Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

A health technology assessment of prion filtration of red cell concentrates to reduce the risk of variant Creutzfeldt-Jakob disease transmission in Ireland

26 January 2011

Safer Better Care

About the Health Information and Quality Authority

The Health Information and Quality Authority is the independent Authority which has been established to drive continuous improvement in Ireland's health and social care services. The Authority was established as part of the Government's overall Health Service Reform Programme.

The Authority's mandate extends across the quality and safety of the public, private (within its social care function) and voluntary sectors. Reporting directly to the Minister for Health, the Health Information and Quality Authority has statutory responsibility for:

Setting Standards for Health and Social Services - Developing person centred standards, based on evidence and best international practice, for health and social care services in Ireland (except mental health services)

Social Services Inspectorate - Registration and inspection of residential homes for children, older people and people with disabilities. Inspecting children detention schools and foster care services. Monitoring day and pre-school facilities*

Monitoring Healthcare Quality - Monitoring standards of quality and safety in our health services and investigating as necessary serious concerns about the health and welfare of service users

Health Technology Assessment - Ensuring the best outcome for the service user by evaluating the clinical and economic effectiveness of drugs, equipment, diagnostic techniques and health promotion activities

Health Information - Advising on the collection and sharing of information across the services, evaluating information and publishing information about the delivery and performance of Ireland's health and social care services

**Not all parts of the relevant legislation, the Health Act 2007, have yet been commenced.*

Foreword

Variant Creutzfeldt-Jakob disease (vCJD) is one of a group of rare, progressive fatal non-inflammatory degenerative diseases of the brain affecting humans and animals. The origin of vCJD is linked to the outbreak of a bovine form of the disease, Bovine Spongiform Encephalitis (BSE), which occurred in the United Kingdom (UK) in the 1980s and 1990s. The incidence of BSE and vCJD peaked in the UK in 1992-1993 and 2000, respectively, declining since. However, there is an ongoing risk of vCJD transmission from transfusion of blood or blood products due to donations from sub-clinical carriers of the disease.

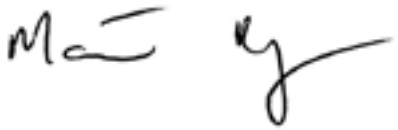
Worldwide there have been five documented cases of transfusion-related vCJD infection, resulting in three deaths from clinical vCJD. All of these cases occurred in the UK prior to the introduction of universal leucoreduction (removal of white blood cells) of blood products. Measures are taken by the Irish Blood Transfusion Service (IBTS) in accordance with national, European Union and international standards to minimise the risks of transmission of vCJD associated with blood transfusion. These include donor deferral policies, importation of plasma from countries with a low incidence of vCJD and BSE and leucoreduction of all blood products. This health technology assessment (HTA) examined the potential for a new technology, prion filtration, to reduce the risk of variant vCJD transmission from transfusion of red cell concentrates (RCC) in Ireland.

In April 2010, the Health Information and Quality Authority (the Authority) agreed to undertake a HTA of prion filtration of RCC in response to a request from the Department of Health and Children. The purpose of this HTA was to evaluate the available evidence on the risk of vCJD transmission from transfusion of RCC in Ireland, the safety and efficacy of prion-removing filters, the costs and cost-effectiveness of implementing a policy of prion filtration and to advise on other issues that may need to be considered prior to a decision regarding the adoption of such a policy.

Work on the HTA was undertaken by the HTA Directorate of the Authority supported by Dr Deirdre Madden, Faculty of Law, University College Cork, who provided the legal and ethical commentary. A multidisciplinary Expert Advisory Group was convened to advise the Authority on conduct of this assessment.

The draft report was reviewed by the Expert Advisory Group in November 2010. The Board of the Authority subsequently approved the report in January 2011 and it was submitted to the Minister for Health. A decision on the adoption of prion filtration will be taken by the Minister following due consideration of all available evidence.

The Authority would like to thank the Evaluation Team, Dr Deirdre Madden, the members of the Expert Advisory Group and all who contributed to the preparation of this report.



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Acknowledgements

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The membership of the Expert Advisory Group was as follows:

Dr Máirín Ryan, Director of Health Technology Assessment, Health Information and Quality Authority (Chairperson)

Dr David Asher, Office of Blood Service and Review, representing the Food and Drugs Administration, United States

Dr Colette Bonner, Deputy Chief Medical Officer, Department of Heath and Children, Ireland

Dr Francesca Brett, Consultant Neuropathologist, Beaumont Hospital, Dublin, representing the National vCJD Surveillance Unit and the Irish Institute of Clinical Neurologists

Matthew Collins, Principal Officer, Blood Policy Unit, Department of Health and Children, Ireland

Dr Patrick Costello, Blood and Tissue Manager, Irish Medicines Board

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Dr Jenny Kieran, Lecturer in Pharmacology and Therapeutics, Trinity College, Dublin, representing the Infectious Disease Society of Ireland

Stephen McMahon, Chairman, Irish Patients' Association

Dr Deirdre Madden, Faculty of Law, University College Cork

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Professor Marc Turner, Consultant Haematologist, Scottish National Blood Transfusion Service representing the UK Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO)

Organisations that assisted the Authority in providing information, in writing or through meetings, included:

Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO, UK)

Coombe Women & Infants University Hospital, Dublin

Department of Health and Children (Ireland)

Department of Health (UK)

Economic and Social Research Institute

Health Protection Agency (UK)

Health Service Executive

Irish Blood Transfusion Service

Irish Medicines Board

MacoPharma Ltd

Our Lady's Children's Hospital, Crumlin, Dublin

Pall Medical (a division of Pall Europe Ltd)

Prion Working Group (UK)

NBS/MRC Clinical Studies Unit, UK (PRISM Study)

St James's Hospital, Dublin

UK Transfusion Forum

Members of the Evaluation Team:

This HTA was undertaken by members of the HTA Directorate of the Health Information and Quality Authority (Dr Patricia Harrington, Michelle O'Neill, Patrick Moran, Dr Linda Murphy, Dr Conor Teljeur, Dr Máirín Ryan) in collaboration with Dr Deirdre Madden (Faculty of Law, University College Cork) who prepared the chapter on ethical and legal issues.

Conflicts of Interest

None declared

Advice to the Minister for Health

The Health Act 2007 states that one of the functions of the Health Information and Quality Authority is 'to evaluate the clinical and cost-effectiveness of health technologies including drugs and provide advice arising out of the evaluation' to the Minister for Health and the Health Service Executive (HSE).

This health technology assessment (HTA) examined the potential for a new technology, prion filtration, to reduce the risk of variant Creutzfeldt-Jakob disease (vCJD) transmission from the transfusion of red cell concentrates (RCC) in Ireland. vCJD is one of a group of transmissible spongiform encephalopathies (TSEs) – these are rare, progressive, fatal non-inflammatory degenerative diseases of the brain affecting humans and animals.

Arising out of this HTA, the advice to the Minister is as outlined below. There is substantial uncertainty around a number of the key factors that impact on the risk of transmission of vCJD. As it is not possible to screen for vCJD, the prevalence of sub-clinical vCJD in Ireland is unknown, introducing marked uncertainty into estimates of the risk of transfusion-transmitted vCJD. As the economic model includes assumptions about these parameters, the results are subject to uncertainty. Taking into account the assumptions made and the fact that the model tends towards a worst-case scenario, the following conclusions can be drawn.

- In the absence of prion filtration, it is estimated that two individuals (range: 0 – 8) will develop clinical vCJD and die from this disease as a result of exposure to infected red cells in the next 10 years.
- The current available evidence suggests that prion filters are effective in removing prion protein from blood at the levels that would apply to normal clinical or sub-clinical infection. However, based on experimental data, 1 in 10,000 infectious particles could pass through the filter.
- The current available evidence also suggests that prion filtered blood is safe. Some constituents of blood may be removed during the filtration process. Blood establishments may need to alter their specifications for RCC in order for filtered units to comply. Clinically, some transfusion-dependent patients may require additional units of prion-filtered RCC.
- It is predicted that prion filtration of all RCCs will initially cost €11 million per annum and, over a 10-year time period, will prevent two deaths from vCJD and result in 19.4 discounted life years gained.
- The introduction of prion filtration, either for all transfusion recipients or for limited patient sub-groups, was found to be not cost-effective by traditional standards of cost-effectiveness. The incremental cost-effectiveness ratio (ICER) of prion filtration is €2.6 million per life year gained.
- There is a precedent for blood safety interventions that are not cost-effective by traditional standards to be widely implemented by blood transfusion services (for example, nucleic acid testing [NAT] for HIV, Hepatitis B and Hepatitis C).

- Limiting prion filtration to any selected patient sub-group (for example, infants less than one year, patients with haemoglobinopathies*) is unlikely to result in any health gain (that is, no infections prevented), irrespective of cost. Ethically, a policy of universal prion filtration would be preferable to limited introduction for specific patient sub-groups on the basis of equity and fairness.
- European Union and national legislation specifies that 'all precautionary measures' be adopted to safeguard blood supplies from viral infection. However, there is no definition or concrete interpretation of what these 'precautionary measures' entail and the extent to which the measures must be reasonable and proportionate to the health threat in question.
- Under the Liability for Defective Products Act 1991, a producer may be liable for damage caused by a defect in his product. The potential for legal consequences for the Irish Blood Transfusion Service (IBTS) would need to be considered in the event that a person could prove that they had contracted vCJD from a blood transfusion received in the State and that prion filtration would have minimised this risk.
- Given the likely number of clinical cases (two deaths, range: 0 – 8) and in the context of a finite healthcare budget, consideration must be given to the existing technologies and services that may need to be displaced should a decision be made to introduce prion filtration, at a cost of up to €11 million per annum.

**Haemoglobinopathies are inherited blood disorders and include the thalassaemias and sickle-cell disease.*

Executive summary

1 Background

General information on HTA

The Health Information and Quality Authority (the Authority) is an independent Authority reporting to the Minister for Health and was established on 15 May 2007. The Authority is the statutory organisation in Ireland with a responsibility to carry out national health technology assessments (HTAs) and to develop guidelines for the preparation of HTAs across our health system.

Health technology assessment is a form of health research that generates information about the clinical and cost-effectiveness of health interventions (technologies), as well as information on their wider impact. The term 'technology' includes drugs, medical equipment, diagnostic techniques, surgical procedures, and public health programmes, for example, cancer screening programmes. This information is for use by the public, service providers and policy makers. The main issues investigated as part of any HTA are:

- Does the technology work?
- For whom does it work?
- What is the benefit to the individual?
- At what cost?
- How does it compare to the alternative options available?

Background information on this HTA

On 16 March 2010, the Department of Health and Children asked the Authority to undertake a HTA of prion filtration to reduce the risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) from the transfusion of red cell concentrates (RCC). The HTA will inform a decision as to whether or not prion filtration of RCC should be adopted as a standard approach by the Irish Blood Transfusion Service (IBTS).

Patients who require blood transfusions rarely receive the whole blood that has been donated. Rather, the donated whole blood is processed into its constituent parts that can then be specifically administered according to the clinical need of the patient. These constituent parts include red blood cells (referred to as units of red cell concentrates or RCC), platelets and plasma.

vCJD is one of a group of rare, progressive and ultimately fatal conditions known as prion diseases – described in more detail in section 4 of this executive summary. They are thought to be caused by an abnormal form of a naturally occurring protein in the brain – this protein is called the prion protein. This abnormal form of the protein is potentially infectious.

The risk for secondary transmission of vCJD via transfusion of blood and blood products is recognised as a significant risk, in that people who have been infected with the abnormal prion protein may not have developed clinical vCJD at the time of donation.[1-3] Worldwide, five cases of secondary transmission of vCJD from transfusion of blood or blood products have been identified.[3] Blood transfusion services in every country have taken steps to further assure the safety of their blood supplies since these risks have been identified.

Prion filters are new technologies that have been developed in recent years. According to their manufacturers, they substantially reduce any residual infectious prion protein that may be present in donated blood, rendering it safer for transfusion to its intended recipient.[4] The IBTS has proposed adoption of prion filtration of RCC as an additional safety control measure. A decision on the adoption of prion filtration of RCC will be made by the Minister for Health, following due consideration of all available evidence.

2 Objectives

The terms of reference of this HTA are to:

(a) describe the epidemiology of vCJD in Ireland

(b) examine the current risk of contracting vCJD from a blood transfusion in Ireland

(c) examine the current controls and practices in place to prevent the transmission of vCJD via transfusion

(d) examine the current evidence of efficacy and safety for prion-removing filters

(e) examine the costs and cost-effectiveness associated with the implementation of prion filtration of red cell concentrates in the Irish Blood Transfusion Service

(f) advise on other issues which may need to be considered prior to the introduction of such a policy

(g) advise on the appropriateness of using prion filters in sub-groups of the transfused population only, and the potential costs associated with this.

3 Methodology

This HTA was conducted using the general principles of HTA and employing the processes and practices used by the Authority in such projects. In summary:

- The terms of reference of the HTA and the specific questions to be addressed were agreed between the Authority, the former Minister for Health and Children and the Department of Health and Children.
- An expert advisory group (EAG) was established.
- An evaluation team was appointed comprising internal Authority staff. Dr Deirdre Madden, Faculty of Law, University College Cork, provided legal and ethical commentary.
- A review of the relevant literature was conducted. Other data were obtained from a range of Irish and international experts and included dossiers submitted by the commercial companies manufacturing prion filters.
- An independent economic model developed in the United Kingdom (UK) was adapted to the Irish setting. This model makes it possible to calculate the future costs and health benefits of introducing this technology. More details of how this model was adapted are included in section 7 of this executive summary.

4 Epidemiology of vCJD in Ireland

vCJD is one of a group of diseases known as transmissible spongiform encephalopathies (TSEs), or prion diseases.[5] These are rare, progressive and fatal non-inflammatory degenerative diseases of the brain affecting humans and animals. They are considered to be caused by an abnormal form of a naturally occurring protein in the brain (the prion protein) that has been acquired through infection.

CJD is the most common TSE affecting humans. A new variant form of CJD – termed vCJD – was first described in 1996.[6] The incubation period of vCJD (the time between first acquiring the infectious protein to the time of developing clinical disease) is uncertain. This period could be up to 40 years in some individuals.[3]

Experts agree that the origin of vCJD is linked to an earlier outbreak of Bovine Spongiform Encephalopathy (BSE) in the UK.[7-9] BSE was first reported as a new prion disease in cattle in 1987, with incidence peaking in the 1992-1993 period.[8] In Ireland, incidence peaked in 2002 and was significantly lower than in the UK. A similar decline in new cases has also been documented.

Worldwide, at the time of this report, there have been 216 definite or probable recorded deaths from vCJD, of which 170 have been in the UK. The annual number of deaths peaked in 2000 at 28, declining since.[10] There have been four deaths from vCJD recorded in Ireland to date. Two of these cases are thought to have originated in the UK as the individuals resided there for long periods during the BSE 'at-risk' period (1980 to 1996).[11]

There may be a genetic pre-disposition to developing clinical vCJD. To date, all confirmed clinical cases of vCJD have occurred in individuals in a specific genotype (MM) that occurs in roughly 40% of the population. The remaining 60% of the population (non-MM) may be carriers of infection and have the potential to develop clinical vCJD, albeit after a much longer incubation period. One possible case of clinical vCJD occurred in such a patient. However, the diagnosis was not confirmed.[12]

Currently, there is no screening test that reliably identifies individuals that have been infected with vCJD, but who have not yet developed the disease.[13;14] These individuals are referred to as 'sub-clinical' or 'pre-clinical' carriers of the disease and are at risk of transmitting vCJD through blood donation. Estimates of sub-clinical infection in the UK suggest that the prevalence could be as high as 237 infections per million population (95% CI* 49 to 692). These estimates have wide confidence intervals and ongoing studies suggest that the true figure may be lower.[7] No testing studies have been conducted in Ireland. Experts agree that the likely prevalence of sub-clinical infection in Ireland is substantially lower than in the UK, in line with the substantially lower incidence of clinical disease observed here.

It is possible that sub-clinical carriers of vCJD may transmit the disease to others through transfusion of donated blood or blood products. A significant portion of the infectivity of the prion protein in human blood is thought to remain in the leucocyte (white cells). Removal of these cells from transfusion products could therefore reduce the risk of vCJD transmission. A policy of leucocyte filtration (leucoreduction) of all blood products (universal leucoreduction) was implemented in Ireland in 1999,[1;15] in addition to a number of other jurisdictions.

Worldwide, five cases of vCJD transmission from blood donors who subsequently developed vCJD have been identified. These cases all occurred in the UK. Four cases relate to the transfusion of non-leucoreduced red blood cells between 1996 and 1999, three of whom died from clinical vCJD and one from unrelated causes. One case relates to vCJD transmission from infected factor-concentrates in a haemophilia patient who died from unrelated causes. No further cases of transfusion-related vCJD have been identified in the UK since the introduction of universal leucoreduction.[3]

At the time of this report, no cases of vCJD arising from transfusion of blood or blood products have been identified in Ireland. However, one Irish blood donor developed clinical vCJD shortly after making a donation. The components of this donation were transfused to two recipients.[16]

The Irish Blood Transfusion Service has taken several measures to reduce the risk of transmission of vCJD via transfusion of blood and blood products. These include donor deferral policies, importation of plasma from countries with a low incidence of vCJD and BSE, and leucoreduction of all blood products.

*See glossary.

5 Efficacy of prion-removing filters

A number of prion-removing filters have been developed to further reduce the risk of vCJD transmission from transfusion of red cell concentrates (RCC) by substantially reducing (or eliminating) any residual prion protein present in donated blood. The use of such filters would complement existing measures adopted to contain the risk of transmission.

At the time of this report the commercially available Conformité Européenne (CE)-marked prion-removing filters are the P-Capt™ prion-removing filter (MacoPharma Ltd) and the Leukotrap Affinity Plus® combined leucocyte and prion-removing filter system (PRF2BE) (Pall Medical). In October 2010, the Macau Blood Transfusion Service in China became the first service to adopt prion filtration as a routine process following a decision to use the P-Capt™ filter to filter RCC donated by Caucasians at risk of carrying the infectious prion protein. In the UK, the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) has concluded that there is now sufficient evidence that these filters remove infectivity. They have recommended that in the UK, prion filtered RCC should be provided to those born since 1996, subject to satisfactory completion of an ongoing clinical trial.[17] At the time of this report a decision in relation to this had not been taken by the UK authorities.

As there is no specific test to detect the presence of infectious prion in donated blood, the assessment of the efficacy of prion-removing filters is limited to experimental animal models.[13] The relevance and applicability of these studies to the potential infectivity in human red cell concentrates is uncertain.

Studies of the efficacy of the filter resins and prototype versions of the commercially available prion filters have been published. Data supporting the efficacy of the commercially available P-Capt™ filter have also been published. All published studies and data have been sponsored by the respective device manufacturers.

Data for the P-Capt™ filter suggest that a greater than 99.9% reduction in infectivity is achieved following filtration of blood that has been artificially spiked with infectivity at levels much greater than would be seen in clinical infection. These studies are termed ‘exogenous’ studies. In other studies, no animals developed prion disease following injection of blood that had been filtered after collection from infected animals. These are referred to as ‘endogenous’ studies. Data on prototype and pre-marketed versions of the Pall filter suggest that a greater than 99.9% reduction in infectivity is also achievable in exogenous studies. No data on the currently marketed version of the Pall filter (PRF2BE) had been published at the time of this report.

Prior to their routine adoption, the need for independent safety and efficacy studies of the final commercially-available blood product device has been strongly advocated.[3;13;14] Satisfactory completion of such studies is required prior to the adoption of a prion filter by the IBTS.

The Health Protection Agency (HPA) in the UK was commissioned by the UK Blood Services Agency to conduct an independent assessment of the efficacy of the CE-marked prion filters. The IBTS is a partner in this study.[18] This assessment replicates the manufacturer-sponsored in-vitro studies using the final commercially-available product.[19] To date, only exogenous independent studies of the P-Capt™ filter have been completed. These exogenous studies are known to be ‘artificial’ in that they

involve testing a blood sample that has been spiked with levels of prion infection much higher than would be present in clinical situations. Even if the independent exogenous studies could not replicate the published studies, the objective was to establish if the prion removing capacity of the filters was sufficient to remove the level thought to be present in human leucoreduced red cells from an individual with clinical or sub-clinical vCJD infection.

The independent assessment of the P-Capt™ filter exogenous studies reports lower efficacy results than those reported by the manufacturers. However, the amount of infectious prion removed generally far exceeded the expected exposure levels from blood donated by people with sub-clinical vCJD infection.

Independent validation of the previously published endogenous studies for the P-Capt™ filter has commenced in 263K scrapie-infected hamster and BSE sheep models.

Pending the independent assessment of the endogenous animal model studies, the UK Prion Working Group has concluded from the combined available evidence that, when used in conjunction with universal leucoreduction and other risk reduction strategies, prion filters have the capacity to remove infectivity from blood at levels greater than those expected from donors with sub-clinical vCJD infection. This has been accepted as an interim finding by SaBTO in the UK.[17] However, current evidence suggests that 1 in 10,000 infectious particles could pass through the filter. A conservative approach would, therefore, assume that residual infectivity would remain at this level following prion filtration of leucoreduced RCC from an infected donor.

6 Safety of prion-removing filters

Published studies have indicated that prion-removing filters may alter the quality and composition of RCC that are passed through them. Mean post-filtration haemoglobin levels are reduced by 8-9 grams per unit, or up to 20%. An increase in haemolysis that may be due to the filter has also been reported.[20;21]

These alterations could in theory render some units outside of current quality control product specifications. The reduction in haemoglobin content is of significance for laboratory practice and potentially of clinical significance for some transfusion recipients. In the event of a decision to adopt universal prion filtration, blood transfusions laboratories may have to negotiate amended specifications for their products in order to maintain the validation of their process. Some transfusion-dependent patients may require the administration of additional units of RCC to counter the reduction in haemoglobin content associated with the filter.

7 Cost-effectiveness and budget impact of universal prion filtration of red cell concentrates

Economic evaluation in HTA involves the comparative analysis of alternative courses of action. When comparing two or more technologies, the question that arises is: what is the additional cost for the additional benefit achieved? To answer this question, the incremental cost-effectiveness of the technology compared to the alternative is calculated, with the results presented as an incremental cost-effectiveness ratio (ICER).[22] The ICER of A (prion filtration) compared to B (no prion filtration) can be calculated as follows:

$$ICER = \frac{(Cost_A - Cost_B)}{(Effect_A - Effect_B)}$$

In this HTA, the additional costs and health benefits associated with the introduction of universal prion filtration of RCC are compared with the usual standard of care (i.e., no prion filtration). The health benefit of prion filtration is the impact of the technology on patient survival and is measured in life years gained (LYG).

No published economic evaluation of prion filtration was identified during a systematic literature search. To provide context for this HTA, however, a limited review of published cost-effectiveness analyses examining other blood safety initiatives was conducted.

One such blood safety initiative is nucleic acid testing (NAT). This is a specific test that screens donated blood for viral infections including HIV, Hepatitis B and Hepatitis C. It is used in addition to other tests (viral antigen / antibody serology) that are already in use to screen blood for these infections. NAT is primarily used to detect donations from those in the early period of infection, before the standard serological tests become positive. Adding NAT to the current strategy of viral serological testing was not found to be cost-effective by traditional measures, with ICERs ranging from €300,000 to €47 million per quality-adjusted life year (QALY).[23-27] Despite this, NAT has been implemented by many transfusion services including the IBTS.[28]

Cost-effectiveness in blood safety strategies does not compare easily with other interventions where cost-effectiveness is typically an order of magnitude less. In Ireland, examples of technologies that were adopted following a determination of their cost-effectiveness include:

- population-based colorectal cancer screening using faecal immunochemical test (FIT) (€1,696/QALY)[29]
- Human papillomavirus (HPV) vaccination of 12-year-old girls to reduce the risk of cervical cancer (€17,383/LYG)[30]
- universal infant pneumococcal conjugate vaccination (€5,997/LYG)[31] and
- universal hepatitis B vaccination of infants (€37,018/LYG).[32]

Economic analyses carried out in HTAs typically use models to project the future health benefits and costs of an intervention. The economic analysis in this HTA was conducted using a model independently developed by the UK Department of Health for an equivalent HTA. This model was provided to the Evaluation Team and

adapted to the Irish setting. National guidelines for the economic evaluation of health technologies in Ireland as published by the Authority were applied. In summary:

- a cost-effectiveness analysis was used
- the perspective of the evaluation was the publicly funded healthcare system
- the study comparator was routine practice in the IBTS, that is, no prion filtration
- a timeframe of 10 years was used for costs and vCJD exposure with health outcomes modelled to full life expectancy for infected recipients
- a standard discount rate of 4% was applied to both costs and benefits
- a range of data parameters (inputs) required to populate the model was agreed with the Expert Advisory Group.

A probabilistic sensitivity analysis (PSA) was performed to allow the main parameters to vary within defined ranges, thereby allowing uncertainty to be encompassed in the model. A conservative approach to selecting the model parameters was adopted so that results are closer to a worst-case scenario.

The costs used in the cost-effectiveness model related to the incremental cost of prion filtration, that is, added costs over and above the current operational costs. Cost savings related to the reduced consumption of existing resources were included where appropriate. When estimating the marginal unit cost for the intervention, the costs of procurement, processing, storage and distribution of prion-filtered RCC were included as appropriate. Cost data were provided by the IBTS, the Department of Health and Children and the manufacturers of the prion filters. The majority of costs related to recurring annual costs.

In the absence of universal prion filtration in Ireland, it was estimated that over 10 years there will be:

- 45 (range: 2-142) infected donors of whole blood
- 70 (range: 3-222) transfusion recipients of infected units of RCC
- 7 (range: 0-24) of the recipients of infected RCC who are susceptible to clinical vCJD
- 3 (range: 0-10) of the recipients susceptible to clinical vCJD who survive 5 years post-transfusion
- 2 (range: 0-8) of the susceptible recipients surviving 5 years post-transfusion who survive long enough to develop clinical vCJD and die from the disease resulting in 19.7 (range 0.0-96.1) life years lost.

The confidence intervals for infections encompass zero meaning that there may be no infections, even in the absence of prion filtration. Due to the long incubation period of vCJD and the older age profile of transfusion recipients, infected patients will often die of other causes before the onset of clinical vCJD. The wide confidence intervals reflect the considerable uncertainty which arises due to the prevalence of subclinical vCJD in Ireland being unknown.

The incremental cost effectiveness ratio (ICER) associated with universal prion filtration of RCC was estimated at €2.6 million per life year gained. This figure takes into account the average cost of applying a policy of universal prion filtration over the 10-year period as well as the average number of life years gained. Prion filtration is therefore not cost-effective by traditional standards for cost-effectiveness. Of note, however, other blood safety strategies found not to be cost-effective have been implemented widely in developed countries.

The cost-effectiveness model is subject to a number of limitations that may impact on the results or their interpretation. There is substantial uncertainty around both the suitable point estimates and the associated ranges of probable values for many of the key model parameters. The cost-effectiveness results reflect the conservative approach adopted (that all genotypes can develop the disease). Universal prion filtration could therefore have a true ICER that is far higher than €2.6 million per life year gained. The costs considered were limited to the direct costs to the IBTS and the HSE. Costs to the individual (for example, out-of-pocket expenditure related to treatment or transport to appointments) or to society (for example, lost productivity in those diagnosed with vCJD) were not considered.

Over a five-year timeframe, the estimated budget impact of implementing prion filtration ranged from €51.6 million to €55.9 million depending on the filter model adopted.

8 Patient sub-group analysis

Selective implementation of prion filtration of red cell concentrates (RCC) for sub-groups of the transfused population could be considered as an alternative to universal prion filtration. This consideration might arise if universal prion filtration is deemed not cost-effective or the total cost of implementing a policy of universal prion filtration is not considered affordable. Transfusing selected sub-groups of the population could be more cost-effective than in the population as a whole. Such a selective implementation would have a lower budget impact, as smaller numbers of RCC would be filtered.

On the basis of a number of biological and clinical arguments outlined in the HTA, the following patient sub-groups were chosen for analysis. These sub-groups may derive a greater health gain arising from a policy of prion filtration of RCC when compared with the overall transfused population. Alternatively, they could be viewed as the sub-groups with the greatest potential for harm if universal prion filtration is not implemented. The patient sub-groups are:

- all children under 1 year
- all children under 2 years of age
- all children and adolescents under 16 years of age
- patients with haemoglobinopathies
- combinations of patients with haemoglobinopathies and paediatric sub-groups.

The cost-effectiveness analysis of universal prion filtration was repeated at a sub-group level. The key parameters for the sub-group models were identical to those used in the model for universal filtration. The only difference in the models was the number, age profile and average number of units transfused per recipient of prion filtered blood.

There was no sub-group for which prion filtration prevented any cases of vCJD in the point estimate. The 95% confidence interval predicted a range of 0 to 3 cases prevented in one of the sub-groups examined (children less than 16 years plus patients with haemoglobinopathies). Under the base-case assumptions regarding the prevalence of pre-clinical vCJD, limiting prion filtration to any selected sub-group is not cost-effective and will not result in any health gain, irrespective of the cost.

A budget impact analysis over a five-year timeframe was performed for each of the sub-groups examined in this HTA. The five-year budget impact ranged from €4.1 million to €15.2 million, depending on the sub-group and the filter used.

The IBTS currently supplies a wide range of blood products to over 70 hospitals. If prion-filtration of RCC is introduced on a limited basis for selected patient sub-groups, this will increase the complexity of the supply chain process. Based on discussions with the IBTS, it would be logistically feasible. However, the risk of harm (vCJD transmission) from transfusion of a single non-prion filtered unit to an individual would be miniscule compared to the potential negative consequences, including death, should a transfusion be delayed in a critically ill patient while prion-filtered product was sourced.

9 Ethical issues

New medical technologies often raise ethical and social dilemmas as society comes to understand the implications of their application. Decisions to implement new technologies have implications for resource allocation because choosing a particular medical technology may imply abandoning existing technologies or may lead to the re-allocation of resources, potentially limiting or depriving service-users of existing services.

In acknowledging the reality that blood transfusions are not risk free, it is important to note the devastating harm they have caused in the past. Included are those with haemophilia, von Willebrand disease and women treated with Anti-D blood products who were infected with Hepatitis C – and also those with haemophilia who were infected with HIV – as a result of transfusion of infected blood products in Ireland from the late 1970s to early 1990s.[33;34] Measures are taken by the IBTS in accordance with national, international and EU standards to minimise the risks associated with blood transfusion. However, harm and deaths caused as a result of transfusion of infected blood products in the past has created a legacy which must be borne in mind in considering new blood safety strategies.

There may be significant ethical considerations relating to the denial of a technology to a proportion of the population if it is known to reduce risk. Universal prion filtration of RCC would be preferable to its limited introduction for selected sub-groups from the perspective of equity and fairness. Selection of a sub-group should only occur on foot of a decision not to introduce universal prion filtration. Prioritisation of sub-

groups of the population is not without precedent in our health system (for example, HPV vaccination and the use of age thresholds for screening programmes). Sub-group selections are generally on the basis of clinical and biological criteria and aim to maximise population health gain.

In the context of the sub-groups identified in this HTA, there may be sound ethical justifications for prioritising the implementation of prion-filtered RCC for children (for example, those less than 1 or less than 2 years of age). As the longest survivors of transfusions, these patients would have the greatest potential for health gain if transmission of vCJD was prevented. There may also be sound ethical reasons to provide filtered blood to patients with haemoglobinopathies as their high transfusion burden and near normal life expectancy place them at higher risk of exposure to and development of clinical vCJD. However, this report estimates that selective prion filtration of RCC for any sub-group identified is not cost-effective and unlikely to prevent any deaths by vCJD, regardless of the cost.

It is estimated that universal prion filtration would initially cost €11 million per annum preventing two deaths from vCJD arising from transfusion of vCJD-infected RCC over 10 years. Based on this analysis, universal prion filtration is not cost-effective at the present time. If this intervention was implemented despite not being cost-effective, the financial resources for implementation would have to be found from within the existing health budget. In that event, consideration would have to be given to the ethical issues arising from the discontinuation or re-allocation of existing services.

10 Legal issues

The IBTS is responsible for the processing and supply of blood products in the State. This responsibility is discharged in compliance with the EU Directive 2002/98/EC which was transposed into Irish law in SI 360 of 2005. The 2002 Directive states that for human blood and blood components:

> in order to safeguard public health and to prevent the transmission of infectious diseases, all precautionary measures during their collection, processing, distribution and use need to be taken making appropriate use of scientific progress in the detection and inactivation and elimination of transfusion transmissible pathogenic agents.

There is no definition or concrete interpretation of what these 'precautionary measures' entail and the extent to which the measures must be reasonable and proportionate to the health threat in question.

Under the Liability for Defective Products Act 1991 (which transposed into Irish law the EU Product Liability Directive) a producer may be liable for damage caused by a defect in his product. This is a strict liability offence. Although exemptions pertain, based on limited case law in other jurisdictions, these do not appear to extend to defective products manufactured and used in the course of a specific medical service financed entirely from public funds.

The extent to which the possibility of litigation should influence policy makers is open to debate. The potential for legal consequences for the IBTS would need to be considered in the event that a person could prove that they had contracted vCJD from a blood transfusion received in the State and that prion filtration would have minimised this risk.

11 Conclusions

This HTA has reviewed the evidence regarding prion filtration of red cell concentrates (RCC). Current evidence suggests that the filters are safe and will remove almost all residual risk of vCJD transmission with the caveat that 1 in 10,000 infectious particles may pass through the filter. Furthermore, the residual risk of vCJD transmission through transfusion of platelets (which cannot be prion filtered) will remain.

There is substantial uncertainty around a number of the key factors that impact on the risk of transmission of vCJD. As it is not possible to screen for vCJD infection, the prevalence of subclinical vCJD in Ireland is unknown introducing marked uncertainty into estimates of the risk of transfusion-transmitted vCJD. As the economic model includes assumptions about factors such as the prevalence of subclinical vCJD, the results are therefore subject to uncertainty.

In Ireland the risk of acquiring vCJD from RCC transfusion in the absence of prion filtration is low. It is estimated that two people (range: 0-8) will die from clinical vCJD as a result of an exposure to infected blood in Ireland during the next 10 years. Due to filter-induced reductions in haemoglobin, introduction of universal prion filtration may necessitate changes in the specifications for filtered RCC units and an additional transfusion burden for transfusion-dependent patients.

It is predicted that the prion filtration of all RCCs will initially cost €11 million per annum and, over a 10-year time period, will prevent two deaths from vCJD and result in 19.4 discounted life years gained. The incremental cost-effectiveness ratio (ICER) of prion filtration is €2.6 million per life year gained. Introduction of prion filtration for selected patient sub-groups results in lower ICERs, but also a much lower probability of any life years gained. As a comparison, population-based colorectal cancer screening had an estimated ICER of €1,696 per quality-adjusted life year (QALY) compared to a policy of no screening. This screening was estimated to cost €15 million per annum at full implementation, averting 160 cases of colorectal cancer and 270 deaths from the disease in year 10 of the screening programme.[29;35]

Introduction of prion filtration for either all transfusion recipients or for limited sub-groups was found to be not cost-effective by traditional standards of cost-effectiveness. However, other blood safety interventions considered not cost-effective by traditional standards have been implemented previously, for example, NAT testing for HIV, Hepatitis B and Hepatitis C.

Introducing limited prion filtration for selected patient sub-groups may involve additional logistical issues associated with product distribution and supply. Failure to introduce prion filtration may be associated with a risk of liability in the case of vCJD transmission from RCC.

The cost of universal prion filtration is substantial, with estimated initial costs of €11 million per annum. This financial cost of further minimising what is at most likely to be a low risk is high compared to the likely benefits. In the context of a finite healthcare budget, consideration must be given to the existing technologies and services that may need to be displaced should a decision be made to introduce prion filtration at a cost of up to €11 million per annum.

Technical Report

A health technology assessment of prion filtration of red cell concentrates to reduce the risk of variant Creutzfeldt-Jakob disease transmission in Ireland

26 January 2011

Technical Report

1. Introduction and terms of reference

1.1 Introduction

On 16 March 2010, the Department of Health and Children asked the Health Information and Quality Authority (the Authority) to undertake a health technology assessment (HTA) of prion filtration to reduce the risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) from transfusion of red cell concentrates (RCCs). This was to inform a policy decision as to whether or not prion filtration of RCC should be adopted as a standard approach by the Irish Blood Transfusion Service (IBTS).

vCJD is one of a group of degenerative disorders of the nervous system known as transmissible spongiform encephalopathies (TSEs), or prion diseases.[5] TSEs are considered to be caused by an abnormal form of a naturally occurring protein in the brain (the prion protein) acquired through infection. Their origin, presentation and epidemiology are discussed in detail in chapter 3.

vCJD is a relatively recently identified disease, first described in 1996. The occurrence of other forms of CJD (e.g., sporadic CJD and iatrogenic CJD) has been documented for much longer.[5;6] Experts now agree that the origin of vCJD is linked to an earlier outbreak of Bovine Spongiform Encephalopathy (BSE) in the UK.[7-9] BSE was first identified as a new prion disease in cattle in 1987 with a peak incidence of 3,500 new cases per month in the 1992-1993 period.[8] To date, there have been 170 recorded deaths from vCJD in the UK alone. The annual number of deaths peaked in 2000 at 28, declining since then.[10] In Ireland, there have been four documented deaths from vCJD. Two of these individuals were long-term residents in the UK(11) during the at-risk period for dietary exposure to BSE (1980-1996).[15;36]

There is a potential for secondary transmission of vCJD via transfusion of blood products.[1-3] The incubation period of vCJD (the time between first acquiring the infectious protein to the time of developing clinical disease) is unknown. This period could be up to 40 years in some individuals.[37] Worldwide, five cases of secondary transmission of vCJD from transfusion of blood or blood derivatives have been identified to date. All occurred in the UK. Four cases arose following transfusion of non-leucodepleted red cells between 1996 and 1999; three developed clinical vCJD, the fourth died from unrelated causes.[3] The fifth case relates to a haemophilia patient who received factor concentrates manufactured from plasma pools collected during the at-risk period; this patient died from unrelated causes.[12] Having adopted several precautionary measures, blood safety agencies around the world took further steps to assure the safety of their blood supplies following confirmation of the risk of vCJD transmission via blood products. Risk-reduction measures include: excluding donors who have resided in the UK for significant periods during the at-risk BSE epidemic years; excluding donors who themselves have received transfusions; importing plasma from countries perceived to have a lower risk of vCJD; and removing specific cells and components from donated blood considered to contain a significant portion of the infectivity.[18] Further details of these measures are described in chapter 3.

Prion filters are new technologies designed for the filtration of red cell concentrates (RCCs). According to their manufacturers, they remove infectious prion protein that may be present in donated blood, rendering the transfused blood safer to the recipient.[4] The total number of primary vCJD cases in Ireland has been relatively small. The risk of new cases appears to be receding based on the presumed association with the BSE epidemic in the UK.[1] However, there remains the risk that some blood donors have sub-clinical or pre-clinical disease (that is, infected with the abnormal prion, but will not, or have yet to, develop any clinical manifestation of the disease).

With the exception of a recent decision to introduce selective prion-filtration in Macau, China, prion-filtration has not as yet been adopted as a standard process by any other blood transfusion service. In the UK, the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) has concluded that there is now sufficient evidence that these filters remove infectivity. It has recommended that, in the UK, prion-filtered RCC should be provided to those born since 1996, subject to satisfactory completion of clinical trials.[17] No decision had been taken by the UK authorities in this regard at the time of this report. In order to safeguard the blood supply further against the risk of transmission of vCJD via blood transfusion, the Irish Blood Transfusion Service has proposed the use of prion filters in the production of RCC in Ireland as an additional measure to existing controls.

1.2 Terms of reference

A decision on the adoption of prion filtration of RCC will be taken by the Minister for Health, following due consideration of all available evidence.

Use of the filters in Ireland would likely incur a significant financial cost. A decision to invest in this technology requires consideration of a number of issues including:

- an assessment of the available evidence with regard to the safety and efficacy of the filters
- the estimated risk of acquiring vCJD via blood transfusion in Ireland
- the current controls to safeguard the blood supply against this risk
- the cost-effectiveness, budget impact and organisational issues associated with introduction of prion filtration and
- the ethical, legal and other relevant issues.

The terms of reference of this assessment are to:

a) describe the epidemiology of vCJD in Ireland

b) examine the current risk of contracting vCJD from a blood transfusion in Ireland

c) examine the current controls and practices in place to prevent the transmission of vCJD via transfusion

d) examine the current evidence of efficacy and safety for prion-removing filters

e) examine the costs and cost-effectiveness associated with the implementation of prion filtration of red cell concentrates in the Irish Blood Transfusion Service

f) advise on other issues which may need to be considered prior to the introduction of such a policy

g) advise on the appropriateness of using prion filters in sub-groups of the transfused population only, and the potential costs associated with this.

Further background information on the use of blood products in Ireland, the associated risks and the role of the Irish Blood Transfusion Service is included in Appendix 1.

2 Methodology

2.1 Overall approach

Following an initial scoping of the technology, the terms of reference of this assessment were agreed between the Authority and the Department of Health and Children.

The Authority convened an expert advisory group (EAG) comprising representation from relevant stakeholders including the Department of Health and Children, Irish Blood Transfusion Service, Health Service Executive, Irish Medicines Board, clinicians with specialist expertise, representatives of patients' organisations and international experts in blood transfusion and HTA. The Group was chaired by the Authority's Director of Health Technology Assessment. The role of the EAG was to inform and guide the process, provide expert advice and information and to provide access to data where appropriate. A full listing of the membership of the EAG can be seen on pages vi and vii of this report. The terms of reference of the EAG were to:

- contribute to the provision of high quality and considered advice by the Authority to the Minister for Health and Children
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to the Authority regarding the scope of the analysis
- support the Evaluation Team led by the Authority during the assessment process by providing expert opinion and access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate
- contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

The Authority appointed an evaluation team comprised of internal staff to carry out the assessment. Dr Deirdre Madden of the Faculty of Law at University College Cork provided ethical and legal commentary and wrote these sections of the report.

The terms of reference of the project were agreed by the EAG at the initial meeting. Interim findings from the assessment and issues to be addressed including the parameters for the cost-effectiveness model were discussed at subsequent meetings. A final draft report was reviewed by the Group and approved by the Board of the Authority on 26 January 2011. The final report was submitted to the Minister for Health.

2.2 Literature review

A review of the relevant literature was conducted as part of the HTA. Appropriate articles were retrieved to inform the description of the epidemiology of vCJD in Ireland, to describe the risk of acquiring vCJD from a blood transfusion and to assess the current controls in place to prevent this occurrence.

A systematic review of the literature was performed to assess the available evidence in relation to the efficacy and safety of prion-removing filters and to ensure that that all relevant studies in relation to the technology were included in the HTA. Full details of the search system used are included in Appendix 2.

2.3 Documentation and data review

Data to inform the HTA was sourced from a number of organisations, including the:

- Irish Blood Transfusion Service
- Department of Health and Children
- Health Service Executive
- Irish Medicines Board
- Economic and Social Research Institute
- Coombe Women & Infants University Hospital, Dublin
- Our Lady's Children's Hospital, Crumlin, Dublin
- St James's Hospital, Dublin.

Two commercially available, CE (Conformité Européenne) marked prion-removing filters were identified at the time of conducting this HTA. The companies who manufacture and supply these filters (MacoPharma Ltd and Pall Medical) were invited to submit price quotations as well as dossiers in support of the safety, efficacy and use of their products to the Evaluation Team.

There is significant, ongoing research in the UK in relation to vCJD. The potential use of prion filtration by UK blood services to reduce the risk of vCJD is also being considered. Data, and where appropriate, documentation was sought and obtained from a number of UK sources, including:

- the Department of Health
- the Health Protection Agency
- Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO)
- the Prion Working Group
- 'Prion-filtered vs Standard Red cells in Surgical and Multi-transfused Patients' (PRISM study).

2.4 Cost-effectiveness and budget impact analysis

To assess the cost-effectiveness of introducing prion filtration of red cell concentrates (RCC) by the IBTS, future costs and outcomes must be predicted using an economic modelling approach. An independent model developed by the UK Department of Health was provided to the Evaluation Team and then adapted and populated with data relevant to the Irish setting. Data were obtained from literature review, published trials and Irish databases. Expert opinion was sought when published data were unavailable, or where the data were conflicting. The UK model was adapted to incorporate uncertainty around parameter estimates by allowing parameters to vary within plausible ranges. All data inputs were approved by the EAG. Results are presented as a most likely outcome along with confidence bounds indicating the range of probable outcomes. The confidence bounds indicate possible best and worst case scenarios given the selected parameter ranges. Details of the model and the parameter inputs are provided in chapter 6 and appendices 4, 5 and 6.

A budget impact analysis (BIA) of a policy of introducing prion filtration in Ireland was also performed as part of this HTA. Data were obtained from a number of sources to inform this assessment, including the Department of Health and Children, IBTS, HSE and the manufacturers of the prion-removing filters. Details of the BIA model and parameter inputs are provided in chapter 6.

A sub-group analysis was conducted to examine the appropriateness of selective prion filtration of RCC for limited sub-groups of the population. These sub-groups were selected on the basis of plausible clinical and biological arguments and were endorsed by the EAG. Data to inform the population estimates for these sub-groups were obtained from the ESRI, the IBTS, Our Lady's Children's Hospital, Crumlin, and by review of the literature. The key parameters for the sub-group models were identical to those used in the model for universal filtration. The only difference in the models was the number, age profile and average number of units transfused per recipient of prion filtered blood. Details of the sub-group section and analysis are provided in chapter 7.

2.5 Ethical and legal considerations

A review of the ethical and legal considerations surrounding the adoption or non-adoption of prion filtration of RCC in Ireland was conducted by Dr Deirdre Madden. This review considered the epidemiology of vCJD, the safety and efficacy of the prion filters and the cost-effectiveness and budget impact of both universal and restricted implementation of prion filtration as well as the discussions with the EAG. Details of this review are included in chapter 8.

3. Epidemiology

3.1 Introduction

The purpose of this section is to:

- review the aetiology of vCJD
- describe the prevalence of clinical and sub-clinical vCJD
- examine the potential for future clinical cases of vCJD
- describe the risk of vCJD transmission via blood or blood products
- review the incidence of transfusion-transmitted vCJD
- describe the current controls to prevent transfusion-transmitted vCJD.

3.2 Overview of vCJD and its origin

Variant Creutzfeldt-Jakob disease (vCJD) is classified as a transmissible spongiform encephalopathy (TSE). This is a group of rare, progressive, fatal non-inflammatory neurodegenerative diseases that affect humans and animals.

Animal examples of TSEs include:

- natural scrapie of sheep and goats
- bovine spongiform encephalopathy (BSE)
- feline spongiform encephalopathy
- chronic wasting disease of cervids (elk, moose, deer)
- transmissible mink encephalopathy (TRIE).[38;39]

In humans, TSEs include:

- Kuru
- Gerstmann-Stäussler-Scheinker syndrome (GSS)
- Fatal familial insomnia (FFI)
- Creutzfeldt-Jakob disease (CJD), of which there are at least four forms – sporadic CJD, familial CJD, iatrogenic CJD and variant CJD.[5;38]

TSEs are thought by many authorities to be prion diseases that are transmitted by infectious proteins. Unlike traditional infectious agents such as viruses and bacteria, the infectious agents are resistant to heat, ultraviolet and ionizing radiation, as well as disinfectants such as formaldehyde and gluteraldehyde.[40] The normal prion protein (PrP^{c}) found in neuronal tissue has unknown physiological properties. In TSE infection, this normally occurring protein is transformed into an insoluble and proteinase-resistant isoform (PrP^{Sc}), which may form the major component of the transmissible agent.[40] A form of CJD with variably protease-sensitive abnormal prion protein has also been recently described.[41] Accumulation of abnormal prion in the brain is accompanied by spongiform degeneration, ultimately manifesting as clinical disease.

The most common human prion disease is Creutzfeldt-Jakob disease (CJD). Most cases are sporadic (80-85%), with an unknown mode of transmission. Other cases are familial (approximately 15%), and a small number transmitted by medical procedures.[5] The spread of human prion disease through consumption of infected material has been documented. Historically, the kuru disease was transmitted by cannibalistic rituals in New Guinea. More recently, the emergence of vCJD has been associated with the consumption of BSE-infected beef. Human prion diseases remain relatively uncommon, leading to fewer than 100 deaths each year in the UK,[42] that is, 1 to 1.5 deaths per million of the population per annum.[8]

Epidemiological surveillance of CJD was reinstituted in the UK in 1990 to identify any changes in the occurrence of this disease after an epidemic of bovine spongiform encephalopathy (BSE) in cattle.[6] In 1996, 10 recently identified, atypical cases of CJD were reported.[6] These cases had a different neuropathological profile than had previously been described for CJD. Other distinguishing features included the young age of the patients (usually less than 45 years) on presentation, the clinical findings and the absence of abnormal electroencephalogram (EEG) findings typical of other CJD forms. The authors concluded that this was a newer variant form of the disease and hypothesised that infection through exposure to BSE was the most plausible interpretation for their findings.

Experts now concur that the emergence of vCJD in the mid 1990s was linked to an earlier outbreak of BSE in the UK.[8;42] BSE, a novel prion disease first reported in cattle in the UK in 1987, had a peak incidence rate of 3,500 new cases per month in 1992-1993.[8] Evidence of the link between BSE and vCJD includes that:[8]

- vCJD has occurred predominantly in the UK, the country with the largest BSE epidemic in cattle
- the biochemical profile of the proteinase-resistant isoform of the prion protein (PrP^{Sc}) in the brain in vCJD is very similar to that of the PrP^{Sc} in the brain in cattle and some other animals infected with BSE
- experimental infection of macaque monkeys with BSE produces a neuropathological profile closely resembling that of vCJD in humans
- experimental transmission studies of BSE and vCJD in wild-type and transgenic mice have revealed that the infectious agent in vCJD has very similar biological properties to the BSE agent.

The World Health Organization, in its summation of the evidence of a link between the two, states that 'the most likely cause of vCJD is exposure to the BSE agent, most plausibly due to dietary contamination by affected bovine central nervous system tissue'.[9]

A summary of the differences between clinical cases of sporadic CJD and vCJD is provided in Table 3.1.[5]

Table 3.1 Comparisons of variant CJD and sporadic CJD^

Clinical Feature	Variant CJD	Sporadic CJD
Mean age of onset	29 years	60 years
Length of survival	14 months	4 months
Early psychiatric symptoms	Common	Unusual
Painful sensory symptoms	Common	Rare
Later cerebellar ataxia	All	Many
Dementia	Commonly delayed	Typically early
Electroencephalogram	Non-specific slowing	Biphasic and triphasic periodic complexes
MRI*	Signal in pulvinar region of thalamus	Signal in basal ganglion and putamen
Cerebrospinal fluid	14-3-3 concentration high in 50% of patients	14-3-3 concentration high in most patients
Histopathology of brain	Many florid plaques	No amyloid plaques
Immunostaining of tonsils	Positive	Negative
Polymorphism at codon 129	All homozygotes (M/M)	Homozygosity and heterozygosity

** MRI changes are accepted as part of diagnostic criteria for variant CJD but not sporadic CJD*

^ ***Source:*** *Reprinted with permission from Elsevier (The Lancet Neurology. 2005; 4(10): pp.638)* [5]

With regard to polymorphism at codon 129 (Table 3.1):

- All probable and definite clinical cases of vCJD have been homozygous (MM) at codon 129. Sub-clinical infection with PrP^{Sc} has been identified in individuals with other polymorphisms.[3]
- A possible case of clinical vCJD was diagnosed in a patient who was heterozygous (MV) at codon 129. Diagnosis was performed on the basis of characteristic clinical onset and progression, exclusion of other diagnoses, and MRI findings. Sporadic CJD was judged unlikely given the combination of young age, clinical features, MRI findings, and absence of pseudoperiodic complexes on EEG. Autopsy was not performed, precluding a definite diagnosis.[12]

The human prion protein gene (designated *PRNP*) responsible for the coding of the prion protein is thought to play an important role in vCJD. Mutations of this *PRNP* gene have not been identified in vCJD, but all confirmed clinical cases of the disease have been homozygous for methionine (MM) at the polymorphic codon 129. However, based on European data, only approximately 40% of the general population have this genotype, indicating perhaps a genetic risk factor for vCJD.[42] Due to limited Irish data, European population estimates for the ***PRNP*** gene pool were used in this study. Whether clinical vCJD may yet occur, perhaps with longer incubation periods, in the other codon 129 genotypes (MV or VV) is uncertain.[8] Other TSEs have shown longer incubation times in subjects who have been heterozygous (MV) or valine homozygous (VV).[42] It is not yet known if clinical cases of vCJD from the remaining 60% of the population who show these genetic subtypes could emerge in the future.

3.3 Number of vCJD cases identified in Ireland and internationally

The European CJD surveillance network coordinated by the UK National CJD Surveillance Unit based in Edinburgh[43] conducts epidemiological surveillance for CJD. Currently, 25 collaborating centres from European Union Member States, European Free Trade Association (EFTA) countries, and eight additional countries worldwide provide data from national registries.

Table 3.2 outlines the reported worldwide cases of vCJD, updated to October 2010.[16] Worldwide there have been 216 deaths from vCJD in 11 countries since vCJD was first identified, 170 of which have been in the UK. Due to the link between the incidence of the disease and the UK epidemic of BSE in the 1980s and 1990s, the cumulative residence in the UK for a period greater than six months in the BSE 'at-risk' period (1980-1996) is also shown.

Table 3.2 Worldwide cases of vCJD [16]

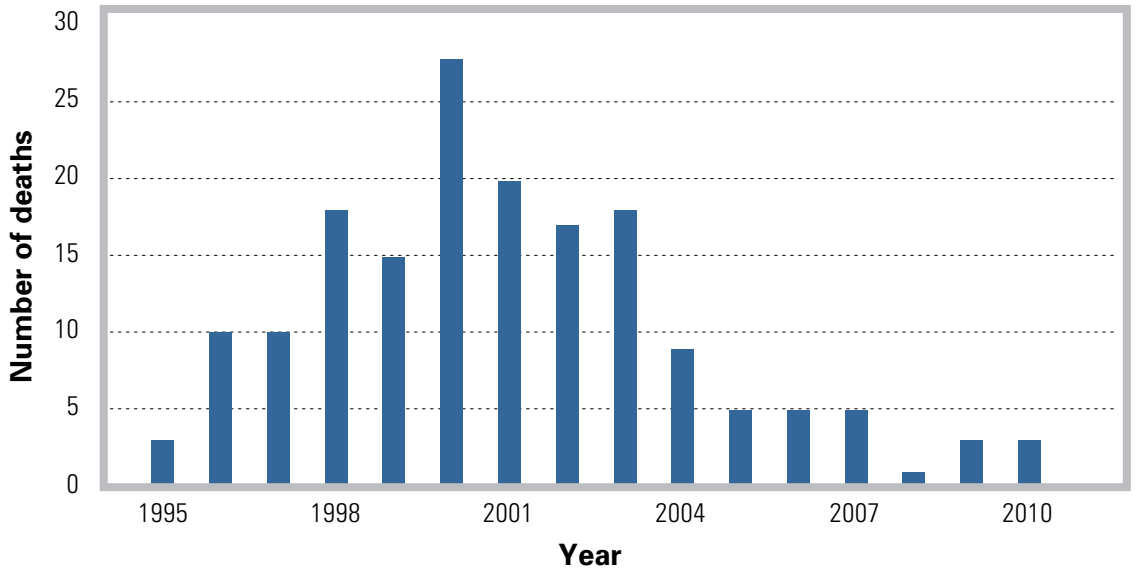
Country	Total number of primary cases including (number alive)	Cumulative residence in UK > 6 months during period 1980-1996
UK	174 (4)	174
France	25 (0)	1
Ireland	4 (0)	2
Italy	2 (1)	0
USA*	3 (0)	2
Canada	1 (0)	1
Saudi Arabia	1 (0)	0
Japan**	1 (0)	0
Netherlands	3 (0)	0
Portugal	2 (0)	0
Spain	5 (0)	0

** The third USA patient was born and raised in Saudi Arabia, and had lived permanently in the USA since late 2005. According to the USA case report, the patient was most likely infected as a child when living in Saudi Arabia.[16]*

*** The case from Japan had resided in the UK for 24 days in the period 1980-1996.[16]*

The largest number of cases of vCJD has occurred in the UK. A breakdown of the numbers of deaths from vCJD identified from 1995 to date is shown in Figure 3.1

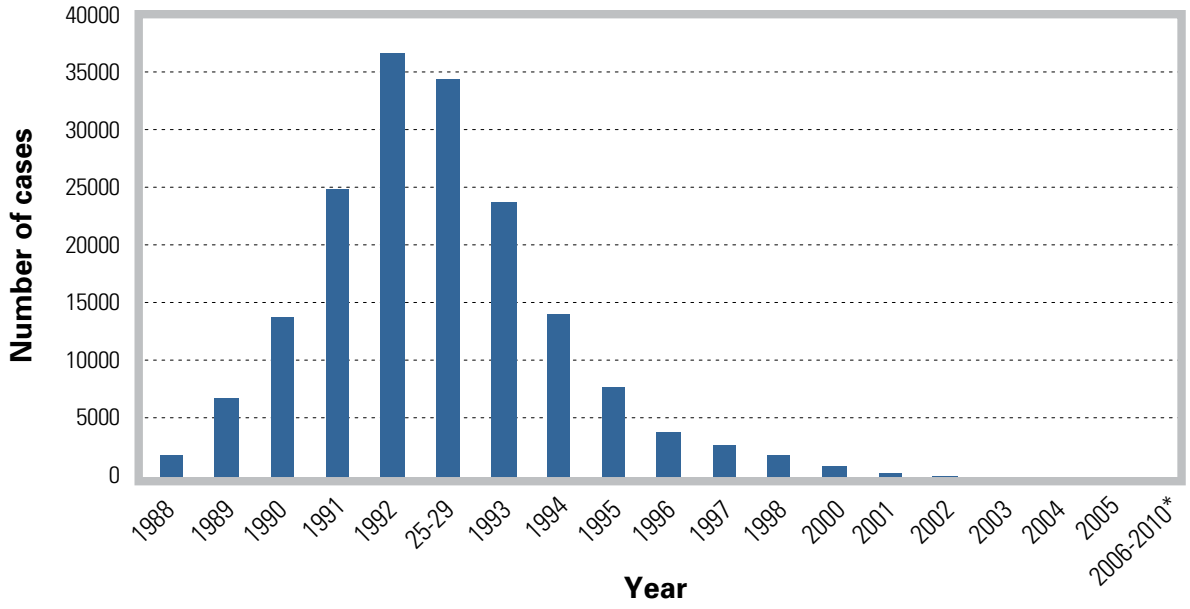
Figure 3.1 Number of definite or probable deaths from vCJD in the UK between 1995 and 2010* [10]



** Figures as of 2 December 2010. A further four people with definite or probable vCJD are still alive.*

The annual number of definite or probable deaths from vCJD in the UK peaked in the year 2000, declining since then. A similar trend has been documented for confirmed cases of BSE in animals, with the peak incidence occurring in 1992-1993, some seven to eight years earlier (see Figure 3.2).[44]

Figure 3.2 Number of confirmed cases of BSE in the UK each year from 1988 to date[44]*



** As of 1st November 2010*

Four cases of clinical vCJD have been notified to the Health Protection Surveillance Centre in Ireland (see Table 3.3).[11] Two of these cases are thought to have originated in the UK as the individuals resided there for prolonged periods between 1980 and 1996.[11;45]) Two further cases were considered to be indigenous, that is, the cases presented in two people who had never spent significant time outside of Ireland.[46]

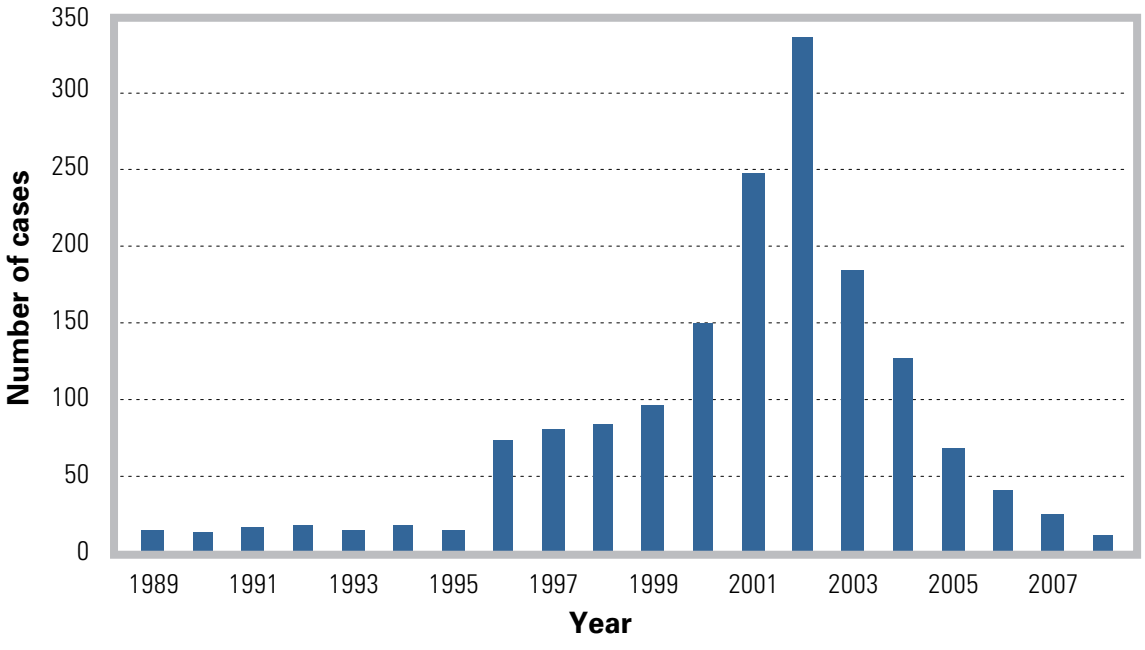
Table 3.3 Details of confirmed clinical cases of vCJD in Ireland

Case	Year of death	Age group	Cumulative residence in UK > 6 months during period 1980-1996
1	1999	25-34	✓
2	2005	20-24	x
3	2005	55-64	✓
4	2006	20-24	x

With four documented cases of vCJD, Ireland has the second highest prevalence in the world, after the UK.[47] The per-capita prevalence of the disease in Ireland is estimated at 1:1,000,000.[18] This is second to the UK, where with 174 cases identified and an estimated population of 58.5 million, the equivalent figure is 1:350,000. In France with 25 cases and an estimated population of 60 million, the prevalence is 1:2,400,000.

The incidence of BSE in animals peaked in Ireland in 2002, 10 years later than the UK. The incidence was an order of magnitude lower than the UK, with a peak incidence of over 300 new cases per annum, compared to over 36,000 new cases in the UK. However, a similar decline in new cases has been documented in recent years (see Figure 3.3).[48]

Figure 3.3 Number of confirmed cases of BSE in Ireland each year from 1989 to date[48]



3.4 Assessment of likely future occurrence of the disease

An assessment of the total number of future clinical cases of vCJD that might occur in Ireland was published in 2003 by Harney et al..[36] This study used an established mathematical model based on infectivity of bovine tissue (calculated from UK data) and the relative exposure to BSE-contaminated meat. The authors estimated one to two future cases of clinical vCJD disease in Ireland (95% CI*: 0-15). Exposure could be from BSE-infected indigenous beef products or imported UK beef products and taking into account the proportion of the Irish population who resided in the UK during the at-risk period of 1980 to 1996. Three clinical cases of vCJD have been reported since this study published.[11] A similar modelling study published in the UK in 2003, estimated that there could be 40 future clinical cases (95% CI: 9-540) in the UK based on the existing vCJD case data.[49] Consistent with the Irish modelling study, this point estimate has underestimated the subsequent reported deaths in the UK (n=49). However, for both studies, the observed number of cases has been well within the bounds of the predicted number of cases.

The limitations of the Harney study were discussed by the authors in their study. Notably, all cases of the disease to date have been homozygous for methionine (MM) on codon 129 of the human prion protein gene *(PRNP)* gene,[36] and the analyses assumes that the remaining 60% of the population are not susceptible to the disease or have a longer incubation period. The incubation period in homozygous individuals is generally shorter than in heterozygous individuals for other TSEs such as kuru and sporadic and iatrogenic CJD.[5;37] If this were the case with vCJD, then these individuals would appear to have either a longer incubation period for the disease to manifest, or may have decreased susceptibility.[49] Longer incubation periods are likely to result in a lower per capita incidence of the disease, since infected individuals have an increased probability of dying from other causes as they age.[49] Decreased susceptibility to the disease would also result in a lower per-capita incidence of the disease.[49]

The estimates case for Ireland assumed that the source of BSE, infected meat and bone meal fed to animals which then themselves became infected, had been eradicated from the food chain. Although this meat and bone meal had been banned from the diet of ruminants in Ireland since 1990, it was not banned from the diet of other animals until 2001. If vCJD could be contracted from other animals, there could in theory be an increase in the number of future cases.[36]

Of note, the modelling studies estimate only the total number of future clinical cases of vCJD.[36;49] They do not estimate the number of people who may be sub-clinical carriers of the disease. The number of people with sub-clinical infection who may go on to develop clinical disease is unknown. While patients with sub-clinical infection may never suffer adverse effects themselves, they retain the possibility of transmitting the disease to others, as a result of iatrogenic transmission via surgical procedures, such as tonsillectomy or appendicectomy, or as a result of blood donation.[36]

The study by Harney et al., assumed that Irish exposure to BSE infectivity arose from exposure to indigenous BSE infected meat products, exposure from UK imported products and exposure from travel to the UK in the at-risk period of 1980-1996. The relative proportion of risk attributable to each of these factors was assessed at 2:2:1, respectively.[36] A separate report commissioned by the IBTS in 2003 suggested that the Harney study overestimated the level of risk attributable to indigenous beef as it

**Confidence interval, see Glossary.*

did not take into account local slaughter and consumption practices.[50] It concluded that the combined risk of exposure of Irish people to BSE-infected meat products (indigenous beef, imported beef and travel to the UK) was 0.5% that of the risk of exposure in the UK.

3.5 Prevalence of sub-clinical vCJD infection in the UK

In the UK, attempts have been made to estimate the total number of individuals who may be carriers of sub-clinical vCJD infection. These individuals are at risk of further transmitting the disease, iatrogenically or through blood donation. There is no currently accepted blood test that reliably identifies individuals that have been infected with vCJD.[13;14]

Lymphoreticular accumulation (e.g., in appendices, tonsils, spleen and lymph nodes) of prion protein is a consistent feature of vCJD at autopsy and has also been demonstrated in the pre-clinical phase of the disease. Immunohistochemical accumulation of prion protein in the lymphoreticular system is the only technique that has been shown to reliably predict neurological disease in animal prion disorders.[7] In a major retrospective UK study by Hilton et al., samples from 16,703 patients (14,964 appendectomies, 1,739 tonsillectomies) were tested for the presence of abnormal prion protein (PrP^{Sc}) using immunohistochemistry. Of the adequate samples, three appendix samples tested positive, giving an estimated prevalence of 3/12,674 or 237 per million (95% CI: 49–692 per million). Two of the positive appendix samples in this study were found to be from patients who were valine homozygous (VV), indicating that individuals in this genetic sub-group are susceptible to vCJD infection. The third positive appendix sample could not be genotyped.[7] The true prevalence may be higher than reported in these studies as screening tests of lymphoid tissues could fail to detect some vCJD infections due to the non-uniform distribution of abnormal prion protein or from samples taken early in the incubation period.

Further studies, also in the UK population, have been carried out to try to refine the estimate of the prevalence of sub-clinical disease. No positive results were found in 63,007 tonsil samples from the National Anonymised Tonsil Archive (NATA) when tested using enzyme immunoassay.[51] Of these, 32,661 were from a cohort born between 1961 and 1995. This included 12,753 from the birth cohort in which most vCJD cases have arisen (1961-1985) and 19,908 from the 1986-1995 cohort that would have been also exposed to bovine spongiform encephalopathy through infected meat or meat products. In the 1961-1985 cohort, the prevalence of zero (95% CI: 0 to 289 per million) was lower than, but still consistent with the results of the Hilton appendix study.[7;51] To confirm the reliability of these findings, confirmatory testing using immunohistochemistry has been completed for over 10,000 tonsil samples, including 9,160 from the 1961-1985 birth cohort. One specimen showed a single, strongly positive follicle, but was negative on further testing. This positive result [1:9,160] would indicate a prevalence of 109 per million (95% CI 3-608 per million) which again, although lower that than the point estimate from the Hilton appendix study, is not inconsistent with it (237 per million; 95%CI: 49-692 per million).[7;52]

The Spongiform Encephalopathy Advisory Committee (SEAC) in the UK, has advised the UK Department of Health that estimates based on the Hilton appendix survey alone would represent a 'a reasonable, pragmatic and precautionary working scenario'

for the prevalence of sub-clinical infections in the UK.[53] It notes, however, that because of the wide confidence intervals, the appendix and tonsil data sets are not inconsistent with each other.[54]

However, it has been argued that if the estimated prevalence from the appendix study is accurate, there should be a substantially higher incidence of vCJD infection than is being experienced with the clinical data alone.[37] The discrepancies could be due to a proportion of those infected not developing clinical disease, or a delay in the development of the disease in a proportion of those infected due to genetic variations. By applying these hypotheses to a mathematical model to predict future clinical cases of the disease, the authors suggest that a possible maximum five-fold increase in future cases could occur. They note, however, the considerable uncertainty around this.[37]

Ongoing monitoring of tonsil samples as well as a further appendix study have been recommended in the UK to:

- refine the calculated prevalence of sub-clinical infection
- assess the risk of disease transmission
- establish the need for, and effectiveness of, the very costly measures that have already been introduced on a precautionary basis to reduce the potential risk of transmission of infection from infected individuals to others and to
- determine whether further risk reduction measures are necessary.[7;51;55;56]

3.6 Prevalence of sub-clinical vCJD infection in Ireland

There are no published estimates for the prevalence of sub-clinical disease in the Irish population. Preliminary data on sub-clinical infection from the Hilton appendix study became available at the time of reporting of the Harney study. These data were adapted to the model being used by the Harney team resulting in an increase from the 95% confidence interval estimate of 0-15 future cases of clinical vCJD in Ireland to a potential of 0-46 future cases.[36] It should be noted, however, that this preliminary data differed from the final reported data on completion of the Hilton study. It should also be noted that these revised estimates of clinical plus sub-clinical infection by Harney et al. take into account the potential for reduced exposure of the Irish people to BSE infection from indigenous beef, although not to the extent postulated by Comer.[50]

3.7 Risk of transmission of vCJD via blood transfusion

There remains the possibility that individuals who have been infected with vCJD and who are sub-clinical carriers of the disease may transmit the disease to other individuals through blood donation.[36] In contrast with vCJD, there have been no published cases of sporadic CJD transmission through transfusion of blood components or plasma.[1;2;57]

Modern medicine rarely involves transfusion of whole blood. Rather, donated whole blood is processed into its constituent parts that can then be specifically administered according to the clinical need. Studies have indicated that infectivity differs according to the blood component. In a risk assessment report for the UK Department of

Health, it was estimated that half of the infectivity in whole blood is in the plasma, and the remainder equally split between the red cells and buffy coat (white cells and platelets).[58] By refining the processing techniques to reduce or eliminate unnecessary components, vCJD infectivity can be reduced without impacting on the clinical benefit of the blood product. For red cell transfusions, these techniques have included removing white cells (leucoreduction) and reducing the plasma content of the final product.

3.8 Incidence of vCJD acquired through transfusion of red cells

In the UK, 18 patients who developed clinical vCJD have been identified as previous blood donors. Sixty-six recipients of their blood have been identified, 21 of whom are still alive.[3;59] Of those who died, infection with vCJD prions has been confirmed at post-mortem in four cases. Three of these recipients developed clinical vCJD, while the fourth died from causes unrelated to vCJD five years post-transfusion.[3] All four patients received transfusions of non-leucoreduced red blood cells suspended in plasma (red cell standards) between 1996 and 1999. Two of the cases of clinical vCJD were associated with transmission from the same donor. The three patients who developed clinical vCJD were all methionine homozygous (MM) at codon 129 of the human prion protein gene *(PRNP)* gene. The patient who died from unrelated causes was heterozygous (MV),[2] providing evidence that individuals who are valine homozygous (VV) or heterozygous (MV) are also susceptible to infection. Blood processing techniques have since been refined to reduce the white cell and plasma content of red cell transfusions, with product now supplied as leucoreduced red cell concentrate (RCC).

No clinical cases of vCJD arising from transfusion of blood or blood products have been identified in Ireland.[16] However, one donor developed clinical symptoms of vCJD shortly after making a blood donation. This donation was leucoreduced. The recipient of the red cell components died shortly after the transfusion from unrelated causes. The recipient of cryoprecipitate manufactured from the donation survived the illness that necessitated the transfusion.[18]

3.9 Incidence of vCJD acquired through transfusion of other blood components and blood products

To date, no recipient of pooled plasma has developed vCJD,[2;3] although the possibility cannot be ruled out particularly since its production requires large volume plasma pools with many patients receiving products from this pool.[2] In the UK, certain plasma products, manufactured using plasma from donors who later developed vCJD, may have exposed people who received them to infectivity and an increased risk of developing vCJD.[60] This plasma was used to manufacture factor VIII, factor IX, antithrombin, intravenous immunoglobulin G, albumin, intramuscular human normal immunoglobulin and Anti-D. For public health purposes, patients who received these products were notified that they had been at increased risk of exposure to vCJD.[60] There is one recorded case in the UK of a haemophilia patient (heterozygous [MV] at codon 129) who, at post-mortem, showed signs of accumulation of the abnormal prion protein in his spleen. This patient had not developed clinical vCJD and had died from unrelated causes. The investigation of the case indicated that the most likely

infectious agent was factor concentrates manufactured from plasma pools sourced in the UK during the BSE 'at-risk' period (1980 to 1996).[60;61]

3.10 Current controls to prevent the transmission of vCJD via transfusion of blood products

A number of measures have been taken by transfusion services to reduce the risk of transmission of vCJD from transfusion of blood or blood products. These include the following.

- Exclusion of donors who lived in the UK for a specified time during the at-risk period (1980-1996). This measure has been introduced in several countries, including the US and France.[2] In Ireland, individuals who have resided in the UK for a period of at least one year between 1 January 1980 and 31 December 1996 are excluded from donating.[62] This policy has been in place since November 2004. The period of time living in the UK has been reduced incrementally from five years to one year since April 2001.
- Exclusion of donors who themselves have received a blood transfusion. In Ireland, all potential donors who themselves received a blood transfusion outside the Republic at any time in the past are excluded.[62] Donors who received a transfusion (other than autologous units) in Ireland since 1980 are also excluded.
- Exclusion of donors who have undergone certain procedures. This is to minimise the risk of iatrogenic transmission. In Ireland, individuals who have undergone certain procedures in the UK are excluded including: neurosurgery, eye surgery, laser eye surgery, appendicectomy, tonsillectomy, adenoidectomy, splenectomy, lymph node biopsy and root canal treatment (unless the dentist used single use disposable files and reamers).[62]
- Use of plasma imported from countries where the incidence of BSE is an order of magnitude less than the UK and Ireland, and where the risk of vCJD is deemed very low. In Ireland, 98.5% of the plasma used is sourced from the USA, and shipped to Vienna for virus inactivation (SD-plasma). The remainder is sourced within Ireland for use by the Liver Transplant Unit in St Vincent's University Hospital, Dublin.[18]

These risk reduction methods are intended to reduce the potential for secondary transmission of vCJD from sub-clinical donors infected due to exposure to BSE infected meat in the UK or from receipt of infected blood. An ongoing risk of transmission, albeit at a lower level, is assumed to prevail from donors who acquired the infection from consumption of indigenous meats, or contaminated meat consumed outside of the BSE 'at-risk' window. The implementation dates of current measures adopted in Ireland and in the UK are illustrated in Table 3.4.

Table 3.4 Measures adopted in Ireland and the UK to reduce the risk of transmission of vCJD via blood products

Preventative measure	Year of introduction in Ireland[62]	Year of introduction in the United Kingdom
Universal leucoreduction of RCC	1999	1999[1]
Programmes to implement best practice for hospital transfusions	2001[63]	2001[64]
Exclusion of donors who had spent five or more years in the UK during the at-risk period (1980-1996)	2001	N/A
Exclusion of donors who had previously received blood transfusions outside of respective country	2002	N/A
Importation of plasma for manufacture of blood products from low-risk BSE countries	N/A	1997[1]
Importation of plasma for transfusion from low-risk BSE countries (limited in the UK to patients under the age of 16 or born after 1995)	2002	2002[1]
Exclusion of donors who spent three or more years in the UK during the at-risk period	2004	N/A
Exclusion of donors who spent one or more years in the UK during the at-risk period	2004	N/A
Exclusion of donors who had received any blood transfusion (other than an autologous transfusion) since 1980	2004	2004[1]
Exclusion of donors who underwent certain high risk procedures in the UK since 1980	2004	2004
Exclusion of donors who underwent root canal treatment in the UK since 1980 (unless dentist used only single-use disposable files and reamers)	2006	N/A
Importation of fibrinogen made from US-sourced plasma to replace cryoprecipitate made from Irish plasma	2009	N/A

In 1999, the Irish Blood Transfusion Service introduced universal leucoreduction (that is, leucoreduction of all blood components) through the use of leucocyte removing filters. The purpose of universal leucoreduction is to reduce the infectivity of domestic blood products or red blood cells, with a goal of reducing the transmission of vCJD.[65] The efficacy of leucoreduction in removing TSE infectivity from whole blood concentrates has been assessed using scrapie-infected hamster models.[65] A mean reduction of 42% (SD: 12) of the total TSE infectivity in endogenously infected blood was reported. The authors concluded that while leucoreduction is necessary to remove white-cell-associated TSE infectivity from blood, by itself it is not sufficient to remove all blood-borne TSE infectivity as a substantial part of the TSE infectivity is not associated with white cells.[65] In a further study following the same protocol, leucoreduction removed 72% of TSE infectivity.[66] Although infectivity was reduced in both studies, leucoreduction by itself is not seen to be sufficient to eliminate the risk completely.

Current World Health Organization guidelines make the following statement in regard to vCJD and leucoreduction:[67]

> Leukoreduction is known to remove some TSE infectivity from endogenously infected blood and might be expected to lower risk from labile blood components for transfusion without abolishing risk completely. Leukoreduction is already used widely in some countries, largely for other reasons. Unfortunately, recent studies found substantial endogenous infectivity remaining in plasma after blood of scrapie-infected hamsters was passed through a commercial leukoreduction filter.

3.11 Key messages

- Experts agree that the origin of vCJD is linked to the outbreak of BSE that occurred in the UK in the 1980s and 1990s.
- The UK has had the highest incidence of clinical vCJD disease, with 170 deaths reported to date. In Ireland, there have been four reported deaths since the disease was identified. The incidence of the disease has declined in recent years in the UK.
- All confirmed clinical cases of vCJD have occurred in individuals with the MM genotype at codon 129. However, other genotypes (MV and VV) have been shown to be susceptible to, and may be carriers of, the infection. A case of possible clinical vCJD has occurred in an individual who was heterozygous at codon 129, although is unconfirmed because autopsy could not be performed.
- The precise number of sub-clinical carriers of vCJD in the population is not known. UK estimates indicate that the prevalence of sub-clinical infection could be as high as 237 per million (95% CI: 49-692). However, there is considerable uncertainty associated with this result. Prevalence estimates have varied depending on the tissue sampled and the analytical technique used. When used in conjunction with other model assumptions, reported estimates from modelling studies over-predict the number of clinical cases that have occurred. No prevalence studies have been conducted in Ireland. It is likely however that this prevalence is substantially lower than in the UK.
- Worldwide, five cases of transfusion-associated vCJD transmission from donors who subsequently developed vCJD have been identified. These cases all occurred in the UK. Four cases relate to the transfusion of non-leucoreduced red blood cells between 1996 and 1999, three of whom died from clinical vCJD and one from unrelated causes. One case relates to vCJD transmission from infected factor concentrates in an individual with confirmed pre-clinical vCJD who died from unrelated causes. Both individuals who died from unrelated causes were MV heterozygous at codon 129.
- There is an ongoing risk of vCJD transmission from transfusion of blood or blood products due to donations from sub-clinical carriers of the disease.
- The Irish Blood Transfusion Service has taken several measures to reduce the risk of transmission of vCJD via transfusion of blood or blood products. These include donor deferral policies, importation of plasma from countries with a low incidence of vCJD and BSE and leucoreduction of all blood components.

4 Efficacy of prion filters

4.1 Introduction

The purpose of this section is to:

- provide background on the development of prion filters and the tests used to assess their efficacy
- examine the available evidence used by the commercial developers of these filters to demonstrate their efficacy
- examine the available evidence from an independent UK assessment of the efficacy of prion filters and
- discuss the applicability of the efficacy data to potential clinical transmission of vCJD from donated RCC in humans.

4.2 Background

The known cases of vCJD transmission associated with blood transfusion have occurred following the administration of non-leucocyte reduced red blood cell products[3] or factor components manufactured from infected plasma.[60] Universal leucocyte reduction was introduced by the Irish Blood Transfusion Service in 1999 to in part reduce the risk of transmission of vCJD from blood products. However, leucoreduction does not completely remove infectivity from whole blood (see section 3.10).[65-67] A number of specially designed prion-removing filters have been developed to further reduce the risk of vCJD transmission from transfusion of red cell concentrates by substantially reducing (or eliminating) any residual prion protein that might be present in donated blood. The use of such filters would complement existing measures adopted to contain the risk of transmission.

In general, before a medical device can be marketed in the EU, it must carry the 'CE' (Conformité Européenne) mark.[68] This indicates that the manufacturer is satisfied that the product conforms to the essential requirements in the relevant European Directives for that device, including that it is safe, of an acceptable quality, and fit for its intended purpose (as stated by the manufacturer), and that the manufacturer has signed the necessary declaration of conformity. For all but the lowest-risk devices, the manufacturer's conformity assessment must be verified pre-market launch by an independent certification organisation, known as a Notified Body.[68] Clinical trials are not required to acquire CE marking.[13]

At the time of this report, two systems incorporating a prion-reduction filter had been commercialised and CE marked. Only those filters that were CE marked at the time of this report were considered for inclusion in the assessment. However, we are aware that there is at least one other filter in development (Asahi Kasei Medical). The MacoPharma P-Capt™ Prion Capture filter (MacoPharma Ltd), hereafter referred to as the P-Capt™ filter, was CE marked in September 2006 and is designed to be used in sequence with a leucoreduction filter. The Pall Leukotrap® Affinity Plus Prion and Leucocyte Reduction Filter System (Pall Medical, a division of Pall Europe Ltd), hereafter referred to as the PRF2BE filter system, was CE marked in September 2009.

This product was developed from a first-generation prion-reduction filter that was CE marked in 2005.

A literature search was performed to review the published evidence on efficacy of prion-removing filters (see Appendix 2). Additionally, Pall Medical and MacoPharma Ltd were invited to make submissions in relation to their products. Published independent validation studies performed on the efficacy of these filters by other research groups were also reviewed.

4.3 Tests for filter efficacy

Assessment of the efficacy of prion filters is hampered by the lack of a specific test that can detect the presence of infectious prion in donated blood.[13] Indeed, current testing is not even sufficiently sensitive to detect infectivity in people with clinical vCJD.[14;69] In the absence of a specific screening test to detect infectious prion in donated blood, determination of the efficacy of prion-removing filters is limited to exogenous and endogenous studies in experimental animal models. Efficacy results are presented as log reductions in infectivity. A 1-log reduction means a 90% reduction in infectious load, a 2-log reduction means a 99% reduction and a 3-log reduction means that the infectious load is reduced by 99.9%.

Exogenous studies using a brain homogenate (10% weight/volume) prepared from 263K scrapie-infected hamsters have been used by manufacturers to test filter efficacy ('brain-spike' studies). The brain homogenate is inoculated into human red cell concentrate (RCC) providing blood with very high levels of infectivity.[13] Samples of the infected blood are assayed before and after prion filtration at multiple 10-fold dilutions using bioassays to assess infectivity and immunoassays (Western blot) to detect abnormal prion protein. The bioassays involve intracranial injection of a 0·04–0·08 ml sample into hamsters to find the maximum dilution at which infection occurs. Results are usually based on the dilution at which half of the test animals become infected; this is expressed as the ID_{50} (50% infectious dose) units/ml.[19]

The correlation of animal model studies using brain homogenate with human blood infectivity is uncertain.[14] TSE infectivity derived from brain tissue may not be partitioned in the same way as endogenous TSE infectivity and therefore, may not provide a model which accurately represents the fractionation of a prion agent present naturally.[70] Different TSE agents may also differ in terms of their physiochemical properties, and it has been suggested that transmission of 263K scrapie may not accurately reflect vCJD transmission in humans. A second TSE agent, a mouse-adapted BSE (BSE-301V), has been proposed as a more feasible model to investigate vCJD transmission between humans.[71] This agent has been included in independent studies performed by the Health Protection Agency (HPA) in the UK.

Studies have also assessed the impact of different techniques for preparing the brain homogenates, as these may impact on the findings. Specifically, the effect of different levels of centrifugation in preparing the homogenate has been examined as part of the assessment of filter efficacy.

Endogenous studies have been developed to assess the level of prion reduction that can be achieved using the peripheral blood of 263K scrapie-infected hamsters. Whole blood is collected from pre-infected animals and processed into a single unit

of red cell concentrate (RCC) in accordance with standard practice for the production of human RCC. Pre- and post-filtration samples of this unit are tested for infectivity by inoculation of the RCC into healthy hamsters with observation of the animals over time.[72;73] Due to the low baseline infectivity of the whole blood samples (which is likely to be more relevant to human RCCs than brain spikes), quantification of prion removal is generally limited to little more than a 1-log reduction in infectivity.[3]

4.4 Efficacy studies of the P-Capt™ filter

The original P-Capt™ prototype was developed by screening a large peptide-based combinatorial library for ligands that could bind prion protein and TSE infectivity in the presence of red cells and plasma.[19] The efficacy of the resin in column and commercial filter format has been demonstrated in the exogenous and endogenous studies described below. A summary of these studies is shown in Table 4.1. The commercialised form of the developed filter (P-Capt™) was CE marked in September 2006. This filter is intended to be used in sequence with a leucoreduction filter, for the prion-reduction of leucoreduced RCC.

A 3- to 4-log reduction in ID_{50} per ml was obtained in bioassays for the prototype ligand resins packed in column format when challenged in exogenous studies using hamster-brain-derived 263K scrapie spiked in leucoreduced human red cells. Despite repeated passage through successive columns, 0.01% of the exogenous infectivity remained following filtration.[73] When the ligand resin was reformulated in a commercial filter format, a comparable 3-log reduction in infectivity was reported. However, the study result depended on the preparation of the brain spike, with only a 1-log reduction noted for the ultra-centrifuged sample.[4] The capacity of the ligand resin to remove infectivity from hamster-brain-derived 263K scrapie was confirmed using Western blot assays in further exogenous studies both when the resin was assembled in experimental column and commercial filter formats.[73;74] The binding capacity of the commercial filter for prion infectivity was determined to be 1.5 x 107 ID_{50}.[75]

The efficacy of the prototype ligand resins (L13: best-performing resin in exogenous studies; L13A: variation of L13 capable of being produced on a commercial scale) in removing infectivity from leucoreduced 263K scrapie-infected hamster whole blood was tested in an endogenous efficacy study.[66] No animal inoculated with the final flow-through from the L13 resin (96 animals) or the L13A resin (100 animals) developed the disease during 540 days of observation. Infectivity was reduced to below the limit of detection (0.2ID/ml) with a greater than 1.22 log ID per ml reduction in challenge infectivity reported for the two column types. In contrast, leucoreduction alone removed only 72% of input infectivity while 15 of the 99 animals in the control challenge were infected with 263K hamster scrapie.[66]

Table 4.1 Summary of efficacy studies for MacoPharma prototype and P-Capt™ filters

Author (published)	Filter type	Exogenous infectivity studies	Endogenous infectivity studies	Notes
Gregori et al. 2006[73]	Prototype ligand resins in column format	**Bioassay:** reduction in infectivity titre of 263K scrapie by 3.0-4.3 log ID_{50}/ml **Western blot:** strong abnormal prion signal reduced to below the limit of detection		Testing of prototype resins in columns to determine optimal resin and volume required. Brain spike sample centrifuged at 12,000g
Gregori et al. 2006[66]	Prototype ligand in column format		After 540 days observation, transmission of abnormal prion from 263K scrapie in inoculated hamsters was: 0/96 L13 filtered blood 0/100 L13A filtered blood 15/99 pre-filtered controls	Optimal ligand resin (L13) and its manufacturing scale derivative (L13A) tested in column format. Infectivity reduced to below the limit of detection (0.2ID/ml)
Gregori et al. 2006[74]	P-Capt™ filter L13A in filter format	**Western blot:** comparable reduction in 263K scrapie from brain homogenate for both column and filter format		Ligand resin maintained its performance when reformatted into commercial filter format
Lescoutra-Etchegaray et al. 2009[4]	P-Capt™ filter	**Bioassay:** 263K scrapie from brain infectivity spike: 14,000g spike: 3-log reduction Ultra-centrifuged sample: 1-log reduction		Brain spike studies using two different sample preparations (14,000g-treated spike and an ultra-centrifuged sample). Results were seen to be dependent on spike preparation

4.5 Development and efficacy studies of the PRF2BE filter system

Pall adapted its existing red cell leucoreduction filter materials using a proprietary surface modification technique that resulted in sheets of material with a high affinity for prion proteins and the associated TSE infectivity. By interweaving standard and modified media, a combined filter capable of concurrent reduction of prions and leucocytes was developed.[19]

A number of variations of the Pall filter have been developed. These include a prototype leucoreduction filter with prion reduction capability; the Pall Leukotrap Affinity Prion Reduction filter system (PRF1BU) intended for prion reduction of single units of leucoreduced red cells; and the currently marketed PRF2BE filter system intended to be used for concurrent prion and leucocyte reduction of red cell units. The PRF1BU filter was originally commercialised by the company and CE marked in 2005. It has since been replaced by the PRF2BE filter system which was CE marked in September 2009.

Exogenous and endogenous studies in experimental animal models have been reported for the prototype filter and the PRF1BU.(76) Bioassay results for the prototype filter indicated a 3.7-log reduction in infectivity from 263K scrapie-infected brain homogenates. A very strong abnormal prion signal was reduced to below the limit of detection on the Western blot following filtration.[72] Western blot assays for the PRF1BU demonstrated a mean log reduction of 2.9 (SD: 0.7) in prion protein concentrations when tested under a range of operational conditions. Bioassay results were not reported.[77]

Endogenous infectivity studies were conducted using the prototype filter and the PRF1BU system. For the prototype filter, no transmission of abnormal prion was detected within a 300-day incubation period in any of 35 animals following inoculation of filtered RCC, compared to 6 of 43 animals in the pre-filter control group. In a Western blot assay of the endogenous blood, a barely visible pre-filtration signal was reduced to below the level of detection in the post-filtration sample.[72] This finding was confirmed using a novel sensitive cell culture-based infectivity assay to measure prion infectivity.[76] However, for the PRF1BU system, while no transmitted disease was noted by the 200-day observation time (0/413 transmitted disease versus 6/187 for the filtered and unfiltered cohorts, respectively)[77], 3 of the 413 animals receiving filtered RCC had developed scrapie by the 300-day observation time (compared to 7/187 cohort receiving unfiltered RCC).[76] Evidence of residual infectivity was also evident for the PRF1BU system when tested using the novel sensitive cell culture-based infectivity assay.[76]

No in vivo studies demonstrating the exogenous or endogenous efficacy of the PRF2BE commercial filter system have been published. However, an independent endogenous infectivity study using scrapie-infected sheep has been completed in France by the Etablissement Français du Sang and is expected to be published in 2011.[78] A summary of the studies outlined in this section is shown in Table 4.2.

Table 4.2 Summary of information on efficacy studies for Pall prototype filter, PRF1BU and PRF2BE filter systems

Author (reference)	Filter type (number of prion-removing layers)	Exogenous infectivity studies	Endogenous infectivity studies	Notes
Sowemimo-Croker et al. 2005[72]	Prototype	**Bioassay:** 3.7-log reduction in infectivity **Western blot:** strong abnormal prion signal reduced to below the limit of detection	No transmission of abnormal prion in 35 animals @300 days (vs. 6/43 infected in pre-filtered group)	Brain spike sample centrifuged at 3,000g
Sowemimo-Croker et al. 2006[77]	PRF1BU	**Bioassay:** none **Western blot:** mean log reduction in concentration of abnormal prion of 2.9 ± 0.7 when tested over a range of operational conditions	No transmission of abnormal prion in 413 animals infected post inoculation @200 days (vs. 6/187 in the pre-filtered group)	Brain spike sample centrifuged at 5,000g
Sowemimo-Croker et al.[76]	PRF1BU		3/413 animals infected post inoculation @300 days (vs. 7/187 in the pre-filtered group)	This is a continuation of the 2006 study which reported infectivity to 200 days, with results updated to 300 days
Ortolano et al. 2009	PRF2BE	No peer-reviewed published studies	No published studies	Unpublished confidential results assessing efficacy using a novel conformation-dependent immunoassay

4.6 Independent validation of efficacy studies

The need for independent safety and efficacy studies prior to the universal adoption of blood product devices has been strongly advocated.[3;13;14] The purpose of the independent validation is to replicate the in-vitro studies that enabled CE certification using the final commercially available product. Such studies could also include appropriate clinical studies not performed to date and evaluate feasible quality control measures to verify the ongoing efficacy of the device during routine blood processing.[19]

The Health Protection Agency (HPA) in the UK was commissioned by the UK Blood Services Agency to conduct an independent assessment of the exogenous prion filter efficacy studies. The IBTS is a partner in this study.[18] Results from the independent assessment are intended to inform a decision regarding the capacity of the filters to remove the infectivity thought to be present in human leucoreduced red cells to a level sufficient to reduce or eliminate the risk of vCJD transmission. This decision would inform recommendations regarding the clinical use of prion filters.

Manufacturers of these filters were requested to assess their devices against an earlier set of specifications that had been produced by the UK Blood and Tissues Service.[79] Manufacturers that could meet these specifications were invited to submit their data so that their devices would be independently assessed. The MacoPharma P-Capt™ filter was the only device for which data were submitted and which was assessed.[17]

P-Capt™ filters were tested in exogenous studies using hamster brain-derived 263K scrapie spiked in leucoreduced red cell concentrate (RCC). Two spike preparations were used: a crude brain homogenate and a sonicated sample in order to replicate the published manufacturer's studies, with each assay performed in triplicate. Bioassay results indicated a mean log reduction in infectivity of 1.3 ID_{50} per gram of undiluted brain (range 0.3-1.5) and 0.3 ID_{50} (range 0.0 to 1.0) for the crude and sonicated samples, respectively.[80] The study was repeated using a different TSE sample: a mouse-brain derived BSE-301V spike (sonicated only) again with assays performed in triplicate. Bioassay results indicated a mean log reduction in infectivity of 2.1 ID_{50} per gram of undiluted brain (range 1.4 to 2.4).[71]

These results suggest that the efficacy of the filter in reducing infectivity appears to depend on the TSE agent used and on the method of preparation of the brain spike. Results also differed between individual filter lots with negligible clearance of infectious prion noted in two of the nine assay runs. The results of the assessment by the HPA also differ considerably from the published data. In particular, the result of the 263K sonicated brain spike assay (0.3-log reduction, range 0.0 to 1.0) differs markedly from the published 3 to 4-log reduction noted by the manufacturers.(73) Explanations for these discrepancies included potential variability between the filters, differences in the blood used for the filtration runs and differences in the accessibility of the prions within the spike preparations. The results from these studies are outlined in Table 4.3. This table also illustrates the corresponding number of units of infectious TSE that would be removed based on these mean log reductions in infectivity.

Table 4.3 Estimated reduction in TSE infectivity based on exogenous brain spike bioassays for the P-Capt™ filter

TSE spiking agent	Mean log reduction in infectivity (ID_{50}/ml)	Estimated infectious units removed/unit LR RCC
Crude 263K	1.3 (0.3-1.5)	9.00×10^8
Sonic 263 K	0.3 (0.0-1.0)	5.95×10^5
BSE 301V	2.1 (1.4-2.4)	1.18×10^9

BSE – Bovine spongiform encephalopathy; LR - leucoreduced; RCC – Red cell concentrate; TSE – Transmissible spongiform Encephalopathies.

The significance of these findings and the reason for the discrepancy between the findings of this independent study and that of the filter manufacturers is uncertain. All process runs are within the specification of acceptance recommended by the filter manufacturer. The apparent failure of the filter to remove any significant amount of prion material in two of the nine assay runs (one each sonic 263K and crude 263K assay) remains a concern, particularly if these exceptions mimic the pattern of vCJD transmission through donated blood in humans.

The HPA has commenced endogenous studies to assess the efficacy of the P-Capt™ filter in 263K scrapie-infected hamster and BSE sheep models. These studies will not report for a further two to three years.

4.7 Relevance of efficacy studies to transmission of vCJD in humans

The capacity of the prion filters to reduce infectivity has varied according to the TSE strain and the method of preparing the brain spike sample and between published and independent validation studies. The results of the animal models must be interpreted within the context of the ability of the filters to remove prion protein from a TSE-infected unit of human RCC.

The exogenous infectivity studies involve challenging these filters with levels of TSE infectivity more than 2×10^6 times higher than would be expected from a TSE-infected unit of human RCC.[73] As the prion-reducing filters are affinity matrices with a fixed binding capacity, it is possible that they would not bind all of the challenged infectivity in the spiked samples, but that they would have adequate binding capacity to bind all infectivity in a TSE-infected unit of human RCC. The number of infectious TSE units estimated to be present in a unit of leucoreduced RCC from a donor with sub-clinical vCJD is in the order of 100 to 200 ID.[81] As illustrated in Table 4.3, the filter has the capacity to remove infectious prion far in excess of this, although some uncertainty remains based on the lower average reduction in infectivity results obtained for the sonicated 263K scrapie spikes.

In the exogenous brain spike study by Gregori et al., a small fraction of brain infectivity (1 in 10,000 infectious doses) could not be removed by the filter resin.[73] To assess the relevance of this and the general relevance of brain-derived infectivity spikes to the clinical situation, endogenous studies using leucoreduced scrapie-infected peripheral blood are used. As noted in section 4.4, infectivity from leucoreduced whole blood was reduced by more than $1.22 \log_{10}$ ID to below the limit of detection of the assay (0.2ID/ml) in studies by the filter manufacturer with no animal developing the disease

within 540 days. Independent validation of the endogenous studies reported by the manufacturers has not been performed at the time of this report.

Pending the independent validation of the endogenous animal model studies, the UK Prion Working Group has concluded from the combined available evidence that prion filters have the capacity to remove infectivity from peripheral blood at levels greater than those expected from donors with sub-clinical vCJD infection. This has been accepted as an interim finding by SaBTO in the UK.[17] However, current evidence suggests that 1 in 10,000 infectious particles would remain following filtration. A conservative approach would, therefore, assume that residual infectivity would remain at this level following prion filtration of leucoreduced RCC from an infected donor.

4.8 Key messages

- Two prion-removing filters have been commercially developed and awarded CE marks.
- CE marking of devices is limited to demonstration of biocompatibility. Neither the efficacy of the device in terms of the final product (e.g. reduced infectivity of filtered human blood) nor the clinical safety of this product is considered as part of the CE process.
- Studies of these devices rely on animal brain tissue (brain-spiking or exogenous studies) and animal peripheral blood models (endogenous studies) to assess their efficacy. The relevance of this to vCJD infectivity of human blood is uncertain.
- Data to support the efficacy of the filter resin in reducing infectivity from vCJD has been published for prototypes of both filters and for the current commercially available P-Capt™ filter.
- No peer-reviewed studies have been published to date to demonstrate the efficacy of the currently marketed PRF2BE filter system.
- Independent validation of safety and efficacy data has been recommended before a filter is considered for routine adoption by blood transfusion services. In the UK, satisfactory completion of an independent study was a requirement for a recommendation by SaBTO to the UK Department of Health regarding the adoption of prion filtration.
- Validation of the exogenous studies has been undertaken for the P-Capt™ filter. Although reporting lower efficacy levels than suggested by the manufacturers, the amount of infectious prion removed generally far exceeded the expected exposure levels from peripheral blood of donors with sub-clinical vCJD infection. However, the apparent failure of the prion filter to remove any significant amount of prion material in two of the nine assay runs in the independent exogenous study remains a concern. Independent validation of the endogenous studies is planned.
- Similar independent validation studies would be required for the PRF2BE filter system prior to any decision to adopt this technology into routine blood processing in Ireland.
- When used in conjunction with universal leucoreduction and other existing risk reduction strategies, current evidence suggests that the filters will remove almost all residual risk of vCJD transmission with the caveat that 1 in 10,000 infectious particles would remain following filtration.

5. Safety of prion-reduction filters

5.1 Introduction

This purpose of this section is to examine the:

- quality control standards used to assure the quality of red cell concentrates (RCCs)
- evidence of the quality of RCCs post prion filtration
- evidence on clinical outcomes post-transfusion of prion filtered RCCs.

5.2 Background

The potential for a prion filter to alter or reduce the quality of the filtered RCC with negative consequences for the transfusion recipient must be considered as part of this assessment. Issues in the evaluation of the quality and safety of prion filtered RCCs include:

- a potential alteration in the quality of the RCC, perhaps as a result of the filter process retaining blood components or as a result of the filter altering the composition of the RCC
- the possibility that the filtered RCC could induce the formation of new antigens (neoantigens) that could be clinically significant to the recipient, inducing adverse effects.[19]

A number of in-vitro and in-vivo studies have been carried out, or are underway, to assess the impact of prion filtration on the safety and quality of filtered RCC. The in-vitro studies evaluate the effect of prion filtration on the red blood cell component levels. The in-vivo studies monitor the development of new antibodies as well as the occurrence of adverse events in recipients of transfusions or RCC that have been prion filtered. The results of these studies are summarised in later sections of this chapter.

5.3 Quality control standards for red cell concentrate

EU directive 2004/33/EC[82] sets standards for the quality and safety of blood and blood components with the frequency of sampling for all measurements determined using statistical process control methods. Red cells that are leucocyte reduced and stored in additive solution should:

- have a volume that is sufficient to maintain haemoglobin and haemolysis levels within specification for the duration of storage
- have a haemoglobin content of not less than 40g per unit
- demonstrate a haemolysis level of less than 0.8% of the red cell mass at the end of the shelf life (as haemolysis increases over time, control measures specify the maximum level permitted at the end of shelf life)
- have a leucocyte count of less than 1×10^6 per unit.

The IBTS adopts a process monitoring system based on the UK and Council of Europe Guidelines where a minimum of 90% of tested leucocyte depleted red cell products stored in additive solution should meet the specification for leucocyte count and 75% meet the specifications for volume, haemoglobin and haemolysis levels. In this system, at least 1% of produced products are tested, with haemolysis levels tested in four products per month.

5.4 In-vitro studies of red cell quality for the P-Capt™ filter

A 2008 study conducted by the Irish Blood Transfusion Service (IBTS) reported the in-vitro assessment of leucodepleted red cell concentrates filtered using the P-Capt™ filter. Thirty-six units of leucodepleted red cell concentrates in SAG-M (additive solution) were prepared under standard 'bottom and top' (BAT) processing conditions. Twenty-four units were prion filtered with 12 units acting as a control; 50% of these units were subsequently irradiated on day 14.[20] The quality of the blood was assessed at seven-day intervals up to day 35.

A significant reduction in haemoglobin (Hb) levels was recorded for the prion filtered units, with a mean reduction of approximately 9g Hb/unit equating to a 22.5% loss of haemoglobin noted. This reduction was attributed to retention of red cells in the dead space of the filter. As a consequence, the haemoglobin concentration of a number of the filtered units was below the specified 40g Hb/unit. As expected, haemolysis levels increased with shelf life and were higher for irradiated than non-irradiated units. A significant increase in haemolysis was reported for the filtered units compared to the non-filtered controls. While non-irradiated packs remained within European technical specifications for haemolysis (<0.8%) at day 28, and up to day 35, two filtered and irradiated units had haemolysis levels that exceed this limit by the end of the storage period.[20]

The occurrence of new or more frequent adverse events associated with transfusion of prion-filtered RCC may only become apparent following wide-spread adoption of the technology and would necessitate careful post-marketing surveillance.

The effectiveness of individual prion-removing filters cannot be directly measured as part of process validation or during routine process monitoring. Clotting factors II and IX have been suggested as potential process control measures for prion filtration as these are bound by the filter resin via a parallel, but distinct, process. In this study, a 41.6-fold reduction in prothrombin levels in post filtered samples was recorded.[20]

Wiltshire et al. conducted an in-vitro study for the NHS Blood and Transplant Service that assessed the quality of the filtered components, the impact of prion filtration on blood group antigens and the operational use of the prion filters.[21] Following standard processing using both BAT and 'top and top' (TAT) methods, 272 units of leucodepleted RBC were passed through the P-Capt™ filter. Filtration resulted in a 6 to 9% reduction in haematocrit and an average loss of 7 to 8g of haemoglobin per filtered unit. In that study, 58% of BAT and 99% of TAT units contained more than 40g haemoglobin after filtration. The authors noted that the specification for minimum haemoglobin content would need to be decreased from 40 to 36g per unit before 75% of BAT units would comply with process control measures.

The authors estimated that certain cohorts of transfusion-dependent patients may require additional units of red cells to compensate for the lower haemoglobin content per unit. Estimates ranges from one to two extra donor exposures per year for babies and smaller children, to four to five additional donor exposures per year for adults and larger children. On an annual basis, this could translate to use of an additional 10,000 to 15,000 units of RCC in the UK[21] where between 1.9 and 2 million units of RCC were produced in 2009.[83]

Filtration was associated with a significant increase in haemolysis. This was detectable immediately after filtration, was significantly higher in BAT-processed units, and increased throughout storage. However, more than 75% of filtered units had less than 0.8% haemolysis.[21]

Prothrombin was assessed as a process control measure for filter integrity with median removal of 95.8% and 98.5% for TAT and BAT processed units, respectively. No evidence of any immunologic changes of clinical relevance to the RBC membrane after filtration was noted.[21]

The median filtration time was between 55 and 60 minutes. Processing losses from filter failure or incomplete filtrations were 5.9%. As a result of this, changes were made by the manufacturers to the outlet tubing to improve drainage. This new configuration was subsequently tested by the Scottish National Transfusion Service using 125 BAT units. No filter blockages were observed, the mean filtration time had reduced to 37.5 minutes and haemoglobin loss was reduced from a mean of 7 to 8g per unit to 6 to 7g per unit.[21]

5.5 In-vitro studies of red cell quality for Pall filters

A study published in 2005 [84] evaluated the effect of the Pall PRF1BU on previously leucoreduced red cell units prepared in accordance with standard UK practice. The filtered units were found to have statistically significant higher percentage haemolysis levels, lower haemoglobin levels and a smaller volume than the pre-filtered units. The filter retained a mean volume of approximately 55ml, associated with a loss of 20 to 24% of the original haemoglobin content per unit.

Similar results were obtained in an in-vitro study that investigated the quality of red cells processed under routine conditions and filtered using the PRF2BE filter system. Filtered units in the BAT-processed groups were found to have a statistically significant reduction in haemoglobin and unit volume compared to the control units. No difference in haemolysis levels was found.[85]

No significant changes in red cell morphology were noted in a 2006 study following filtration with the PRF1BU filter.[77]

5.6 Discussion of results of in-vitro studies

Studies to date for the P-Capt™ filter indicate that use of the filter is associated with a significant reduction in haemoglobin per unit.[20;21] This is attributed to retention of the red cells in the filter, although the presence of SAG-M in the filter allows the final volume of the units be maintained.[21] Increases in haemolysis were apparent immediately after filtration[20;21], and may be greater in BAT produced units.[21]

Alterations in haemoglobin content may lead to units of prion filtered red cells being outside of specifications for leucocyte-depleted red cell concentrates. The use of a new lower specification of 35g haemoglobin per unit for prion-filtered leucoreduced red cells has been proposed by the IBTS.[20] The EU directive allows the quality and safety of new blood components (in this case, leucoreduced and prion filtered red cell concentrates stored in additive solution) to be regulated by the relevant competent authority (the Irish Medicines Board [IMB] in Ireland), provided the European Commission is notified with a view to Community action.[82] Such a new specification would have to be agreed with the IMB and any European initiatives in this regard coordinated. A further consideration is that the loss of haemoglobin content in filtered units could be clinically significant and result in an increased red cell transfusion requirement for some patients, particularly for those that are transfusion-dependent. It has been proposed that changes in red cell requirements in multi-transfused patients should be assessed in future clinical studies.[20]

The occurrence of new or more frequent adverse events associated with transfusion of prion-filtered RCC may only become apparent following wide-spread adoption of the technology and would necessitate careful post-marketing surveillance.

Prothrombin levels were reduced by more than 95% in both the P-Capt™ in-vitro studies,[20;21] supporting the theory that this could be used as a marker for filter efficacy during validation and ongoing process monitoring studies. Further studies are ongoing in the UK to investigate the use of changes in Factor IX levels as an alternative process control measure – the advantage of this assay is that a commercial CE marked Factor IX assay kit is available.[86]

The IBTS manufactures a limited number of units of a red cell product (suspended in plasma) for intrauterine and neonatal transfusion. Used to treat foetal anaemia, the haematocrit levels and haemostatic content of this product are closely defined. The removal of coagulation factors by the prion filter and the dilution effect of the SAG-M contained in the filter may make it more difficult to achieve these levels and necessitate changes to the manufacture of this blood product.[21]

5.7 In-vivo studies of red cell safety for the P-Capt™ filter

A number of in-vivo studies are ongoing or completed in relation to the transfusion of prion-filtered red cells to determine any potential effect on transfusion recipients. Outcomes evaluated include immunological changes and adverse clinical events. Possible immunological changes included the development of new antibodies specific to prion-filtered red cells, development of pan-reacting red cell antibodies and increases in the rate of alloimmunisation to clinically significant red cell antigens. Clinical outcomes include increases in the rate of well recognised transfusion reaction types and the development of new types of transfusion reactions.

In a post-marketing pharmacovigilance study, units of P-Capt™ filtered blood were processed under normal conditions and stored for up to 42 days in accordance with standard practice. These units were evaluated for changes in red cell antigens prior to their autologous re-infusion to the donors. Red cell recovery rates of at least 75% were reported at 24 hours for all units, with no differences between the filtered and control units. There was no evidence of neoantigenicity (development of new antigens

to the filtered red cells) six weeks after re-infusion of the prion filtered autologous red cells.[87]

An Irish phase I/II open clinical study conducted by the IBTS was published in 2010.[88] Twenty adult patients for whom transfusions were clinically necessary received one unit of prion-filtered RCC.[88] Patients were followed up at 24 hours, six weeks and six months post-transfusion. Clinical effects, liver function tests, red cell antibody screen and direct antiglobulin tests were performed. No adverse events were noted. A further six of these patients underwent re-exposure to a further unit of filtered RCC, and were followed up for six weeks without incident. All units of transfused RCC were filtered with the P-Capt™ filter.

A phase IV open trial using prion filtered red blood cells was conducted by the IBTS in Ireland. A total of 93 adult patients for whom transfusions were clinically necessary received 194 prion filtered RCC that had been filtered using the P-Capt™ filter. Clinical outcomes are monitored in accordance with standard practice for red cell transfusions and potential transfusion-related adverse reactions. No unexpected transfusion reactions have been recorded to date.[89]

The controlled trial 'Prion-filtered vs Standard Red cells in Surgical and Multi-transfused Patients' (PRISM study) is currently underway in the UK. In the first arm of this study, 270 adult medical or surgical patients will receive leucocyte reduced red cell concentrate filtered using the P-Capt™ filter for all elective transfusions deemed clinically necessary from time of admission until discharge and compared to a control cohort of 270 people receiving unfiltered blood. The primary outcomes assessed are the development of any antibodies specific for prion filtered red cells, development of pan-reacting red cell antibodies or alloimmunisation to significant red cell antigens. Secondary data includes any transfusion reactions or atypical symptoms arising during or after the transfusion. By October 2010, recruitment to the filter arm of the trial (n=270) had concluded, with completion of the control arm expected by March 2011. No evidence of increased alloimmunisation to standard red cell antigens (143 filter arm and 152 control arm patients completed follow up so far) has been recorded to date. Equally, no cases have been identified where alloantibodies have formed against prion filtered cells only. There has been a 22% loss to follow up, as patients in this study are elderly and have multiple chronic conditions.[90]

Following the successful completion of the first arm of this study, a second study arm will commence. Multi-transfused patients will be randomised to receive either prion filtered or non-filtered blood for up to six transfusion episodes. Primary outcome measures will be the same as for the first arm. Secondary outcome measures will include the total number of red cell units required over the six transfusion episodes, the total volume of red cells transfused and the mean number of days between transfusion episodes.

5.8 In-vivo studies of red cell safety for the PRF2BE filter system

In-vivo data for the PRF2BE filter system is limited to an autologous study that examined 24-hour percentage recovery of radiolabeled red cells. No significant difference between the test and control groups (mean 83.8% and 86.1%, respectively) was noted.[85;91]

5.9 Key messages

- The use of a prion filter alters the quality of leucoreduced red cell concentrates.
- Mean post-filtration haemoglobin levels are reduced by 8 to 9g per unit, or up to 20%. This appears to be more common in BAT-processed units.
- An increase in haemolysis has been reported due to prion filtration. This appears to be more common in BAT-processed units.
- Some prion-filtered units may fail to meet existing specifications for leucoreduced red cell concentrates due to filter-induced changes in haemoglobin and haemolysis levels. A new specification for prion-filtered, leucocyte depleted red cell concentrates in additive solution may be required.
- The reduction in haemoglobin content may have clinical significance for transfusion recipients. In particular, a number of transfusion-dependent patients may require additional units of RCC to compensate for the lower haemoglobin content per filtered unit.
- Clinical trial (in-vivo) data for adults indicate no immunological changes or additional adverse events associated with transfusion of leucoreduced red cell concentrate that has been prion filtered using the P-Capt™ filter. Further studies are ongoing.
- Clinical trial data for the PRF2BE filter system are limited to an autologous study examining 24-hour recovery of radiolabeled red cells.
- No clinical trials using prion-filtered RCC have been conducted in children, but would be required prior to adoption of prion filtration in this cohort.
- Satisfactory independent safety data will be required by the IBTS for a prion filter prior to its adoption.

6 Cost-effectiveness and budget impact of universal prion filtration of red cell concentrates

6.1 Introduction

This purpose of this section is to:

- provide background on economic evaluation in HTA
- review the use of economic evaluations to assess blood product safety strategies
- evaluate the cost-effectiveness of universal prion filtration of RCC compared to the current policy of no prion filtration using an independent economic model
- evaluate the budget impact of introducing universal prion filtration of RCC.

6.2 Background – economic evaluation

Economic evaluation in HTA involves the comparative analysis of alternative courses of action. In this case, the additional costs and health benefits associated with introducing universal prion filtration of red cell concentrates (RCC) in Ireland are being compared with the usual standard of care (i.e., no prion filtration). The health benefits of prion filtration are defined as the impact of the technology on patient survival and measured in life years gained (LYG).

When comparing two or more technologies, the question that arises is: what is the additional cost involved for the additional benefit achieved? To answer this question, the incremental cost-effectiveness of the technology compared to the alternative is calculated, with the results presented as an incremental cost-effectiveness ratio (ICER).[22] The ICER of A (prion filtration) compared to B (no prion filtration) can be calculated as follows:

$$ICER = \frac{(Cost_A - Cost_B)}{(Effect_A - Effect_B)}$$

One of the implications of making comparisons between the cost-effectiveness of different technologies is that there is a threshold ratio above which a technology may not be considered cost-effective. If a technology has an ICER that is significantly higher than that of other healthcare technologies that are reimbursed, other factors such as the innovative nature of the technology or the wider costs and benefits to patients and society may be taken into consideration.

6.3 Economic evaluation of blood product safety strategies

A systematic search was undertaken to identify existing literature on the economic evaluation of prion filtration to reduce the risk of vCJD. To supplement this, a limited review of the cost-effectiveness and budget impact of other blood product safety strategies was completed. The purpose of the review was to identify and evaluate the methodological and modelling methods used by other groups to assess their relevance, and to set the findings of this HTA in the context of those from HTAs of other blood product safety strategies.

6.3.1 Search strategy

A systematic review was undertaken to identify existing literature on the economic evaluation of prion filtration to reduce the risk of vCJD. This search was performed in August 2010 and updated in November 2010. Details of the search are provided in Appendix 2. To supplement the literature and to provide context to this study, the literature search was extended to include studies that evaluated the economic evaluation of other blood safety strategies.

6.3.2 Cost-effectiveness of prion filtration

No published economic evaluation of prion filtration was identified. Two unpublished reports were identified and are summarised in Appendix 3, Table 1.

An options appraisal in relation to the prevention of transfusion-related vCJD produced by the IBTS was submitted to the Department of Health and Children in April 2009.[18] Options discussed included a 'do nothing' approach (that is, no additional measures), screening all donations for vCJD, and introducing prion filtration of RCC for all, or some of the population. The report predicted that universal prion filtration would cost €9,375,000 per annum and would potentially prevent one infectious donation with an estimated ICER of €4,800,000 per life year gained. No discounting was applied to costs or benefits.

The second study, an economic evaluation to predict the cost and cost-effectiveness of prion filtration in the UK was carried out by the UK Department of Health.[17] Preliminary results were reported in the SaBTO Meeting Minutes of October 2009. A deterministic model was used to estimate cost-effectiveness for a number of best and worst case scenarios depending on low and high estimates related to vCJD prevalence, susceptibility to infection and infectivity in blood.[92] Depending on the scenario modelled, the cost-effectiveness of universal prion filtration of RCC was estimated to range from (£ sterling) £3,000 to £856,000 per life year saved. Selective prion filtration for those younger than 16 years of age was estimated to range from £5,000 to £839,000 per life year saved while providing prion filtration for patients with haemoglobinopathies in addition to those younger than 16 years of age was estimated to range from £8,000 to £1.2 million per life year saved. Discount rates of 3% and 1.5% were applied to costs and outcomes, respectively. A recommendation was subsequently made to the Secretary of State for Health in the UK that selective prion filtration of RCC should be introduced for those born after 1 January 1996. A decision by the Minister is still pending.[17]

6.3.3 Cost-effectiveness of other blood safety strategies

In the absence of published cost-effectiveness studies examining prion filtration, a limited review of the published cost-effectiveness evaluations of other blood safety strategies was conducted to provide context for this study. Further details on these studies are provided in Appendix 3, Table 2.

The cost-effectiveness of various strategies for nucleic acid testing (mini-pool or single donor) for viral infections including HIV, Hepatitis B and Hepatitis C has been evaluated in a number of published studies.[23;24;26;27;93] Adding nucleic acid testing (NAT) to the current strategy of viral serological testing was not found to be cost-effective in any instance, with ICERs ranging from €300,000 to €47 million per quality-adjusted life year (QALY). NAT is used in addition to existing safety measures (donor deferral and viral serological testing) primarily to detect infectious donations given in the early period of infection (pre-seroconversion window) before standard serological tests become positive. That is, the incremental benefit of NAT is limited to the detection of additional cases missed by the existing measures. Despite not being cost-effective, NAT has been adopted by blood transfusion services in most developed countries. NAT was introduced by the IBTS for Hepatitis C RNA in 1999, for HIV RNA in 2002 and for Hepatitis B DNA in 2009.[28]

The cost-effectiveness of pre-operative autologous blood donations compared to standard allogeneic transfusions was evaluated in a 1995 US report. This strategy was found to be not cost-effective with ICERs ranging from (US $) $235,000 to $23 million per QALY.[94]

Cost-effectiveness in blood safety strategies does not compare easily with other interventions where cost-effectiveness is typically an order of magnitude less. Economic evaluations of other interventions in an Irish setting which have adopted following a determination that they were cost-effective include population-based colorectal cancer screening (€1,696/QALY);[29] human papillomavirus vaccination programme at €17,383/life year gained (LYG);[30] universal infant pneumococcal conjugate vaccination at €5,997/LYG;[31] and of universal infant hepatitis B vaccination at €37,018/LYG.[32]

6.4 Methods – economic evaluation and budget impact analysis

An economic evaluation of prion filtration requires the prediction of outcomes and costs that will occur in the future, necessitating an economic modelling approach. Modelling facilitates the combination of data on costs and benefits from different sources and allows these to be extrapolated into the future. The introduction of a prion filtration programme would incur considerable ongoing running costs, while any benefits – such as life years gained – could take many years to accrue. Modelling allows the short-term nature of some costs to be offset against the long-term nature of the benefits in the economic evaluation.

The Budget Impact Analysis (BIA) provides a means to predict the potential financial impact of introducing a new technology into a healthcare system. Whereas an economic evaluation addresses the additional health benefit gained from investment in a technology, BIA addresses the affordability of the technology (e.g., the net annual financial cost of adopting the technology for a finite number of years).[95]

6.4.1 Type of economic evaluation

The preferred economic evaluation type for HTA in Ireland is a cost-utility analysis (CUA) with the outcomes expressed in terms of quality-adjusted life years (QALYs). The use of a cost-effectiveness analysis (CEA) with the outcomes expressed in terms of life-years gained is acceptable when a CUA is an unsuitable choice.[96] No published quality of life data were found for vCJD (or CJD or TSEs). Therefore, a CEA was undertaken in this HTA.

6.4.2 Study perspective

In assessing costs, the perspective adopted is that of the publicly-funded health and social care system. Established in 1965, the IBTS is a state body. It is the sole provider of red cell concentrates (RCC) for transfusion in Ireland and is primarily funded by the sale of blood products to the publicly funded healthcare system. Only direct medical costs (i.e., fixed and variable medical costs associated with the provision of a technology, but excluding indirect costs such as decreased productivity due to disease or death) associated with prion filtration are included in the evaluation. All health benefits accruing to individuals are included in the assessment of outcomes. Adoption of this perspective is consistent with recommended guidelines.[96]

6.4.3 Study comparator

The study comparator is current practice in the IBTS. A series of risk-reduction measures including donor deferral strategies and universal leucoreduction as outlined in Section 3.10 are currently used to minimise the risk of vCJD transmission from RCC. These risk reduction measures form the alternative ('no prion filtration') which is used in the baseline comparison.

6.4.4 Timeframe of the economic evaluation

A timeframe of 10 years was used for this study for measuring costs and exposure to RCC from vCJD infected donors. Health benefits were measured to the point of full life expectancy for infected recipients. Thus, the analysis includes anyone who is predicted to receive infected RCC over a 10-year period. Life years gained is not restricted to the 10-year timeframe, but is measured to the point of natural life expectancy.

The number of people with primary infection through exposure to BSE-infected meat will not increase and, over time, will decline to zero. However, it may take up to two generations before the risk of transmission through blood donated from this cohort disappears. Cases of secondary infection through blood transfusion and iatrogenic exposure are precluded from donating blood based on current deferral policies. The risk of infected blood being donated can therefore only decrease over time.

The prevalence of vCJD is very low with only four diagnosed cases in Ireland over 15 years. With such small numbers, a short timeframe of five years might not be long enough for cases of secondary infection to occur. We have used a time frame of 10 years for exposure to enable a large enough cohort of exposed individuals to be

identified from which to determine the possible health benefits of prion filtration. The cohort of exposed individuals is then followed to full life expectancy.

6.4.5 Description of the economic model

The economic analysis was conducted using an economic model independently developed by the UK Department of Health and used to estimate the cost-effectiveness of prion filtration of RCC in the UK. This model was provided to the Evaluation Team, so that it could be adapted to the Irish setting and populated with Irish data. The UK model is deterministic and estimates cost-effectiveness for a number of best and worst case scenarios. It was converted into a probabilistic model which allows the inherent uncertainty around parameter estimates to be incorporated. A range of data parameters (inputs) were required in order to develop this approach and provide an estimate of the likely outcomes and costs in Ireland.

The cost-effectiveness model is composed of two distinct components: the transmission model and the costs model. The transmission model estimates the exposure of transfusion recipients to infected RCC, and the likely impact of introducing prion filtration to reduce that exposure. The costs model estimates the cost of introducing prion filtration as a function of the number of units of RCC filtered, taking into account filter, staff and other resource costs.

6.4.6 The transmission model

This component of the model is constructed to mimic the real-life process of blood donation, processing, transfusion and post-transfusion survival. Parameters that the model takes into account include:

- the prevalence in the donor population of pre-clinical vCJD
- the probability that the infectivity will be removed by processing of the RCC (i.e. leucoreduction and prion filtration)
- the susceptibility of recipients to being infected and
- whether recipients survive long enough post-transfusion to develop clinical vCJD.

The probabilistic model uses simulation to allow the main parameters to vary within defined ranges thereby allowing uncertainty to be encompassed in the model. This is of particular importance as, given the rarity of vCJD and the limited data available on its characteristics, there is substantial uncertainty regarding a number of the model parameters. The model has been developed as a micro-simulation to allow parameters to vary within a simulation, but also across infected donors.

The key parameters are defined in Appendix 4 and along with justification for the choice of distributions used in each case.

Transmission model structure

The transmission model has been developed using micro-simulation and stochastic modelling. Details of the model are provided in Appendix 5. The key parameters are allowed to vary within the defined distributions, so that outputs can include both a point estimate and confidence bounds for the estimate of future cases and life years saved.

Parameter uncertainty can arise within simulation, by year, by individual or by unit of RCC. Prevalence and susceptibility are set for each simulation on the presumption that these parameters do not vary by year or individual. The number of donors infected with vCJD varies from year to year. The number of donations and the infectivity of those donations are varied by infected donor. Type of processing, residual plasma and effect of leucoreduction are varied by unit of infected RCC. Age, gender, genotype and post-transfusion survival are varied by recipient.

The point estimates presented are median values and accompanied by the 2.5th and 97.5th percentiles (as confidence bounds). The model was developed and executed in the open source statistics package R.[97]

Model parameters

A wide range of input parameters were required for the transmission model. For each parameter, the most likely value and a range of uncertainty around this value were determined. The data sources and assumptions used in deriving the parameter values are outlined in detail in Appendix 4. The primary source of information was through literature review. In translating published estimates into parameter values, a critical consideration was the applicability to the Irish context. The number of worldwide cases of vCJD number in the hundreds with only five confirmed cases of vCJD resulting from the transfusion of infected blood products. Much of the data on infectivity and transmission are derived from animal studies. The limited data on the topic has been acknowledged by allowing for substantial uncertainty in the model. In the absence of comparable data, we have assumed that the two models of filter have the same efficacy. All values, ranges and distributions of the model parameters were endorsed by the Expert Advisory Group.

For the key parameters, the following Table 6.1 outlines the distributions used, the point estimates and the associated confidence bounds.

Table 6.1 Point estimate, range and distribution of parameter estimates

Parameter	Distribution	Median (95% range)
National prevalence of pre-clinical vCJD (cases)	Beta	149 (33 - 406)
Susceptibility to developing clinical vCJD (%)	Beta	10.0 (8.8 – 11.1)
Donations per infected donor (units per annum)	Sampled	1 (1 – 4)
Percentage of collected units used (%)	Beta	89 (86 - 92)
Infectivity of vCJD infected blood (ID/ml)	Gamma	9.9 (0.7 – 31.6)
Residual plasma (ml) -TAT	Normal	20.3 (13.6 – 26.2)
- TAB	Normal	9.2 (4.9 – 13.5)
Infectivity removed by leucoreduction (%)	Beta	50.0 (32.5 – 67.5)
Incubation (years) - MM homozygous	Normal	7.6 (5.6 – 9.6)
- non-MM homozygous	Beta	21.2 (16.5 – 29.1)
Percentage population MM homozygous	Beta	39.2 (34.5 – 44.0)
Probability of infectious doses after prion filtration	Beta	0.00007 (0.000003 – 0.00037)
Discount rate (%)	-	4

6.4.7 Cost component of cost-effectiveness model

Cost data are used in the cost component of the cost-effectiveness model and as the basis for the budget impact analysis (BIA).

The costs used in the cost-effectiveness model related to the incremental cost of prion filtration, that is, added costs over and above the current operational costs, or baseline. Cost savings related to the reduced consumption of existing resources were included, as appropriate. Costs considered in estimating the marginal unit cost for the intervention included the cost of procurement, processing, storage and distribution of prion-filtered RCC. Costs were provided by the IBTS, the Department of Health and Children and the manufacturers of the prion filters. The majority of costs related to recurring annual costs. Set-up costs were limited to validation of the PRF2BE filter system. No additional capital investments related to the introduction of prion filtration were identified by the IBTS.

Satisfactory independent safety and efficacy data must be available for a prion filter to be considered for adoption by the IBTS. As there are no published independent safety and efficacy studies for the PRF2BE filter system, it is assumed that it cannot be adopted until such studies are completed. We have assumed that such studies will take three to four years and that the PRF2BE filter system can be adopted after that time.

The data sources, methods and assumptions to derive the cost inputs are described in detail in Appendix 6. In the cost-effectiveness analysis a discount rate of 4% was applied to both costs and outcomes. A summary of the costs associated with the implementation of universal prion filtration using either the P-Capt™ filter or the PRF2BE filter system is outlined in Table 6.2.

Table 6.2 Estimated costs inputs (exclusive of VAT) for universal prion filtration using the P-Capt™ filter or PRF2BE filter system

Item	P-Capt™ Filter	PRF2BE	Source
Unit Cost of Filter			
Filter cost per unit	€55	€43.70*	Fannin Scientific/ Pall Medical
Additional consumables cost per unit			
Factor IX assay	€0.06	€0.06	IBTS
Wafers	€2.73	€2.73	IBTS
Waste bins	€0.12	-	IBTS
Incineration	€0.26	-	IBTS
Classic 3-bag blood collection system (no filter)	-	€6.95	Pall Medical
Current leucoreduction filter bag system	-	-€8.82**	IBTS
Annual staffing costs			
Medical Laboratory aides (3)	€206,384	€206,384	IBTS
Senior Medical Scientist (1)	€88,690	€88,690	IBTS
Other direct costs			
Processing cost per unit (excluding prion filtration)	€248.71	€248.71	DoHC
Additional cost per unit of leucoreduced plasma	-	€9.87	IBTS
Initial validation costs	-	€7,508	IBTS

** Filter price estimated based on quoted price in sterling for purchase of 150,000 filter units from year two onward.*

*** Weighted average cost based on the contract price for existing leucoreduction filter systems purchased by the IBTS.*

6.4.8 Sensitivity analysis of the economic evaluation

In a cost-effectiveness analysis, the use of a probabilistic sensitivity analysis is recommended to determine the impact of varying the values of key parameters within plausible ranges. As the structure of the transmission model is inherently stochastic, the output is equivalent to a multivariate probabilistic sensitivity analysis.

A univariate sensitivity analysis shows how influential each parameter is and how sensitive the results are to fluctuations in each parameter. This is particularly relevant in this study as the key parameters are defined as distributions rather than point estimates. Given the uncertainty around the parameters themselves, it is important to understand how this translates into uncertainty about the results. Each parameter in turn is fixed at its upper and lower bounds while all the other parameters are varied as per the fully probabilistic model. The variance in results due to each parameter can be displayed as a tornado plot that makes the results of the univariate analysis easy to interpret.

There is no uncertainty about the discount rate in the fully probabilistic model, but uncertainty is incorporated as part of a univariate sensitivity analysis. The discount rate

may vary between 0 and 6%. In line with the other parameters, the 95% confidence bounds are used for the upper and lower parameter values in the univariate sensitivity analysis. A beta distribution is used for discounting that results in lower and upper bounds of 1.7% and 5.7%, respectively.

6.4.9 Budget impact analysis

The BIA is conducted from the perspective of the publicly-funded health and social care system and reports the costs for each year in which they occur. In this case for a timeframe of five years whereas the timeframe required in the economic evaluation is longer at 10 years.

The data for the BIA are the same as those used in the cost-effectiveness analysis with the difference being that prices are inclusive of VAT, and no discounting is applied. All items are subject to VAT at 21% apart from the cost per unit of the processed RCC, which is classified as VAT exempt. The results are reported as the annual cost of implementing universal prion filtration. The analysis takes into account the projected changes to demand for RCC due to the changing size and age profile of the Irish population.[98]

Prion filtration of RCC represents an additional step in the processing of RCC. Because of differences between the two filters (prion filter only versus a combined leucocyte reduction and prion filter), the position of the filters within the processing cycle and the requirements for additional consumables differ. The calculations used in this study take into account cost-offsets where appropriate so that the incremental and total costs of introducing prion filtration are equivalent.

6.5 Results

Results are presented for a 10-year timeframe for the potential number of transmissions of vCJD through infected blood products in the absence of prion filtration as well as the number of infections prevented and the number of life years gained by adopting universal prion filtration. The 10-year discounted cost and the incremental cost-effectiveness ratio (ICER) of adopting universal prion filtration are reported. Finally, the results of the budget impact analysis over five years are presented.

6.5.1 No prion filtration (current practice)

Based on the input parameters, it is estimated that there will be 45 infected donors in the next 10 years and they will contribute a total of 70 infected units (see Table 6.3). In the absence of prion filtration it is estimated that there will be seven recipients susceptible to developing clinical vCJD, two of whom will die from clinical vCJD. The other five susceptible recipients of infected RCC will die before the onset of clinical disease. There was at least one transmitted infection in 84% of simulations. The life years lost will be 19.7 years. The confidence bounds for all of the estimates are wide and all encompass zero (i.e. that there will be no future cases). The upper bound for the number of infected recipients dying from vCJD is 8. Due to the long incubation period of vCJD and the older age profile of transfusion recipients, infected patients

who survive post-transfusion will often die of other causes before the onset of clinical vCJD. In many cases, an infection will not result in any life years lost.

Table 6.3 Predicted number of transmitted infections and life years lost over 10 years if prion filtration of RCC is not implemented

Outcome	Median	(95% CI)
Infected donors	45	(2 - 142)
Transfusion recipients:		
Infected units	70	(3 – 222)
Susceptible to clinical vCJD	7	(0 – 24)
Susceptible and surviving 5 years post-transfusion	3	(0 – 10)
Susceptible and dying from vCJD	2	(0 – 8)
Life years lost (discounted)	19.7	(0.0 – 96.1)

6.5.2 Cost-effectiveness

It is estimated that universal prion filtration of RCC over 10 years will prevent two deaths from clinical vCJD. Prion filtration is estimated to prevent 98.8% of potential cases. Over the 10-year timeframe there will be 1.55 million units of RCC filtered at a discounted cost of €68.2 million (see Table 6.4).

Table 6.4 Predicted infections prevented and life years gained over 10 years by universal prion filtration

Outcome	Median	(95% CI)
vCJD deaths prevented	2	(0 – 8)
Life years gained (discounted)	19.4	(0.0 – 95.2)
Units processed (millions)	1.55	(1.54 – 1.56)
Cost (€ millions) (discounted)	68.2	(61.8 – 75.0)

The use of a probabilistic model makes it possible to compute the probability of different outcomes. There is a 23.7% chance that in the absence of prion filtration there will be no deaths from vCJD due to transfusion with infected RCC over the 10-year timeframe. There is a 96.7% chance that all vCJD deaths will be prevented by universal prion filtration.

An incremental cost-effectiveness ratio (ICER) can be used to quantify the additional cost of a life year gained by the introduction of universal prion filtration. The effectiveness is measured as the life years gained and, in 23% of simulations the life years gained is zero. As the ICER is a ratio, if the denominator is zero a value of infinity is returned. That is, an infinite amount of money must be spent to achieve a health gain. To compute the ICER in this case we divide the average cost across simulations by the average life years gained across simulations.

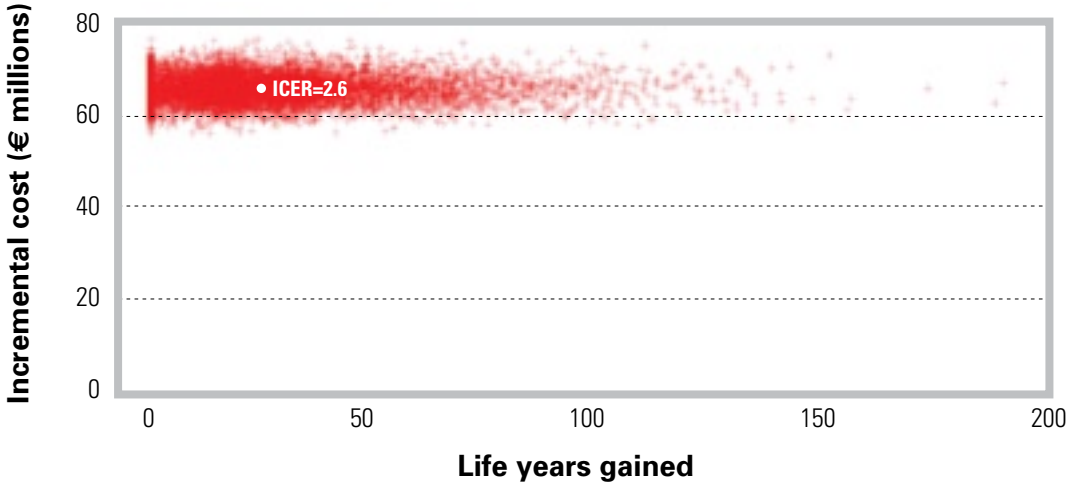
This approach does not allow for the computation of confidence bounds from the model output. The ICER is €2.6 million per life year gained (see Table 6.5).

Table 6.5 Incremental cost-effectiveness ratio for universal prion filtration

Outcome	Estimate
ICER (€ million/life year gained)	2.6

Figure 6.1 plots the cost of prion filtration against the life years gained by adopting filtration. In 76.3% of simulations, prion filtration prevented at least one death from vCJD. Given the shorter life expectancy post-transfusion coupled with the older age profile of transfusion recipients, not all cases of prevented infections will result in life years gained.

Figure 6.1 Cost-effectiveness of universal prion filtration



The cost-effectiveness acceptability curve (CEAC) for universal prion filtration is provided in Figure 6.2. The CEAC shows the probability that prion filtration is cost-effective over a range of willingness-to-pay thresholds. The probability of cost-effectiveness is zero below a willingness-to-pay threshold of €232,000 per life year gained. The probability of cost-effectiveness is 0.08 at a willingness-to-pay threshold of €1million per life year gained. The probability of cost-effectiveness exceeds 0.5 at a willingness-to-pay threshold of €3.5 million per life year gained.

Figure 6.2 Cost-effectiveness acceptability curve for universal prion filtration

If only the P-Capt™ filter is considered, the 10-year discounted cost of prion filtration would be €80.3 million (74.7-85.6) generating an ICER of €3.01 million per life year gained.

6.5.3 Budget impact analysis

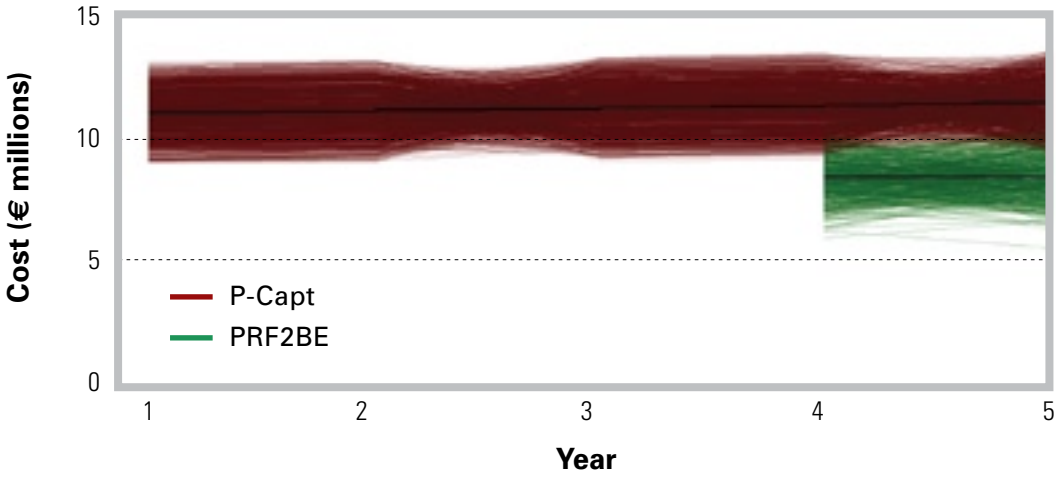
The results of the BIA are shown in Table 6.6. As the PRF2BE filter system cannot be adopted until at least year four, the total budget impact of the PRF2BE filter system is a combination of the budget impact of the P-Capt™ filter and the PRF2BE filter system.

Table 6.6 Annual cost of universal prion filtration of RCC for the P-Capt™ and PRF2BE filters

Year	Cost (€ millions)			
	P-Capt™		PRF2BE	
	Median	(95% CI)	Median	(95% CI)
1	11.0	(9.4 - 12.6)	-	-
2	11.1	(9.4 - 12.7)	-	-
3	11.2	(9.5 – 12.8)	-	-
4	11.3	(9.6 – 12.9)	8.5	(7.0 – 10.1)
5	11.4	(9.7 - 13.1)	8.6	(7.0 - 10.3)
Total	55.9	(50.7 – 61.1))	51.6	(46.3 – 57.6)

In almost all simulations, the annual cost of prion filtration is lower for the PRF2BE filter system than the P-Capt™ filter (see Figure 6.3). The annual cost is lower with the P-Capt™ filter in 1.1% of simulations in the fifth year. The year-on-year increase in cost reflects increasing demand for red cell concentrates due to an ageing population.

Figure 6.3 Variation in estimated annual costs of universal prion filtration using the P-Capt™ and PRF2BE filter models



The disaggregated costs for the implementation of the P-Capt™ filter and PRF2BEfilter systems are presented in Table 6.7 with a breakdown of costs by category for the two filters presented in Figure 6.4.

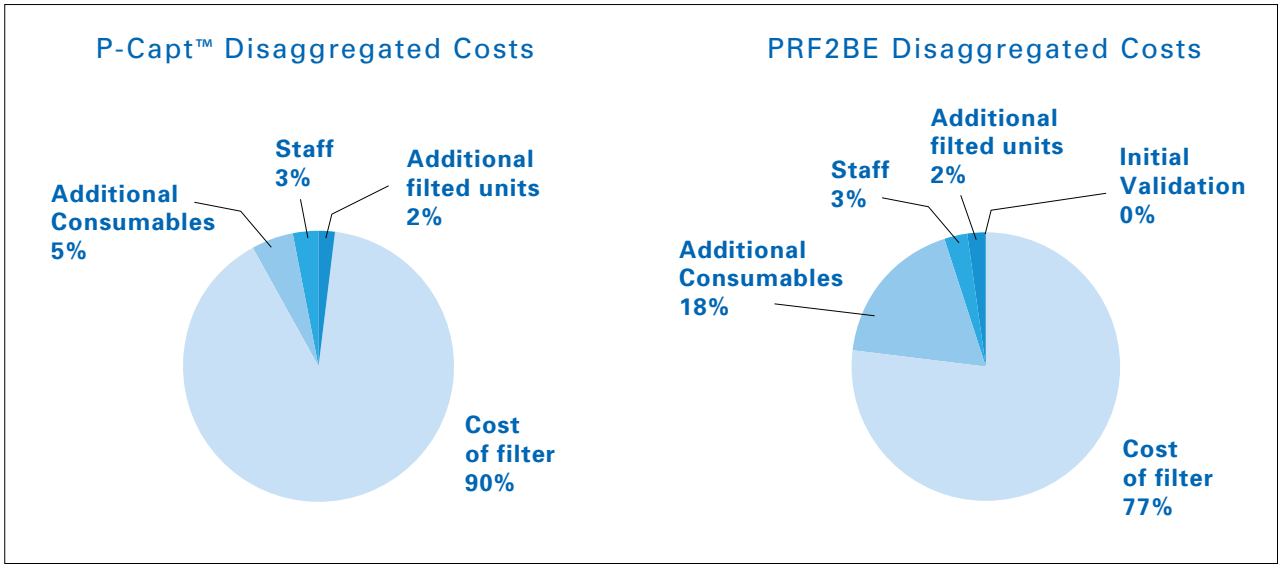
Table 6.7 Annual disaggregated direct costs associated with use of the P-Capt™ and PRF2BE filters

Disaggregated direct costs* of prion filtration (€ 000's)										
	P-Capt™ Filter					PRF2BE Filter System				
Year	1	2	3	4	5	1	2	3	4	5
Filter cost	9,910	10,010	10,110	10,210	10,314	-	-	-	7,843	7,923
Additional consumables										
Factor IX assay	11	11	11	12	12	-	-	-	12	12
Wafers	492	497	502	507	512	-	-	-	507	512
Waste bins	21	21	22	22	22	-	-	-	-	-
Incineration	46	47	47	48	48	-	-	-	-	-
3 bag classic system	-	-	-	-	-	-	-	-	1,290	1,303
Staffing costs										
Medical laboratory aides	206	206	206	206	206	-	-	-	206	206
Senior medical scientist	89	89	89	89	89	-	-	-	89	89
Other direct costs and savings										
Cost of additional units	184	186	188	190	192	-	-	-	190	192
Cost of separate leucoreduced plasma						-	-	-	7	7
Cost savings	-	-	-	-	-	-	-	-	-1,638	-1,655
Initial set up costs	-	-	-	-	-	-	-	-	8	-
Total additional cost	10,960	11,062	11,160	11,266	11,372	-	-	-	8,512**	8,588

** All costs inclusive of VAT where relevant.*

*** Assumed that PRF2BE filter system could be adopted beginning in year 4 or year 5 following satisfactory completion of independent safety and efficacy studies. Initial set up costs are relevant to the first year of use.*

Figure 6.4 Five year costs of prion filtration by category for the P-Capt™ and PRF2BE filters



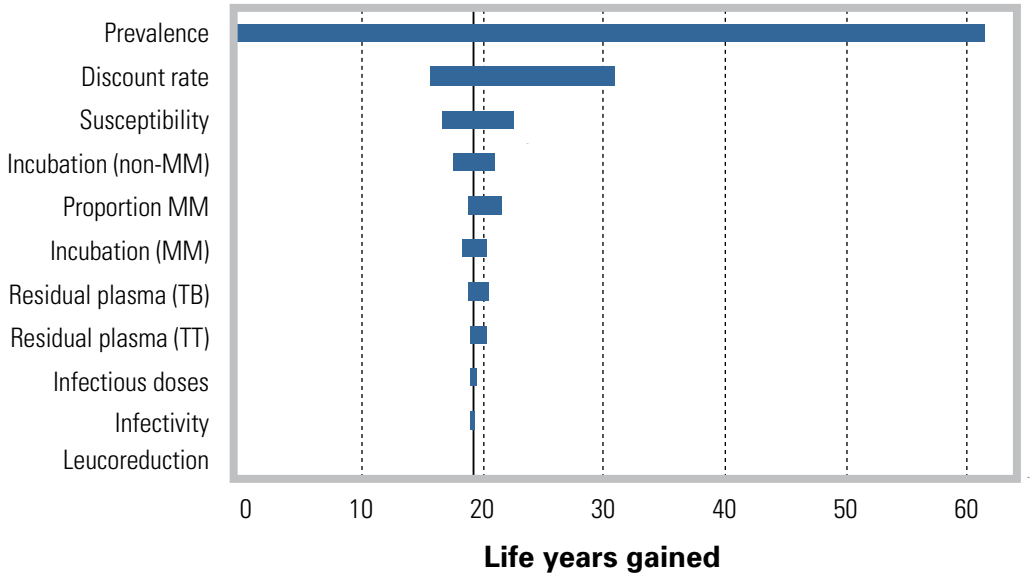
6.6 Univariate sensitivity analysis

Univariate sensitivity analyses were carried out separately for effectiveness, the incremental cost-effectiveness ratio and the budget impact analysis.

6.6.1 Effectiveness

Ten parameters were identified that might have a significant impact on the number of life years gained (Figure 6.5). The most influential parameter is the estimate of prevalence. This was expected as this parameter directly dictates the potential number of infected RCC donations. As prion filters are estimated to be efficacious and prevent most potential infections, a higher number of infected donors translates directly into a higher number of life years saved. In the base case, the prevalence is 149 cases nationally resulting in 19.4 life years gained. If the prevalence is only 33 infected individuals nationally, then there are unlikely to be any life years gained. If, however, there are 406 infected people nationally, the point estimate is that 61 life years will be saved – three times the base case estimate. The next most influential parameter is the discount rate. Varying the discount rate causes the health benefits to fluctuate between 15.7 and 30.7 life years gained. The third most influential parameter is susceptibility which dictates the number of exposed recipients who will potentially go on to develop clinical vCJD. The parameter has significant influence, particularly given the narrow range of values used. All of the remaining parameters have a relatively small impact on the estimate life years gained, which is reassuring. Uncertainty in the estimate of life years gained is predominantly caused by uncertainty in the estimate of prevalence.

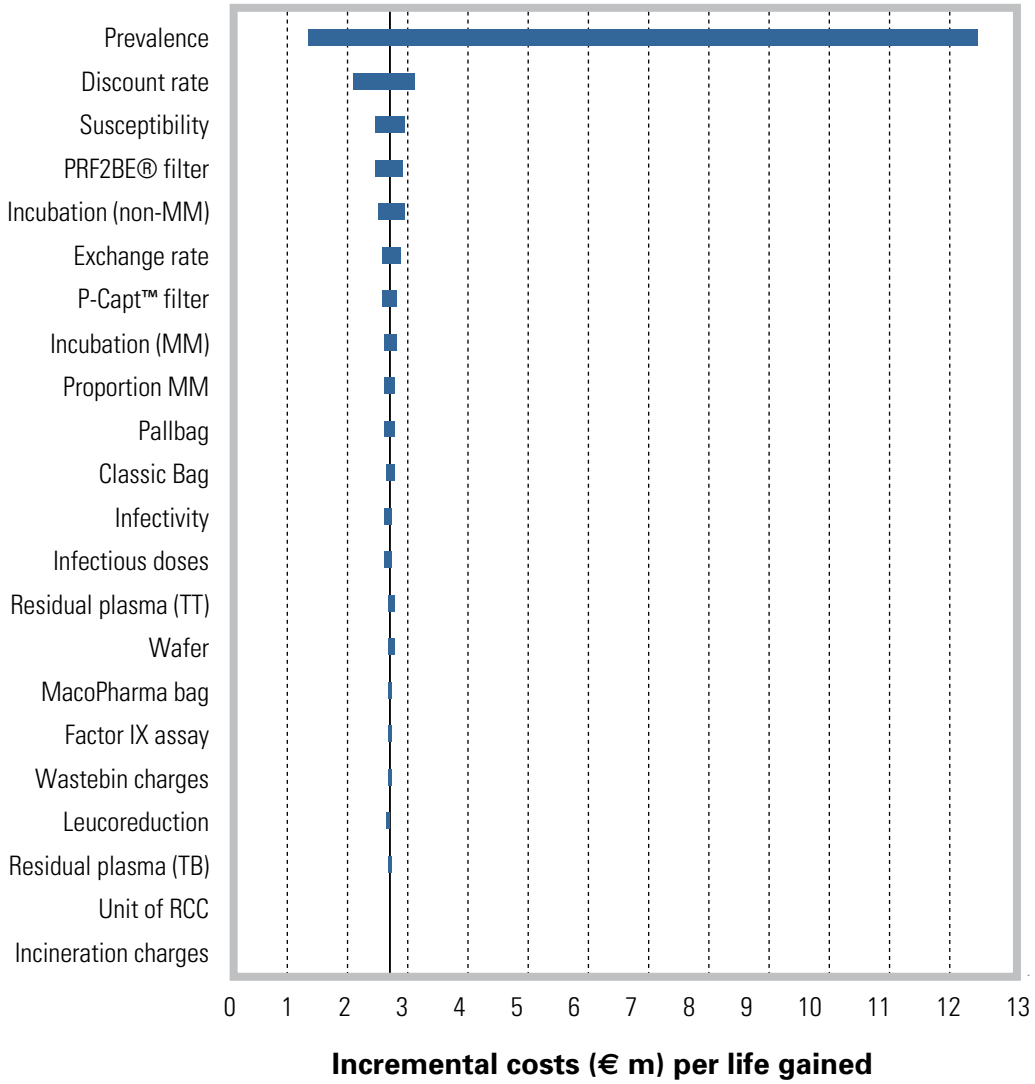
Figure 6.5 Univariate sensitivity analysis of life years gained



6.6.2 Incremental cost-effectiveness ratio

A univariate sensitivity analysis was carried out to assess the influence of different parameters on the ICER (Figure 6.6). Prevalence is the single most influential parameter that impacts on the ICER. If the prevalence of sub- or pre-clinical vCJD nationally is 33 cases, then the ICER will be close to €12.3 million per life year gained. If, on the other hand, the prevalence is 406 cases nationally, then the ICER will be €1.3 million per life year gained. The discount rate is the next most influential parameter with an ICER of €2.0 million per life year gained when the discount rate is at its lowest value.

Figure 6.6 Univariate sensitivity analysis of the ICER

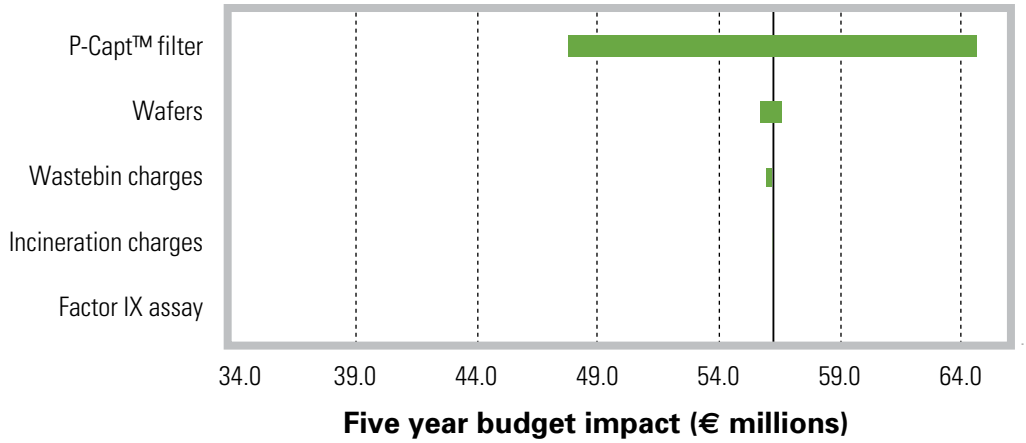


6.6.3 Budget impact analysis

A univariate sensitivity analysis was carried out to assess the influence of different parameters on the results of the BIA. Due to differences between the two filter models (combined leucoreduction and prion filtration versus prion filtration only), there are a number of costs associated with one filter model and not the other.

The influence of parameters on the cost of the P-Capt™ Filter is shown in Figure 6.7 below. Variation in the cost is almost entirely due to variation in the cost of the filter itself with other consumables having a minor impact.

Figure 6.7 Univariate sensitivity analysis of five year budget impact for the P-Capt™ Filter



The most influential parameter affecting the budget impact of the PRF2BE filter system is the price of the filter itself. Varying the price of the filter by ±20% causes a ±15% fluctuation in the total cost. The second most important parameter is the euro to sterling exchange rate. Prices for the PRF2BE filter system after the first year are quoted in sterling and hence exposed to fluctuations in the exchange rate. The exchange rate variability can be substantial and significantly impact on the total cost of prion filtration causing a ±7% fluctuation in the budget impact. Of the remaining parameters, only the cost of the Pall and classic bags have any substantial impact on the overall cost of universal prion filtration.

6.6.4 Discount rate

In this analysis the discount rate was set at 4% and was not varied in the probabilistic sensitivity analysis. However, a recent economic evaluation of prion filtration in the UK adopted a discount rate of 3.5% for costs and 1.5% for benefits. Reducing the discount on benefits whilst leaving a higher discount on costs will increase the cost-effectiveness. The impact of adopting differential discount rates was tested by running the model with discounts rates of 3.5% and 1.5% for costs and benefits, respectively. This approach reduced the ICER from €2.6 million per life year gained to €1.7 million per life year gained.

6.7 Conclusions

The cost-effectiveness and budget impact of various blood safety strategies have been evaluated in a number of studies. Overall, the evidence base is limited, with the majority of measures found to be not cost-effective when compared to the traditional measures of cost-effectiveness used for other healthcare interventions.

A cost-effectiveness model was developed to predict the impact on vCJD outcomes and costs of introducing universal prion filtration. Based on the model assumptions and input parameters, it is likely that over a 10-year period in the absence of universal filtration 70 people will receive infected RCC; seven will be susceptible to clinical vCJD; three will survive to five years post-transfusion; and two will present with clinical vCJD and die from the disease. Introduction of universal prion filtration is likely to prevent both deaths with the discounted life years gained being 19.4 years. The median incremental cost-effectiveness ratio is €2.6 million per life year gained.

The estimate of life years gained is influenced primarily by the prevalence parameter. The only data available on sub-clinical prevalence are based on limited samples from the UK. Extrapolation of the UK estimate to the Irish population is based on the assumption that the relative difference in prevalence will be equal to the relative difference in observed clinical cases of vCJD between the two countries.

The annual budget impact depends on the model of filter chosen, initially costing €11 million per annum and ranging between €8.5 million and €11.4 million by the fifth year. The total costs are most influenced by the cost of the filters and the exchange rate between the euro and sterling in the case of the PRF2BE filter system. Steps to reduce the cost of prion filtration could be achieved by reducing the cost of the filter, with uncertainty reduced by removing exchange rate variability by obtaining prices in euro rather than sterling.

The cost-effectiveness model is subject to a number of limitations that may impact on the results or their interpretation. These limitations are discussed in the following sections.

6.7.1 Availability, robustness and quality of data to populate transmission model

The cost-effectiveness of prion filtration has been estimated using a comprehensive modelling approach. The accuracy of the cost-effectiveness results depends on both the accuracy of the input parameters and the manner in which the model combines those parameters.

There is substantial uncertainty around both the suitable point estimates and the associated ranges of probable values for many of the key model parameters. The uncertainty is inherent in the context of vCJD as it is a new and extremely rare condition. It will take considerable time for the natural history of the disorder to be well defined. Hence, much of the available data are derived from animal studies with the significant assumption that it is appropriate to extrapolate from these results to human blood transfusion.

The disparity between observed and expected cases of vCJD has enabled experts to modify their opinions on the transmission of vCJD. For example, modelling of the

current and future cases of vCJD in the UK has been used to determine plausible estimates for some parameters such as susceptibility. The choice of point estimates for a number of parameters has been pragmatic and guided by expert opinion (e.g. infectivity). The uncertainty is captured in the wide ranges of probable values that parameters can take and is reflected in the wide confidence bounds of the results. When assessing each of the outcomes, it is important to look not only at the point estimates, but also at the ranges of probable values each outcome can take.

6.7.2 Limitations of the economic model

The cost-effectiveness model was developed to mimic the process of blood donation, processing and transfusion. The model combines the input parameters to estimate outcomes such as life years gained and costs. The model is stochastic in nature to reflect the randomness associated with factors that impact on the true process (e.g. blood donations are of varying volume, processing does not always remove the same volume of plasma). Models of real-life processes are simplifications and generally make a number of assumptions. Greater model complexity does not ensure greater accuracy and generally model transparency is preferred. We have endeavoured to include the factors that were felt to be most likely to have a large impact on the findings. A deterministic model was acquired from the UK Department of Health that was revamped to be fully stochastic and to allow for potentially important factors such as the possibility of a 'super-donor' – people who donate three or four times a year over a number of years.

The quality of the model is difficult to assess other than to evaluate the plausibility of the results and by comparison to other estimates of the same outcomes. The only study to estimate future cases of vCJD in Ireland estimated that there would be one to two future clinical cases.[36] The number of vCJD cases in the UK and Ireland appear to have peaked and is now tailing off. Until now, cases of vCJD have been driven by primary infection through consumption of BSE-infected beef. There is a large cohort who may never develop vCJD, but are carriers and can infect others. Infection through blood products appears to be associated with shorter incubation periods and hence may represent a much more efficient mode of infection. It is possible that a second wave of vCJD will occur due to secondary transmission through infected blood products. The estimates used in this study produce predicted numbers of clinical cases that are within the confidence bounds of the study by Harney et al. – the only comparator available.[36] As such, we can conclude that the results of this study do not conflict with other published estimates.

One of the main assumptions that impacts on the number of clinical cases is the susceptibility to developing clinical vCJD. To date, all deaths have been in MM-homozygotes. In assuming the potential for vCJD in non-MM homozygotes, we may be overestimating the number of infections transmitted through blood transfusion. However, given the much longer incubation period that we have applied to non-MM homozygotes, a prevented infection in that genotype will rarely result in life years gained. For the model to be consistent with observed clinical vCJD, the choice of a higher susceptibility would have to be coupled with either a longer incubation period or a lower susceptibility for the non-MM population. While the results of this study may be closer to a worst-case scenario, they should not be viewed as improbable.

The cost-effectiveness results reflect the conservative approach adopted and prion filtration could have a true ICER that is far greater than €2.6 million per life year gained.

6.7.3 Costs and cost perspective

Consistent with national HTA guidelines, this HTA was conducted from the perspective of the publicly-funded health and social care system. The costs considered were limited to the direct costs to the IBTS and the HSE. Costs to the individual (e.g. out-of-pocket expenditure related to treatment or transport to appointments) or to society (e.g., lost productivity in those diagnosed with vCJD) were not considered.

6.7.4 Outcome measure

A cost-utility evaluation with outcomes presented as quality-adjusted life years (QALYs) saved is recommended in national HTA guidelines. This allows changes in both the quantity of life and the quality of that life to be incorporated in a single outcome measure. As no published quality of life data were identified for vCJD, CJD or any other TSE, cost-effectiveness was evaluated with outcomes reported in life years gained.

Variant CJD typically affects younger people, is uniformly fatal and has an average course of only 14 months from diagnosis to death. This relatively short timeframe and the considerable morbidity associated with the condition makes the use of a QALY as an outcome measure of limited relevance as it is likely that the mortality loss would dominate. In this context, use of life years gained instead of QALYs is unlikely to have impacted on the findings of the economic evaluation.

6.7.5 Discounting

Discounting is a technique that allows comparison between costs and benefits that occur at different times. It reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Following national guidelines, a discount rate of 4% was adopted for costs and outcomes in the cost-effectiveness analysis. Consistent with recommendations from the Department of Finance, the discount rate was not varied in the probabilistic sensitivity analysis.

The application of the same discount rate to both costs and outcomes is not without controversy, particularly when potential benefits do not accrue for a long time, such as in vaccination programmes and other preventative public health strategies. A recent economic evaluation of prion filtration in the UK adopted a discount rate of 3.5% for costs and 1.5% for benefits.

The effect of discounting is not inconsiderable in this HTA. Owing to the long incubation period following infection with vCJD, benefits from prion filtration (life years saved) do not occur for many years. Prion filtration is predicted to result in 19.4 (95% CI: 0 to 95.8) life years gained with discounting compared to 39.6 (95% CI: 0-219.5) life years gained without discounting. Use of a higher discount rate would translate into a lower number of estimated life years gained. By applying the differential

discount rates used in the UK, the ICER for universal filtration was estimated to be €1.7 million per life year gained. While this represents a substantial reduction from the estimate of €2.6 million per life year gained, prion filtration would still be considered not cost-effective by traditional standards for cost-effectiveness.

6.8 Key messages

- Economic evaluation in HTA involves the comparative analysis of alternative courses of action. In this HTA, the additional costs and health benefits associated with the introduction of universal prion filtration are compared with the usual standard of care (i.e. no prion filtration).
- There are no published cost-effectiveness analyses evaluating prion filtration. Other blood safety strategies found not to be cost-effective by traditional standards for cost-effectiveness (e.g. nucleic acid testing [NAT] for HIV, Hepatitis B and Hepatitis C with ICERs ranging from €300,000 to €47million per QALY) have been adopted by blood transfusion services including the IBTS.
- A probabilistic model was used to evaluate the cost-effectiveness of universal prion filtration in Ireland compared to the usual standard of care (i.e. no prion filtration). This model allows the inherent uncertainty around parameter estimates to be incorporated. Values for key parameters for the transmission model were informed primarily through literature review and were endorsed by the Expert Advisory Group.
- If prion filtration is not introduced, it was estimated that in the next 10 years there will be two (range: 0 to 8) recipients who will die from vCJD following transfusion of vCJD-infected RCC correlating with 19.7 (0.0-96.1) life years lost. A further five infected recipients who are susceptible to clinical vCJD will not survive long enough to manifest clinical symptoms.
- Universal prion filtration is predicted to prevent both transfusion-related vCJD deaths. The estimated ICER is €2.6 million per life year gained. The probability of cost-effectiveness only exceeds 0.5 at a willingness-to-pay threshold of €3.5 million per life year gained.
- The estimate initial cost of universal prion filtration is €11 million per annum. Over a five-year timeframe, the estimated budget impact of implementing prion filtration ranged from €51.6 million for the PRF2BE filter system and €55.9 million for the P-Capt™ filter.
- In the univariate sensitivity analysis, effectiveness results were sensitive to the prevalence of subclinical infection while filter cost and the euro-sterling exchange rate were key drivers in the costs model. The ICER is predominantly affected by the estimate of prevalence.
- The discount rate is higher than that used in the UK evaluation of prion filtration. Even by applying the differential discount rates used in the UK, universal prion filtration cannot be considered cost-effective.

7. Patient sub-group analysis

7.1 Introduction

The purpose of this section is to:

- outline the criteria for selection of patient sub-groups that might receive prion filtered RCC, should universal filtration not be implemented
- present the sub-groups that meet the criteria outlined
- present the cost-effectiveness and budget impact analyses of implementing selective prion filtration of RCC for these sub-groups.

7.2 Background

Selective implementation of prion filtration of red cell concentrates (RCC) for sub-groups of the transfused population could be considered instead of universal prion filtration. This consideration might arise if universal prion filtration is not cost-effective or the total cost of implementing a policy of universal prion filtration is not considered affordable and the cost-effectiveness of transfusing limited sub-groups is more cost-effective than in the population as a whole.

The cost-effectiveness of a technology may differ for sub-groups of the population arising from differences in costs, treatment outcomes by treatment setting or due to patient heterogeneity (e.g. differences in baseline risk associated with age, gender, genetic predisposition etc.). It is possible that a technology may be cost-effective in one sub-group, but not in others. The selection of eligible sub-groups for a technology should be defined before evaluation and should be based on plausible biological, clinical or care-setting arguments. The intention is to obtain greater population health benefits for the same or lower costs.

7.3 Sub-group selection criteria

After consultation with the EAG, the following criteria were considered when selecting sub-groups for prion filtration.

- **Risk of contracting vCJD:** the patient sub-groups chosen should reflect those who have the greatest potential for harm, that is, those who are at greater risk of developing clinical vCJD from a blood transfusion. Limiting prion filtration to those at higher risk would leverage the greatest health gain on a population basis. For example, groups with a disproportionately high transfusion burden (including premature infants, elderly patients and patients who are multi-transfused as a consequence of their underlying disease) may leverage a greater health gain as a result of prion filtration.

- **Prior exposure:** the risk of vCJD infection from consumption of BSE-infected beef in Ireland was theoretically eliminated following implementation of final safety measures in January 2001. The potential exposure to vCJD for individuals born since that date is limited to iatrogenic infection or secondary infection through blood products. Due to a lower baseline risk, this sub-group may benefit more from a policy of prion filtration when compared to the general population.
- **Survival considerations:** at a population level, the greatest health gain would be leveraged by restricting prion-filtration to those groups with a mean life expectancy that exceeds the incubation period of vCJD. This is considered to be seven years in those in the susceptible genotype (MM) and considerably longer in other genotypes.
- **Ability to implement selective prion filtration for the defined sub-groups:** consideration should be given to logistical issues and costs associated with targeted or phased introduction of prion filtration.

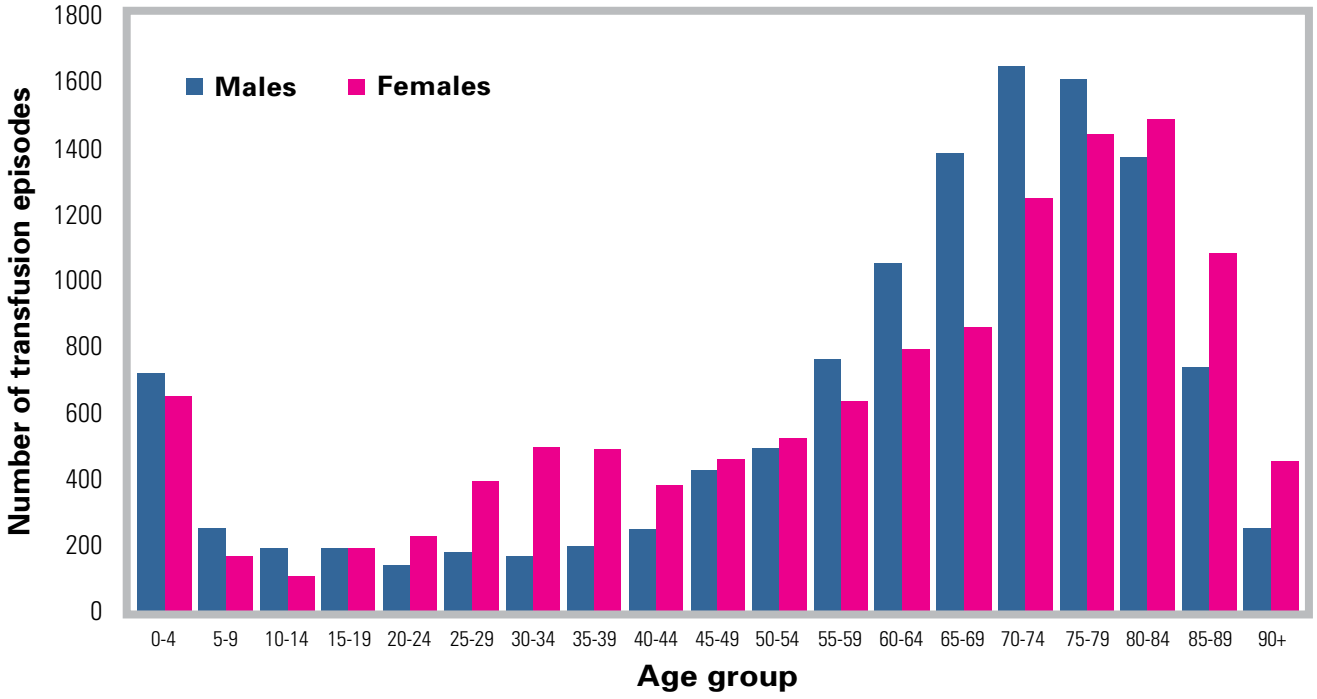
It is appropriate to examine transfusion demographics in Ireland to identify those groups with a disproportionately higher transfusion burden. The additional selection criteria above (actual risk of contracting vCJD, theoretical prior exposure from means other than a transfusion, survival considerations and logistical issues) are then applied to these demographics to determine those sub-groups that may derive greater benefit from a policy of prion filtration as compared to the general population.

7.4 Transfusion demographics

National data on transfusion practice was obtained from the Hospital In-Patient Enquiry system (HIPE) (see Figure 7.1).[99] Data in the HIPE system is limited to records of transfusion episodes from the discharge summary of hospital inpatients (including day-case episodes) from 57 hospitals. Although underestimating the total number of transfusions,[28] the age and gender profile of transfusion recipients is consistent with national audit data from 2001[100] and published audit data from other countries.[101]

Transfusion burden differs by age. An early peak occurs in those aged 0 to 4 years, mainly due to transfusion of neonates and infants less than six months of age. This then tapers off, increasing again in older ages. In the 2001 audit of transfusion practice in Ireland, the median age of transfusion recipients was 68 years (61 and 75 years for males and females, respectively).[100] This is consistent with a median age of 69 years reported in a UK study[101] and 69.9 years in a study of RCC transfusion recipients in Denmark and Sweden.[102]

Figure 7.1 Transfusion episodes by age and gender recorded on the HIPE database for 2006 to 2008 inclusive*



** Source: HIPE National Files 2006, 2007, 2008*

** Data limited to inpatient transfusion episodes only; transfusion episodes in emergency departments are not included. A maximum of one principal diagnosis and 19 secondary diagnoses or procedures are recorded per admission; transfusion episodes may therefore be under-recorded.*

7.4.1 Population aged 50 years and over

Between 2006 and 2008, approximately 70% of transfusion episodes recorded in the HIPE system occurred in those aged 50 years and older, with 56% occurring in those aged 65 years and older (Figure 7.1).[99] A major cohort study of transfusion recipients has shown that patient survival post-transfusion decreases with increasing age at first transfusion. Those in the 65 to 79 age bracket had a one-year survival rate of 72%, and the corresponding survival rate for those aged 80 years and more was 61%.[102] The mean life expectancy of this transfused population was less than 10 years.[18]

At a population level, this cohort is likely to derive little additional health gain from a policy of prion filtration when compared to the overall population. Applying the selection criteria above, the cohort is as likely as the general population to have prior exposure to vCJD from consumption of BSE-infected beef. Significantly, even for those with a susceptible genotype, mean post-transfusion life expectancy is similar to the considered incubation period for developing clinical vCJD following transmission, that is, 7 years (SD 1-32) for MM individuals, and at least 15 years from non-MM individuals.

7.4.2 Population aged less than 16 years

Children younger than 16 years of age receive approximately 4% of the RCC transfused annually. Children older that one year of age typically receive standard issue RCC, making this cohort more difficult to identify when treated in general

hospitals. A number of specialist products are prepared by the IBTS specifically for use in intrauterine transfusions and the neonatal population. Details of these products and their supply are outlined in Appendix 7.

The paediatric population may broadly be divided into two clinically distinct populations: those less than two years of age and those that are two years of age and older. Among the younger cohort (<2 years), those that survive the initial condition that necessitated the transfusion usually revert to normal life expectancy with no further transfusion requirements. Low-birth weight neonates are disproportionately transfused with RCC compared to the general neonate and paediatric populations and the population as a whole. The overall rate of transfusion of live born infants was 0.9%.[100] Transfusions are also common among children less than one year of age undergoing cardiothoracic surgery. A review of 2009 transfusion data from Our Lady's Children's Hospital, Crumlin, indicated that children less that one year of age accounted for 41.4% of those transfused, with children less than two years of age accounting for 51.2% of the transfused paediatric population. However, as dosing is weight-based, these cohorts accounted for only 18.6% and 25.4% of the number of units of RCC transfused, respectively.[103]

As a sub-group of the population, selective prion filtration of RCC for children less than two years or age is likely to have greater potential for health gain when compared to the overall population. This sub-group is more likely to be transfused, represents the longest living survivors of transfusion and will not have been exposed to vCJD through diet. The older cohort (≥2 years) are more clinically diverse. Life expectancy and the need for ongoing transfusions are linked to the underlying clinical condition.[103]

From an ethical and logistical perspective, the use of special measures specifically for paediatric transfusions is not without precedent. To minimise the risk of transfusion-transmitted infection and other transfusion-related adverse events, additional safety measures are employed by the IBTS in the preparation of blood products intended for transfusion to the foetus or children under four months of age. RCC must be:

- prepared from blood donated by non-first time donors who have provided at least one previous donation within the past two years that was negative for all mandatory microbiological markers
- CMV sero-negative
- prepared in CPDA-1 (instead of SAG-M) for exchange or intra-uterine transfusions (to ensure adequate coagulation proteins)
- provided as Pedipacks, (five pre-packed aliquots from a single blood donation) to enable sequential top-up transfusions over the shelf life of the red cells (35 days) while limiting donor exposure, or
- five days old or less for large volume, exchange or intra-uterine transfusions (ensuring optimal red cell function and minimising supernatant potassium levels).[104]

The selective introduction of prion filtration for RCC transfusion in a paediatric population has also been considered by the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) in the UK. Although stating a preference for universal implementation on the basis of equity, SaBTO has recommended limiting use of prion-filtered RCC to those born since 1 January 1996.[17] In the UK, a ban on the use of mammalian meat

and bone meal in animals for human consumption was introduced from January 1996, eliminating dietary exposure from vCJD for those born since that date.[105] A similar ban was introduced in Ireland from 1 January 2001[106]. Aside from the lower baseline risk of vCJD, this paediatric cohort would have a longer post-transfusion life expectancy, maximising the overall population gain from such a policy.

SaBTO has noted that any policy in relation to prion filtration should to be kept under review as additional data emerges, and has recommended targeted safety studies of prion-filtered RCC in children prior to adoption of the technology. Limiting supply of prion-filtered RCC to those born after a certain date will provide logistical supply challenges to ensure the supply is guaranteed for this cohort and to minimise inappropriate use. However, there is precedent of such supply in the UK: in 2002 a policy of providing methylene-blue treated imported plasma for those born after 1 January 1996 was introduced. This was extended to include the treatment of those up to 16 years of age in 2005.

7.4.3 Multi-transfused population

There are a number of patient groups that are multi-transfused (that is, require ongoing maintenance transfusions of RCC as part of their clinical management). These could, in theory, derive greater health gain from a policy of prion filtration when compared to the general population. Included are patients with haemoglobinopathies, those with bone marrow failure secondary to disease, cytotoxic chemotherapy or irradiation and patients with anaemia secondary to chronic renal failure. A number of these cohorts also require transfusion support with other blood products including platelets and plasma.

With the exception of patients with haemoglobinopathies, the survival of this multi-transfused cohort is lower than for those with fewer transfusions. A median survival of eight months has been reported for multi-transfused patients exposed to 80 or more donors (RCC, platelets, and other blood products), with overall survival of 38% at 12 months and 29% at 24 months.[107] Even with a susceptible genotype (MM), these patients are likely to die from their underlying disease before any symptoms of vCJD are manifest.

Haemoglobinopathies are inherited blood disorders and include the thalassaemias and sickle-cell disease. The majority of patients with B-thalassaemia major, a severe form of thalassaemia, require lifelong regular transfusion of RCC at two- to four-weekly intervals as a mainstay of their management.[108] The majority of patients with severe sickle cell disease require intermittent RCC transfusion to treat specific severe complications of the disease or in preparation for surgery. However, a smaller percentage of patients require ongoing maintenance transfusions (including exchange transfusions) for stroke prevention as part of their management.[109]

HIPE data from 2005 to 2009 indicate an average of 546 inpatient discharges per annum for patients with haemoglobinopathies (thalassaemias, sickle cell disease or other hereditary haemolytic anemias) for which a transfusion episode was recorded. Almost 85% of these episodes were in patients aged 19 years and younger, with 60% of episodes in those aged nine years and younger.[99] The majority of the paediatric patients with haemoglobinopathies are managed at our Lady's Children's Hospital, Crumlin, Dublin. Details of RCC use by this cohort are outlined in Appendix 7.

As a sub-group, patients with haemoglobinopathies may derive a greater health gain from a policy of prion filtration of RCC when compared to the overall population. Due to a higher transfusion burden, this sub-group has an increased risk of exposure to vCJD through infected blood and a higher risk of contracting vCJD. Their risk of prior dietary exposure to vCJD may be lower than the general population, as many of these patients were born after 1996. In contrast with other multi-transfused patients, those with haemoglobinopathies have a near normal life expectancy relating to their underlying condition.[110] In Ireland, this transfused population has increased year on year, with patients expected to have ongoing transfusion requirements as they age. The majority are currently managed in the paediatric setting. However, older patients will ultimately transfer to adult care settings.

7.4.4 Selection of sub-groups for analysis

On the basis of the biological and clinical arguments outlined, the following were chosen for sub-group analysis. These sub-groups may derive a greater health gain arising from a policy of prion filtration of RCC when compared with the overall transfused population. Alternatively, they could be viewed as the sub-groups with the greatest potential for harm if universal prion filtration is not implemented.

The sub-groups are:

- all children under 1 year
- all children under 2 years of age
- all children and adolescents under 16 years of age
- patients with haemoglobinopathies
- combinations of patients with haemoglobinopathies and paediatric sub-groups.

7.5 Cost-effectiveness analysis

The cost-effectiveness analysis for universal prion filtration was repeated at a sub-group level. The key parameters for the sub-group models were identical to those used in the model for universal filtration (see Table 6.1). The only difference in the models was the number, age profile and average number of units transfused per recipient of prion filtered blood.

7.5.1 Estimating sub-group populations

The age-sex profile of blood transfusion recipients was extracted from the Hospital In-Patient Enquiry (HIPE) system and averaged for the years 2006-2008.[99] It was possible to extract the annual number of transfusions in each age band using the HIPE data.

Inclusion of the haemoglobinopathy sub-group requires information on the prevalence of RCC transfusions and the life expectancy of patients with haemoglobinopathies. Data on transfusion episodes was obtained from the HIPE database. Life expectancy data were adapted from a 1994 US study.[111] At that time the life expectancy

was calculated as 42 years and 48 years for males and females, respectively. It was noted that great progress had been made on reducing mortality and it can be expected that further gains have been made in the period since the study was reported. That study found few patients survived beyond 50, whereas evidence from HIPE indicates patients surviving into their 70s and 80s. Survival was estimated to fall halfway between that reported in the US study and that observed in the general Irish population. The estimated life expectancy at birth for patients with haemoglobinopathies is 57 years and 63 years for males and females, respectively.

The number of transfusion recipients will be affected by changes in population, particularly given the ageing of the Irish population. Projections for the population from 2011 to 2021 were used to estimate changes in the demand for transfusions.[98] Projections are published for a range of migration and fertility scenarios. For this study, the M0F1 scenario was selected as the projected population for 2011 most closely resembles the estimated current population. The M0F1 scenario assumes zero net migration and current fertility pattern.

7.5.2 Cost-effectiveness analysis results

There was no sub-group for which prion filtration prevented any cases of vCJD in the point estimate (see Table 7.2). The 95% confidence interval predicted a range of 0 to 3 cases (under 16s plus haemoglobinopathies) prevented. Due to the small size of the sub-groups in terms of transfusion episodes, the probability of vCJD transmission is low. For example, even for the largest sub-group defined (combination of children less than 16 years old plus patients with haemoglobinopathies) there was only a 36% probability of life-years being saved (see Table 7.3).

Compared to universal filtration for which approximately 1.6 million units of RCC would be filtered over 10 years, only 29,000 to 415,000 units will be filtered depending on the sub-group. The greatly reduced burden of filtering is reflected in the discounted cost over 10 years which ranges from €5.9 million to €20.1 million, depending on the sub-group under consideration, compared to €68.2 million for universal filtration. However, the reduced cost is counterbalanced by the fact that filtering for sub-groups is less likely to prevent any transmission of vCJD.

Table 7.2 Outcomes over 10 years for introducing prion filtration of RCC for selected sub-groups

Sub-group	Infections prevented	Life years saved (discounted)	Units processed (1,000s)	Discounted cost (€ millions)
<1s	0	0	65	5.9
	(0 - 1)	(0 – 24)	(63 – 66)	(5.6 – 6.3)
<1s and patients with haemoglobinopathies	0	0	109	7.7
	(0 – 2)	(0 – 39)	(107 – 111)	(7.2 – 8.1)
<2s	0	0	83	6.5
<2s and patients with haemoglobinopathies	(0 – 1)	(0 – 25)	(81 – 85)	(6.2 – 6.9)
	0	0	122	8.3
	(0 – 2)	(0 – 40)	(120 – 124)	(7.8 - 8.8)
<16s	0	0	398	19.3
	(0 – 2)	(0 – 45)	(393 – 404)	(17.6 – 20.9)
<16s and patients with haemoglobinopathies	0	0	415	20.1
	(0 – 3)	(0 – 49)	(409 – 421)	(18.3 – 21.8)
Patients with haemoglobinopathies	0	0	29	4.0
	(0 – 1)	(0 – 19)	(28 – 29)	(3.9 - 4.1)
Universal	3	19	1550	68.2
	(0 – 10)	(0 – 95)	(1544 – 1556)	(61.8 – 75.0)

The probability of life years gained due to prion filtration ranges from 12% for patients with haemoglobinopathies to 36% for the combination of under 16s plus patients with haemoglobinopathies (see Table 7.3). For all sub-groups the probability of life years gained is substantially lower than universal filtration. To take into account the large number of simulations in which there were zero life years gained, ICERs were computed as the average cost divided by the average life years gained across simulations. The ICERs are all in excess of €1.3 million per life year gained.

Table 7.3 Probability of life years saved and incremental cost-effectiveness ratio by sub-group

Sub-group	Probability of life years saved (%)	ICER * (€ millions/ life year gained)
<1s	16	1.56
<1s + patients with haemoglobinopathies	25	1.34
<2s	18	1.56
<2s + patients with haemoglobinopathies	26	1.37
<16s	34	2.17
<16s + patients with haemoglobinopathies	36	2.11
Patients with haemoglobinopathies	12	1.99
Universal	77	2.61

** Calculated as the average cost divided by the average life years gained across simulations*

7.6 Budget impact analysis

Consistent with the budget impact analysis (BIA) for a policy of universal prion filtration, a five-year time period was adopted for the sub-group BIA. As before, the data for the BIA are the same as those used in the cost-effectiveness analysis with the difference being that prices are inclusive of VAT, and no discounting is applied. All items are subject to VAT at 21% apart from the cost per unit of the processed blood as which is exempt from VAT. The results are reported as the annual cost of implementing prion filtration for each sub-group. Results for the P-Capt™ filter and PRF2BE filter system are reported separately (see Table 7.4).

Table 7.4 Budget impact of introducing prion filtration for sub-groups

Sub-group	Cost per annum (€ million)									
	P-Capt™					PRF2BE				
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
<1s	0.8	0.8	0.8	0.8	0.8	-	-	-	0.8	0.8
	(0.8 - 0.9)	(0.8 - 0.9)	(0.8 - 0.9)	(0.8 - 0.9)	(0.8 - 0.9)	-	-	-	(0.7 - 0.9)	(0.7 - 0.9)
<1s and patients with haemoglobinopathies	1.1	1.1	1.1	1.1	1.1	-	-	-	1.0	1.0
	(0.9 - 1.2)	(0.9 - 1.2)	(0.9 - 1.2)	(0.9 - 1.2)	(1.0 - 1.2)	-	-	-	(0.9 - 1.2)	(0.9 - 1.2)
<2s	0.9	0.9	0.9	0.9	0.9	-	-	-	0.9	0.9
	(0.8 - 0.1)	(0.8 - 0.1)	(0.8 - 0.1)	(0.8 - 0.1)	(0.8 - 0.1)	-	-	-	(0.8 - 1.0)	(0.8 - 1.0)
<2s and patients with haemoglobinopathies	1.2	1.2	1.2	1.2	1.2	-	-	-	1.1	1.1
	(1.0 - 1.3)	(1.0 - 1.3)	(1.0 - 1.3)	(1.0 - 1.3)	(1.0 - 1.3)	-	-	-	(1.0 - 1.3)	(1.0 - 1.3)
<16s	2.9	2.9	2.9	3.0	3.0	-	-	-	2.7	2.7
	(2.5 - 3.4)	(2.5 - 3.4)	(2.5 - 3.4)	(2.5 - 3.4)	(2.5 - 3.4)	-	-	-	(2.2 - 3.2)	(2.2 - 3.2)
<16s and patients with haemoglobinopathies	3.0	3.0	3.0	3.1	3.1	-	-	-	2.8	2.8
	(2.6 - 3.5)	(2.6 - 3.5)	(2.6 - 3.5)	(2.6 - 3.5)	(2.6 - 3.6)	-	-	-	(2.3 - 3.3)	(2.3 - 3.4)
Patients with haemoglobinopathies	0.5	0.5	0.5	0.5	0.5	-	-	-	0.5	0.5
	(0.5 - 0.5)	(0.5 - 0.5)	(0.5 - 0.5)	(0.5 - 0.6)	(0.5 - 0.6)	-	-	-	(0.5 - 0.5)	(0.5 - 0.5)
Universal	11.0	11.1	11.2	11.3	11.4	-	-	-	8.5	8.6
	(9.4 - 12.6)	(9.4 - 12.7)	(9.5 - 12.8)	(9.6 - 12.9)	(9.7 - 13.1)	-	-	-	(7.0 - 10.1)	(7.0 - 10.3)

Note – 95% confidence bounds in parentheses

The budget impact of selective prion filtration of RCC for limited patient sub-groups differs for the two models of the filter, although the difference is small for sub-groups with low volume use of filters. The estimated budget impact of selective prion filtration of RCC ranged from €0.5 million per annum for patients with haemoglobinopathies only to €3.1 million (P-Capt filter) to provide filtered RCC to those less than 16 years of age in addition to patients with haemoglobinopathies.

7.7 Logistical issues

The IBTS currently supplies a wide range of blood products to over 70 hospitals. If prion-filtration of RCC is introduced on a limited basis for selected patient sub-groups, this will increase the complexity of the supply chain process. However, based on discussions with the IBTS, it would be logistically feasible. It is anticipated that prion-filtered product would need to be over-produced to ensure its availability at a local level. Similar to current practice with CMV-negative RCC, unused short-dated product would be diverted for use in the general population to minimise out-dating. Increased costs due to wastage would therefore not be anticipated. However, there would be a cost implication for unnecessarily providing prion-filtered products to those outside the designated sub-groups. This was included as part of the cost-effectiveness and budget impact analysis, where production of prion-filtered RCC was inflated by 10% (<2 year old) to 25% (<16 years; patients with haemoglobinopathies; combination sub-groups) compared to a scenario of no prion filtration.

Limited introduction of prion-filtered RCC for selective sub-groups could have implications for the reporting of haemovigilance events. Transfusion of a blood component that does not meet appropriate requirements is classified as an 'Incorrect Blood Component Transfused' (IBCT). Although reporting of IBCTs is not mandatory under EU legislation, IBCTs are reportable to the National Haemovigilance Office under professional responsibility.[112] The risk of harm (vCJD transmission) from transfusion of a single non-prion-filtered unit to an individual would be miniscule compared to the potential negative consequences, including death, should a transfusion be delayed in a critically ill patient while a prion-filtered product was sourced.

7.8 Discussion

There are a number of important issues when considering the limited introduction of prion filtration of RCC for selected patient sub-groups. There may be significant ethical considerations relating to denying a technology to a proportion of the population if it is known to reduce risk. Selection of a patient sub-group should only occur on foot of a decision not to introduce universal prion filtration. There are a range of criteria that could be used to define suitable patient sub-groups, but some of these may be conflicting. If the intention is to maximise health gain (i.e. life years gained) then younger populations stand to gain most from risk reduction. If the intention is to achieve the greatest reduction in risk, then the multi-transfused may be more appropriate.

The results of the cost-effectiveness analysis indicate that under the base-case assumptions regarding the prevalence of pre-clinical vCJD, limiting prion filtration to any selected patient sub-group is not cost-effective and is unlikely to result in any health gain, irrespective of cost.

7.9 Key messages

- Consideration may be given to the selective introduction of prion-filtered RCC for limited patient sub-groups if a policy of universal prion filtration is found not to be cost-effective or cost-effective, but not affordable.
- Criteria for the selection of sub-groups should be based on plausible clinical and biological arguments.
- Patient sub-groups identified included those <1, <2 or <16 years of age, patients with haemoglobinopathies and combinations thereof.
- In the UK, SaBTO has made a recommendation to the Department of Health for the selective implementation of prion filtration for those born since 1 January 1996.
- Under the base-case assumptions regarding the prevalence of pre-clinical vCJD, limiting prion filtration to any selected sub-group is not cost-effective and is unlikely to result in any health gain, irrespective of cost.
- The risk of harm (vCJD transmission) from transfusion of a single non-prion-filtered unit to an individual would be miniscule compared to the potential negative consequences, including death, should a transfusion be delayed in a critically ill patient while prion-filtered product was sourced.

8 Ethical and legal issues

8.1 Introduction

The purpose of this section is to:

- review the general principles of medical ethics and describe their relevance to the allocation of healthcare resources
- examine the ethical issues arising from a decision to provide, or not provide prion filtration for either all red cell recipients, or selected patient sub-groups
- examine the potential legal issues relating to blood safety initiatives.

8.2 Background

New medical technologies often raise ethical and social dilemmas as society comes to understand the implications of their application. Decisions to implement new technologies have implications for resource allocation because choosing a particular medical technology may imply abandoning existing technologies or may lead to the re-allocation of resources potentially limiting or depriving service-users of existing services. In the context of health policy, such as considerations as to whether to introduce screening for disease, or the provision of a vaccine, ethical principles must take account not only of the application of the principles to individuals but also the benefit, costs and risks to the public.

The importance of good health is something that is uncontroversial amongst policy-makers. However, the action to be taken in furtherance of good health at the expense of the State is a topic that has exercised many governments, activists, academics and medical practitioners alike. The legal and moral responsibility of the State to prevent disease as well as promote good health amongst its citizens is the subject of longstanding debate.

Decision makers must balance both individual and wider societal interests in making their decision. Technology should thus be seen in context as societal and ethical effects will vary according to cultural norms and the structure of the health service within which the decision is being made. Ethical analysis seeks to understand the situation in its morally relevant aspects, not provide an immediate solution to an ethical dilemma. Ethical analysis therefore assists decision making by providing insight into these issues and enabling the interpretation of information in a policy-relevant way.

Where resources are limited and it is impossible or impracticable to provide universal services, any decision to re-allocate resources within the public health system or to allocate services to one group rather than another is a decision that must be open to strict scrutiny and accountability. Our society starts from the basic premise that every citizen has a right to life but we must also understand that the meaning of rights is contingent on the availability of resources needed for respecting those rights. When resources are limited, corresponding rights to those resources also become limited. The difficulty lies in trying to ensure fairness and ethical justice in the rationing process. Many criteria play a role in decision making in this context:

- the societal wish to maximise general population health
- distribution of health in the population as many societies may wish to prioritise vulnerable population groups such as the poor, the severely ill, children, pregnant women
- specific societal preferences that target preventative over curative treatments, or the provision of acute care in life-threatening situations
- budgetary constraints and the costs of implementation
- political criteria such as the influence of interest groups and legacy issues.

The background to the work of the Irish Blood Transfusion Service is explained in detail in Appendix 1 of this report. In acknowledging the reality that blood transfusions are not risk free, it is important to note the devastating harm caused to those with haemophilia and von Willebrand disease who received contaminated blood products and women who received contaminated Anti-D in the 1970s, 1980s and early 1990s. Some of those patients with haemophilia became infected with HIV, while patients with haemophilia, von Willebrand disease and women receiving Anti-D were infected with Hepatitis C as a result of contaminated blood. Measures are taken by the IBTS in accordance with national, EU and international standards to minimise the risks associated with blood transfusion. However, the memory of the harm and deaths caused as a result of infected blood supplies has created a legacy that has influenced decisions regarding the introduction of blood safety strategies, including those not found to be cost-effective by traditional standards of cost-effectiveness. This legacy must be borne in mind in considering any new technology which might reduce or minimise the risk of vCJD transmission by blood transfusion.

In making difficult decisions, ethical principles can come into conflict and it becomes necessary to balance competing concerns. There is no national or international consensus on the correct approach to this balancing exercise. The emphasis in the literature on this issue is on ensuring that the decision-making process itself is fair, open and inclusive of all perspectives. It is important that the decision maker is as transparent as possible in relation to the ethical stance taken and the values underpinning the decision.

8.3 General principles of medical ethics

There are a number of approaches to medical ethics but one of the most widely used frameworks in recent years is that advocated by Beauchamp and Childress, known as 'the Four Principles'.[113] The principles are:

- autonomy
- beneficence
- non-maleficence
- justice.

The principles are important in every situation to which they apply, but no single principle is of itself absolute and the principles may come into conflict with each other in certain cases. For example, there may be a conflict between autonomy and

beneficence where an individual chooses not to undergo treatment which is clinically in their best interests, or a conflict may arise in relation to allocation of healthcare resources between benefit for an individual and benefit to society. In cases of conflict a balance must be found which prioritises the achievement of the primary objective and minimises any negative impacts as far as possible.

Autonomy: the word autonomy literally means self-rule, in other words making one's own deliberate decisions. In the medical context, respect for autonomy is of vital significance in relation to consulting with and informing patients about their healthcare and their choices. It requires doctors to obtain informed consent from patients before any treatment or intervention (except in cases of incapacity or medical emergency). It also requires patient confidentiality to be maintained, appropriate behaviour to be practised and good communication methods to be used between patients and healthcare professionals.

Beneficence and non-maleficence: these are sometimes considered together as two sides of the same coin although in some situations one of these duties may exist without the other. The ultimate aim in healthcare is to produce net benefit over harm, while recognising that inevitably some risk of harm may exist when any medical intervention takes place. Beneficence is the traditional Hippocratic duty to prioritise patients' best interests, while non-maleficence is the duty not to cause harm or risk of harm to patients. These duties mean, for example, that those who treat patients must be appropriately qualified as otherwise the risk of causing harm becomes disproportionate. Healthcare professions therefore undertake to provide appropriate training and education to prospective and current practitioners to ensure adequate protection of patients.

Justice: this is generally synonymous with fairness and may be described as the moral obligation to act on the basis of fair adjudication between competing claims. This may be subdivided into three categories of obligations: distributive justice which involves the fair distribution of resources; rights-based justice which involves respect for people's rights; and legal justice which involves respect for morally acceptable laws. There are many moral conflicts that can arise in this context, for example how to decide between equally deserving patients as to provision of a scarce resource. There are also issues in regard to the wider use of resources, conscious that payment must be made for those resources either by the patient, an insurer or the State. In the context of a public health programme, this raises issues in relation to equity of access and the rationale or justification for selection of particular population groups.

8.4 Allocation of resources in healthcare

If healthcare is considered to be a social good, the method of allocation must be addressed as many legitimate but contradictory goals may exist. The development of any national strategy to deal with resource allocation must first decide how much resources are available nationally to deal with healthcare. That is essentially a political question. If no additional resources are available for the proposed new intervention or treatment, then resources must be taken from within existing budgets to pay for its cost. Once the resources become available, it must then be determined how the resources are to be divided between all of those that need them.

There are a number of different theories of justice, for example, utilitarianism, egalitarianism, libertarianism and contractarianism. When applied to healthcare, each of these theories provides guidance on a just system of healthcare distribution. However, the application of these various theories of justice, while useful in stimulating discussion about priorities and objectives of the healthcare system, nevertheless are not perfect. Each theory ranks values differently, from equality to liberty and prioritisation of certain groups and so on. The difficulty is how to choose between these theories in determining how to prioritise scarce resources. Regardless of which theory is chosen, some groups and individuals will benefit and others will not.

8.5 Prion filtration

The ethical principles outlined above have relevance in the context of a decision whether or not to introduce prion filtration, and if so, whether it should be introduced at a universal level or for specific sub-groups of the population only.

- The principle of respect for autonomy necessitates that patients and service-users are informed regarding any risks, benefits and alternatives to any proposed treatment prior to making a decision about whether to avail of that treatment. It is not common practice in Ireland and many other jurisdictions at present to seek specific informed consent for blood transfusions as it is generally implied from the consent given by the patient to medical treatment of which the transfusion forms part. However, in keeping with the principle of respect for autonomy, it would be best practice to inform recipients of the risks, benefits and alternatives to transfusion in order to enable them to make an informed choice as to whether or not to accept the transfusion.
- Beneficence requires that decisions are made and treatment services are provided in the best interests of patients. This is complied with where transfusions are given on the basis of clinical need.
- Non-maleficence in this context means that as far as possible, services or treatments are not provided where the risk of harm to the patient outweighs the potential benefit, and that all reasonable precautions are taken to ensure the safety of the blood products used for transfusion.
- Justice in this context means that the decision to allocate resources should be fair and should not either favour or impose undue burdens on any sector of the population.

As discussed elsewhere in this Report, there are essentially three options available in relation to the provision of prion filtered blood:

- No implementation.
- Universal implementation. Although universal implementation would be preferable to sub-group implementation from the perspective of equity and fairness, it is estimated that the annual cost of this would initially be €11 million with a predicted prevention of two deaths of vCJD infection after filtering for 10 years. This results in an ICER of €2.6 million for each life year gained. Based on this analysis, universal implementation is not cost-effective at the present time. If this intervention was implemented despite not being cost-effective, the financial resources for implementation would have to be found from within the existing health budget. Should this happen, consideration would have to be given to the ethical issues arising from the discontinuance or re-allocation of existing services.
- Sub-group implementation. There are specific patient sub-groups that might benefit from receiving filtered blood. As explained in chapter 7, criteria considered when identifying sub-groups included increased risk of contracting vCJD, lack of prior exposure through diet up to 2001, survival rates, implementation challenges and transfusion demographics. The sub-groups considered include:
  - children < 1 year of age
  - children < 2 years of age
  - children < 16 years of age
  - patients with haemoglobinopathy
  - combination of the above.

If consideration is given to implementation in a sub-group of the population there are ethical considerations to be borne in mind. The most important of these is equity as favouring one sub-group over another could be said to inherently contradict the ethical principle of justice. However, on the other hand, prioritisation of sub-groups of the population, particularly vulnerable groups such as children, is not without precedent in our health system and does have societal support in other contexts such as HPV vaccination and the use of age thresholds for screening programmes. These selections are generally done on the basis of clinical as well as age criteria when, for example, a higher prevalence of disease occurs in a particular sub-set of the population or increased effectiveness occurs with a particular sub-group. On this basis therefore the potential for greatest gain is maximised by the choice made.

In the context of the sub-groups identified in chapter 7, there may be sound ethical justifications for prioritising the implementation of filtration of blood for children (<1 or <2 years of age) on the basis that this would have the greatest potential for health gain over the life-span of this sub-group as the long-term consequences of transfusion infections would be avoided. However, there may also be sound ethical reasons to provide filtered blood to patients with haemoglobinopathies on the basis that, due to their increased level of exposure to transfusion, this group is at the highest risk of

contracting vCJD. In comparison to other patients who receive multiple transfusions, patients with haemoglobinopathies have a near normal life expectancy relative to their underlying medical condition. Therefore, this group might be said to be on a par with the paediatric non-haemoglobinopathy cohort, other than on age criteria which in itself may not be a sufficient ethical distinction to draw in this context.

It is important to note that, as stated earlier, funding prion filtration for any of these sub-groups would require the re-allocation of funds from elsewhere in the healthcare budget, with a lower societal impact since it would only affect a small proportion of the population. The evidence and analysis presented in this report estimates that filtering for sub-groups is not cost-effective and is unlikely to prevent any transmission of vCJD.

8.6 Legal issues

The IBTS is responsible for the processing and supply of blood products in the State. This responsibility is discharged in compliance with the EU Directive 2002/98/EC which was transposed into Irish law in SI 360 of 2005. This sets standards for, amongst other things, the testing, storage, and traceability of blood products. EU Directive 2004/33/EC sets out technical requirements for blood and blood products including standards for the quality and safety of blood supplies. The 2002 Directive states that:

> in order to safeguard public health and to prevent the transmission of infectious diseases, all precautionary measures during their (blood and blood components) collection, processing, distribution and use need to be taken making appropriate use of scientific progress in the detection and inactivation and elimination of transfusion transmissible pathogenic agents.

There is no definition or concrete interpretation of what these 'precautionary measures' entail and the extent to which the measures must be reasonable and proportionate to the health threat in question.

Under the Liability for Defective Products Act 1991 (which transposed into Irish law the EU Product Liability Directive) a producer may be liable for damage caused by a defect in his product. The Act removes to a large extent the concept of fault and the question of whether the producer took reasonable steps to alleviate the risk. A producer may not be liable under the Act in certain limited circumstances, such as where the producer establishes that the product was neither manufactured by him for sale or any form of distribution for an economic purpose nor manufactured or distributed by him in the course of his business.* However, based on limited case law in other jurisdictions, this exemption does not appear to extend to defective products

*Section 6 of the Act. The producer is freed from all liability if he proves: that he did not put the product into circulation; that the defect causing the damage came into being after the product was put into circulation by him; that the product was not manufactured for profit-making sale; that the product was neither manufactured nor distributed in the course of his business; that the defect is due to compliance of the product with mandatory regulations issued by the public authorities; that the state of scientific and technical knowledge at the time when the product was put into circulation was not such as to enable the defect to be discovered. On this point, the Member States are permitted to take measures by way of derogation; in the case of a manufacturer of a component of the final product, that the defect is attributable to the design of the product or to the instructions given by the product manufacturer.

manufactured and used in the course of a specific medical service which is financed entirely from public funds.[114]

The extent to which the possibility of litigation should influence policy makers is open to debate. The potential for legal consequences for the IBTS would need to be considered in the event that a person could prove that they had contracted vCJD from a blood transfusion received in the State and that prion filtration would have minimised this risk.

8.7 Key messages

- Decisions to implement new technologies may have implications for resource allocation of existing technologies and services. Such decisions should be guided by ethical principles that take into account the application of the principles to individuals, but also the benefit, costs and risks to the public.
- Blood transfusions are not risk free. Measures are taken by the IBTS in accordance with national, EU and international standards to minimise the risks associated with blood transfusion. However, harm and deaths caused as a result of transfusion of infected blood products in the past has created a legacy which must be borne in mind in considering new blood safety strategies.
- In making difficult decisions, ethical principles can come into conflict and it becomes necessary to balance competing concerns. In cases of conflict, a balance must be found that prioritises the achievement of the primary objective and minimises any negative impacts as far as possible.
- A policy of universal prion filtration would be preferable to limited introduction for specific sub-groups on the basis of equity and fairness. However, given the finite healthcare resources, any such decision must be made in the context of the ethical issues arising from the discontinuance or re-allocation of existing services.
- Although inherently contradicting the ethical principle of justice, selective introduction of a technology is not without precedent, has societal support in other contexts and has the potential to maximise health gain depending on the choice made.
- European Union and national legislation specifies that 'all precautionary measures' be adopted to safeguard blood supplies from viral infection. However there is no definition or concrete interpretation of what these 'precautionary measures' entail and the extent to which the measures must be reasonable and proportionate to the health threat in question.
- Under the Liability for Defective Products Act 1991, a producer may be liable for damage caused by a defect in his product. This is a strict liability offence. The potential for legal consequences for the IBTS would need to be considered in the event that a person could prove that they had contracted vCJD from a blood transfusion received in the State and that prion filtration would have minimised this risk.

9 Summary and conclusions

9.1 Introduction

Health technology assessment is a tool that is increasingly being used internationally. It supports evidence-based decision making around the optimum use of resources in healthcare services. How healthcare resources are allocated is of growing importance given finite healthcare budgets and increasing demand for the services provided. Judicious investment and disinvestment decisions are essential to ensure that overall population health gain is maximised.

In examining a technology, traditional questions addressed by HTA include: Does the technology work? For whom does it work? At what cost? Is it cost-effective? A further consideration is the budget impact, or affordability, of the technology. Increasingly, decision makers must choose between competing technologies. The decision to invest in a new technology may necessitate rationalisation or withdrawal of existing services.

A decision to introduce prion filtration of red cell concentrates (RCCs) in the Irish Blood Transfusion Service (IBTS) requires consideration of the above issues. A number of other factors must also be taken into account. Blood safety is of paramount concern in any health service. The possibility that a blood or blood products could be infected with an agent that could ultimately prove fatal to the transfusion recipient is a very serious issue.

What must also be considered is the scale of the risk. It is likely that the prevalence of pre-clinical and sub-clinical vCJD in Ireland is low and that the corresponding risk of transfusion-transmitted infection is extremely low. The threat of BSE and vCJD appears to be receding both in Ireland and internationally, as evidenced by a decline in the number of new cases. However, there is considerable uncertainty surrounding the prevalence of vCJD and the likelihood of future cases. Several measures have already been adopted by the IBTS to mitigate the risk of vCJD transmission. Introduction of a further safety measure in the form of prion filtration must be viewed in the context of these measures and of the underlying risk.

The specific questions that a decision maker may ask when considering adoption of prion filtration as a routine measure could therefore be summarised as:

1. What is the likely prevalence of vCJD in the Irish population?
2. What is the current risk that vCJD may be transmitted via a blood transfusion in Ireland?
3. Are the measures taken by the IBTS sufficient to prevent transfusion-related transmission of vCJD?
4. What is the evidence that prion filters as a new technology are effective?
5. Is the filtered blood safe to administer?
6. Is it cost-effective to introduce prion filtration as an additional safety measure?
7. What would be the overall cost of providing prion-filtered red cell concentrates?

8. Is it appropriate to consider selective introduction of prion filtration for limited sub-groups of the population based on their increased risk of infection or their greater potential for health gain?

9. What are the ethical and legal issues to be considered to support a decision to invest in, or not to invest in, this new technology?

These questions have been addressed in this HTA, and are summarised in the sections that follow.

9.2 Prevalence of vCJD in Ireland

Experts agree that the origin of vCJD as a disease is linked to the outbreak of BSE that occurred in the UK in the 1980s and early 1990s. The incidence of BSE peaked in the UK in 1992-1993, declining since. The incidence of BSE infection in Ireland peaked in 2002 and was an order of magnitude lower than in the UK, with a peak incidence of over 300 new cases per annum, compared to over 36,000 new cases in the UK. Worldwide there have been 216 deaths from vCJD in 11 countries since vCJD was first identified, 170 of which have been in the UK. There have been four deaths from vCJD in Ireland, two of which are considered to have originated in the UK.

All confirmed clinical cases of vCJD have occurred in individuals with the MM genotype at codon 129. However, other genotypes (MV and VV) have been shown to be susceptible to, and may be carriers of the infection. A case of possible clinical vCJD has occurred in an individual who was heterozygous at codon 129, although is unconfirmed because autopsy was not performed.

The prevalence (expressed as the number of potential cases per million population) of pre-clinical or sub-clinical infection is unknown. A number of prevalence studies have been carried out in the UK, with others ongoing. Estimates of prevalence from these studies range from zero (95% CI: 0-289 per million) to a high of 237 per million (95% CI: 49-692), with results varying depending on the tissue sampled and the analytical technique used. In modelling studies, reported estimates of the prevalence of sub-clinical disease over-predict the number of clinical cases that have occurred. There are no such prevalence studies in Ireland, although it is accepted that the prevalence is likely to be substantially less than in the UK. Therefore, there is a high degree of uncertainty around any estimates of the likely pre-clinical or sub-clinical infection in the Irish population. Also unknown is the proportion of those infected that will go on to develop clinical disease and the interval between infection and clinical disease, particularly for non-MM homozygous individuals.

9.3 Risk of transmission of vCJD via blood transfusion

It is known that vCJD has a long incubation from the time of infection to the development of clinical symptoms. In people with a particular genetic subtype, MM homozygous on the prion protein encoding gene (approximately 40% of the population), the incubation period could be up to 10 years long. In the remaining 60% of the population that are heterozygous at this gene (MV) or valine homozygous (VV), the incubation period appears to be much longer.

It is known that vCJD can be unwittingly transmitted by transfusion of infected blood donated by those who have sub-clinical or pre-clinical vCJD. Worldwide to date, five cases of vCJD transmission from blood donors who subsequently developed vCJD have been identified. These cases all occurred in the UK. Four cases relate to the transfusion of non-leucoreduced red blood cells between 1996 and 1999, three of the recipients died from clinical vCJD and one from unrelated causes. One case relates to vCJD transmission from infected factor concentrates in an individual with confirmed pre-clinical vCJD who died from unrelated causes. Both individuals who died from unrelated causes were MV heterozygous at codon 129.

There is an ongoing risk of vCJD transmission from transfusion of blood or blood products due to donations from sub-clinical carriers of the disease.

9.4 Measures taken to prevent secondary transmission of vCJD

Several measures have been implemented by the IBTS to prevent the secondary transmission of vCJD via transfusion of blood or blood products. These include the exclusion of potential donors who resided in the UK during the BSE at-risk period (1980 to 1996), and the exclusion of donors who themselves have received a blood transfusion. Leucoreduction of red cell concentrates removes half of the potential infectivity from donated blood. There have been no reports of transfusion-transmitted vCJD since the introduction of universal leucoreduction of red cell concentrates in the UK and Ireland in 1999. Further measures to safeguard transfusion of plasma products are in place with the importation of treated plasma sourced from countries with a very low risk of vCJD and BSE. These measures do not alter the underlying prevalence of vCJD – rather they serve to reduce the risk of secondary transmission from infected donors.

9.5 Evidence of effectiveness of prion-removing filters

It is not currently possible to test human blood for the presence of the abnormal prion protein associated with vCJD. This increases the complexity of evaluating the efficacy of prion-removing filters. Testing strategies require the use of animal models: using exogenous studies – 'spiking' blood with very high concentrations of prion protein and assessing the level of removal with a filter, or 'endogenous' studies by injecting laboratory animals with infected blood and observing them over time to establish if they develop disease.

Two filters have obtained the CE mark and are marketed as prion-removing filters: the P-Capt™ filter and the PRF2BE filter system. It is not necessary to conduct a clinical trial to obtain a CE mark. Data to support the efficacy of the filter resin in reducing infectivity from vCJD has been published by the manufacturers of the devices for prototypes of both filters and for the current commercially available P-Capt™ filter. In the exogenous spiking studies, a 3-log reduction in infectivity has been reported. In the endogenous studies, no animal exposed to infected blood that has been passed through the P-Capt™ filter has developed clinical disease. At the time of this report, there had been no published studies to demonstrate the efficacy of the currently marketed PRF2BE filter system.

Independent validation of efficacy data has been recommended before a filter is considered for routine adoption by blood transfusion services. In the UK, satisfactory completion of an independent study was a requirement for a recommendation by SaBTO to the UK Department of Health regarding the adoption of prion filtration. The UK Health Protection Agency (HPA) has independently validated the exogenous spiking studies assessing the efficacy of the P-Capt™ filter. Although reporting lower efficacy levels than suggested by the manufacturers, the amount of infectious prion removed generally far exceeded the expected exposure levels from peripheral blood of donors with sub-clinical vCJD infection. However, the apparent failure of the prion filter to remove any significant amount of prion material in two of the nine assay runs in the independent exogenous study remains a concern. Independent endogenous studies to validate the efficacy of the P-Capt™ filter are currently underway. Similar independent exogenous and endogenous validation studies would be required for the PRF2BE filter system prior to any decision to adopt this technology into routine blood processing in Ireland.

The results from the exogenous studies confirm the capacity of the prion-removing filters to remove infectivity at levels many orders of magnitude higher than expected in the peripheral blood of donors with sub-clinical vCJD. Current evidence suggests that 1 in 10,000 infectious particles are not retained by the filter. A conservative approach would, therefore, assume that residual infectivity would remain at this level following prion filtration of leucoreduced RCC from an infected donor. In the absence of evidence to the contrary, it was assumed that for the purpose of this HTA both filter models have the same efficacy.

9.6 Filter safety

Published studies have indicated that prion-removing filters alter the quality and composition of RCC that are passed through them. Reports indicate that mean post-filtration haemoglobin levels are reduced by approximately 20%, or 8-9 grams per unit. Exposure to the filter may cause an increase in haemolysis and may occur more frequently in bottom-and-top processed units. Introduction of universal prion filtration of RCC may necessitate a reduction in the haemoglobin specification of this new product in order to meet ongoing process control measures. A reduction in the haemoglobin content of units of RCC may have clinical consequences for transfusion-dependent individuals, necessitating transfusion of additional units to counter the reduction in haemoglobin content associated with use of the filter. No change in haemoglobin specification would be required if prion filtration were introduced for limited sub-groups of the population as large volume units could be specifically selected by the IBTS for prion filtration.

Currently available clinical trial data for the P-Capt™ filter suggest no increase in antibody generation or adverse events associated with transfusion of prion-filtered RCC in adults. Trials in this regard are continuing.

Clinical trial data for the PRF2BE filter system are limited to an autologous study examining 24-hour recovery of radiolabeled red cells.

No clinical trials using prion-filtered RCC have been conducted in children.

9.7 Cost-effectiveness of prion filtration

Economic evaluation in HTA involves the comparative analysis of alternative courses of action. In this case, the additional costs and additional health benefits associated with introducing prion filtration of red cell concentrates (RCCs) as a standard practice in Ireland is being compared with the usual standard of care (i.e. no prion filtration).

There are no published cost-effectiveness analyses evaluating prion filtration. Other currently implemented blood safety strategies have been found to be not cost-effective when compared to traditional standards used for other healthcare interventions. Depending on the intervention, incremental cost-effectiveness ratios (ICERs) have ranged from €300,000 to €47 million per quality-adjusted life year (QALY).

A cost-effectiveness analysis was conducted using a UK-developed independent economic model that was adapted and populated with Irish-relevant data. A probabilistic model was used to ensure that the inherent uncertainty around the parameter estimates is incorporated in the findings. Values for parameter estimates were informed primarily through literature review and were endorsed by the Expert Advisory Group. Cost data were provided by the IBTS and the filter manufacturers. A conservative approach was adopted, so that the point estimates are closer to a worst case scenario. A 10-year timeframe was used along with a discount rate of 4% for costs and benefits.

Given the underlying assumptions of the model, if prion filtration is not introduced, it was estimated that there will be two (95% CI: 0 to 8) deaths from vCJD arising from transfusion of vCJD-infected RCC over the next 10 years correlating with 19.7 (95% CI: 0.0-96.1) life years lost. A further five infected recipients who are susceptible to clinical vCJD will not survive long enough to manifest clinical symptoms. Adoption of universal prion filtration is predicted to prevent these two deaths. The estimated incremental cost-effectiveness ratio (ICER) is €2.6 million per life year gained and is considered not cost-effective by traditional measures of cost-effectiveness.

Universal prion filtration of RCC would initially cost €11 million per annum. Over a five-year timeframe, the estimated budget impact of implementing prion filtration ranged from €51.6 million for the PRF2BE filter system to €56.0 million for the P-Capt™ filter.

In the univariate sensitivity analysis, efficacy results were sensitive to the prevalence of sub-clinical infection, while filter cost and the euro-sterling exchange rate were key drivers in the costs model.

9.8 Cost-effectiveness of and budget impact of selective prion filtration for limited patient sub-groups

The possibility of selective introduction of prion filtered RCC for limited sub-groups was considered in the event that a policy of universal prion filtration was found to be not cost-effective, or cost-effective but not affordable. Patient sub-groups were identified in advance on the basis of plausible biological and clinical arguments that reflected underlying differences in the risk of acquiring vCJD or differences in the potential for harm, should infection occur. Four key patient sub-groups were chosen: all children under 1 year of age; all children under 2 years of age; all children and adolescents under 16 years of age; and patients with haemoglobinopathies.

Selective introduction of blood safety policies is not without precedent in Ireland and internationally. There was no patient sub-group for which prion filtration prevented any cases of vCJD in the point estimate. The 95% confidence interval predicts a range of 0 to 3 cases (children and adolescents under 16 years plus patients with haemoglobinopathies) prevented, however, the probability of any life years being gained is substantially lower than for universal filtration. The ICERs for all sub-groups were in excess of €1.3 million per life year gained and as such, would be considered not cost-effective when compared to other healthcare interventions funded on the basis of cost-effectiveness evaluations. Reflecting the smaller number of RCC units to be filtered, the estimated annual budget impact ranged from €0.5 million to €3.1 million per annum. However, as stated, no health gain is predicted for any sub-group, irrespective of the money spent.

The risk of harm (vCJD transmission) from transfusion of a single non-prion-filtered unit to an individual would be miniscule compared to the potential negative consequences, including death, should a transfusion be delayed in a critically ill patient while a prion-filtered product was sourced.

9.9 Ethical and legal issues

Potential ethical and legal issues arising from a decision to adopt, or not adopt prion filtration were considered as part of this HTA.

Given a finite healthcare budget, a decision to invest in prion filtration may have implications for the resource allocation of existing technologies and services, potentially limiting or depriving service-users of existing services. Any decision to re-allocate resources within the public health system or to allocate services to one group rather than another is a decision that must be open to strict scrutiny and accountability. While recognising that blood transfusion is not risk-free, consideration must be given to the harm that resulted from the transfusion of Hepatitis C and HIV-infected blood products in Ireland in the 1970s, 1980s and 1990s when reviewing any technology that has the potential to increase the safety of blood products.

Based on this analysis, universal implementation of prion filtration is not cost-effective. If implemented despite being not cost-effective, the financial resources would have to be found from within the existing healthcare budget. Should this happen, consideration would have to be given to the ethical issues arising from the discontinuation or re-allocation of existing services. Selective adoption of prion filtration for limited sub-groups would inherently contradict the ethical principle of justice. However, such a policy is not without precedent within the healthcare setting, has societal support in other contexts and has the potential to maximise health gain depending on the choice made. There may be sound ethical arguments to support the limited introduction of prion filtration for those most at risk or for those who would derive the greatest health gain. However, prion filtration of RCC was not found to be cost-effective for any patient sub-group in this analysis.

The IBTS supplies blood products in compliance with EU and national legislation. EU directives specify that 'all precautionary measures' be adopted to safeguard blood supplies from viral infection. However, the interpretation of what these 'precautionary measures' entail and the extent to which measures must be reasonable and proportionate to the health threat is not certain. Under the Liability for Defective Products Act 1991, a producer may be liable for damage caused by a defect in his product. This is a strict liability offence. The potential for legal consequences for the IBTS would need to be considered in the

event that a person could prove that they had contracted vCJD from a blood transfusion received in the State and that prion filtration would have minimised this risk.

9.10 Conclusions

This HTA has reviewed the evidence regarding prion filtration of red cell concentrates (RCCs). Current evidence suggests that the filters are safe and will remove almost all residual risk of vCJD transmission with the caveat that 1 in 10,000 infectious particles may remain following filtration. Furthermore, the residual risk of vCJD transmission through transfusion of platelets (which cannot be prion filtered) will remain.

In Ireland the risk of acquiring vCJD from RCC transfusion in the absence of prion filtration is low. It is estimated that two people will die from clinical vCJD as a result of an exposure to infected blood in Ireland during the next 10 years. Due to filter-induced reductions in haemoglobin, introduction of universal prion filtration may necessitate changes in the specifications for filtered RCC units and an additional transfusion burden for transfusion-dependent patients.

In evaluating the cost-effectiveness of this technology, it was necessary to determine the risk of transmission through infected RCCs and the cost of adopting the technology. There is substantial uncertainty around a number of the key factors that impact on the prevalence and risk of transmission of vCJD.

It is predicted prion filtration of all RCCs will initially cost €11 million per annum and, over a 10-year time period, will prevent two deaths from vCJD and result in 19.4 discounted life years gained. The incremental cost-effectiveness ratio (ICER) of prion filtration is €2.6 million per life year gained. As a comparison, population-based colorectal cancer screening had an estimated ICER of €1,696 per QALY compared to a policy of no screening. This screening was estimated to cost €15 million per annum at full implementation, averting 160 cases of colorectal cancer and 270 deaths from the disease in year 10 of the screening programme.[29;35]

Introduction of prion filtration for selected patient sub-groups results in lower ICERs, but also a much lower probability of any life years gained. Introducing limited prion filtration for selected sub-groups may involve additional logistical issues associated with product distribution and supply.

Introduction of prion filtration for either all transfusion recipients or for limited sub-groups was found to be not cost-effective by traditional standards of cost-effectiveness. However, other blood safety interventions considered not cost-effective by traditional standards have been implemented previously, for example, NAT testing for HIV, Hepatitis B and Hepatitis C. Failure to introduce prion filtration may be associated with a risk of liability in the case of vCJD transmission from RCC.

The cost of universal prion filtration is substantial, with estimated initial costs of €11 million per annum. This financial cost of further minimising what is at most likely to be a low risk is high compared to the likely benefits. In the context of a finite healthcare budget, consideration must be given to the existing technologies and services that may need to be displaced should a decision be made to introduce prion filtration at a cost of up to €11 million per annum.

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11 Glossary of terms and abbreviations

Adverse event
Any adverse change in health or side-effect that occurs in a person undergoing treatment or investigation or who participates in a clinical trial while the patient is receiving the treatment (study medication, application of the study device, etc.) or within a pre-specified period of time after their treatment has been completed.

Aetiology
The causes or origin of disease and the factors which produce or predispose toward a certain disease or disorder.

Albumin
The most abundant protein in human plasma.

Amyloid plaque
Build up of protein based plaque in the brain.

Assay
Test to determine the presence, absence, or quantity of one or more components in a sample.

Asymptomatic
Without symptoms. For example, an asymptomatic infection is an infection with no symptoms.

Bovine spongiform encephalopathy
See **BSE**.

BSE
A fatal, neurodegenerative disease in cattle, commonly known as mad-cow disease

Budget impact analysis
Analysis of the financial consequences of adoption and diffusion of a new healthcare intervention within a specific healthcare setting or system.

CE (Conformité Européenne) marking
A mandatory conformance mark on medical devices placed on the single market in the European Economic Area (EEA). The CE marking certifies that a product has met EU consumer health and safety requirements.

CI
See **Confidence interval**.

CJD
A degenerative neurological disorder that is incurable and invariably fatal.

Clotting factors
See **Coagulation factors**.

Coagulation factors
A series of blood plasma proteins (I to XIII) involved in the production of a fibrin clot to stop bleeding.

Codon 129 of the *PRNP* gene
A group of nucleotides (codon) on the prion protein gene. This codon appears to act as a genetic susceptibility factor for vCJD.

Cohort
A group of subjects with a common defining characteristic.

Confidence interval
This refers to the range of values within which the true prevalence or percentage is likely to lie. These intervals provide an estimate of the uncertainty about underlying parameters given data. For example a 95% confidence interval has a 95% chance of including the true value for that parameter. As the amount of data increases, confidence intervals for parameters get narrower in width.

Cost-effectiveness
A form of economic analysis that compares the relative costs and outcomes (effects) of two or more courses of action.

Creutzfeldt-Jakob disease
see **CJD**.

DOH
Department of Health (UK).

DoHC
Department of Health and Children (Ireland).

Donor deferral
see **Donor exclusion**.

Donor exclusion
The non-acceptance of a potential donor based on lifestyle criteria or prior possible exposures to pathogens.

Economic model
Simplified mathematical model representing the inputs and processes involved in the introduction and use of medical technologies in the health system to help predict resource usage.

Effectiveness
How well a given intervention works in routine clinical use.

Efficacy
How well a given intervention works under ideal conditions (clinical trials or laboratory tests).

Encephalopathy
Disease, damage, or malfunction of the brain.

Endogenous infectivity
Infectivity due to transfusion of blood from other infected animals.

Epidemiology
The study of factors determining the causes, frequency, and distribution of diseases in a community or specified population.

EuroCJD
European Creutzfeldt Jakob Disease Surveillance Network.

EuroScan
International Information Network on New and Emerging Health Technologies.

Exogenous infectivity
Infectivity where the infectious material was introduced artificially into the extracted blood (usually by mixing with brain material taken from infected animals).

Fibrinogen
Blood plasma protein involved in coagulation. Also called Factor I (see also **Coagulation factors**).

Haematocrit
The proportion of blood volume that is occupied by red blood cells.

Haemoglobin
A protein found in red blood cells that carries oxygen from the lungs to the cells throughout the body.

Haemoglobinopathies
Range of blood disorders due to a genetic defect that result in abnormal structure of the haemoglobin molecule.

Haemolysis
The breakdown erythrocytes (red blood cells) with release of haemoglobin.

Haemophilia
Group of hereditary genetic disorders that impair the body's ability to control blood clotting or coagulation.

Hb
See **Haemoglobin**.

Hct
See **Haematocrit**.

Heterozygous
Possessing two different forms of a particular gene, one inherited from each parent.

Homozygous
Possessing two identical forms of a particular gene, one inherited from each parent.

HPA
Health Protection Agency (UK).

HPSC
Health Protection Surveillance Centre (Ireland).

HPV
Human papillomavirus (HPV) is the most common sexually transmitted infection. Some HPV types can cause cervical cancer.

HTA
Health technology assessment.

Human papillomavirus
See **HPV**.

Iatrogenic Creutzfeldt-Jakob disease
See **iCJD**.

IBTS
Irish Blood Transfusion Service.

ICER
Incremental cost-effectiveness ratio.

iCJD
Iatrogenic Creutzfeldt-Jakob disease, acquired through a medical or surgical treatment or a diagnostic procedure,

ID
The number of organisms necessary to cause disease.

ID_{50}
The number of organisms necessary for 50% of those exposed to develop the disease.

IMB
Irish Medicines Board.

In-vitro
A procedure performed in-vitro is performed not in a living organism but in a controlled environment, such as in a test tube or Petri dish.

In-vivo
In-vivo is experimentation using a whole, living organism.

Leucodepletion
See **leucoreduction**.

Leucoreduction
The process by which leucocytes (white blood cells) are removed from donated blood.

Life year gained
see **LYG**.

Log-reduction
A way to express levels of decreased biological contamination in liquid using the logarithmic scale. A 1-log reduction is nine out of 10 and would be equivalent to a 90% reduction. A 2-log reduction would be 99 out of 100 or 99% reduction and a 3-log reduction would be 999 out of 1000 or 99.9% reduction.

Look back study
Study to trace all blood and blood products donated by a person who subsequently developed vCJD.

LYG
Life year gained refers to a single year prolongation of a patient's life by means of a certain intervention. It is used to compare the cost-effectiveness of different medical interventions.

Lymphoreticular prion protein
Prion protein accumulated in the lymphoreticular system (includes the lymphatic system and the spleen).

MET
see **Methionine**.

Methionine
An amino acid that can be encoded in genes.

MRC
Medical Research Council (UK).

NBS
National Blood Service (UK).

Neonate
Newborn baby less than one month old.

NeuroCJD
The Extended European Collaborative Study Group of CJD.

Optimal use of blood products
A system to ensure the safe, clinically effective and efficient use of donated blood and to prevent unnecessary transfusions, that comprises guidelines, systematic application of guidelines in practice, and systematic audit of blood use.

Pall Leukotrap® Affinity Plus
see **PRF2BE filter system**.

P-CAPT™
The MacoPharma P-Capt™ Prion Capture filter (MacoPharma Ltd) was CE marked in September 2006 and is designed to be used in sequence with a leucoreduction filter.

Plasma
The yellow liquid component of blood in which the blood cells in whole blood are normally suspended. It makes up about 55% of the total blood volume.

PMCA
An amplification technique to multiply misfolded prions to a level where they can be detected.

Pre-clinical
See **Sub-clinical**.

PRF2BE filter system
The Pall Leukotrap® Affinity Plus Prion and Leucocyte Reduction Filter System (Pall Medical, a division of Pall Europe Ltd) was CE marked in September 2009. This product was developed from a first-generation prion-reduction filter that was CE marked in 2005.

Prion
A disease-causing agent that is neither bacterial nor fungal nor viral and contains no genetic material. A prion is a protein that occurs normally in a harmless form. By folding into an aberrant shape, the normal prion turns into a disease-causing agent. It then co-opts other normal prions to become rogue prions

Prion disease
See **TSE**.

Prion filter
A device that filters blood and extracts prion proteins.

PRISM trial
Clinical trial to investigate the safety of using blood that has been passed through the P-Capt prion filter: Trial of Prion-filtered versus Standard Red Cells in Surgical and Multi-transfused Patients (PRISM).

PRNP
Prion protein gene.

Probabilistic sensitivity analysis
See **PSA**.

Protein misfolding cyclic amplification
See **PMCA**.

Prothrombin
A protein found in blood that is necessary for blood clotting. Also called Factor II (see also Coagulation Factors).

PrP^{Sc}
Misfolded form of prion protein. PrP^{Sc} are disease-specific proteins seen in certain human and animal neurodegenerative diseases (prion diseases).

PSA
A type of sensitivity analysis where probability distributions are applied to a plausible range of values for key parameters to capture uncertainty in the results.

QALY
A universal health outcome measure that captures changes in both the quantity of life (mortality) and quality of that life (morbidity) as a single measure. It enables comparisons of the cost-effectiveness of a diverse range of medical interventions.

Quality-adjusted life year
See **QALY**.

RCC
A unit of blood from which most of the plasma and platelets have been removed leaving only the red cells.

Red cell concentrates
See **RCC**.

Reverse TMER
Reverse Transfusion Medicine Epidemiology Review. Ongoing reviews conducted to inform the UK Transfusion services of all definite and probable cases of vCJD who were reported as blood product recipients (see also **TMER**).

SaBTO
Advisory Committee on the Safety of Blood, Tissues and Organs (UK).

sCJD
Sporadic CJD, where the disease appears even though the person has no known risk factors for the disease. This is by far the most common type of CJD and accounts for at least 85% of cases.

Screening
A strategy used in a population to detect a disease in individuals without signs or symptoms of that disease.

Sensitivity
Sensitivity is a screening statistic that measures the proportion of actual positives which are correctly identified as such (e.g. the percentage of sick people who are correctly identified as having the condition).

Specificity
Specificity is a screening statistic that measures the proportion of negatives which are correctly identified (e.g. the percentage of healthy people who are correctly identified as not having the condition).

Spiked infectivity
See **Exogenous Infectivity**.

Spongiform
Resembling a sponge in being soft and full of cavities.

SPORADIC CREUTZFELDT-JAKOB DISEASE
See **sCJD**.

Sub-clinical
Without clinical manifestations; said of the early stages or a very mild form of a disease where the person may be infected but has no symptoms.

Time horizon
A fixed point of time in the future at which point certain processes will be evaluated. It is used in the economic assessment of a medical intervention.

TMER
Transfusion Medicine Epidemiology Review. Ongoing reviews conducted to inform the UK Transfusion services of all definite and probable cases of vCJD who were reported as blood donors (see also **Reverse TMER**).

Transfusion Medicine Epidemiology Review
See **TMER**.

Transmissible spongiform encephalopathy
See **TSE**.

TSE
Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, are a group of rare degenerative brain disorders characterized by tiny holes that give the brain a 'spongy' appearance that can be seen when brain tissue is viewed under a microscope.

Val
See **Valine**.

Valine
An amino acid that can be encoded in genes.

Variant Creutzfeldt-Jakob disease
See **vCJD**.

vCJD
Variant Creutzfeldt-Jakob disease (vCJD) is a rare and fatal human neurodegenerative condition. As with Creutzfeldt-Jakob disease, vCJD is classified as a transmissible spongiform encephalopathy (TSE) because of characteristic spongy degeneration of the brain and its ability to be transmitted. vCJD was first described in 1996.

Western blot assay
The Western blot is an analytical technique used to detect specific proteins in a given sample.

Appendix 1

Background information

App 1.1 Blood transfusion

Blood donors provide blood as whole blood consisting of a range of cell types with different physiological functions including red blood cells (RBCs), white blood cells (WBCs) and platelets. All of these cells are suspended in a liquid or transport medium called plasma. Their primary functions are as follows:

- RBCs – these cells contain a substance called haemoglobin whose primary function is to carry oxygen throughout the body, and to remove carbon dioxide
- WBCs – these cells defend against infectious agents
- platelets – these cells promote blood clotting and wound healing.[115]

Plasma is the liquid that provides the transport medium for blood cells throughout the body. In addition to suspending the above cells, plasma also contains vitamins, sugars, hormones, fibrinogen, albumin, immunoglobulin, clotting factors and waste products.[115]

Donated blood must be 'typed' to determine its compatibility with potential recipients. The major blood group system is known as the ABO system, where donated blood is categorised as group A, B, O or AB. These categories relate to the presence of antibodies or antigens that develop in human blood in the early stages of life. The second system is the Rhesus system, where an individual is categorised as Rhesus positive or Rhesus negative. The combination of the two systems means that there are a total of eight different major blood types. This is an important consideration as the blood group of the recipient must be compatible with that of the donor.[115]

Whole donated blood is not generally re-transfused to recipients. It is first separated down into its constituent parts, including units of red blood cells (referred to as units of red cell concentrates or RCC), units of platelets and units of plasma. When separated, the components can be stored for a longer time and can be transfused more rapidly than whole blood whilst also providing tailored treatment for patients, that is, the patient can be transfused with the specific component that they lack.

Examples of clinical indications for transfusions of red cell concentrates include:

- loss of blood during surgery and trauma
- side-effects from chemotherapy administration
- anaemia, which could be associated with conditions such as kidney disease, heart disease or liver disease
- anaemia in pregnancy
- haemoglobinopathies – a group of conditions, genetically acquired, that prevents the body from forming proper blood cells.

Platelet transfusions may be indicated in the management of patients with clinically low platelet counts, or patients with leukaemia. Plasma may be indicated for those with clotting difficulties. Pooled plasma may also be used in the production of clotting factors that are indicated in the management of bleeding disorders such as haemophilia and von Willebrand disease. White blood cells are transfused in very limited circumstances to critically ill septic patients with bone marrow failure following chemotherapy.

App 1.2 Irish Blood Transfusion Service

In Ireland, the Irish Blood Transfusion Service (IBTS) is the organisation responsible for collecting blood donations, processing and distributing blood products.

The functions of the IBTS are set out in Statutory Instrument No. 78 of 1965 and Statutory Instrument No. 209 of 1988, and include to:

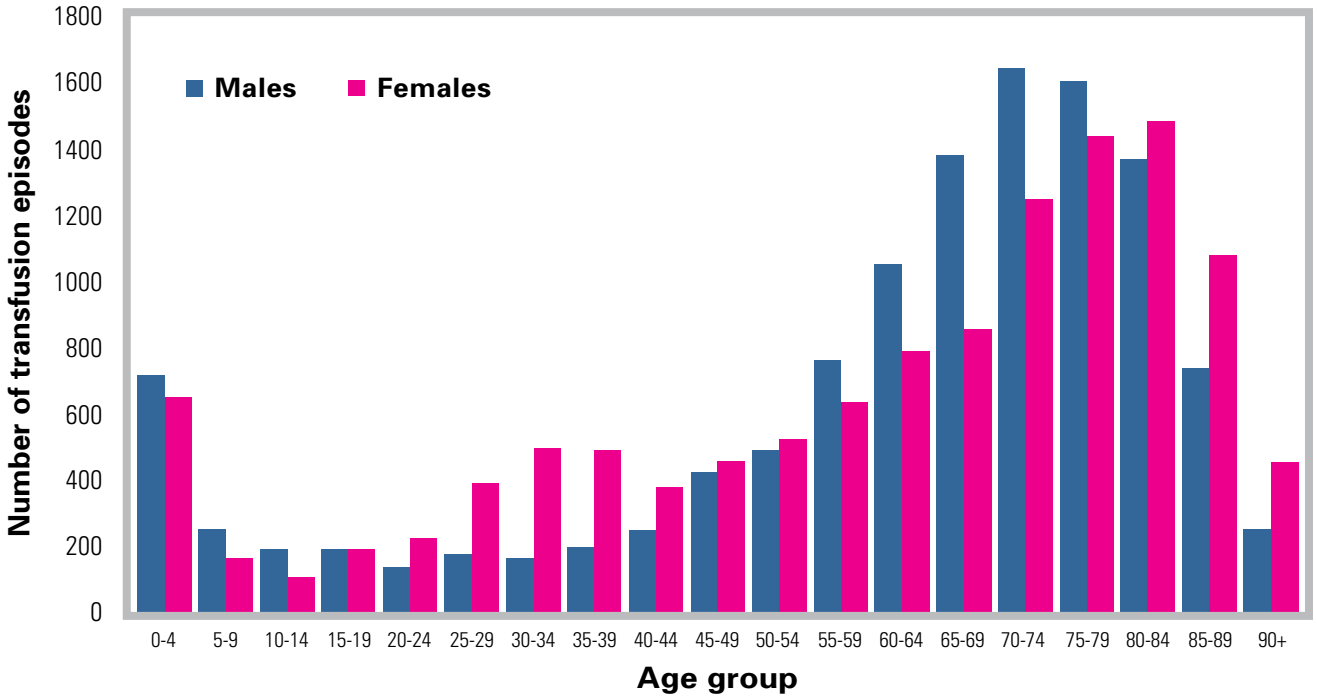
- organise and administer a blood transfusion service including the processing or supply of blood derivatives or other blood products, and also including blood group and other tests in relation to specimens of blood received by the service
- make available blood and blood products
- furnish advice, information and assistance in relation to any aspect of the service to the Minister, any health authority or any hospital authority
- organise, provide, assist or encourage research and the training and teaching of persons in matters relating to blood transfusion and preparation of blood products
- organise and administer a service for obtaining and assessing reports of unexpected or undesirable effects of transfusion of blood or blood components made available by the service.[116]

The European Union (EU) directive 2002/98/EC (transposed into Irish law in Statutory Instrument No. 360 of 2005) sets out further requirements for the processing of blood supplies. Blood establishments of the member states (that is, the IBTS in Ireland) must be 'designated, authorised, accredited or licensed by the Competent Authority for that purpose'.[117] This directive sets standards for blood establishments including responsibilities, personnel, quality management, documentation, record keeping, traceability, adverse events, donor management, testing of donations, storage and transport. Basic testing requirements for donated blood include testing for the ABO system, Rhesus system and mandatory testing for Hepatitis B, Hepatitis C and HIV infection. In Ireland, the Competent Authority is the Irish Medicines Board.

EU directive 2004/33/EC sets out technical requirements for blood and blood products in the member states and defines some of the aforementioned standards.[82] These include defined specifications for the storage, transport and distribution of blood, as well the information obtained from, and provided to potential donors. The directive also includes standards for the quality and safety of blood supplies, and defines acceptable limits for quality control purposes.

The IBTS requires approximately 3,000 blood donations per week or 160,000 units per year to address transfusion requirements in Ireland[115]. Data from the Irish Hospital In-Patient Enquiry Scheme (HIPE) suggest that transfusions are most commonly required in earlier and later years of life. Of those aged between 20-44 years, the transfusion burden is higher among female patients, probably reflecting transfusions required in pregnancy related anaemia. The HIPE data for the years 2006-2008 is illustrated in Figure App1.1.

Figure App1.1 Annual average number of transfusion procedures (including whole blood and packed cells) by age and gender, 2006-2008



Source: HIPE National Files 2006, 2007, 2008

In 2009, the IBTS issued 142,459 units of red cells and whole blood. In 2008, the corresponding figure was 141,364.[28] The IBTS also supplied a wide range of other blood products either manufactured by it (for example platelets, fresh, frozen plasma) or manufactured by third parties (for example imported plasma products or recombinant blood factor concentrates used in bleeding disorders). The organisation bills the individual hospitals and other facilities that it supplies these products to. In 2010 for example, the cost of a supplied unit of red cell concentrate was €248.71 per unit. [118]

App 1.3 Risks associated with blood transfusion

Blood transfusions are not risk free. However, the risk of not receiving a transfusion should outweigh the risk of receiving it. Risks include immune-mediated adverse events, other adverse events and infections. Immune-mediated adverse events occur when the immune system of the recipient attacks components of the blood being transfused, or when the blood causes an allergic reaction. Careful procedures are in place to prevent immune-mediated adverse events associated with mismatches

between the donor and recipient's blood groups. Immune mediated events may include acute or delayed haemolytic reactions, non-haemolytic febrile reactions, acute lung injury or anaphylactoid reactions.[119] Other adverse events include fluid overload or iron overload in those patients who receive multiple transfusions. Viral agents such as Hepatitis B, Hepatitis C and HIV can be transmitted through transfusion of infected donor blood.[119]

In the 1980s and early 1990s, HIV and Hepatitis C infected a portion of blood supplies all over the world with devastating consequences. Worldwide, approximately 40,000 people with haemophilia were infected with HIV,[120] including 106 in Ireland.[33] Also in Ireland, 220 people with haemophilia and 20% of those with von Willebrand disease who received blood products prior to 1990 contracted Hepatitis C.[34] In February 1994, batches of Anti-D immune globulin used in Ireland during 1977 and 1978 were found to be contaminated with Hepatitis C from a single infected donor. A national programme of screening women who had received Anti-D between 1970 and 1994 was commenced to identify possible infection.[121]

The consequences of these infections have been devastating to those infected. Ninety-three people with haemophilia who were infected with HIV or Hepatitis C have since died.[33] Around 1,400 people in Ireland have been infected with Hepatitis C as a result of receiving blood products administered in the State.[122] A Hepatitis C and HIV compensation tribunal was established by the government in 1996 to assess compensation awards to persons infected with either virus as a result of the administration of blood products. Between 1996 and 2008, the total cumulative cost of the tribunal is estimated at €900 million, with approximately 1,000 claims applications pending.[122] Primary care and hospital services are currently provided free of charge by the State to those infected. A range of services, including GP services, all prescribed drugs, medicines and appliances, dental and ophthalmic services, home support, home nursing, counselling services and other services are also provided free of charge to those infected by the Health Service Executive (HSE). These services cost approximately €22 million in 2008.[122] An insurance support scheme for infected persons was established in 2007. This measure addresses the problems faced by the inability of people to purchase mortgage protection and life assurance policies as a result of contaminated blood products being administered to them. The estimated lifetime cost of this scheme is €90 million.[122]

App 1.4 Measures taken by the IBTS to minimise risks associated with blood transfusion

Measures are taken by the IBTS (and blood transfusion services throughout the world) to minimise risks associated with blood transfusion. These measures include the nationally and EU mandated standards, as well as standards adopted by the individual service from time to time. The risk of receiving an incorrect blood component as a result of a blood group mismatch is generally much greater than receiving a transfusion-transmitted infection.[112] In Ireland, in the nine years of operation of the national haemovigilance system (2000-2008) a total of 1,860 serious adverse transfusion reactions or events have been reported.[28] Only 0.3% of suspected transfusion-transmitted infections were confirmed compared to transfusion of incorrect blood component or other serious adverse events which accounted for

57.5% of reports. The confirmed transfusion-transmitted infections consisted of three bacterial infections considered possible/probable and two HBV infections where donor investigations could not be completed.[112]

In Ireland, the current risk of viral transmission from donated blood has been estimated in Ireland as:

- one possibility in 9 million units of blood transfused for HIV
- one possibility in 20.7 million units transfused for Hepatitis C
- one possibility in 750,000 units transfused for Hepatitis B.[123]

Measures taken by the IBTS to reduce these and other risks include:

- donor selection and exclusion criteria to exclude potential donors who may be considered to be at higher risk of contracting an infectious agent[15]
- testing of donated blood for infection. All donated blood is tested for HIV, Hepatitis B, Hepatitis C and syphilis antibodies as well as Hepatitis B surface antigen and anti-HTLV1/11 using serology tests and nucleic acid testing (NAT)[28]
- post-collection processing such as universal leucoreduction (removal of white blood cells) [124] and effective viral inactivation of certain blood products[120]
- exclusion of potential donors for periods of one to 12 months if they have had recent travel to areas where there is a higher prevalence of transfusion transmissible infections such as Dengue, West Nile Virus and malaria.[125]

The risk of vCJD transmission via a blood transfusion must be carefully considered by blood safety agencies everywhere. The introduction of a specific technology – prion filters – may extend the possibility that any remaining risk may be significantly reduced or eliminated.

Appendix 2

Literature search strategies

App 2.1 Search strategy for data on efficacy and safety of prion-removing filters

Published literature was obtained by searching MEDLINE, CINAHL, the Cochrane Library, Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, EBSCO Psychology and Behavioural Sciences Collection and Health Business on the PubMed and EBSCO systems. Regular alerts were established on PubMed and EBSCO and relevant information retrieved via alerts was current to 16 December 2010.

No date restrictions or other filters were applied to limit the retrieval to specific study designs or document types. Given the limited data available on the topic it was decided to conduct a broad search to include as many potentially relevant results as possible.

Topic concepts and associated search terms were decided with input from the project team. A list of the search terms associated with the three chosen concepts is given in Figure App2.1, along with the initial search results from PubMed (Medline) and EBSCO (all other databases).

Figure App2.1 Search terms for review of the literature

Concept	Search terms	Results	
		PubMed	EBSCO
vCJD	Variant Creutzfeldt Jakob Disease	24913	2801
	New Variant Creutzfeldt Jakob Disease		
	V-CJD		
	vCJD		
	Prion		
	Transmissible Spongiform Encephalopathies		
	TSE		
	PrPres		
	PrP		
	PrP^{Sc}		
Blood	Blood	3171465	305328
	Transfusion		
	Erythrocyte		
	Red Blood Corpuscles		
	Red Blood Cell		
	RBCC		
	leukodepletion		
	leucocyte		
	leukocyte		
	leucoreduction		
	RBC		
Filtration	Filtration	1223379	262682
	P-Capt		
	Leukotrap		
	pall		
	MacoPharma		
	Filter		
	affinity ligand resin		
	remove		
	removal		
	reduce		
	reduction		

These terms were combined to produce the following results as outlined in Figure App2.2.

Figure App2.2 Results of combination of terms

vCJD AND Blood		vCJD AND Filtration		vCJD AND Blood AND Filtration	
PubMed	EBSCO	PubMed	EBSCO	PubMed	EBSCO
4867	619	1892	257	694	121

The final search string combining all three concepts was:

(Variant Creutzfeldt Jakob Disease

OR New Variant Creutzfeldt Jakob Disease

OR V-CJD

OR vCJD

OR Prion

OR Transmissible Spongiform Encephalopathies

OR TSE

OR PrPres

OR PrP

OR PrP^{Sc})

AND

(Blood

OR Transfusion

OR Erythrocyte

OR Red Blood Corpuscles

OR Red Blood Cell

OR RBCC

OR leukodepletion

OR leucocyte

OR leukocyte

OR leucoreduction

OR RBC)

AND

(Filtration

OR P-Capt

OR Leukotrap

OR pall

OR MacoPharma

OR Filter

OR affinity ligand resin

OR remove

OR removal

OR reduce

OR reduction)

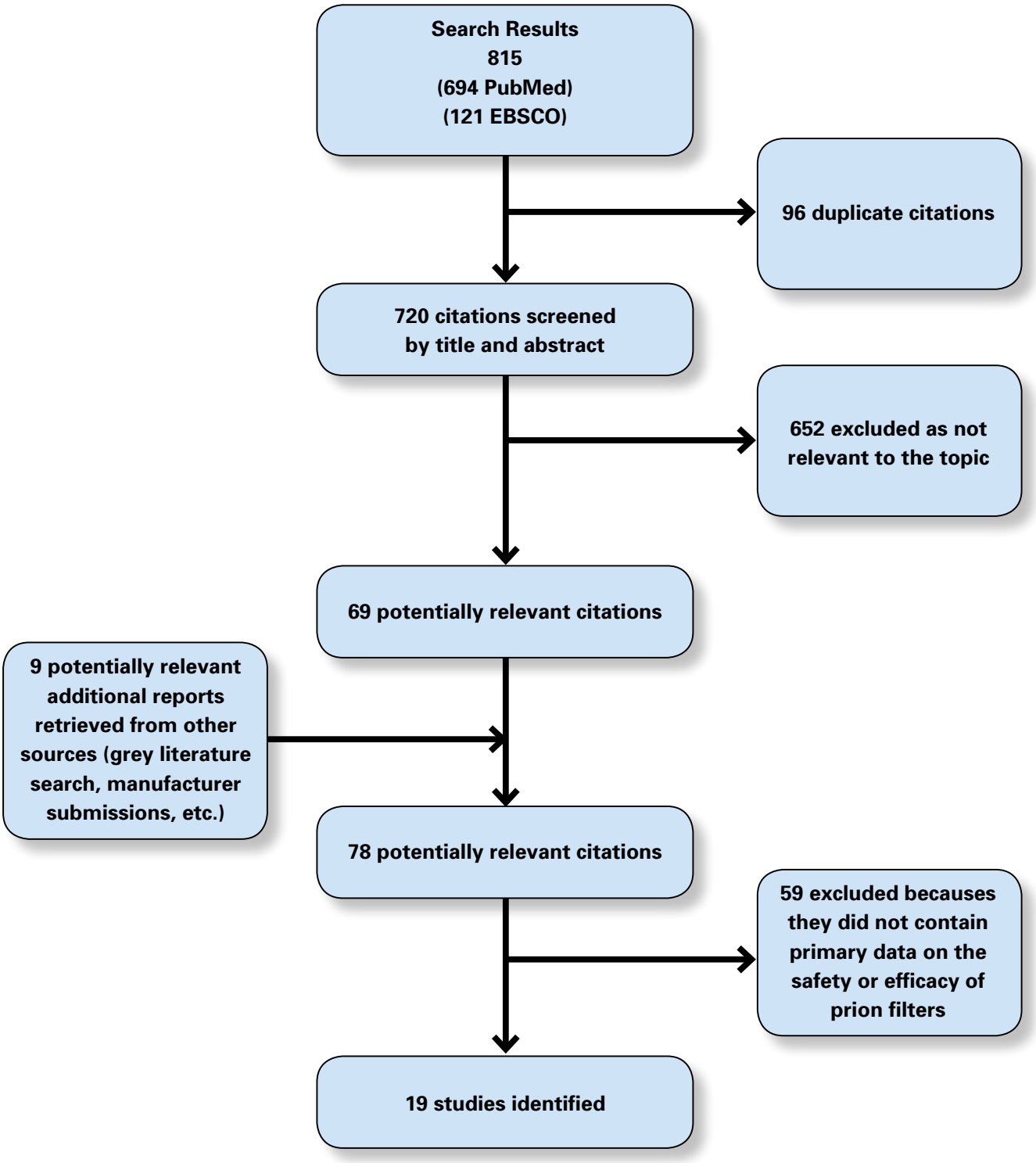
Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other sources, including:

- Google Scholar
- SIGLE
- WHO
- NHS Evidence
- IBTS
- Lenus
- AIeHL
- TRIP database
- Health Protection Surveillance Centre
- Health Protection Agency
- UKBTS
- BBTS Conference 2009
- Prion 2008 & 2009
- EDQM
- SEAC
- SaBTO.

Google and other internet search engines were used to search for additional information. These searches were supplemented by hand-searching the bibliographies and abstracts of key papers, and through contacts with appropriate experts and agencies.

A flowchart illustrating how the studies (reviewed as part of an evaluation of the safety and efficacy of prion filters) were located is included in Figure App2.3

Figure App2.3 Flow chart of included studies (efficacy and safety)



App 2.2 Search strategy for data on economic evaluation of prion-removing filters

The literature search described in App 2.1 was repeated adding a fourth concept – economics – to locate studies specific to the economic evaluation of prion-removing filters. The search terms for this additional concept were:

(Economics

OR Quality of life

OR Cost

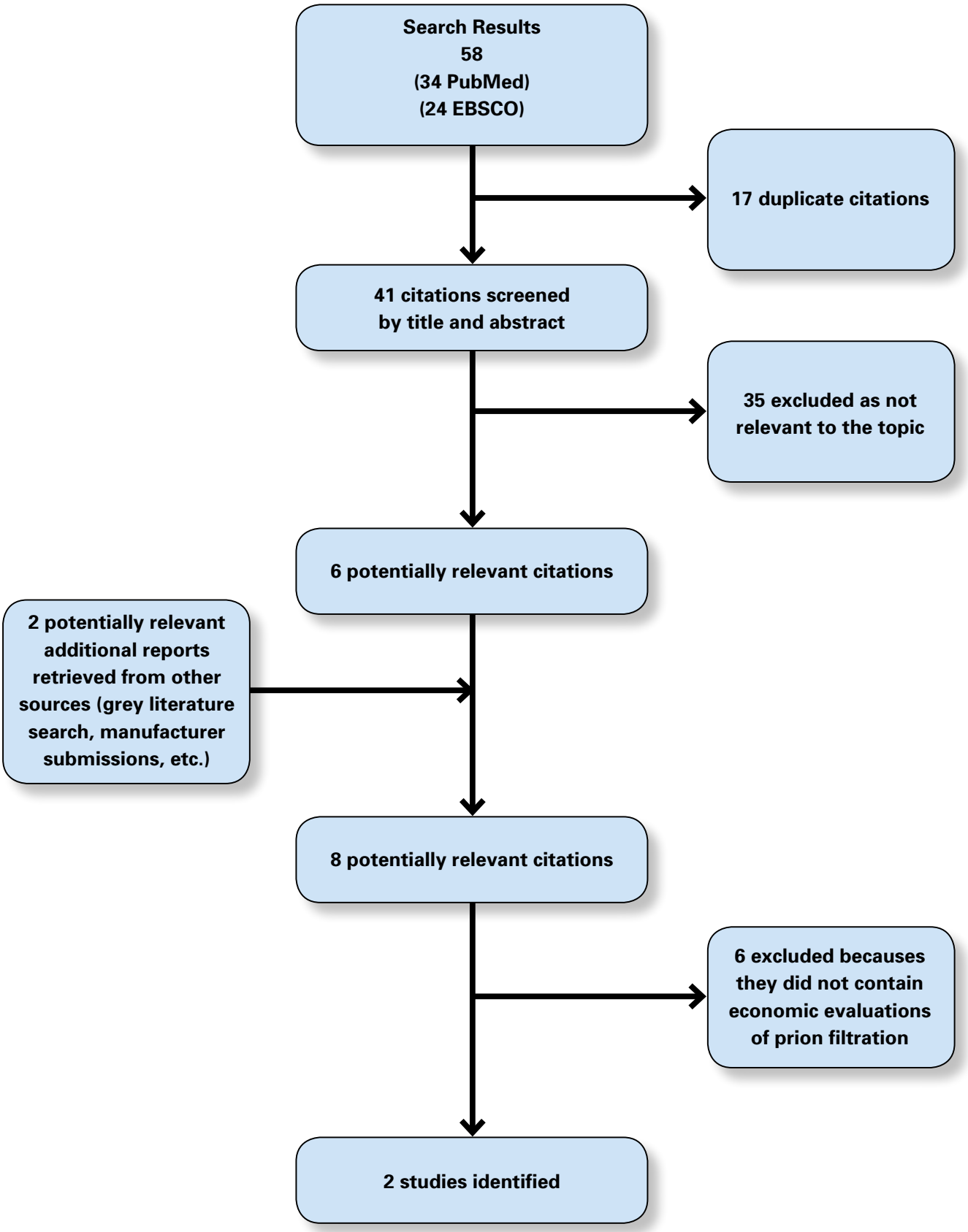
OR Cost analysis

OR Cost effectiveness

OR Economic Evaluation)

The results from the search of PubMed (Medline) and EBSCO (all other databases) are shown in Figure App2.4.

Figure App2.4 Flow chart of included studies (economic evaluation)



Appendix 3

Summary of cost-effectiveness literature on blood safety strategies

Table App3.1 - Summary of cost-effectiveness and budget impact assessments of prion filtration to reduce the risk of transfusion-related vCJD transmission

Authors (Peer reviewed Y/N)	Setting	Scenarios	Assumptions	Outcomes assessed	Annual discount rate	Summary Results	Comments
IBTS [18] (N)	Ireland 2009	Do nothing	- Price of screening test based on estimate from manufacturer. - Additional price per unit processed estimated at €80-100 or approximately €15 million pa (includes device and manufacturing requirements). - Prevalence: worst case assumption of 1 in 100,000 infectious donors in Ireland (1 infectious donation/year, 1.6 infectious donations being transfused). - 85% of donations go to >50 year olds with life expectancy of <10 years. - Incubation period for MM homozygotes (40% of population) >9 years. - Younger patients – up to 50 years gained per recipient per infection prevented, 10% of blood transfusions go to younger patients. Predicted to cost €3 million pa to filter younger patients. Predicted as 5–15% of universal value.	N/A	None specified	€0	Baseline scenario = no filtration, but includes donor questionnaire and LR. Currently, there is no viable screening test available.
		Screen all donations		BIA		€3 million pa	
		Universal prion filtration (P-Capt™ filter)		ICER		€9,375,000 prevents 1 infectious donation. >€10 million/LYG (>50 yrs). €4,800,000/LYG (<50 yrs)	
		Combination of testing and filtration		BIA		€3 million–€18 million pa	
		Filter all cells for children in 2009		BIA		€750k–€2.25m pa	

Table App3.1 continued - Summary of cost-effectiveness and budget impact assessments of prion filtration to reduce the risk of transfusion-related vCJD transmission

Authors (Peer reviewed Y/N)	Setting	Scenarios		Assumptions	Outcomes assessed	Annual discount rate	Summary Results	Comments
SaBTO [17] (N)	UK Ongoing	1. Universal Prion filtration of all red blood cells	Infectivity: High=10ID/ml, Low=1ID/ml. Prevalence: 1 in 4000, 1 in 20,000. Susceptibility (incubation period): MM homozygous =10yrs. Other=20 yrs	- The three scenarios were assessed for eight infectivity, prevalence and susceptibility combinations. - Estimate of benefits based on assessment of the 'currently' understood risk of vCJD transmission through RCCs or plasma included. - Age profile of RCC or plasma recipient population, and likely survival rates considered. For recipients surviving six years post transfusion episode, assumed survival rates reflect the average survival rates for their age group (i.e. no negative effect on life expectancy once they have survived six years post transfusion). - Cost includes costs of procurements, processing, storage and distribution of the intervention, which are expressed as a marginal unit cost for the intervention. - Opportunity costs included.	ICER	3% (costs) 1.5% (life years lost)	1. £3k-£856k/LYS	Baseline scenario = no filtration, but includes donor questionnaire and LR. This study is ongoing. The results presented here are preliminary are included for information purposes only.
		2. Prion filtration of RBCs for < 16s and haemoglobin-opathies					2. £8k-£1.02m/LYS	
		3. Prion filtration of red blood cells for < 16s					3. £5k-£839k/LYS	

BIA=Budget impact assessment; IBTS = Irish Blood Transfusion Service; ICER= Incremental cost-effectiveness ratio; LR = Leucoreduction; LYG = Life-year gained; LYS = Life-year saved; RCC = red cell concentrate; vCJD = variant Creutzfeldt-Jakob disease.

Table App3.2 Summary of published peer-reviewed cost-effectiveness and budget impact assessments of other blood safety strategies

Authors	Intervention	Setting / Year	Scenarios assessed	Outcomes assessed	Annual discount rate	Summary Results	Comments
Cleemput I et al. [126;127]	LR of WB donations to prevent vCJD	Belgium 2004	Universal LR	BIA	N/A	€11.95m pa	Healthcare system perspective.
			Selective LR*			€4.25m pa	
Canadian Coordinating Office for HTA[128]	LR of platelets and RBCs donations to prevent vCJD	Canada 1998	100% pre-storage filtration	BIA	N/A	€46.37m (Canadian $)	Baseline scenario = no filtration. For multi-transfused patients, post-storage LR is predicted as cost saving. Healthcare system perspective.
			100% post-storage filtration in blood bank			$29.95m	
			100% pre-storage filtration at bedside			$20.2m	
Jackson BR et al. [24]	NAT for HIV, HCV, and HBV in WB donations	US 2003	NAT for HIV, HCV Minipool (MP)	ICER	3%	$5.8m/QALY (4.7-7.0)	Baseline scenario = testing protocol required by the FDA before licensure of MP-NAT for HIV & HCV (includes detection of antibodies to HIV, HBV, HCV, HBsAg AHIV p-24 antigen. Societal perspective.
			NAT for HIV, HCV Single donation (SD)			$8.4m/QALY (7.6-9.2)	
			MPNAT for HIV, HCV (no HIV p24 antigen)			$7.6m/QALY (5.7-10.6)	
			SDNAT for HIV, HCV (no HIV p24 antigen)			$9.1m/QALY (7.8-11.2)	
			NAT for HIV, HCV, HBV MP			$4.3m/QALY (2.7-5.8)	
			NAT for HIV, HCV, HBV SD			$7.3m/QALY (6.2-8.4)	
			NAT for HIV, HCV, HBV MP (no HIV p24 antigen)			$6.1m/QALY (3.8-9.5)	
			NAT for HIV, HCV, HBV SD (no HIV p24 antigen)			$7.3m/QALY (5.5-9.9)	
						Net cost = $155m to $558m.	

Table App3.2 continued - Summary of published peer-reviewed cost-effectiveness and budget impact assessments of other blood safety strategies

Authors	Intervention	Setting / Year	Scenarios assessed		Outcomes assessed	Annual discount rate	Summary Results	Comments
Marshall DA et al. [26]	CE of NAT for HBV, HCV & HIV	US 2004	Base case	SS	ICER	3%	-	Baseline scenario = SS which includes HIV p24 antigen, HBsAg, anti-HIV-1, anti-HIV-2, anti-HCV, anti-HBc. Healthcare system perspective.
				SS + MP NAT – p24			$1.5m/ QALY	
				SS + MP NAT			Dominated by SS + MP NAT – p24	
				SS + SD NAT – p24			$7.3m/QALY	
							-	
			Secondary analysis	SS			$1.5m/QALY	
				SS + MP NAT – p24				
				SS + MP NAT			Dominated by next less expensive strategy	
				SS + SD NAT – p24/anti HBc			$5.0m/QALY	
				SS + SD NAT – p24/HBsAg			$1422m/QALY	
				SS + SD NAT – p24			Dominated by next less expensive strategy	

Table App3.2 continued - Summary of published peer-reviewed cost-effectiveness and budget impact assessments of other blood safety strategies

Authors	Intervention	Setting / Year	Scenarios assessed	Outcomes assessed	Annual discount rate	Summary Results	Comments
Korves CT et al.[93]	CE of blood screening strategies for WNV	US 2006	NAT MP of 16 samples followed by testing the samples in a reactive pool by ID NAT	ICER	3%	In areas with high rates of natural WNV transmission, seasonal screening of individual samples and blood for immunocompromised patients is cost saving. ICERS > $1.7 million/ QALY for seasonal screening for all transfusion recipients.	Baseline scenario = screening using a donor questionnaire. Societal perspective.
			NAT MP of 6 samples followed by individual testing of samples in a reactive pool by ID NAT				
			NAT of individual samples by ID NAT				
			Individual NAT on blood donations designated for immunocompromised patients				
			Seasonal targeting for above criteria				
Pereira A [27]	CE of HBV testing for post-transfusion Hep B	EU 2003	Enhanced sensitivity HBsAg assay versus current HBsAg assay	ICER	3%	€0.70m/QALY (0.13-1.664)	Post-transfusion Hep B is HBV transmission due to blood from donors in the HBsAG-negative window period of early infection or from chronic carriers with low levels of HBsAg or mutant forms of HBV not detected by current HBsAg assays. Healthcare system perspective.
			SD HBV NAT versus current HBsAg assay			€5.1m/QALY (1.7-11.6)	
			SD HBV NAT versus enhanced sensitivity HBsAg assay			€47m/QALY (14-113)	

Table App3.2 continued - Summary of published peer-reviewed cost-effectiveness and budget impact assessments of other blood safety strategies

Authors	Intervention	Setting / Year	Scenarios assessed	Outcomes assessed	Annual discount rate	Summary Results	Comments
Borkent-Raven BA et al. [23]	Estimate the ICER of HBV MP-6-NAT and SD Nat versus triplex MP-24-NAT	Netherlands 2009	Triplex MP-6-NAT versus triplex MP-24-NAT	ICER	Future costs = 4%, life-years = 1.5%.	€303,218/QALY (233,001-408,388)	Baseline scenario = sensitive test for HBsAg, triplex MP-24-NAT. The ICER strongly correlates with the age of the transfusion recipient. Societal perspective
			Triplex SD NAT versus triplex MP-24-NAT			€518,995/QALY (399,359-699,120)	
Etchason J et al. [94]	CE of preoperative autologous blood donations	U.S. 1995	Autologous blood donations	ICER	5%	Range from $235,000 to over $23m	Baseline scenario = collection and transfusion of allogeneic unit Societal perspective

BIA = Budget impact assessment; CE = Cost effectiveness; CEA = Cost effectiveness analysis; HBsAg =Hep B surface antigen; HBV – Hepatitis B virus; HCV – Hepatitis C virus; ICER – Incremental cost-effectiveness analysis; LR= Leucoreduction; MP = Mini-pool; QALY – Quality-adjusted life year; SS = Serology screening; SD = Single donor; WNV = West Nile Virus; WB = Whole blood.

Appendix 4

Parameters used in the transmission model

This appendix outlines the key parameters used in the transmission model and how the parameter estimates were derived. Details of the model are provided in Appendix 5

App 4.1 Prevalence of vCJD in the Irish donor population

The prevalence of pre-clinical vCJD in the donor population is a key parameter as it determines the likely number of infected donors entering the donor pool each year and dictates the probable number of infected blood donations over the time horizon of the cost-effectiveness study.

The only study of Irish prevalence was based on a predictive model of clinical cases of vCJD using a combination of Irish and UK data.[36] Two models were presented that estimated there would be 1 (95% CI: 0-15) and 2 (95% CI: 0-46) future cases, respectively. The estimate was restricted to MM-homozygous cases. Since the publication of that study there have been three clinical cases – this figure is well within the bounds for both estimates.

Two prevalence studies in the UK have been reported to date [7;51] and are described in more detail in section 3.5. In a study of appendices, the estimated prevalence of vCJD was 3 in 12,674.[7] In the second study, the prevalence in a study of tonsil tissue was 0 in 85,000. However, additional immunohistochemistry testing on a sub-group of 9,160 from these 85,000 samples found a single positive follicle sample.[52;129] It is likely that the rate of accumulation of prion proteins differs between appendix and tonsil tissues. With the limited data available, it appears that accumulation may occur earlier in the appendix.[51] It is presumed that an individual with vCJD is infective even at the earliest stages of prion protein accumulation. Hence, the results of the appendix study are taken as a more realistic prevalence estimate. The prevalence estimate is also based on the assumption that all positive samples are detected. False-negatives could arise in infected people, for example early in the incubation period before accumulation of abnormal prion protein has occurred. Without any evidence on the false-negative rate, it was assumed that all cases of subclinical vCJD were detected in the Hilton study.

As there are no data on the prevalence of sub-clinical vCJD in Ireland, it is necessary to adapt the UK data to the Irish context. The relative difference in prevalence between Ireland and the UK should be reflected in the relative difference in observed clinical cases of vCJD. A total of four clinical cases of vCJD have been recorded in the Republic of Ireland. However, as noted in section 3.3, two of the cases are thought to have originated in the UK as those individuals resided there for long periods. People who have spent one year or more in total in the UK between 1 January 1980 and 31 December 1996 are ineligible to donate blood in Ireland; two of the four Irish cases would therefore have been ineligible to donate blood. The effectiveness of donor deferral policies in reducing the risk of infected individuals donating blood is open to question. Individuals who do not meet eligibility criteria may mistakenly fail to identify themselves. Individuals who resided in the UK for less than 12 months can

legitimately donate and may be at an increased risk of having subclinical vCJD. It was assumed that there is a homogeneous risk of vCJD infection across the donor population and that the impact of non-eligible individuals donating is negligible.

It is pragmatic to define the Irish prevalence of observed vCJD as two in a population of 4,470,700.[130] As two of the Irish cases are assumed to be UK residents, the UK prevalence of observed vCJD is 176 in a population of 62,008,048.[131] This serves as a crude estimate as we do not take into account the rolling population over the time span of recorded cases and we do not adjust the denominator for the persons ineligible to donate blood. In both cases it would not be feasible to estimate the correct population and the impact on the results would be small. Thus, the relative prevalence of clinical vCJD in Ireland can be computed as:

$$\frac{2/4{,}470{,}700}{176/62{,}008{,}048} = 0.158$$

Multiplying estimated UK prevalence of pre-clinical vCJD by the relative prevalence of clinical vCJD in Ireland gives a prevalence of 37 (95% CI 8-109) per million (i.e. 149 total cases) of pre-clinical vCJD in the indigenous Irish population. This prevalence is well in excess of previous predictions, although it should be noted that this figure includes both MM and non-MM individuals.[36] Whether or not individuals with sub-clinical vCJD go on to develop clinical vCJD is governed by susceptibility (see section App 4.4). It is presumed that the prevalence figure represents the current total number of cases of pre-clinical and sub-clinical vCJD in Ireland that are eligible to donate blood. Individuals acquiring vCJD through blood transfusion cannot enter the donor pool as transfusion recipients are excluded from donating blood. The proportion of the national population with pre-clinical vCJD is sampled from a beta distribution and then converted into a population figure using the binomial distribution.

Parameter	Distribution	Median (95% range)
Prevalence of pre-clinical vCJD	Beta	149* (33 - 406)

** The point estimate quoted is a median and hence differs from the mean which would be computed as 37 x 4.4707 = 165 cases nationally.*

App 4.2 Rate of blood donation

Although most donors donate a single unit of blood in a given year, it is possible to donate every three months. Exceptions are made for some rare blood types, so that a small number of donors can donate more than four times per year; this group accounts for less than 0.03% of donors.[28] If a donor with pre-clinical vCJD donates multiple times in one year, then multiple patients will be exposed to the risk of vCJD infection. The rate of donation for each donor is sampled from the observed donation rates in 2009. A proportion of donors return each year and tend to donate frequently, while others donate only once or twice in their lifetime. A worst case scenario may occur if one or more people infected with vCJD were so-called 'super-donors' – people who donate three or four times a year over a number of years. At the start of each simulation, infected individuals are classed as potential (i.e. they have not donated in the past, but they will in the future), new (i.e. donating for the first time), continuing

(i.e. have donated before) or non-donors (i.e. will never donate). There is a 75% chance of someone being a non-donor. People can transition from potential to new (1.1% chance), new to continuing (29%), new to non-donors (71%), and continuing to non-donors (8%). This approach to modelling donations allows for the possibility of 'super-donors'.

Of the 155,082 units of blood donated in 2009, 142,459 units were issued and fewer than 140,000 were ultimately transfused as red cells into patients.[28] Processed units may be discarded for failing to meet specifications or due to adverse analytical findings. Wastage and outdating mean that not all issued units will be transfused into patients. The difference between processed and transfused units represents a 10% chance that an infected unit of RCC will not be transfused into a patient. The properties of prion-removing filters are such that they reduce the haemoglobin content of blood. Introduction of prion filtration will almost certainly result in larger numbers of units failing to meet specifications for haemoglobin content, although the impact should be acceptably low. A reduction in useable units may be compensated for by increased donation. Thus, the net impact of changed processing may be negligible in terms of exposure to infected units of RCC.

Parameter	Distribution	Median (95% range)
Donations per infected donor (per annum)	Sampled	1 (1 – 4)
Percentage of collected units used (%)	Beta	89 (86 - 92)

App 4.3 Infectivity of blood

The level of vCJD infectivity in blood is a measure of the number of infectious doses contained per millilitre of blood. As there are no data available on infectivity in human blood, estimates of infectivity have been sourced from animal studies, typically involving scrapie in hamsters. Extrapolation to vCJD in humans introduces additional uncertainty, but at present the animal studies provide the best level of evidence.

The Spongiform Encephalopathy Advisory Committee (SEAC) reports that the levels of infectivity in animal studies vary from 1 to 300ID/ml with a large unpublished study using hamster scrapie that suggests a mean infectivity of 10ID/ml with a range of 2 to 24ID/ml.[55] The measured level of infectivity is dependent on whether animals are infected using intracranial (IC) or intravenous (IV) inoculation. Infectivity is frequently measured using IC inoculation with the efficiency of IV inoculation estimated to be between 10% and 100% of the IC method. Thus, the method of inoculation affects the subsequent infectivity estimates. A 2003 report by DNV Consultants for the UK Department of Health suggested use of a mean infectivity of 4ID/ml with a range of 0.1 to 30ID/ml for modelling purposes.[58] More recent attempts to model the observed cases of vCJD have led researchers to conclude that infectivity may be lower than previously thought, as an assumption of high infectivity results in overestimates of clinical vCJD cases.[37] For this study, a Gamma distribution with a wide range is used to encompass the uncertainty with a mean value of 9.9 (95% CI: 0.7 – 31.6) ID/ml. The mean infectivity is a high value and represents a conservative estimate that tends towards a worst case scenario. A Poisson dose-response model is used in line with the UK modelling strategy.[132] Under a Poisson dose-response model, the probability of infection is calculated as $[1-e^{-i}]$ where i is the expected number of infectious doses transfused given the amount of material to have come from an infected donor.

Infectivity may be a function of the disease stage of the donor. Humans are infectious in the pre-clinical phase, but it is unclear if the level of infectivity changes prior to the development of clinical disease.[133] It is possible that humans are not infectious during the first phase of pre-clinical infection, but in the absence of any clear data it is assumed that human blood is equally infectious throughout the pre-clinical phase.

The source of vCJD infectivity in blood is not well understood although it is believed that infectivity may be distributed equally between plasma and white blood cells. Reducing the plasma and white blood cell content in transfused blood should reduce risk of vCJD transmission. Currently there are two types of blood processing in use in the IBTS: top and bottom (TAB) and top and top (TAT). Units of blood processed using TAB have lower mean residual plasma volumes 9.3ml (SD 2.1ml) compared to TAT processed units which have 20.2ml (SD 3.3ml).[21] The ratio of units processed in the IBTS by TAB and TAT methods varies from year to year, although it is intended to move to 10,000 units per annum processed by TAB, with the balance by TAT. A subsequent processing step is the application of a leucoreduction filter which removes residual white blood cells. Animal models suggest that between 42% and 72% of vCJD infectivity can be removed by leucoreduction.[65;66] Universal leucoreduction was introduced by the IBTS in 1999 to mitigate the risk of vCJD transmission.[134]

Parameter	Distribution	Median (95% range)
Infectivity of vCJD infected blood (ID/ml)	Gamma	9.9 (0.7 – 31.6)
Percentage units processed by TAB (%)	-	7.0 (-)
Residual plasma (ml) - TAT	Normal	20.3 (13.6 – 26.2)
- TAB	Normal	9.2 (4.9 – 13.5)

App 4.4 Susceptibility and incubation

Susceptibility is a measure of the likelihood that the recipient of an infected unit of blood will develop clinical vCJD. To date, clinical vCJD has only been confirmed in individuals who are MM-homozygous at codon 129. It is possible that individuals who are not MM-homozygous may have a lower susceptibility and although they may be infected, they may never develop clinical vCJD. Alternatively, individuals who are not MM-homozygous may simply have a longer incubation time before developing clinical vCJD. Susceptibility may be related to age and it has been suggested that younger people are more susceptible to vCJD infection.[135] In the absence of comprehensive exposure data it is not possible to determine a plausible relationship between age and susceptibility.

In projecting the future number of vCJD cases in the UK, Clarke and Ghani showed that current (primary) clinical case numbers could be reconciled with prevalence estimates from the appendix study (see 3.5) with the assumption that development of clinical vCJD is confined to about 10% of MM homozygotes.[37] For this model, a 10% susceptibility was applied to all genotypes on the grounds that susceptibility in non-MM genotypes cannot be discounted. This susceptibility estimate implies that 15 of the 149 sub-clinical cases will eventually become clinical which may be seen as a likely overestimate. However, although 15 cases seems improbable, it is not impossible and is within the predictions of Harney et al..[36] As with the estimate of

infectivity, this represents a conservative estimate for susceptibility that is closer to a worst-case scenario.

Of the three UK cases of clinical vCJD with probable acquisition through blood transfusion, the incubation periods were 78, 94 and 102 months, respectively.[133] Assuming that these figures are representative of incubation periods for infection through blood transfusion in MM-homozygous individuals, a median incubation period of 7.6 (95% CI: 5.6 – 9.6) years can be assumed. In the absence of any data on the incubation period for non-MM homozygous individuals, the model uses a longer positively skewed distribution with a median of 21.2 (95% CI: 16.5 – 29.1) years.

We have adopted a low estimate of susceptibility coupled with a narrow range of possible values. This choice of susceptibility is coupled with the choice of incubation period for non-MM individuals. For the estimated cases of clinical vCJD to correspond to the observed numbers, a shorter incubation period must be matched with a lower susceptibility. Alternatively, a higher estimate of susceptibility could have been adopted, but would have to be offset by a longer incubation period; this would lead to similar estimates of future cases.

Parameter	Distribution	Median (95% range)
Susceptibility to acquiring vCJD (%)	Beta	10.0 (8.8 – 11.1)
Incubation (years) - MM homozygous	Normal	7.6 (5.6 – 9.6)
- non-MM homozygous	Beta	21.2 (16.5 – 29.1)

App 4.5 Filter efficacy

The ability of a prion-removing filter to successfully reduce the level of infectivity is a critical component of the transmission model. Exogenous studies have shown a 3 to 4 log reduction in infectivity after prion filtration.[73] The lower limit of efficacy has been predicted at a 1 log reduction for endogenous infectivity.[4] Independent validation of the efficacy of prion-removing filters has been undertaken by the UK Health Protection Agency (HPA). Although reporting lower efficacy than recorded by the filter manufacturers, a 0.3 to 2.1 mean log reduction was noted depending on the species, TSE strain and method of test preparation used.

The filter efficacy studies use blood samples in which the level of infectivity are orders of magnitude higher than might be found in a unit of blood drawn from a donor with sub-clinical vCJD.[81] Testing of filter efficacy has shown that 1 in 10,000 infectious particles are not retained by the filter.[73] In the transmission model, residual infectivity in leucoreduced RCC ranges from 13 to 661 ID/ml with a maximum of 1200 ID/ml. The data are strongly suggestive that prion filters remove sufficient infectivity with the proviso that 1 in 10,000 IDs will remain in prion filtered, leucoreduced units of RCC.

For the current study it was assumed that the number of infectious doses remaining in a prion filtered unit of RCC follows a beta distribution with a probability of 1/10,000.

Parameter	Distribution	Median (95% range)
Probability of infectious doses after prion filtration	Beta	0.00007 (0.000003 – 0.00037)

Filter failure has not been incorporated into the model. There were no cases of filter failure in the validation tests carried out by the IBTS. Although universal filtration would involve greater numbers of filters and hence a greater risk of one or more failures, it is assumed that the IBTS will have sufficient monitoring in place to detect failures and take appropriate action.

App 4.6 Life years gained

The context in which an individual receives a transfusion of RCC generally entails a greatly reduced survival. Poor survival is primarily due to transfusions being given to patients who are already at an increased risk of death as a consequence of trauma, major operations or serious illness.[102] A Scandinavian study found that 53.4% of transfusion recipients were still alive five years following first transfusion, but only 27% were alive at 20 years.[102] The increased risk continues such that a higher mortality rate is still observed even 17 years post-transfusion. The mortality rate increases with the number of units transfused. Survival in paediatric patients tends to be much higher than in older patients.[136]

There are no Irish data available on survival post-transfusion. The EASTR study in the UK is in an early phase, but provides the source of six-year survival data post transfusion.[101] Given the broad similarities between Ireland and the UK in terms of clinical practice and individual life expectancy, this study uses the UK survival data as a proxy for Irish survival rates.

To estimate the life years saved by preventing a vCJD infection, the model first determines the life expectancy for the transfusion recipient using the Irish life tables.[137] An incubation period specific to the individual's genotype is also calculated using the distribution described previously. If the life expectancy is greater than the incubation period, then the life years saved is the difference between the life expectancy and incubation period. No adjustment is made for quality of life in the final year. In the absence of longer term survival data, it is presumed that if a patient survives to six years post-transfusion then they will achieve normal life expectancy. As life expectancy post-transfusion is compromised, even 20 years after transfusion the model generates a slight overestimate of life years gained.[102]

App 4.7 Discounting

For a cost-effectiveness analysis it is standard practice to compute the present value of future events using discounting. The further away into the future the event occurs, the lower the (discounted) present day value. In this study, standard discounting applies to life years gained and costs at a rate of 4% per annum.[96]

App 4.8 Recipient profile

To predict the probable number of transmitted infections and life years lost in the absence of prion filtration, it is necessary to predict the likely recipients of infected RCC units. The number of transfusion episodes varies by age and gender which entails different exposure by age and gender. The age-gender profile of RCC transfusion recipients was extracted from the Hospital In-Patient Enquiry (HIPE) system and averaged for the years 2006-2008.[99] HIPE data are collected for the public acute hospitals. Private hospitals also perform procedures requiring RCC transfusions and these are not contained in the HIPE data.

Less than 10% of RCC units go to hospitals that are not part of the HIPE system. It is therefore assumed that the HIPE data is broadly reflective of the national age-gender breakdown of transfusion episodes.

The number of transfusion recipients will be affected by changes in population, particularly given the ageing of the Irish population. Projections for the population from 2011 to 2021 were used to estimate changes in the demand for transfusions.[98] Projections are published for a range of migration and fertility scenarios. For this study, we have opted for the M0F1 scenario as the projected population for 2011 most closely resembles the estimated current population. The M0F1 scenario assumes zero net migration and current fertility pattern. The population projections show an increasing number of over 50s in the coming 10 years. As the over 50s are the highest users of blood products, demand for blood is expected to increase by 30% over the 10-year study horizon. The actual number of recipients in any given year is not computed as we assume that each infected unit of RCC will go to a different recipient. Given the anticipated small number of infected units of RCC this is a reasonable assumption.

Exposure is also related to the number of units of RCC received. There is international evidence that the average number of units transfused varies by age.[138] An analysis of transfusion data from St James's Hospital, Dublin, and the Coombe Women & Infants University Hospital, Dublin, suggested that for adults, any relationship between units transfused and age was minor and the variation was insufficient to warrant modelling differential exposure.[139] Furthermore, the increased exposure must be counterbalanced with the fact that receiving more units of RCC is related to poorer survival. In the absence of more comprehensive data it was decided not to weight recipient exposure by the number of units transfused.

There are some circumstances in which a patient could potentially receive multiple infected units of RCC. In the event of an infected donor making multiple donations in one year, the probability of more than one donated unit going to the same individual are negligible unless the donor and recipient are of a rare blood type. The probability increases for recipients of frequent transfusions. Similarly, a patient could receive donations from two different infected donors. A patient receiving multiple units of infected RCC will be at increased risk of acquiring vCJD. For the current model we assume that each infected unit goes to a different recipient which, given the high infectivity of vCJD, corresponds to a worst case scenario.

As the model distinguishes between MM and non-MM homozygous transfusion recipients, it is necessary to characterise patients by genotype. A European study has estimated the proportion of population that is MM-homozygous to be approximately 39%.[140] The proportion of the population that is MM-homozygous is modelled using a beta distribution and allocated to simulated patients using a binomial distribution.

Parameter	Distribution	Median (95% range)
Proportion population MM-homozygous	Beta	39.2 (34.4 – 44.0)

Appendix 5

Model details

The cost-effectiveness model was developed to simulate the likelihood of RCC recipients developing vCJD as a result of being transfused with blood donated by individuals infected with vCJD.

An outline of the cost-effectiveness model is shown in Figure App5.1. The model parameters are input at the outset. These parameters include: population data; age-sex distribution of transfusion episodes; distribution parameters for the key variables; life expectancy data by age and sex; and base-case cost information. At the start of each simulation a national prevalence is estimated; the donor status of infected individuals is allocated; and the national susceptibility to vCJD is calculated. Within each simulation, the model steps through 10 years to predict:

- the number of infected donations
- infectivity post-processing
- number of infected units transfused
- age-sex profile, genotype, post-transfusion survival and susceptibility of recipients
- number of life years gained as a result of prion filtering
- cost of prion filtration.

Discounting is applied to the results from each year and the results are then aggregated to generate a simulation-level result. The median, 2.5th percentile and 97.5th percentile are computed from all simulations for each outcome. These values represent the point estimate, lower and upper bounds, respectively, for each outcome.

The model was run for 100,000 simulations. Three outcome measures (recipients infected, life years gained and cost) were assessed to determine how many simulations were required for the model to converge on a stable result (see Figures App 5.2, App5.3 and App5.4). In all cases, the median, upper and lower bounds all converged within 10,000 simulations.

Figure App5.1 Transmission model

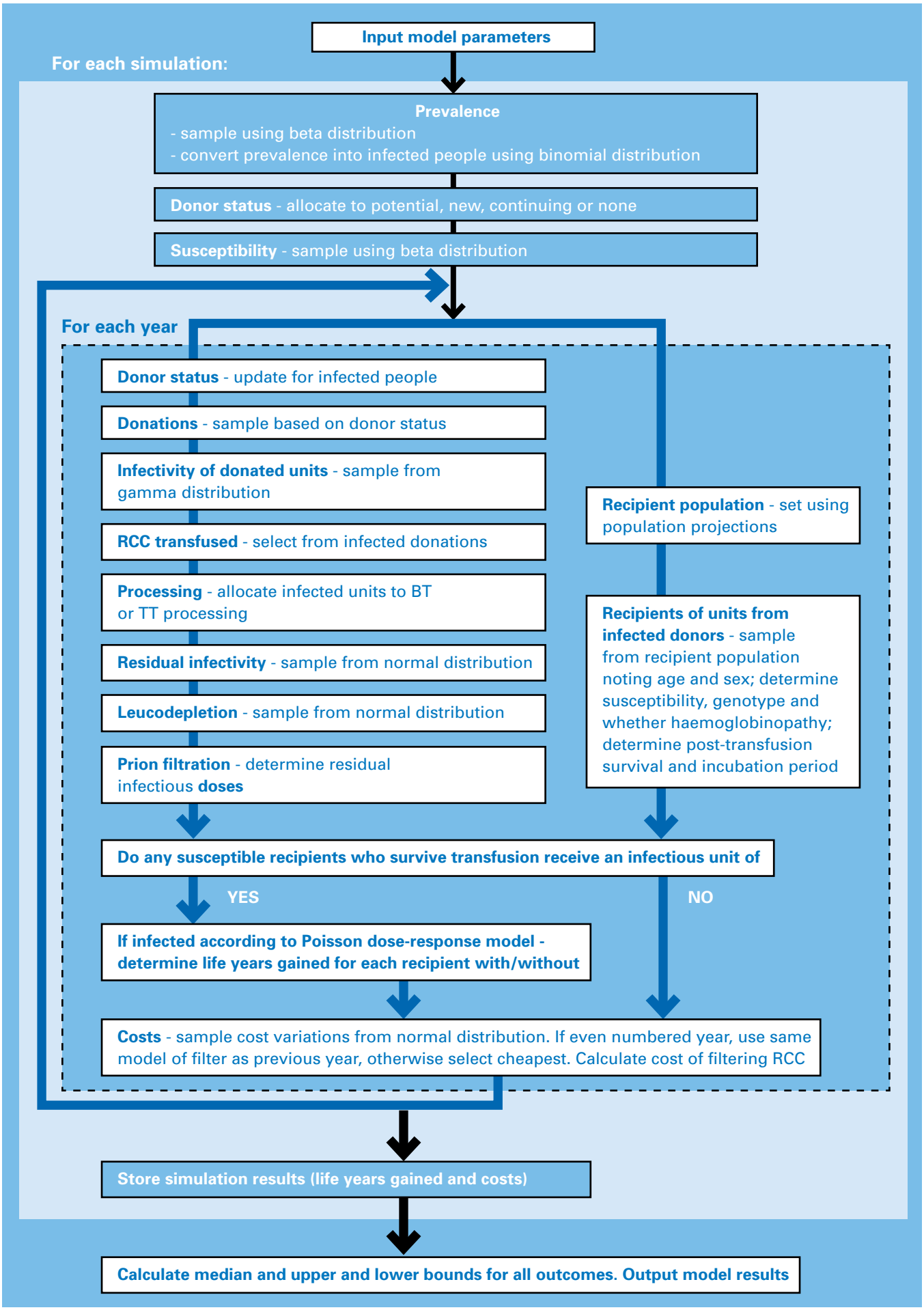


Figure App5.2 Estimate of infected recipients against simulation number

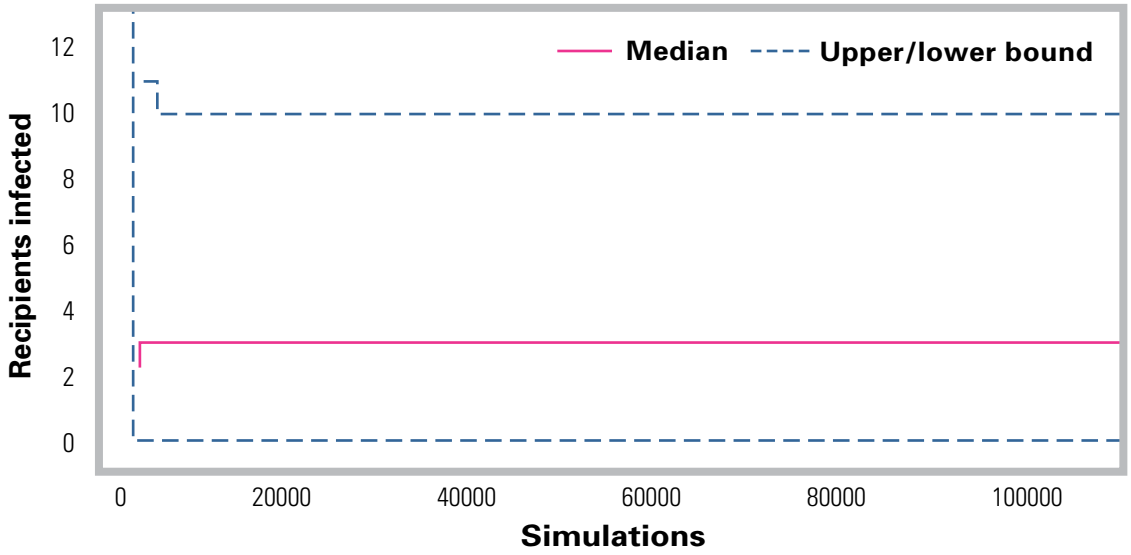


Figure App5.3 Estimate of life years gained against simulation number

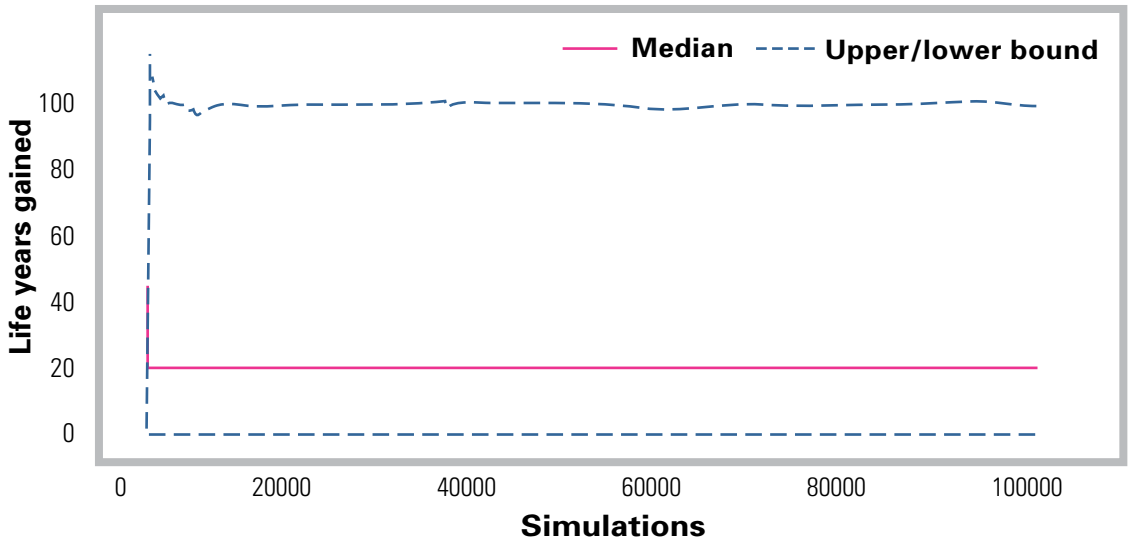
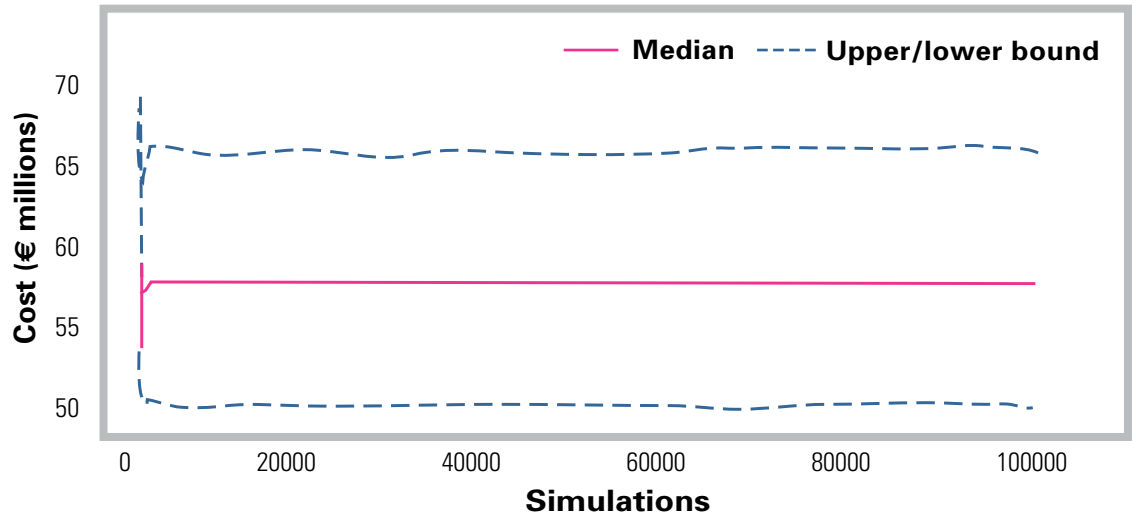


Figure App5.4 Estimate of cost against simulation number



Appendix 6

Cost estimates

App 6.1 Methodology

Set-up, recurring and one-off costs related to the introduction of prion filtration of RCC were identified based on discussions with the IBTS and a review of the process diagrams submitted by the manufacturers of the two prion filters. The costs inputs for the cost-effectiveness model relate to the incremental cost of prion filtration, that is, added costs over and above the current operational costs. Cost savings related to the reduced consumption of existing resources are included as appropriate. Costs considered in estimating the marginal unit cost for the intervention included the cost of procurement, processing, storage and distribution of prion-filtered RCC. Costs were provided by the IBTS, the Department of Health and Children and the manufacturers of the two prion filters.

Consistent with national guidelines, VAT was not applied to costs for the cost-effectiveness analysis. VAT at the relevant rate was applied when assessing the budget impact of introducing prion filtration.[95;96] The perspective adopted was that of the publicly-funded health and social care system. Consistent with this, only direct costs to the IBTS and HSE were included in the analysis.

App 6.2 Assumptions

The costs of filters and consumables are allowed to vary by ±20% from the base case value each year. The distribution of costs for each item is assumed to centre on the base case value and follow a beta distribution ($\alpha = 2$, $\beta = 2$). The price of a number of consumables was quoted in sterling. The exchange rate is assumed to be £1 sterling = €1.1446. Variation in the exchange rate is assumed to follow a normal distribution (mean = 0.982, standard deviation = 0.065) around the previous years' exchange rate. The mean and variation in exchange rate is based on an analysis of exchange rates at the mid-point of each of the last 10 years.[141]

Based on discussions with the IBTS, two-year supply contracts are expected to apply to the purchasing of prion-removing filters. For the cost-effectiveness model, the cost of filters only changes every second year while all consumables vary from year to year. Every two years, at the point of filter costs changing, it is assumed that the IBTS will select from the two filter models based on lowest price. For the BIA, the costs of adopting each brand of filter are modelled separately.

App 6.3 Recurring costs

When calculating the cost of introducing prion filtration, it is the number of units processed that must be considered rather than the number of units transfused. Due to the need for timely processing, testing occurs concurrently with processing. As some bags fail testing or fail to meet product specifications, not all processed bags are distributed for transfusion, also for those distributed, not all will be transfused due

to outdating and wastage. Hence, the number processed is higher than the number transfused. In 2009, approximately 147,000 units of RCC were processed by the IBTS.

Prion filtration is applied to leucodepleted units of RCC. As documented in section 5.4, prion filtration has been associated with a reduction in the haemoglobin content of filtered RCC units. A new specification of 35g haemoglobin per unit has been recommended by the IBTS for prion-filtered RCC. It was assumed in the model that this lower specification would be approved by the Competent Authority (the Irish Medicines Board) for use as a process control measure and that no additional cost adjustments would be required to compensate for the limited number of units that would fail to meet this standard. However, the reduction in haemoglobin content per unit may have clinical consequences for transfusion-dependent patients with a percentage of these patients requiring additional units of RCC annually. Consistent with the UK, it was assumed that this would equate to an increase of 0.5% in the number of units required nationally per annum (e.g., 735 units in 2009).

App 6.4 Prion-removing filters

Two models of prion-removing filter were considered in this assessment: the MacoPharma P-Capt™ filter and the PRF2BE filter system. The cost of these filters is based on prices quoted by the manufacturers as part of a dossier submission to the Evaluation Team in August 2010. For both models, the unit price varies by the annual volume purchased. A discounted 'early adopter' price was quoted for the PRF2BE filter system to be invoiced as free of charge products pro-rated to the list price for the appropriate volume band stated in the price list. This would apply for the first year regardless of volume; this discounted rate was included in the estimate of the costs for year-1 for this filter. For the P-Capt™ filter a reduced price would apply if both Ireland and the UK implemented a process of universal prion filtration. This discounted rate was not applied as the UK has yet to announce a decision regarding adoption of universal prion filtration.

Adoption of the PRF2BE filter system by the IBTS would be contingent on independent efficacy studies. To date no such studies have been published and it is assumed that such a study would take three to fours years to complete. It is therefore assumed that the PRF2BE filter system could be adopted in four to five years' time under the assumption that it will be shown to be equivalent to the P-Capt™ filter. Due to this lag it is also assumed that the early adopter price will no longer apply.

The filter prices were applied to the estimated volume of units to be filtered to calculate the annual cost of purchasing the filters. The unit price varies by volume purchased which introduces anomalies due to economies of scale. Over-ordering can reduce the unit cost. For example, if 147,000 units are required it may be cheaper to order 150,000 due to the incremental reduction in price per unit. For this analysis, if over-ordering reduces the price then it is presumed that over-ordering will be applied and to calculate the unit price the total price is divided by the units required (i.e., the additional filters are treated as unusable).

As prices for the system filter were quoted in pounds sterling the current exchange rate (1.14) was applied to convert the price into euro. Although quoted in pounds sterling, this price was quoted specifically for the Irish market. Therefore, we

need only account for potential differences in the currency exchange rates with no adjustment required for the difference in purchasing power between the UK and Ireland.

App 6.5 Processing of RCC

The two prion filter models have different process configurations with differing implications for consumables required. The processing steps and product generated for the two prion filters and for the current situation (no prion filtration) are outlined in Table App6.1. Donated whole blood is currently processed using one of two standard blood processing methods (top and top [TAT] and top and bottom [TAB]) to separate the blood into its constituent parts (RCC, plasma, buffy-coat [platelets]). Different collection bags, both incorporating leucoreduction filters, are used to collect the donated blood for these two processes. The relative proportion of these processes differs from year to year. In estimating cost savings, its was assumed that the IBTS will move as intended to 10,000 units per annum processed by TAB with the balance processed by TAT.

Table App6.1: Processing steps for the P-Capt™ and PRF2BE Filters

Current		P-Capt™		PRF2BE	
Donation		Donation		Donation	
Leucocyte reduction (Whole Blood)	Process to constituent parts (TAB)	Leucocyte reduction (Whole Blood)	Process to constituent parts (TAB)	Process to constituent parts (TAT)	Process to constituent parts (TAB)
Process to constituent parts	Leucocyte reduction (RCC)	Process to constituent parts	Leucocyte reduction (RCC)	Leucocyte reduction and prion filtration	Leucocyte reduction and prion filtration
		Prion filtration (RCC)	Prion Filtration (RCC)		
Issue	Issue	Issue	Issue	Issue	Issue
LR Plasma, LR RCC	Plasma, Buffy-coat, LR RCC	LD Plasma, PF/ LR RCC	Plasma, Buffy-coat, PF /LR RCC	Plasma, PF/ LR RCC	Plasma, Buffy-coat, PF/ LR RCC

TAB – Top and bottom; TAT – Top and top; LR – Leucoreduced; RCC – Red cell concentrate; PF/LR – Prion filtered, leucoreduced

App 6.6 Additional consumables

As illustrated in Table App6.1, the two prion filter models have different process configurations, with differing implications for consumables required. A common consumable is the Factor IX assay, which is used as a process control measure to indicate filter exposure. It is assumed that 1% of prion filtered units will be selected for testing using Factor IX assays. The cost of the factor IX assay was only available for the UK market (£4.81 exclusive of VAT). This was converted for the Irish market using the latest (July 2010) purchasing power parity index of 129. It was necessary to transfer the UK price as no cost was available from Ireland. This purchasing power

parity index takes account of both the currency exchange rate as well and the different purchasing power of the countries.

Use of the P-Capt™ filter represents an additional process step. No existing step is replaced. Use of this filter would necessitate use of an additional sterile connector device (wafer) to connect the P-Capt™ filter bag and would result in added costs for the IBTS associated with disposal of the additional waste generated. The following additional consumables (all costs provided by the IBTS) will be needed if the P-Capt™ filter is to be implemented:

- Wafers, (a sterile connector) 1 required for each unit of blood, €462.45 per box of 140 inclusive of VAT.
- Waste bins with 22L capacity which equates to approximately 40 bags, cost €5.70, inclusive of VAT. It was assumed that 18 bins per day for 210 annual processing days would be required.
- Incineration charges €2,240 per ton exclusive of VAT, a waste bin of 40 bags weighs approximately 4.6Kg.

The PRF2BE filter system is a combined filter incorporating both a leucoreduction filter and a prion-removing filter. Donated blood must first be collected in a classic 3-bag collection system (no leucoreduction filter). A unit cost of €6.95, exclusive of VAT was quoted by Pall for this bag (TAT or TAB). Use of this collection bag eliminates the need for the current four-bag collection systems (incorporating a leucoreduction filter) for donated blood – this is represented as a cost saving. The current contracted cost to the IBTS for the current four-bag systems were provided to the Evaluation Team inclusive of VAT (€11.95 and €10.59 for the TAB and TAT bag systems, respectively). The estimated costs of these bags, ex-VAT are therefore €9.88 and €8.75, respectively. The relative proportion of these processes differs from year to year. In estimating cost savings, it was assumed that the IBTS will move as intended to 10,000 units per annum processed by TAB.

As with the P-Capt™ filter, a sterile connector will be required to connect the collection bag to the PRF2BE filter system. The additional consumables required to implement this system (costs per the IBTS) is then:

- Wafers, (a sterile connector) 1 required for each unit of blood, €462.45 per box of 140 inclusive of VAT.

It was assumed that no additional waste would be generated by use of the PRF2BE filter system.

The PRF2BE filter system is intended for leucoreduction and prion filtration of RCC. If universal prion filtration is introduced, this standard process would mean that no leucoreduced plasma (for issue as fresh, frozen plasma) would be generated. In 2009, a total of 447 units of frozen plasma were issued for which an additional TAT processing step would be required. Following collection and processing to its constituent parts, a further processing step will be required to generate leucoreduced plasma. Additional consumables in addition to the PRF2BE filter system for each processed unit associated with this step are then:

- Wafers, (a sterile connector) 1 required for each unit of blood, €462.45 per box of 140 inclusive of VAT.
- Leucoreduction filter (€9.87 exclusive of VAT).

As noted, prion filtration has been associated with a reduction in the haemoglobin content of filtered RCC units. This may have clinical consequences for transfusion-dependent patients with a percentage of these patients requiring additional units of RCC annually. Consistent with the UK, it was assumed that this would equate to an increase of 0.5% in the number of units required nationally per annum (e.g. 735 units in 2009). In addition to the additional cost of prion filtering this unit (counted as part of the volume of units processed), the extra cost of these units (currently €248.71 based on the charge to the HSE) to the healthcare system must be accounted for.

App 6.7 Additional staff requirements

The additional staff costs for prion filtration arise when connecting the filter to the leucoreduced RCC bag, hanging the units for filtration and affixing a unit identification number. Sterile docking of a new bag system is a significant step in the blood production process, necessitating multiple quality control checks. If universal prion filtration were introduced, the IBTS estimated that three additional laboratory assistants and one additional senior medical scientist would be required to handle the ensuing production and quality control work. The IBTS pay scale (January 2010) for a laboratory assistant was €28,651 to €34,514 and has a total of 7 increments. The consolidated salary scales available from the Department of Health and Children for public-sector employees were used to calculate pay-related costs for the senior medical scientist. The additional cost of new staff was calculated and adjusted for pay-related costs in accordance with national guidelines, that is, standard PRSI contributions of 10.75%, imputed IBTS pension costs at 17% and general IBTS overheads at 30% of salary were applied.[96]

If prion filtration is selectively implemented for limited sub-groups of the population, the additional salary related costs for the laboratory assistant would be prorated based on the assumption that three laboratory assistants would take six hours to process 520 units. It was assumed that no other additional pay costs would be required.

App 6.8 One-off costs

The PRF2BE filter system has not been validated for use by the IBTS. Introduction of the system would therefore incur validation costs prior to its routine adoption. The validation process involves applying the PRF2BE filter system to 1,000 units of blood. It is presumed that the filters for this validation run will be provided free of charge by the manufacturer. Each filtered unit will have to be tested by Factor IX assay. It is assumed that 100 units will be wasted as part of this validation process, so the opportunity cost at the standard unit price of RCC (€248.71) for these units is included in the calculation.

No additional one-off or capital investments related to the introduction of prion filtration were identified by the IBTS.

Appendix 7

Specialist paediatric red cell products

This appendix describes a number of specialist red cell products provided by the IBTS for the paediatric population and the use of RCC by paediatric patients with haemoglobinopathies in Our Lady's Children's Hospital, Crumlin, Dublin.

App 7.1 Red cell products used by the paediatric population

A number of specialist products are prepared by the IBTS specifically for use in intrauterine transfusions and the neonatal population. A breakdown of the number of such units used in Irish paediatric and maternity hospitals in 2009, together with the number of standard issue RCC that were used in dedicated paediatric hospitals is shown in Table App7.1

Table App7.1 Use of red cell products by the paediatric population (2009)

Product type	Units used
Leucodepleted RC in AS (standard adult unit)	2,258 *
Leucodepleted RC in AS for neonatal use for first 5 days	1,625
Leucodepleted RC in AS (pedipacks)	1,272
Plasma reduced RC (neonatal use)	725
Leucoreduced RC for intrauterine transfusion	30
Leucodepleted whole blood for neonatal use	1
Total	**5,911 ***

Abbreviations: RC- red cells; AS-additive solution.

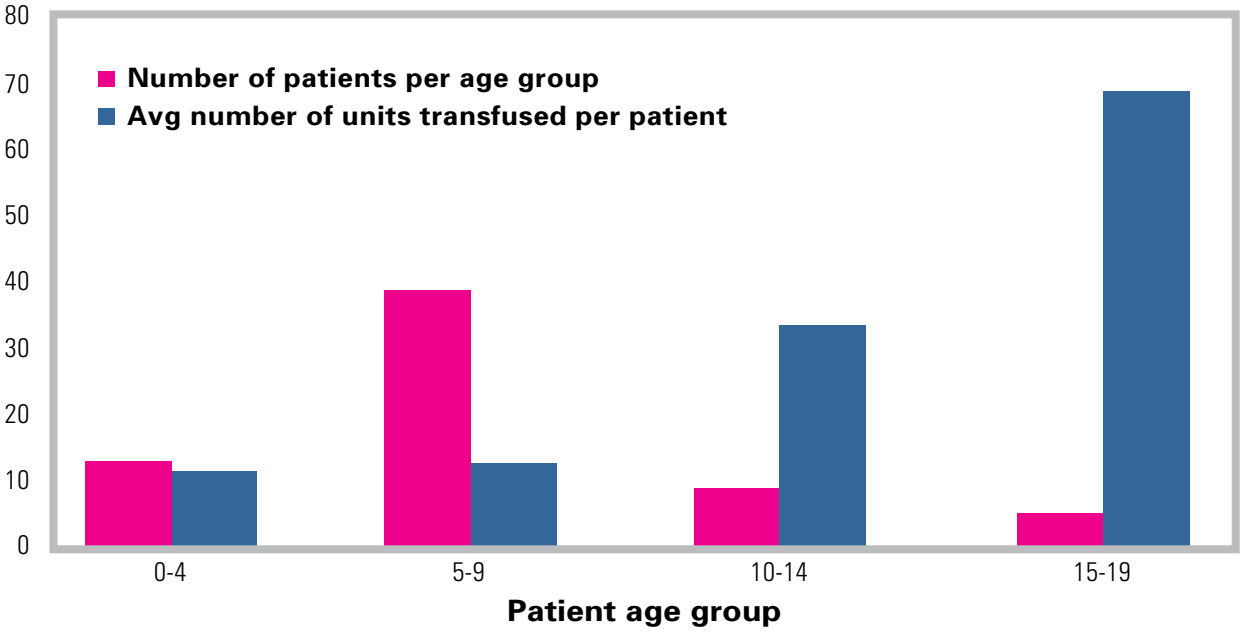
**Count of leucodepleted RC in AS (standard adult unit) is limited to two of the three dedicated paediatric hospitals in Dublin (Our Lady's Children's Hospital, Crumlin and Temple Street Children's University Hospital) and so underestimates use of this product by children treated in general hospitals and leads to an underestimate in the total use of red cell products by the paediatric population. Patients treated in paediatric hospitals may be up to 19 years of age.*

From a logistics perspective, a recommendation to limit the supply of prion-filtered product for those aged less than one year of age would be easy to implement as the products used in this cohort are clearly defined and limited in number. Extending prion-filtered RCC to those less than 16 years of age would represent a greater logistical challenge as older children are transfused with standard issue leucoreduced RCC. Identification of this cohort is more difficult, particularly as many may be transfused in general hospitals.

App 7.2 Use of red cell concentrates by paediatric patients with haemoglobinopathies

Between 400 and 500 paediatric patients with haemoglobinopathies (sickle cell disease) up to 19 years of age are managed at Our Lady's Children's Hospital, Crumlin. Of these, between 40 and 50 are maintained on regular transfusions at three-weekly intervals. In 2009, 65 patients with haemoglobinopathies were transfused a total of 1,228 units of RCC (Figure App7.1). Dosing is weight dependent, so that on average the number of units transfused increases with patient age. The average annual number of units transfused ranged from 11(0-4 years) to 67(15-19 years) units. Individual requirements are highly variable with one patient maintained on exchange transfusions receiving a total of 133 units.[103]

Figure App7.1 Units of red cell concentrate transfused in haemoglobinopathy patients by age



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