakeholders post informal feedback on 19 February 2019

Dear XXX

Further to my previous email dated XXX, we have already received some feedback from stakeholders, for which we are very grateful.

As mentioned in the previous email, SaBTO is planning to hold a public meeting. After some discussion with stakeholders, we believe the most effective way to hear your feed-back is in small groups rather than in one large group. Therefore, I am pleased to inform you that SaBTO will be holding four three-hour face:to:face stakeholder engagement sessions on 12 and 13 March 2019. As previously advised all of these sessions will take place in central London, (venues to be confirmed).

Can you please confirm whether you are able to attend and which date and time you would prefer by 1 March 2019 to SaBTO mailbox (mbSaBTO@dhsc.gov.uk) Could you also let us know how many people will be coming from your organisation?

Whether or not you are able to attend any of the sessions, we welcome any written feedback you have by 13 March, this can be sent to SaBTO mailbox.

On the basis of comments received, we are revising the Lay Summary to clarify some aspects of the summary and we will shortly be circulating a revised version of the Summary.

I do hope you will be able to attend and provide feedback.

We look forward to hearing from you.

James Neuberger

SaBTO Chair

Appendix 4

Information sheet for stakeholder engagement (version 4)

Key points from report

- Following recognition that blood, blood components, tissues and organs donated by infected donors could transmit the agent that leads to vCJD, several measures were introduced in the UK to reduce the risk of vCJD transmission.

- Measures included deferral of high-risk donors, leucodepletion (removal of most of the white cells from blood and plasma) and, for those born after 1995, use of plasma imported from those countries where the risk is lower, and for some indications, the use of platelets from a single donor ('apheresis platelets').

- In the UK, four people have been known to acquire vCJD from blood transfusions with three having died from vCJD (the other died of unrelated causes without any symptoms); the last known case was in 2006 and that patient had received non-leucodepleted blood. There are no known cases of vCJD from plasma or platelets.

- As part of its regular review of guidance, SaBTO established a working group to review the risk measures in place to reduce vCJD. A review from the ACDP (Advisory Committee on Dangerous Pathogens) showed the estimated number of future cases of vCJD to be considerably lower than previously forecast.

- The working party noted the operational issues that had arisen as a result of implementing the guidance: these included the challenges of ensuring a robust supply of plasma that meets current UK quality standards and the challenges and risks that hospitals and blood establishments face in maintaining dual stocks of plasma.

- In 2017, 110,000 units of imported plasma were issued in the UK. The working group estimated that stopping importation of plasma from abroad would slightly increase the risk of recipients of plasma: on average for every 5.1 million units of UK-plasma given, one additional death due to vCJD may occur (approximately 45 years' worth of transfusions).

- Implementation of these recommendations for plasma would reduce the operational challenges for hospitals and would allow the NHS to re-invest the savings which are estimated to be £840 million (undiscounted) over a 50-year period or, on average, £16.5 million per year.

- Other risk reduction measures (such as leucodepletion) will remain in place at this time.

- Clinicians will still be able to prescribe commercial imported plasma products such as OctaplasLG for patients, according to local and national guidelines.

- Clinicians will be able to prescribe apheresis platelets donated by UK donors as clinically indicated.

- The working group reported to SaBTO in January 2019 and the report was accepted. However, before considering the report's recommendations, members of SaBTO wanted to hear the views of all stakeholders before advice is given to Ministers of the four UK nations. All members of SaBTO are very aware of the consequences of transfusion-acquired diseases not only for the individual recipients and their family and friends but also on public confidence.

Please note that the bullet points above represent a summary of much more detailed work and should be read in conjunction with the report

Introduction

SaBTO (Advisory Committee on the Safety of Blood, Tissues and Organs) is an independent Committee that is hosted by the Department of Health and Social Care; members are selected by interview after public advertisement. Members advise health ministers of the four UK nations on safety of blood, cells, tissues and organs. Policies are published on its website (https://www.gov.uk/government/groups/advisory-committee-on-the-safety-of-blood-tissues-and-organs) and are reviewed on a regular basis.

The UK has one of the safest blood supplies in the world, and decisions regarding safety initiatives are taken based on evidence of risk, ethical considerations and operational sustainability; cost is also considered. Where the evidence and/or the risk is not known, SaBTO makes recommendations on a precautionary basis. SaBTO reviews its guidance on a regular basis and also when new information becomes available.

The UK also has one of the world-leading haemovigilance organisations (www.shotuk.org) which is responsible for collection of reports of adverse reactions related to transfusion so that the impact of policy decisions can be monitored.

Around two million units of blood components (red cells, platelets or plasma) are transfused in the UK every year. These may be given as a life-saving emergency treatment, to enable another treatment such as surgery or chemotherapy for cancer, or as the primary treatment for a long-term condition that affects the blood.

Variant Creutzfeldt-Jakob disease & transfusion

Variant Creutzfeldt-Jakob disease, or vCJD, is a neurodegenerative disease arising from the consumption of meat from cows with bovine spongiform encephalopathy (BSE; vCJD is also known as 'mad-cow disease'), which mainly occurred in the 1980s to early 1990s. vCJD may have an incubation period of years to decades and when the first cases of vCJD were seen in the late 1990s there was considerable concern that large numbers of people had been infected and that this could result in many deaths; vCJD is currently untreatable and leads to death in 18 months. By 1996, stringent risk reduction measures were in place to prevent cows with BSE reaching the human food supply, so any individual born after 1st January 1996 should not have been exposed to BSE through food. vCJD has remained a rare disease with 178 cases diagnosed in the UK between 1995 and 2017.

When the first cases of vCJD appeared, there was concern that the disease could be transmitted from one individual to another by the transfusion of blood, blood products or blood components such as plasma and platelets. Although cases of transmission of vCJD from blood transfusion have occurred, there have been far fewer cases than originally forecast. Three people died following transmission of vCJD from two blood donors, who later developed vCJD. Another person who was known to have received a transfusion from a different blood donor (who later developed vCJD) was found to have evidence of vCJD in their spleen and appendix after they died (of another cause); this was presumed to be

because of the transfusion. A fifth individual, who had haemophilia and received many doses of Factor VIII concentrate (a medicinal blood product, not a blood transfusion), including some from a batch where one of the donors was known to have subsequently developed vCJD, was also found to have evidence of vCJD in their spleen when they died (also from another cause). Neither of the latter two cases had symptoms nor evidence of brain disease but the evidence of vCJD in their spleen could represent a pre-clinical form of the disease (before any symptoms became apparent). It should be noted that, although the last known case was diagnosed in 2006, all the recipients infected by blood transfusion had received red cells that had not been filtered to remove white blood cells (leucodepletion or leukoreduction); this protective measure was introduced in 1999, after their transfusions. There have been no reports of vCJD transmission from plasma or platelet transfusion. There have been no cases of transfusion-related transmission anywhere else in the world even though some countries, such as France, have had cases of vCJD.

Transfusion transmission risk reduction measures for vCJD

The UK Departments of Health and UK blood services have introduced several vCJD risk reduction measures for blood, blood products and blood components. These include:

- Since December 1997, all blood components, blood products or tissues obtained from any individual who later develops clinical vCJD have been withdrawn/recalled to prevent their use.
- Since October 1999, white blood cells (which are thought to contain most of the infectious agent that causes vCJD) have been reduced in all blood components used for transfusion, by a process known as leucodepletion or leucoreduction.
- In 2004, all individuals who had themselves received a transfusion of blood components (anywhere in the world) since January 1980 were excluded from donating blood.
- Since 1999, plasma for the manufacture of fractionated plasma products, such as clotting factors and immunoglobulins, has been obtained from non-UK sources.
- Since 1998, synthetic (recombinant) clotting factor for the treatment of haemophilia has been provided to those aged under 16 years, and since 2005 this measure has been extended to all patients for whom it is clinically appropriate.
- Since 2004, plasma for transfusion to those born on or after 1st January 1996 has been obtained from outside the UK.
- Since 2005, provision of platelets collected from a single donor by apheresis for transfusion to those born on or after 1st January 1996.
- In 2009, a minimum of 80% of platelets to be collected from single donors by apheresis, for transfusion to all recipients. This measure was reassessed and rescinded in 2013.

Importation of plasma and provision of apheresis platelets

The importation of plasma and provision of apheresis platelets for certain groups, were introduced as specific measures for individuals born on or after 1st January 1996 as they were considered not to have been exposed to BSE through their diet. Platelets and red cells have short shelf-lives (days and weeks, respectively) so it was considered to be impractical to source these components from non-UK countries with no, or very few cases of BSE.

Plasma has a much longer shelf-life (years) as it can be frozen and can therefore be imported from suitable countries. Apheresis is a way of collecting platelets so that a single donor can provide enough for a therapeutic dose; this is in contrast with platelets collected from whole blood donations as platelets from four donations have to be pooled together to provide a therapeutic dose. Therefore, a patient receiving a dose of platelets sourced by apheresis will be exposed to the infection risk from fewer donors. Some individuals with thrombotic thrombocytopenic purpura (TTP) can receive multiple transfusions with plasma to treat their condition and, therefore, have an enhanced risk of exposure to plasma-borne pathogens including vCJD; these individuals also receive non-UK, pathogen reduced plasma. Since the first appearance of vCJD, the Department of Health and Social Care (DHSC) England has periodically carried out a risk assessment on the predicted number of future infections and associated deaths due to vCJD that could occur from the transfusion of blood components. This risk assessment uses highly precautionary assumptions and is likely to overestimate the impact of the changes. This risk assessment combines assumptions based on the latest understanding of the disease and experimental data, including studies to determine the number of individuals who may have the disease but have not developed clinical symptoms and the results of animal experiments, with the number of deaths due to vCJD that have actually occurred. Since 2006, as more time has elapsed without any further cases due to transfusion the projected number of future deaths estimated by the risk assessment has been revised downwards. In addition, there is now a better understanding of the disease and studies on animals have shown that white cells carry most of the infectivity. This suggests that there is less infectivity in platelets and plasma than first thought and that leucodepletion is an important risk reduction measure, perhaps the most important, for all blood components.

Review of current practice

A working group of SaBTO was established to advise whether the vCJD risk reduction measures in place for individuals born on or after 1st January 1996 and for patients with TTP, of importing plasma and using apheresis platelets, should be maintained, withdrawn for some individuals, or withdrawn altogether. The review, chaired by Dr Stephen Thomas, was set up by SaBTO in 2017 as part of its regular programme of review of advice,

The review considered numerous factors including the revised risk assessment, the equity of the current measures, the operational difficulties of maintaining the measures, and their cost-effectiveness. In considering the ethical aspects of both the current policy and the possible changes, the working group considered the duty to protect the vulnerable from harm, the need to treat all patients fairly, the need for trust and transparency and what level of risk is acceptable to wider society.

There are practical difficulties for hospital departments having to maintain a dual stock of imported and UK plasma and pooled and apheresis platelets to treat each patient group. This increases complexity, risk, cost and wastage of valuable resources. In addition, the number of individuals in this group are growing year on year which compounds these difficulties. The demand for plasma has been rising throughout the developed world to make immunoglobulin preparations used to treat a variety of other diseases. This means that non-UK blood services have little spare plasma to export to the UK, at the same time that UK

blood services require increasing amounts of plasma to support the risk reduction measures. The working group did not consider changing any of the other safety measures and, indeed, assumed that they will remain in place.

The latest UK vCJD blood safety risk assessment was carried out in 2018 under the supervision of the Advisory Committee for Dangerous Pathogens Transmissible Spongiform Encephalopathy (ACDP TSE) subgroup. This expert subgroup and the full ACDP committee are hosted by, but independent of, DHSC England. ACDP TSE gave its support to the risk assessment as providing a highly precautionary estimate of the number of future cases and infections with specific figures for these numbers, while uncertain and subject to revision in the light of further data, considered to be of the right order of magnitude. This position was later agreed by the full ACDP committee in November 2018.

This risk assessment predicts that under current practice the best estimate is that around eight deaths from vCJD could occur over the next 50 years due to plasma transfusions, with around five of those being due to transmissions that have already occurred (the potential worst-case scenario would have around 73 deaths over the next 65 years with 48 of those due to transfusions that have already occurred; the best-case scenario would be no future cases). For platelets, the best estimate is that there could be around eleven deaths from vCJD over the next 55 years as a result of platelet transfusions with five of the transmissions having already occurred (the worst-case scenario estimates around 137 cases over 75 years with 67 having already occurred; the best-case scenario predicts no future cases).

The SaBTO working group used this risk assessment to establish if the risk reduction measures of plasma importation and provision of apheresis platelets are still appropriate. The modelling showed that the impact of these measures was small. If these risk reduction measures were not in place, a further one to two clinical cases may occur due to plasma transfusions that take place over the next 50 years; and for individuals receiving pooled platelets rather than apheresis platelets, an additional three to four cases may occur due to transfusions that take place over the next 60 years (the worst-case scenarios estimated by the model would give around an extra 15 cases for plasma and 45 cases for platelets due to transfusions over the same time period. The best-case scenario would be no additional cases). This means that the additional risk of death from transfusion acquired vCJD would on average be 1 in every 5.1 million units of UK-plasma transfused and 3.1 million units of pooled rather than apheresis platelets transfused. To put these risks in context, the increased risk of death due to an accident while driving from London to Bristol and back (approximately 230 miles) is 1 in 1 million.

The working group then looked at the balance of cost and benefit of these measures to patients and the wider NHS. This was done, for each option, by calculating the overall costs, in terms of the blood components purchased, and patient impact, in terms of premature deaths due to vCJD, measured in Quality Adjusted Life Years (QALYs). QALYs are used to compare the impact of medical treatments using both the length and quality of life that are gained from different procedures. One QALY is the equivalent of one year of life spent in perfect health. In this case, the change in QALYs from using the different blood components was calculated using the number of years of life that would be lost by a patient if they died due to vCJD.

Maintaining importation of plasma for individuals born after 1995 and for individuals with TTP was estimated to cost £31 million per QALY (discounted) more than using UK-sourced plasma (the range from worst- to best-case in terms of clinical cases was £3 million to £2,100 million per QALY) equivalent to £660 million per life saved (undiscounted).

For the maintenance of a supply of apheresis platelets to individuals born after 1995, the cost was estimated to be £7 million per QALY (discounted) more than using pooled platelets (the range from worst- to best-case in terms of clinical cases was £1 million to £490 million per QALY) equivalent to £140 million per life saved (undiscounted).

For context, the National Institute for Health and Care Excellence (NICE) recommends that the NHS funds medicines and other procedures if they cost less than £20,000-£30,000 per QALY.

Proposed recommendations of the paediatric components working group

The preliminary recommendations are that, based only on vCJD risk, the current risk reduction measures for individuals born on or after 1st January 1996 or with TTP be withdrawn. This is due to the revised risk assessment showing that the total number of deaths due to vCJD transmitted by plasma or platelets is predicted to be low and these risk reduction measures would only prevent a small number of additional deaths. Removing the current risk reduction measures (importation of plasma and provision of apheresis platelets) will allow more equal provision of components, less operational complexity and risk, and will allow more resources to be deployed to save lives elsewhere in the NHS. Clinicians will still be expected to follow local and national guidelines on managing individual conditions (such as the British Society of Haematology Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies).

Request from SaBTO

SaBTO will not make recommendations to the UK Departments of Health without first seeking the views of patient groups most affected by the potential cessation of these measures.