Prion reduction filters for red cell concentrates

1. Background

In October 2009, SaBTO recommended that:

> Filtration of red cells be implemented, for those not exposed to BSE through diet (ie those born after 1996). The option to remove this measure should be exercised in the event of (i) further data on prevalence or (ii) filters proven to not be efficacious when used widely; and that this recommendation will be kept under review as further data emerges on prevalence, infectivity and susceptibility and the efficacy of the filters."

The recommendation to implement was dependent on the satisfactory completion of the PRISM A study on the safety of [redacted] filter. The PRISM report was presented to SaBTO in March 2012, and the Committee accepted the conclusion that there were no adverse effects due to the prion filtration of the red cells.

However, since SaBTO's 2009 review, additional work had been undertaken to address the mis-match between the predicted number of cases of transfusion-transmitted vCJD and the number of clinical cases actually seen. The revised risk assessment model, developed by the Department of Health (DH) Health Protection Analytical Team, is based on new evidence on both the prevalence of infection and the infectivity of blood, and on the susceptibility of individuals to infection, and has been endorsed by the Advisory Committee on Dangerous Pathogens TSE[1] Risk Assessment Sub Group. This model formed part of SaBTO's review of the importation of fresh frozen plasma (FFP) in March 2012. The data on prevalence was to be further informed by the outcome of an appendix study which was then still ongoing.

In addition, at the time of SaBTO's March 2012 meeting, preliminary results on filter efficacy were available from two endogenous infectivity studies being conducted on behalf of the UK Blood Services.

2. Current data on vCJD prevalence and filter efficacy

a) Appendix study

The HPA has completed and published the results from the study of the prevalence of abnormal prion protein in stored appendix tissue. This was performed by analysis of 32,441 UK appendix samples collected since 2000 during surgery on patients born between 1941 and 1985. Of these, 16

[1] TSE: transmissible spongiform encephalopathy

samples were judged to be "positive", which indicates a central prevalence estimate very close to 1 in 2,000 in this age cohort (95% Confidence Interval approximately 1 in 1,1250 to 1 in 3,500).

These results are not significantly different from previous studies, and are within (but at the upper limit of) the estimations used in the latest modelling on transmission risk by blood components. An updated paper on the cost effectiveness of [redacted] filter, using this risk assessment model, may be found at Annex A. The version of this paper that was reviewed by SaBTO in March 2012 incorporated the updated evidence on infectivity and susceptibility, with a relatively wide range of prevalence estimates. The annexed update of the cost effectiveness paper takes into account the latest data on prevalence, and uses a narrower range.

(A position statement by the Advisory Committee on Dangerous Pathogens TSE Risk Assessment Subgroup on the occurrence of vCJD and prevalence of infection in the UK population is published at:
https://www.wp.dh.gov.uk/transparency/files/2012/08/ACDP-statement-vCJD-occurrence-and-prevalence-Jul-2012.pdf)

Further proposed appendix studies of vCJD prevalence are being considered as follows:

a) to examine appendices removed pre-1980, to establish whether the prevalence of prion protein seen in the population study was also present in the pre-BSE era; and

b) to examine appendices from those born after 1 January 1996, in order to validate the assumption that this cohort is unexposed to BSE. The results of this study will be important to the ongoing feasibility studies on supply of a low risk blood supply from "Club 96" donors.

The UK Blood Services Prion Working Group (PWG) and the Advisory Committee on Dangerous Pathogens have expressed their support for these proposed studies, which are currently subject to consideration by the DH Research & Development Directorate. Each study would take up to three years to complete.

b) Hamster study

In this study, the efficacy of filtration in removing TSE infectivity was tested in hamsters. The research will be published in detail in a peer reviewed journal in due course.

c) Sheep study

The BSE sheep study being conducted at Roslin Institute is not due to finish until 2014. This research will be published in detail in a peer reviewed journal in due course.

3. Effectiveness and cost effectiveness

The DH Health Protection Analytical Team has supplied a revised version of the paper presented to SaBTO in March 2012 (see Annex A). Given the results of the latest HPA appendix study, the paper now focuses on the 'high prevalence' scenarios for the calculation of cost effectiveness. It should be noted that the cost effectiveness calculations in this paper are based upon a filter that is 100% effective.

The modelling used data on post-transfusion survival derived from the EASTR[2] study. The data used were from the original five-year follow up work, and the 10-year follow up data will become available in Spring 2013. The SaBTO Prion Sub Group considered whether these additional data would make a significant difference to the assessment of cost effectiveness. The new data are likely to show reduced post transfusion survival time (due to causes unrelated to vCJD), decreasing the potential gain from using the filter, and therefore reducing the calculated cost-effectiveness of the filter.

4. Alternative filters

PWG are aware of two other manufacturers that are (or have been) developing prion reduction filters.

5. Review and recommendation

The SaBTO Prion Sub Group met on 23 November to review the latest evidence as summarised above, and to prepare advice to SaBTO.

NOTE: Some material has been redacted from this paper and annex for legal reasons. SaBTO may be in a position to publish this at a later date.

[2] Epidemiology and Survival of Transfusion Recipients

Annex A

PRION FILTRATION OF RED BLOOD CELLS: EFFECTIVENESS AND COST-EFFECTIVENESS

PREFACE

In 2009, SaBTO recommended the implementation of prion filtration of red blood cells for patients born after 1 January 1996, subject to satisfactory results of clinical trials. The cost-effective calculations at that time were based on combinations of high and low estimates of the prevalence of infection with vCJD, the infectivity of blood, and the susceptibility of individuals to infection.

In March 2012, the Health Protection Analytical Team in the Department of Health submitted a paper reviewing the potential cost-effectiveness of prion filtration of red blood cells. This paper reflected subsequent research which led to a significant reduction in the assumed infectivity of red blood cells. Also when that analysis was produced, interim results from the Health Protection Agency (HPA)-led appendix survey had identified 7 positive samples in roughly 22,000 tested.

The Risk Assessment model, which has been endorsed by the Advisory Committee on Dangerous Pathogens (ACDP) Transmissible Spongiform Encephalopathy (TSE) Risk Assessment Subgroup, takes 30,000 sets of values within reasonable ranges for vCJD prevalence, infectivity and susceptibility to clinical disease, and estimates the number of clinical vCJD cases that could result from future red cell transfusion. To maintain consistency with what has been seen so far, the analysis removes scenarios in which more than 9 such clinical cases would have appeared before 2011[3], and uses the remaining combinations to provide a range for the number of cases that could be prevented by stopping future red blood cell-borne transmissions.

The cost-effectiveness calculations considered three scenarios for the number of cases and life-years that might be saved by an effective prion reduction filter. The lower and middle scenarios were based on the interim results of the appendix survey, whereas the "high" scenario was based on a hypothetical result of the survey finding 15 positive samples.

Since then, the appendix survey has been completed, and 16 positive samples have been found from a total of approximately 32,000. This is clearly very close to the previously-hypothetical result of 15 in 30,000. The following paper therefore re-works the previous analysis so that all scenarios are based on this prevalence.

[3] This compares with the 3 cases actually detected. We adopt this precautionary approach to allow for cases having been missed, and/or under-ascertainment of blood-borne linkage (eg due to infected donors remaining asymptomatic).

Introduction

The Spongiform Encephalopathy Advisory Committee (SEAC – dissolved in March 2010) and SaBTO have considered prion filtration on a number of occasions, in the context of different assumptions about the underlying risk of vCJD infection through transfusion of blood components. This note reviews the requirements of a prion filter outlined by the two committees. It then assesses the cost-effectiveness of this intervention under different scenarios, and for different groups of recipients. All calculations use cost estimates as provided. They suggest that none of these interventions meets the standard cost-effectiveness threshold of £25,000 per Quality-Adjusted Life-Year (QALY) gained, for any group and in any scenario. Finally, we set out estimates for the maximum cost at which each intervention *would* meet such a criterion.

Background: existing effectiveness criteria

The extant SEAC working assumptions predicted that at least a 3 log (1000x) reduction in the infectivity of blood (in addition to that achieved by leucodepletion alone) could be needed to provide substantial clinical benefit in terms of preventing transmission of vCJD. This reflected the understanding that an infected unit might contain a large number of infectious doses, so that a large reduction would be needed to reduce the chance of transmission. SEAC also stressed that in order to validate manufacturers' claims, it is important that these should be reproducible by independent experimentation.

As tests are carried out on animals, the extent to which the results will apply to human blood transfusion is not clear. It is therefore desirable that reductions of this scale should be demonstrated using more than one experimental model to give a greater confidence that there will be clinical benefit for human transfusion.

In practice, reductions of the order of 3 logs could only be demonstrated experimentally using blood "spiked" with infectivity, providing starting levels much higher than would be expected in normal transfusion of red blood cells. However, such experiments show that a filter has the capacity to remove endogenous infectivity, not necessarily that it will bind it. It is therefore also essential to show that any filter will also reduce endogenous infectivity in blood, even though a large reduction could not be demonstrated and quantified.

As well as showing demonstrable efficacy in removal of infectivity, it is important that the filtration process does not significantly reduce the therapeutic benefits of the transfusion. SaBTO's recommendation[4] that those who have not been exposed to BSE through diet should receive red blood cells that have undergone prion filtration was accordingly subject to satisfactory results from the PRISM A safety study.

[4] SaBTO 8 (27 October 2009)

To illustrate cost effectiveness this paper presents calculations for 100%, 75%, 50% and 25% filter efficacy.

Revised assumptions on infectivity and future vCJD cases

The ACDP Subgroup has reconsidered both the underlying assumptions and the results of vCJD transmission models. The Subgroup endorsed revised assumptions on the likely levels of infectivity in human blood, primarily based on analysis by Gregori *et al*[5]. This suggests levels of infectivity substantially lower than had previously been assumed, of the order of 1 Infectious Dose per unit of red cells prior to leucodepletion. (Leucodepletion is likely to reduce infectivity, but it remains uncertain by how much.) The requirement for a 3 log reduction has not formally been re-evaluated, but appears more stringent than would be required by this latest understanding. With lower starting levels, even a 1 log reduction could reduce transmission risks by ~ 90%, depending on the dose-response.

The Health Protection Analytical Team in DH has developed a revised set of scenarios for the potential future number of blood-borne vCJD cases (and the number that might yet be prevented by stopping new transmissions), taking account of this recent evidence and the continued absence of new clinical cases attributable to transfusion. The resulting scenarios are still precautionary, but can be reconciled with the number of cases seen to date. The underlying methodology, and the resulting scenarios, were considered by the ACDP Subgroup at its meetings of 14th July 2011, 10th January 2012 and 25 May 2012. They were endorsed as providing the best available way of assessing the benefit of further interventions, given current evidence. Specific figures for future cases are subject to revision in the light of further data on post-transfusion survival, but were considered to be of the right order. As well as providing new estimates for future cases (and infections), these new scenarios have substantially different properties to those previously used, with most of those infected developing symptoms only after prolonged incubation periods, if at all.

Quantifying benefits of stopping new transmissions

The Risk Assessment model for Red Cell transfusion provides an estimated range for the number of potential vCJD clinical cases that would result from transmissions taking place after 2012[6] (and which would therefore be potentially preventable):[7]

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[5] Gregori L Yang H and Anderson S (2011): Estimation of variant Creutzfeldt-Jacob disease infectivity titers in human blood. *Transfusion* 2011 Jan 3, doi: 10.1111/j.1537-2995.2011.03199.x

[6] The model is not updated for 2012. The estimated number of cases is from the end of 2011 onwards. The plan is to update the calibration year when 10 year survival become available from EASTR study.

[7] These are taken from the majority of model runs having susceptibility to clinical disease of about 50%, and long IPs for almost all those susceptible.

Table 1: Estimated number of vCJD clinical cases resulting from potential red cell concentrate-borne transmissions after 2012

	Preventable cases		
	Lower bound	Central estimate	Upper bound
Cases	30	180	500

These "preventable" cases would be spread over several decades, with incidence peaking at about 7 (for the central estimate) in around 2040-2050.

We estimate that each of these cases would, on average, cause the loss of 18[8] symptom-free life-years, resulting in a range of 540 to 9000 life-years lost in total, with a central estimate of 3240. As an approximation, we have regarded these as equivalent to QALYs for the purpose of cost-effectiveness calculations, though in general the loss of QALYs will be less (due to individuals being in less-than-perfect health for other reasons). We assume that the quality of life is zero once clinical symptoms of vCJD emerge, and that there will be no cure or effective treatment that will benefit these cases.

This calculation is subject to a number of caveats. Most obviously, these life-years would only be saved if the intervention is 100% effective in preventing new transmissions. Furthermore, the number of life-years saved per case is highly dependent on the assumed survival rates following transfusion. For the purpose of the model, we have divided recipients into ten-year cohorts and considered males and females separately. We have projected the available EASTR data (which extends to 6 years post-transfusion) to predict the survival rates, assuming that the survival rate will be the same as the average of years 4 to 6 after transfusion until normal survival by age becomes a limiting factor[9]. Further survival data from the EASTR study, which now extends to 10 years post-transfusion, should be available during 2013. Even so, long-term survival will remain subject to significant uncertainty. Nevertheless, the estimate of 18 life-years per case should represent (if anything) an over-estimate.

These life-years would be in the future and so, for cost-benefit purposes, need to be converted to 2012 terms. This process has two stages. First, the number of years saved following the clinical onset need to be converted to the terms of the time of onset of symptoms, and then a further allowance also needs to be made to bring these years saved back to a 2012 equivalent figure.

Using a discount factor of 1.5% - as standard for health benefits - we estimate that we need to divide the number of cases by a factor of 1.6 to bring them to 2012 terms, and then each prevented case will save 14 symptom-free

[8] The life-years figures in this paper only relate to direct cases. Onward transmission through surgery may add approximately an extra 15% to the life-year estimates.
[9] We have done this by applying actuarial survival rates for the general population to the proportion surviving the 6 years for which EASTR data are available, and using this figure once it becomes lower than the straight line projection.

life years (discounted). These potential vCJD cases could lead to the following total number of life-years lost, discounted to 2012 equivalent:

Table 2: Estimated number of vCJD symptom-free life-years lost resulting from potential red cell concentrate-borne transmissions after 2012

	Scenario for preventable cases		
	Lower bound	Central estimate	Upper bound
Discounted symptom-free Life years	263	1575	4375

Cost-effectiveness of specific filtration options

The cost-effectiveness of any intervention will depend markedly on the recipients "targeted". Those who would otherwise have good life-expectancy will be more likely to become clinical cases if infected, *and* suffer a greater loss of life-years if they do develop clinical vCJD. The following tables start with the group for whom the prion filtration would be most cost-effective, and then consider the marginal cost-effectiveness of extending it to others.

Children

From the Risk Assessment model, we estimate that about 11.5% of future cases would relate to children. Given the typical incubation periods from the model, preventing these would provide a benefit of approximately 40 life-years per clinical case (or 28 years, discounted). These give the following range of estimates for the total number of discounted life-years associated with these cases:

Table 3: Estimated number of vCJD symptom-free life-years lost resulting from potential red cell concentrate-borne transmissions to children after 2012

	Scenario for preventable cases		
Recipients: children	Lower bound	Central estimate	Upper bound
Discounted symptom-free life years	60	362	1006

We estimate that about 68,500[10] filtered units per annum would have to be transfused for about 20 years to achieve these benefits, at a cost of [redacted][11] per unit (roughly [redacted] per year). The standard cost-effectiveness

[10] This and subsequent numbers of units do not allow for the possible need to import extra units as a result of loss of haemoglobin during the prion filtration process.
[11] Costs of prion filtration provided by NHSBT, February 2010. These costs include both the price of the filter and the cost of extra processing by NHSBT.

methodology discounts costs at a higher rate than benefits, at 3.5% per annum; this gives a discounted cost of just over [redacted].

Table 4: Cost per vCJD symptom-free life-year resulting from potential red cell-concentrate borne transmissions to children after 2012 saved by prion filtration[12] with different degrees of prion filter effectiveness.

		Scenario for preventable cases		
Recipients: children		Lower bound	Central estimate	Upper bound
Cost per life-year	100% effectiveness	[redacted]	[redacted]	[redacted]
	75% effectiveness	[redacted]	[redacted]	[redacted]
	50% effectiveness	[redacted]	[redacted]	[redacted]
	25% effectiveness	[redacted]	[redacted]	[redacted]

As can be seen, the cost per life-year saved falls well above the threshold of £25,000, even for children, and even in the most "generous" scenario for the number of cases prevented.

Adult Sickle Cell and Thalassaemia patients

If we extend the previous policy to include these groups of often highly transfused patients, we estimate that - again assuming filtration to be 100% effective - this would save 1.9% of the remaining cases, with an average of 16 life-years per case (13.7 discounted life-years). This gives the following number of life-years saved:

Table 5: Estimated number of vCJD symptom-free life-years lost resulting from potential red cell concentrate- borne transmissions to adult sickle-cell and thalassaemia patients after 2012

	Scenario for preventable cases		
Recipients: sickle cell / thalassaemia	Lower bound	Central estimate	Upper bound
Symptom-free life years	4	26	72

We estimate that this would involve an extra 39,500 units being filtered per year, though the combined unit cost would be reduced to [redacted]. The resulting extra cost over 20 years, again after 3.5% discount, is around [redacted]. This would result in the following costs per symptom-free life year:

[12] The filtration is assumed to be 100% effective. The figures will increase with a decrease of the effectiveness of prion filtration.

Table 6: Cost per vCJD symptom-free life-year resulting from potential red cell concentrate-borne transmissions to adult sickle cell and thalassaemia patients after 2012 saved by prion filtration

		Scenario for preventable cases		
Recipients: sickle cell / thalassaemia		Lower bound	Central estimate	Upper bound
Cost per life-year	100% effectiveness	[redacted]	[redacted]	[redacted]
	75% effectiveness	[redacted]	[redacted]	[redacted]
	50% effectiveness	[redacted]	[redacted]	[redacted]
	25% effectiveness	[redacted]	[redacted]	[redacted]

As can be seen, the cost per life-year saved falls well above the threshold of £25,000, even for this group, and even in the most "generous" scenario for the number of cases prevented.

Universal filtration

If filtration were then extended to universal implementation, a further 2.03 million units would need to be filtered for 20 years. However, the overall unit cost would reduce substantially, to [redacted] per unit over 20 years. After applying the discount of 3.5%, this equates to an additional cost of [redacted]. Subtracting the number of life-years already saved under the previous options from the total results in the following calculations:

Table 7: Estimated number of vCJD symptom-free life-years lost resulting from potential red blood cell-borne transmissions to other adults after 2012, and cost per year saved by prion filtration

		Scenario for preventable cases		
Extension to all recipients		Lower bound	Central estimate	Upper bound
Total Life years		263	1575	4375
Remaining life years		198	1187	3297
Cost per remaining life year	100% effectiveness	[redacted]	[redacted]	[redacted]
	75% effectiveness	[redacted]	[redacted]	[redacted]
	50% effectiveness	[redacted]	[redacted]	[redacted]
	25% effectiveness	[redacted]	[redacted]	[redacted]

Interestingly, the large reduction in *unit* cost means that these figures are somewhat more favourable than for the sickle cell / thalassaemia patients, suggesting that if the measure was cost-effective for that group, it would be cost-effective for all recipients. However, the robustness of this conclusion would need further investigation of the relative survival rates. In any case,

either intervention would fall well outside the normal cost-effectiveness threshold, even in the "upper bound" scenario.

Cost-effectiveness thresholds for all interventions

So far, we have calculated the number of life-years saved by each intervention, and then estimated cost-effectiveness using the stated costs as provided. None of the potential interventions fell within the standard cost-effectiveness threshold of £25,000 per life-year saved. It is also informative to consider the "reverse" calculation, to ascertain the maximum total cost under which each intervention *would* meet the standard threshold, including both the price of a filter and any extra cost of processing the blood.

The table below presents these figures:

Table 8: Maximum Total Costs (£ per unit) meeting 'standard' cost-effectiveness threshold of £25000

Intervention: Prion Filtration		**Maximum cost per filter (£)**		
Effectiveness of Filtration	Recipient group covered	Lower bound	Central estimate	Upper bound
100%	Children	1.5	9.0	25.0
	Sickle cell / thalassaemia	0.2	0.6	1.8
	Extension to all	0.2	1.0	2.8
75%	Children	1.1	6.7	18.7
	Sickle cell / thalassaemia	0.1	0.5	1.3
	Extension to all	0.1	0.7	2.1
50%	Children	0.7	4.5	12.5
	Sickle cell / thalassaemia	0.1	0.3	0.9
	Extension to all	0.1	0.5	1.4
25%	Children	0.4	2.2	6.2

	Sickle cell / thalassaemia	0.05	0.2	0.4
	Extension to all	0.04	0.2	0.7

These figures only consider the cost-effectiveness as a vCJD risk reduction measure, and do not take into account other risks such as viral infection.

Non-exposed donors

The paper has considered the benefits of prion filtration to reduce the vCJD risk. As people born after 1 January 1996 become blood donors, they are assumed to present an alternative source of "safer" red blood cells as they are presumed not to have been exposed to dietary vCJD risk. However, it seems highly unlikely that we will be able to regard them as entirely risk-free. As well as the risk of transfusion-borne infection, and the (unproven) possibility of maternal vCJD infection, there is also the potential risk of transmission through neurosurgery and dentistry. These latter risks appear very difficult to eliminate, and would not be mitigated by measures such as donor deferral.

At present, there is no direct evidence on the differential in vCJD prevalence for this post-1996 birth cohort, and there will be a significant delay before any evidence becomes available. If the risk from this prospective group of donors is considered acceptable, this may constitute an alternative risk reduction measure once this group donates in sufficient quantities. Analysis of this possibility is under way, led by a working group of the UK Forum, but lies outside the scope of this paper. Such evidence is not expected for 3 to 4 years if a proposed specific prevalence study of this group is approved.

It is then possible that the risk reduction measures might be considered for implementation until this lower-risk cohort is able to meet demand. In this case, the cost-effectiveness for this shorter period of time would broadly be the same as for the 20 year period used in the calculations.

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November 2012