EFFECTIVENESS AND COST-EFFECTIVENESS OF APHERESIS AND ADDITIVE SOLUTION AS A VCJD RISK REDUCTION MEASURE IN THE PRODUCTION OF PLATELETS

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Note: some commercially confidential data have been withheld.

1. Summary

SaBTO has previously considered collection of platelets by single-donor apheresis as a vCJD[1] risk reduction measure, as each unit exposes patients to fewer donors than those produced by pooling four whole blood donations. SaBTO's predecessor committee, the Advisory Committee on the Microbiological Safety of Blood, Tissues and Organs for Transplantation, set a target of 80% of platelets to be produced by apheresis. In 2009 "SaBTO recommended that the UK Blood Services should move as far as possible towards 100% apheresis platelets, but that as a minimum, 80% of platelets should be collected by apheresis"[2] following a review of the feasibility of increasing the percentage further. All four UK Blood Services currently meet this requirement.

Since this recommendation, there have been developments in the understanding of vCJD which affect the assumptions that informed the previous recommendation, most notably concerning the infectivity of a whole blood donation and the prevalence of vCJD in the UK population. This note reviews the effectiveness of apheresis as a vCJD risk reduction measure, and considers the cost-effectiveness of maintaining the requirement for 80% of platelets to be collected in this way. It also considers the potential introduction of additive solution (for pooled platelets, or both pooled and apheresed) to replace the current production method of suspending platelets in donated plasma.

All cost-effectiveness calculations use cost estimates as provided by NHSBT and calculations of effectiveness set out in a recent paper to the TSE[3] Risk Assessment Subgroup of the Advisory Committee on Dangerous Pathogens (ACDP). The results suggest that maintaining the current requirement of 80% apheresis does not meet the standard cost-effectiveness threshold of £25,000 per Quality-Adjusted Life-Year (QALY) gained, and that in many scenarios use of additive solution would more than offset the increased risk of transmission caused by reducing the use of apheresis.

The paper focuses on vCJD risk. Annex A presents a paper by NHS Blood and Transplant (NHSBT) that considers the broader benefits and disbenefits of procuring platelets by apheresis and from pooling, and then the benefits and disbenefits of

[1] vCJD: Variant Creutzfeldt Jakob disease
[2] Minutes, SaBTO 7 (14 July 2009)
[3] TSE: transmissible spongiform encephalopathies

suspending platelets in plasma and in additive solution. This informs the safety framework at Annex B.

2. Background

To date, 177 cases of clinical vCJD have been identified in the UK. Of these, three have been related to blood transfusion. All three of these relate to a transfusion of non-leucodepleted red cells. While there have been no identified cases relating to the transfusion of platelets, there is still a recognised risk that transfusions could transmit vCJD, as suggested by animal models.

Information from the Transfusion Medicine Epidemiology Review (TMER) shows that there were three known vCJD cases who had donated platelets, all of whom had contributed to pooled platelet units. All four recipients of these units have died with interval from transfusion to death ranging from 2 to 9 years, and none developed vCJD. Also, two known clinical vCJD cases had received platelets. The first received 103 donor exposures in total from all components transfused over two transfusion episodes (25 of these from platelets) and had undergone a liver transplant. The second case received one unit of pooled platelets, as well as 22 units of red cells and 22 units of fresh frozen plasma (FFP). None of the platelet donors have gone on to develop vCJD, although the donor of one of the red cell units received by the second case did develop vCJD. Further detail on these cases is presented in Annex C.

In the calendar year 2012, the four UK Blood Services issued 311,737[4] units of platelets. As a result of SaBTO's recommendation, just over 80% were procured by apheresis, with donors attending specific apheresis centres across the country. The remainder were produced by pooling platelets collected from four normal whole blood donations, which can be collected either at centres or any other blood donation session. NHSBT currently have just under 12,000 active apheresis donors.[5]

At present, platelets are suspended in plasma from a platelet donor. In the case of apheresis, sufficient platelets and plasma are collected together while other blood components are returned. For a unit of pooled platelets, some plasma accompanies the platelets from each donor, with a further quantity being added from one of the four donors to enable proper suspension.

In some European countries, additive solution is used as an alternative method of suspension. If so, some plasma is still required for the platelets to be clinically effective, but the quantity is significantly reduced.

Table 1 shows some information from NHSBT's quality monitoring of platelet units, along with information on the plasma content in a unit.

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[4] Figure taken from the Annual SHOT Report 2012, available at http://www.shotuk.org/home/.
[5] NHSBT have 11,952 active apheresis donors on 22 August 2013 (Source: e-mail correspondence with NHSBT).

Table 1. Information on composition of a unit of platelets

	Volume mean (SD) mL/unit	Platelet yield mean (SD) x 109/unit	White Blood Cells mean (SD) x 106/unit	Plasma - current mean mL/unit[6]	Plasma – in additive sol[n] mean mL/unit[6]
Apheresis	198.8 (15.1)	292.2 (38.4)	0.41(13.79)	164 mL	85
Pooled	298.0 (25.5)	316.5 (44.6)	0.34 (0.3)	241	85
Specification	N/A	> 240	< 5		

(Data from NHSBT; plasma data provided May 2013; other data from quality monitoring April-June 2013)

3. Modelling future vCJD cases associated with transfusion

Since 2009, the ACDP TSE Risk Assessment Subgroup has reconsidered the underlying assumptions which informed these earlier decisions on apheresis. In particular, the Subgroup endorsed revised assumptions on the likely levels of vCJD infectivity in human blood, primarily based on analysis by Gregori *et al*[7]. This suggests a level of infectivity substantially lower than had previously been assumed. This reduction reduces the potential disbenefits of pooling. In the previous scenarios, a single infected contribution to a pooled unit would contain more than enough infectivity to infect the recipient with vCJD. Each unit pooled from four donations would thus carry four times the vCJD risk of one sourced from a single donor. For scenarios with lower infectivity per donation, this is no longer true. This can be illustrated by a simple example:

> Suppose an infected whole blood donation contains 3 Infectious Doses (IDs) associated with the plasma, with none attached to the platelets. For an apheresed unit in plasma suspension, using a Poisson dose-response model,

[6] Under the current production method for pooled platelets, 177mL of the plasma come from a single donor, and 21ml from each of the other three donors. If additive solution is used, there would be an equal amount of plasma from each donor (21mL). For apheresis platelets estimating plasma and anticoagulant volumes is more difficult, since the anticoagulant ratio used varies. The figures calculated are based on whole blood being anticoagulated at an average ratio of 1:10 (1/11) for Gambro. Assuming an average haematocrit of 0.45 (most donors are male), this equates to the percentage of plasma that is anticoagulant being 15% for Gambro. Data on platelets in PAS is estimated based on a 65% proportion of PAS as required for use in PI systems and estimated final volumes of component as this component is not yet produced routinely.

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

the amount of plasma in the unit would give a probability of 0.85 of transmitting the infection. For a pooled unit, the probability is 0.86 if the donation used to provide the plasma for suspension is infected, or 0.21 if one of the three other donations (which also contribute residual plasma) is infected. If there is no difference in the prevalence of infection amongst donors, the relative risk is then:

Apheresis: pooling risk ratio = 0.85 / (0.86 + 3 x 0.21) = 0.57

An apheresed unit would thus carry about 0.6 the vCJD risk of a pooled unit. Avoidance of pooling would retain an advantage, but this would be less than in the previous analysis, where the risk ratio was 0.25.

The Health Protection Analytical Team in the Department of Health has developed a revised set of scenarios for the future number of vCJD cases that might be associated with platelet transfusion - and the number that might yet be prevented by stopping new transmissions - taking account of this and other recent evidence[8]. The underlying methodology follows that for red blood cells and FFP previously endorsed by the ACDP TSE Risk Assessment Subgroup and published on the government website[9]. The Subgroup endorsed the adaptation of this methodology to cover platelet transfusions by correspondence in July/August 2013. The resulting scenarios are still precautionary, and may change as our understanding of the science develops, but can be reconciled with the number of cases seen to date. The risk assessment[10] covers a wide range of scenarios as regards both the level and distribution of blood-borne infectivity. In particular, the scenarios allow for the possibility of some infectivity being associated with platelets per se, rather than all risk being associated with the accompanying plasma.[11]

This change tends to increase the benefit of apheresis. Taking the previous example, if one of the 3 IDs in an infected donation were associated directly with platelets, an apheresed unit would carry half (rather than 0.6) the vCJD risk of a pooled unit.

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[8] In particular the prevalence of vCJD in the UK, as measured by a study led by the Health Protection Agency, in which samples of appendix tissue taken during surgery were tested for presence of abnormal prion protein (2012) See, http://www.hpa.org.uk/hpr/archives/2012/news3212.htm#bnrmlprn

[9] Bennett PG and Daraktchiev M (2013): vCJD and transfusion of blood components: an updated risk assessment. Health Protection Analytical Team, Dept of Health https://www.gov.uk/government/publications/vcjd-and-transfusion-of-blood-components-updated-risk-assessment

[10] "Modelling potential vCJD transmission via platelet transfusions" Health Protection Analytical Team, Department of Health, August, 2013.

[11] Advice from TSE Subgroup members on this point is taken to supersede earlier advice from SEAC that infectivity would be associated with plasma and leucocytes. It reflects in particular findings from ovine models of transmission, which do not show the risk of transmission to be dependent on the volume of plasma transfused.(See McCutcheon *et al*, 2011: All clinically-relevant blood components transmit prion disease following a single blood transfusion: A sheep model of vCJD http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0023169). However we received no specific advice as to how infectivity might be split between plasma and platelets.

Gregori *et al* suggest that the infectivity in a 500-mL unit of vCJD-infected blood should be of the order of only a few infectious doses, and some infectivity will be associated with the leucocytes. In view of the uncertainty about this figure, this paper focuses on scenarios where the total infectivity across platelets and plasma is 3 IDs, but our full range of scenarios allows the infectivity to vary between 1 and 6 IDs.

4. Effectiveness of continuing 80% apheresis

Initial scenarios in the risk assessment assume that a leucodepleted whole blood donation would potentially contain 3 Infectious Doses. We use this to indicate the total infectivity associated with the plasma and platelets, while allowing the infectivity specifically associated with the platelets to vary between 0 and 1 ID. This range allows the transmission in an apheresis unit to become almost certain, and enables us to consider options where apheresis appears a more effective vCJD risk reduction measure than additive solution and vice versa.

Ignoring any effects due to differentials in donor age profiles, Table 2 shows the expected number of "potentially preventable" clinical vCJD cases that would result, i.e. those resulting *from transfusions that have not yet taken place*. The options considered allow the *future* proportion of units collected by apheresis to vary from the current 80% to 20%. The latter is identified as the absolute minimum level of apheresis required to meet the demand from patients receiving HLA- or HNA-matched units and from neonates. This table also shows the corresponding numbers of future infections (in brackets) to provide a comparison with numbers of clinical cases. As can be seen, in these scenarios the large majority of those infected would die of other causes rather than developing symptoms of vCJD.
These potentially preventable clinical cases can develop as late as the 2070s, reaching their peak around the 2040s, and we anticipate that they would mostly result from infections over the next twenty years.

Table 2: *Estimated numbers of potentially preventable future clinical cases (and infections) from platelet-borne transmissions, with different percentages collected by apheresis*

Future % Apheresis	Infectivity associated with platelets (IDs per whole blood donation)			
	0	**0.1**	**0.25**	**1**
80%	47 (1275)	50 (1381)	53 (1505)	63 (1830)
50%	56 (1518)	61 (1692)	68 (1914)	89 (2605)
35%	60 (1639)	66 (1848)	75 (2119)	103 (2993)
20%	65 (1761)	72 (2004)	82 (2323)	116 (3380)

From this we see that increasing infectivity associated with platelets can significantly increase the expected numbers of clinical cases. As shown by the differences between rows, it also increases the benefit from maintaining a high level of apheresis.

Since 2009, HPA have published a paper providing updated estimates of prevalence of vCJD in the UK population. This reports a higher prevalence among those born before 1961 than among those born between 1961 and 1985, although this difference is not statistically significant. Following the introduction of various measures, we would expect prevalence among those born after 1985 to be lower, with possible negligible risk among those born after 1996. As a result, there is a higher probability of vCJD infection among older donors than younger.

It is known that apheresis donors tend to be older than whole blood donors. As younger donors have less exposure to vCJD (through the introduction of measures to reduce dietary risk), this leads to a potential *disadvantage* for apheresis, reducing the benefit of lowering the number of donor exposures. It is not clear how this difference in age distributions might change, particularly if the proportion of apheresed platelets changes, although it seems unlikely that the disadvantage will grow significantly. In view of this uncertainty, we consider two alternative sets of estimates, one ignoring the donor age differential (Table 2), and the other introducing the maximum possible donor age effect. The latter set of calculations for preventable cases is presented in Table 3, with the corresponding numbers from Table 2 shown in brackets for comparison.

Table 3: Estimated numbers of potentially-preventable future clinical cases from platelet-borne transmissions with maximum effect of donor age differential

Future % Apheresis	Infectivity associated with platelets (IDs per whole blood donation)			
	0	**0.1**	**0.25**	**1**
80%	67 (47)	72 (50)	77 (53)	91 (63)
50%	71 (56)	78 (61)	87 (68)	115 (89)
35%	72 (60)	80 (66)	90 (75)	123 (103)
20%	72 (65)	80 (72)	92 (82)	129 (116)

Comparing the two sets of figures, we see that the older age distribution of apheresis donors leads to a larger number of cases. Looking down the columns, we see that it also leads to a smaller increase in the number of cases as the apheresis percentage reduces. This difference in age distributions could substantially reduce the benefit of maintaining a high level of apheresis.

As noted on the tables, all figures reported so far are central estimates derived (directly or indirectly) from multiple model runs sampling from ranges for input parameters[12]. All are therefore subject to substantial intrinsic uncertainty. Nevertheless, the central estimates provide a good sense of the *comparisons* between different scenarios, and the effect of different options. Uncertainties are given greater prominence in the final sections that consider cost-effectiveness.

5. Platelet additive solution

At present, platelets are suspended in donated plasma. An alternative production method is to suspend the platelets in additive solution. Under this method, there would still be some donated plasma in a unit of platelets, but the volume would be much reduced. This is therefore an alternative vCJD-risk reduction measure, which could be used for pooled platelets or for all platelets[13,14].

To illustrate the potential impact, the following tables show expected numbers of potentially-preventable cases without use of additive solution, with its introduction for

[12] We only consider combinations that would lead to no more than 3 clinical cases of vCJD having arisen before the end of 2012 to recognise that no known cases have been caused by transfusion of platelets, but allowing for a small number to have taken place but not to have been diagnosed.
[13] This measure was previously considered, but did not significantly affect the probability of transmission of vCJD under previous assumptions on the overall level of vCJD infectivity in a whole blood donation and was therefore not recommended.
[14] For pooled platelets, we considered the case of creating two units of platelets suspended in additive solution from a pool of 8 donations as well as creating single units from pools of four. We found that the risks were very similar for these two alternatives. This paper only presents results for pools of four.

pooled units, and for both pooled and apheresed[15]. This uses an illustrative scenario as in the penultimate column of Tables 2 and 3, with 2.75 IDs in the plasma of an infected whole blood donation, and 0.25 IDs attached to the platelet content. Table 4(a) and 4(b) respectively have no donor age differential and maximum differential.

Table 4. Potentially-preventable clinical cases with 0.25IDs associated with platelets and 2.75IDs with plasma in an infected whole blood donation

a) Without donor age differential

Future % Apheresis	Production Methods		
	All suspended in plasma	Pooled in additive, apheresis in plasma	Universal use of additive
80%	53	49	46
50%	68	57	55
35%	75	61	59
20%	82	65	64

b) With maximum age differential

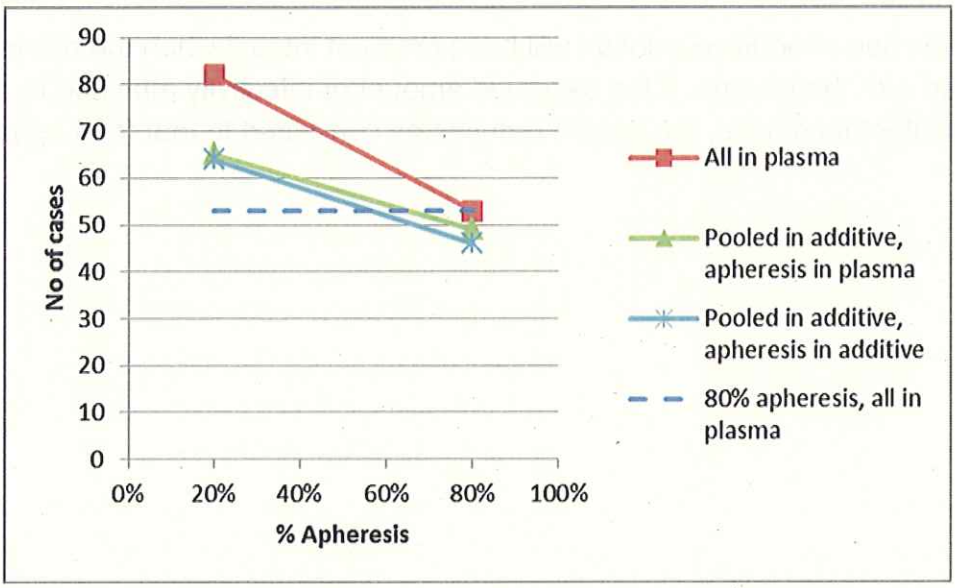
Future % Apheresis	Production Methods		
	All suspended in plasma	Pooled in additive, apheresis in plasma	Universal use of additive
80%	77	71	66
50%	87	73	70
35%	90	73	71
20%	92	72	71

Figures 1(a) and 1(b) show these results in graphical form: the horizontal line represents the status quo of 80% procurement by apheresis, and no use of additive solution.

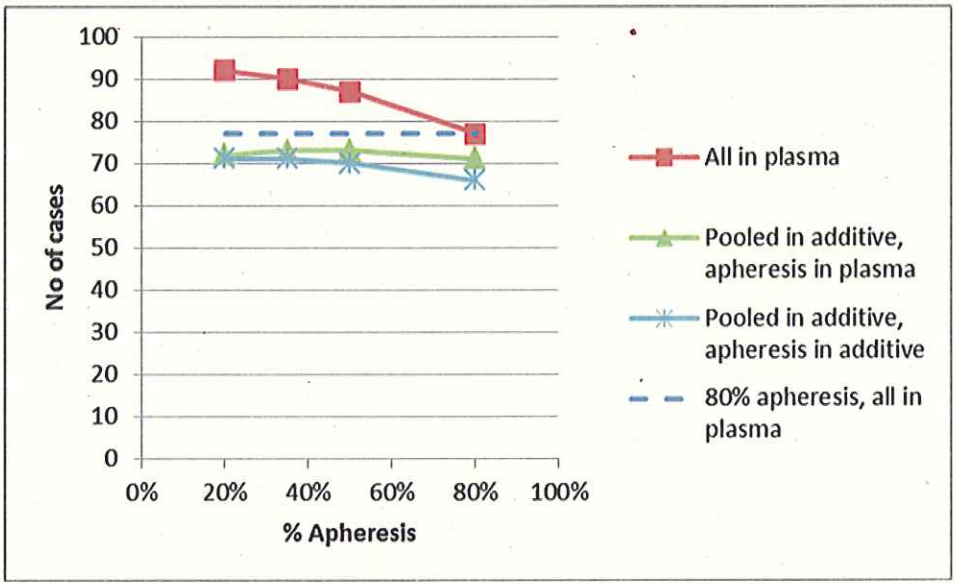
[15] NHSBT and SNBTS have indicated that, for clinical reasons, they would be unlikely to introduce suspension in additive solution for pooled platelets only.

Figure 1. Potentially preventable cases as a function of production method

a) Without age differential



b) With maximum age differential



As can be seen, introduction of additive solution can provide a marked reduction in vCJD cases in this scenario.

- If differentials in donor age are ignored (Figure 1(a)), then full use of additive solution would leave transmission risk below those currently estimated unless procurement by apheresis fell to below about 60%.

- With maximum allowance for the age differential, Figure 1(b) shows that use of additive solution would keep risk levels below the status quo for *any* mix of pooling and apheresis.

The introduction of additive solution will have greatest impact when the risk is mostly associated with the plasma. If the assumed amount of infectivity attached to the platelet content increases, the benefit reduces as compared to that from apheresis.

6. Summary of findings on effectiveness

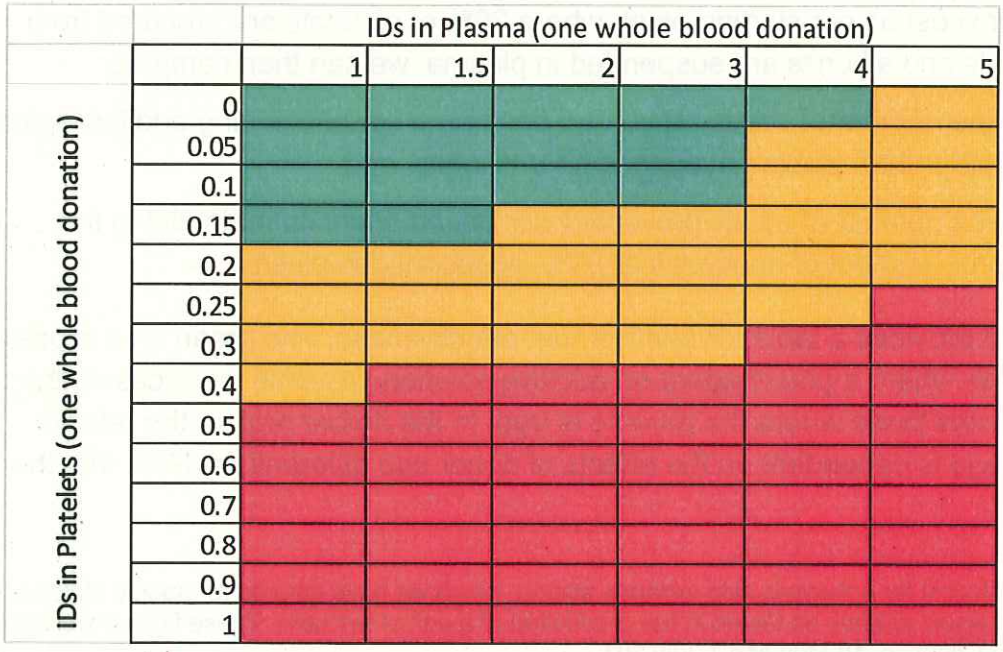
The risk assessment referred to earlier repeats similar calculations for many infectivity scenarios, and uses these to compare two specific situations:

(a) use of apheresis is reduced to 20% (the minimum acceptable for other reasons), but all units use additive solution rather than plasma suspension; and

(b) the status quo, in which 80% of platelet procurement is through apheresis, but all units are suspended in plasma.

The results of this comparison are summarised in Figure 2. The two axes vary the infectivity inputs for plasma and platelets. The resulting space is then divided into three regions. Toward the top-left corner (colour-coded green), there would be fewer clinical cases in situation (a). In other words, introducing additive solution is more effective in reducing vCJD risk than maintaining apheresis at its current high level. Toward the bottom right (coded red) the reverse is true. In the intermediate scenarios (coded amber) the relative advantage is dependent on the effects of donor age differentials.

Figure 2: Effectiveness of maintaining 80% apheresis with all units in plasma; compared to 80% pooled with all units in additive solution



7. Cost and cost-effectiveness calculations

So far, we have considered the *effectiveness* of apheresis and additive solution in reducing expected numbers of vCJD cases. We now consider their *cost-effectiveness*.

NHSBT advise that the cost of producing a unit of platelets from pooling buffy coats is £[redacted]. This includes the cost of direct staff time, bacterial screening, hire of relevant machines and various consumables. The corresponding cost for a unit collected by apheresis varies from £[redacted] to £[redacted] depending on the volume being collected[16]. The additional cost of using additive solution is £[redacted] per unit, for apheresed or pooled platelets[17].

These costs do not include any capital costs (such as NHSBT accommodation used for a collection session), one-off costs (such as project costs, communication, staff recruitment/redeployment/training/redundancy; we are advised that there would not be significant costs from changing the use of current suites) or changes in recurrent costs (e.g. travel and venue hire costs of mobile sessions; donor management, logistics and HR and other support services). These costs could be large, but are expected not to have a material impact on the cost-effectiveness of retaining the current level of apheresis.

Using these figures, we can extend the calculations that led to Figure 2 above. From this information, we can see that the cost will be least when we have the maximum number of units being produced from pooled platelets. If we use this position of minimum cost as our starting point, where 20% of platelets are procured from apheresis and all units are suspended in plasma, we can then compare:

(a) The number of cases prevented *per pound spent* on using additive solution rather than plasma suspension for all units; and

(b) The number of cases prevented *per pound spent* on maintaining the procurement of apheresis at 80%, suspended in plasma.

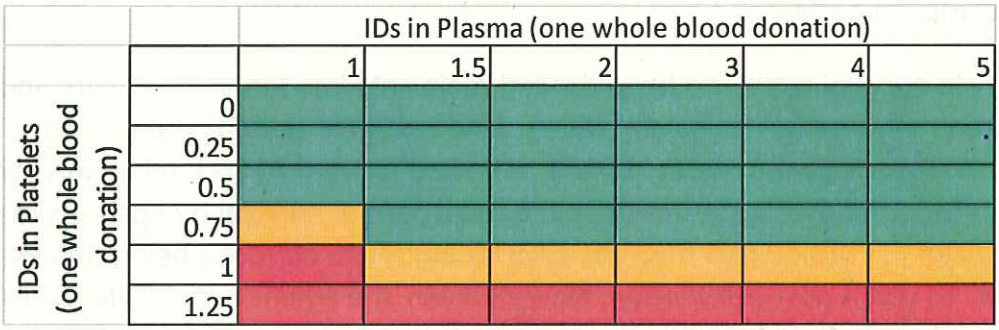
Figure 3 provides a table for relative cost-effectiveness. The green area represents scenarios where a pound spent on additive solution prevents more cases, the red area shows those where the reverse is true. In the amber region, the relative advantage is dependent on the effects of donor age differentials. Note that the

[16] The unit cost for apheresis also includes testing, which we have ignored for pooled platelets as the donation would already be tested in the production of a unit of red cells. These figures were provided by NHSBT finance, 10 May and 1 July 2013.

[17] We do not have any indication to indicate that the costs for the other UK Blood Services will be significantly different from these figures provided by the NHSBT finance. It will be assumed for the purposes of this work that these costs could be safely extrapolated from the NHSBT figures.

vertical axis is slightly extended as compared with that in Figure 2, in order to capture the boundaries between regions completely.

Figure 3: Cost-effectiveness of 80% apheresis with all units in plasma; compared to 80% pooled with all units in additive solution



These analyses give an indication of the *relative* effectiveness and cost-effectiveness of apheresis and additive solution. We also need to consider how the options perform in *absolute* terms of cost per life-year saved.

Such calculations are, of course, subject to many uncertainties. Expected numbers of secondary clinical cases (with onsets spread over several decades) will depend critically on the inputs chosen, particularly on levels and distribution of infectivity, susceptibility of recipients to clinical vCJD and incubation periods between infection via transfusion and onset (if any) of symptoms. To give a better sense of this variability, the calculations will show the ranges obtained from runs of the simulation model, not just the central estimates resulting.

In estimating the life-years lost per clinical vCJD case, we carry across calculations previously presented for cases due to transmission via red cell transfusion.[18] These suggest that each of these clinical cases would, on average, entail the direct loss of 18 symptom-free life-years (i.e. years without symptoms of vCJD). [19] As an approximation, we have regarded these as equivalent to Quality-Adjusted Life-Years (QALYs) for the purpose of cost-effectiveness calculations, though in general the number of QALYs lost 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

[18] Bennett and Daraktchiev (2013, op cit).

[19] In general, recipients of platelets have worse survival prospects than recipients of red cells or FFP. This suggests that the figure used may be an over-estimate. However, shorter survival also reduces the chance of developing vCJD symptoms, so the life-years per case should be relatively stable. These figures were used in "Prion filtration of red blood cells: effectiveness and cost-effectiveness", SaBTO 18 (10 December 2012).

symptoms of vCJD emerge, and that there will be no cure or effective treatment that will substantially mitigate the effect of this disease.

For the purpose of this analysis, we have assumed that just over 260,000[20] units of platelets will continue to be transfused each year. Given an increase in usage over the last few years, this may be an underestimate for some years. However, the cost-effectiveness calculations should not be affected, given use of the same assumption when estimating costs.

To estimate survival rates, we have divided recipients into ten-year cohorts and considered males and females separately. The available EASTR data (which extends to 6 years post-transfusion) are projected forward by assuming survival rates similar to the average of years 4 to 6, until normal survival by age becomes a limiting factor[21]. Further data from the EASTR study are currently being analysed to extend to 10 years post-transfusion. 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 current (2013/14) terms. Using a discount rate of 1.5% - as standard - for health benefits, the original estimates need to be divided by a factor of 1.7, given that they are spread over a period of decades. Each case prevented would save 14 *discounted* symptom-free life years.

As an illustration, Table 5 shows the estimated discounted number of life-years that would be lost in the scenario in Table 4, where 0.25 IDs are attached to the platelet content of an infected donation and 2.75 IDs are in the plasma[22]. The figures in brackets represent 95% intervals around the best estimate, from the simulation model runs.

[20] The Annual SHOT Report 2011, available at http://www.shotuk.org/home/, provides a figure of 260,278. The 2012 report was not available in time to inform the current analysis.

[21] This is done 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.

[22] This scenario uses a middle value in our range of total infectivity in plasma and platelets combined. It allows for some infectivity to be in the plasma, but takes a value below the midpoint of our range in view of the previous assumption that there was no infectivity associated with "pure" platelets. Cost-effectiveness calculations for other scenarios appear in Annex B.

Table 5. Potentially-preventable discounted life-years lost in scenario with 0.25IDs associated with platelets and 2.75IDs with plasma in an infected whole blood donation

a) Without age differential

Future % Apheresis	Production Methods		
	All suspended in plasma	Pooled in additive, apheresis in plasma	Universal use of additive
80%	448 (88 - 1120)	411 (80 - 1026)	384 (75 - 959)
50%	570 (112 - 1424)	476 (93 - 1190)	460 (90 - 1148)
35%	631 (123 - 1576)	509 (100 - 1272)	497 (97 - 1243)
20%	692 (135 - 1729)	542 (106 - 1354)	535 (105 - 1338)

b) With maximum age differential

Future % Apheresis	Production Methods		
	All suspended in plasma	Pooled in additive, apheresis in plasma[23]	Universal use of additive
80%	649 (128 - 1619)	595 (117 - 1484)	556 (109 - 1387)
50%	731 (144 - 1824)	611 (120 - 1524)	589 (116 - 1470)
35%	757 (149 - 1887)	611 (120 - 1523)	597 (117 - 1488)
20%	773 (152 - 1928)	606 (119 - 1510)	598 (117 - 1492)

At present, UK Blood Services procure 80% of platelet units by apheresis, and suspend all units in donated plasma. Under this scenario, if we assume the maximum age differential, we expect a loss of 649 life-years. Moving to 20% apheresis and suspending (only) pooled platelets in additive solution, then we expect to reduce this to 606, a saving of 43 life years. More generally, we can estimate

[23] In this scenario, the transmission probability for an infected apheresis unit (suspended in plasma) is lower than for a pooled unit (suspended in additive solution). However, the age differential leads us to assume that a larger proportion of apheresis donors are infected. In the other columns one of these effects is dominant, leading to a consistently increasing or decreasing number of cases as we increase the apheresis percentage. In this column, these two effects combine to produce a maximum number of cases in the middle of our range for the apheresis percentage.

gains or losses of life-years from moving to each alternative method by subtracting the number in the cell for the given alternative from the number in the status quo cell.

SaBTO has adopted a "safety framework" to inform its decisions about the introduction or withdrawal of safety measures. Under this framework, we consider the cost-effectiveness of a measure for recipients aged 60 or under. A separate "equity cost relating to the provision for over-60s" is also calculated, where a value is attached to the life-years saved among these older patients and subtracted from the cost of implementing the measure for the patient group. We therefore need to identify the costs and life-years saved for the two groups separately.

We estimate that around 1.2% of projected clinical vCJD cases would relate to patients who are over 60 at transfusion, and that on average these cases each result in the loss of just 0.2 life-years. Applying these estimates to the numbers of cases in Table 4, and discounting the cases, always results in fewer than 0.1 life-years being lost.

Throughout, life-years lost are the result of infections that might happen over a number of years. For this analysis, we assume that they would take place over the next 20 years. Allowing for wastage of 9.32%[24], they would arise from the production of around 287,000 units a year, or around 5.74 million units in total.

Table 6 presents the resulting costs for the different levels of apheresis (future costs are discounted using the standard rate of 3.5% for costs):

Table 6. Unit costs, and total cost of platelets over the next 20 years, by future percentage of apheresis

Future Percentage of platelets collected by apheresis	Unit cost - pooled	Unit cost - apheresis	Total cost: all in plasma	Total cost: all in plasma (discounted)	Total cost: pooled in additive (discounted)	Total cost: all in additive (discounted)
80% apheresis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% apheresis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35% apheresis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% apheresis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Unit costs represent only those costs which can be expected to vary in line with activity in the short to medium term and therefore exclude fixed costs and overheads

[24] Wastage rate of 9.32% provided by NHSBT finance, 5 July 2013.

Our estimated discounted cost for the status quo, with 80% procured by apheresis and all suspended in plasma, is £[redacted]m. Subtracting this from the other figures gives an estimate of the discounted change in cost from moving to any alternative situation. Also, we estimate that 39% of platelets are transfused to patients aged over 60[25]. Table 7 shows the total discounted cost over 20 years under each production method, calculated separately for patients over and up to 60.

Table 7. Change in discounted total cost of platelet procurement over the next 20 years by patient group and future percentage of apheresis

Future Percentage of platelets collected by apheresis	Patients over 60			Patients up to 60		
	Total cost: all in plasma (discounted)	**Total cost: pooled in additive (discounted)**	**Total cost: all in additive (discounted)**	**Total cost: all in plasma (discounted)**	**Total cost: pooled in additive (discounted)**	**Total cost: all in additive (discounted)**
80% apheresis	£[redacted]m	£[redacted]m	£[redacted]m	£[redacted]m	£[redacted]m	£[redacted]m
50% apheresis	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m
35% apheresis	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m
20% apheresis	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m	-£[redacted]m

We can now consider the equity cost associated with universal provision, as well as the cost-effectiveness, as estimated for patients aged up to 60.

The equity cost is calculated by subtracting £30,000 for each discounted life-year saved among the over-60s from the discounted cost of implementing a measure (Table 7). However, this is normally shown as an annual amount, and so the calculations from these tables need to be converted back. The results are shown in Table 8.

[25] Wells AW, Llewelyn CA, Casbard A, *et al* (2009): The EASTR Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. *Transfusion Medicine*, 2009, 19, 0-0. (data on transfusions to patients aged over 60 was provided by A. Wells)

Table 8. Equity cost of changing the method of collection/production of platelets

Future Percentage of platelets collected by apheresis	Production method		
	All in plasma	**Pooled in additive**	**Universal use of additive**
80% apheresis		£[redacted]k	£[redacted]k
50% apheresis	-£[redacted]k	-£[redacted]k	-£[redacted]k
35% apheresis	-£[redacted]k	-£[redacted]k	-£[redacted]k
20% apheresis	-£[redacted]k	-£[redacted]k	-£[redacted]k

We only present one table of equity costs, without any ranges. This is because the numbers of life-years are all under 0.1, and so have minimal impact on the equity cost calculation.

The cost-effectiveness can be calculated by dividing the costs in Table 7 by the corresponding number of life-years saved (effectively in Table 5). We first consider the cost-effectiveness of maintaining 80% apheresis and introducing suspension of platelets in additive solution. These figures are shown in Table 9.

Table 9. Cost effectiveness of introducing suspension in additive solution while retaining 80% apheresis (£/life-year saved, discounted)

a) Without age differential

Future Percentage of platelets collected by apheresis	Production method	
	Pooled in additive	**Universal use of additive**
80% apheresis	£[redacted]k (£[redacted]k to £[redacted]k)	£[redacted]k (£[redacted]k to £[redacted]k)

b) With maximum age differential

Future Percentage of platelets collected by apheresis	Production method	
	Pooled in additive	**Universal use of additive**
80% apheresis	£[redacted]k (£[redacted]k to £[redacted]k)	£[redacted]k (£[redacted]k to £[redacted]k)

Here we see situations where the lower end of the broader cost-effectiveness range is close to the acceptability threshold. However, this is not the most desirable option in this scenario, or indeed in any of those we have considered.

We now consider the cost-effectiveness of reducing the percentage of units procured by apheresis, which involves a reduction in the overall cost of the platelets. These figures are shown in Table 10.

Table 10. Cost effectiveness of reducing the percentage of platelets procured by apheresis for alternative production methods (£/life-year lost, discounted)

a) Without age differential

Future Percentage of platelets collected by apheresis	Production method		
	All in plasma	**Pooled in additive**	**Universal use of additive**
50% apheresis	£[redacted]k (£[redacted]k to £[redacted]k)	£[redacted]k (£[redacted]k to £[redacted]k)	£[redacted]k (£[redacted]k to £[redacted]k)
35% apheresis	£[redacted]k (£[redacted]k to £[redacted]k)	£[redacted]k (£[redacted]k to £[redacted]k)	£[redacted]k (£[redacted]k to £[redacted]k)
20% apheresis	£410k (£[redacted]k to £[redacted]k)	£[redacted]k (£[redacted]k to £[redacted]k)	£[redacted]k (£[redacted]k to £[redacted]k)

b) With maximum age differential

Future Percentage of platelets collected by apheresis	Production method		
	All in plasma	**Pooled in additive**	**Universal use of additive**
50% apheresis	£[redacted]k (£[redacted]k to £[redacted]k)	-£[redacted]k (-£[redacted]k to -£[redacted]k)	-£[redacted]k (-£[redacted]k to -£[redacted]k)
35% apheresis	£[redacted]k (£[redacted]k to £[redacted]k)	-£[redacted]k (-£[redacted]k to -£[redacted]k)	-£[redacted]k (-£[redacted]k to -£[redacted]k)
20% apheresis	£[redacted]k (£[redacted]k to £[redacted]k)	-£[redacted]k (-£[redacted]k to -£[redacted]k)	-£[redacted]k (-£[redacted]k to -£[redacted]k)

For all the rows in Table 10(a), the figures show the amount **saved** for each life-year lost as a result of changing the production regime. As a result, a large number is preferable, as it means that there is less health loss for a given cost saving. To take an example, the bottom left cell in Table 10(a) says that we would expect to save £[redacted] for each extra symptom-free life-year lost. Alternatively, we could say that the cost-effectiveness of maintaining apheresis at 80% rather than reducing it to 20% is £[redacted] per life-year saved.

In Table 10(b), we see negative figures: these indicate the desirable situation in which cost is being saved while simultaneously reducing life-years lost – a "double win".

8. Cost-effectiveness of alternative infectivity scenarios

Figures from Tables 5, 6, 8, 9 and 10 appear within the safety framework provided in Annex B. This Annex also shows the corresponding results for two other scenarios, one for a lower assumed level of infectivity (0 IDs in the platelet content and 1 in the plasma) and one for a higher level (1 ID in the platelet content and 5 in the plasma).

Across the full range of scenarios, reducing the percentage use of apheresis, combined with all units being suspended in plasma, always produces a saving of over £30,000 per extra life-year lost. This is above the normal threshold, and so represents an improvement in cost-effectiveness.

For the low- and medium-risk infectivity scenarios, introducing additive solution results in life-years being saved while money is saved, making the total package obviously attractive. However, in the high-risk infectivity scenario introducing additive solution makes the reduction in each level of apheresis less cost-effective.

In summary:

- Maintaining the proportion of platelet units procured by apheresis at 80% is not cost effective in any of the scenarios considered.
- Although the introduction of additive solution is not always cost-effective, it does always reduce the number of cases that we would expect.
- An overall package of reducing the level of apheresis and introducing additive solution is always more cost-effective than the current baseline.

Health Protection Analytical Team September 2013

Department of Health

Annex A - Comparison of apheresis and pooled platelets – background information and additional considerations

1. Efficacy

In vitro studies do not show any consistent difference for the majority of routinely measured parameters between platelets derived from apheresis and whole blood, and all meet current standards [1]. One direct comparison of functional laboratory parameters showed better ADP preservation and collagen-induced platelet aggregation, and a more rapid in vitro haemostatic response when measured on the PFA 100 test system, for apheresis platelets compared to pooled BC-derived platelets [2]. The significance of this data for patients is however unclear.

Regarding clinical data, several studies have compared Corrected Count Increments (CCI) after transfusion of apheresis or whole-blood derived platelets. This is a measure of the rise in platelet count following transfusion, corrected for size of the recipient and the dose given. Heddle, in a systematic review, compared apheresis, platelet-rich plasma (PRP)-derived (a production method used in the USA and Canada but no longer in Europe) and buffy-coat (BC)-derived platelets and found a significant difference between apheresis and PRP platelets (apheresis higher) but no difference between apheresis and BC platelets [3]. The Trial to Reduce Alloimmunisation to Platelets (TRAP) found that the type of platelet component had no relation to inter-transfusion interval [4]. In a study on bone marrow transplant patients comparing apheresis platelets with PRP and BC platelets, there was no significant difference between the 3 types of component in either 1 hour- or 24 hour-CCI [5]. A further study in thrombocytopenic patients comparing apheresis with BC pooled platelets stored for up to 6.5 days also showed no difference in CCI and transfusion intervals [6].

In summary, there does not appear to be any significant difference in clinical efficacy between apheresis and pooled platelets, except for patients refractory to platelet transfusion due to alloimmunisation to HLA antigens (who will continue to require HLA matched apheresis platelets).

2. Leucodepletion Quality Monitoring

The efficacy of leucodepletion of blood components is assessed by testing a proportion of components using flow cytometry and monitoring using statistical process control. The more 'in control' a production process is, the fewer components will require to be tested.

The 'production process' monitored in this way for apheresis platelets is the individual apheresis machine, whereas the process for pooled platelets is considered as the production from one manufacturing site per day; the former is a significantly greater number than the latter therefore more testing is required. In addition, the leucodepletion process is more robust for the pooling process, reducing the number requiring testing further.

Each UK Blood Service uses different pack types for both apheresis and pooled platelets, and has different quality monitoring protocols, as can be seen in the following table.

Table A1: Leucodepletion quality monitoring – UK data 2012

		No. issued	No. tested	% tested
Apheresis	**All UK blood services**	**137,960**	**76,336**	**55.3**
Pooled	**All UK blood services**	**44,983**	**10,312**	**22.9**

Data from SACBC – *Note: Summary data are given here*

As can be seen, apheresis components undergo approximately twice as much monitoring as pooled platelets. The cost of testing is approximately £6 per test, therefore increasing the proportion of pooled platelets compared to apheresis could significantly reduce the cost to Blood Services of LD monitoring.

3. Bacterial screening

NHSBT implemented bacterial screening of platelet component from February 2011, with all components being screened from July 2011. Other UK Blood Services implemented several years prior to this.

All services use the BacT/Alert system, in which samples are taken from packs and incubated within the system for the length of the shelf life of the platelet component. The system will flag at 10 minute intervals whenever a sample begins to show a positive reaction, or 'initial reactive'. Further tests are done on the sample to confirm whether the test is truly positive, and also components are recalled from blood centres if still in stock, or hospitals if issued, both to prevent transfusion and to confirm the result.

For apheresis platelets, other associated platelet units are recalled (there are usually 2 or 3 packs manufactured from a single donation; the mean number of units produced from each donation for NHSBT in 2012 is 2.14). For pooled platelets, there will be recall of the 4 red cell units from the 4 donations which went to make the pooled platelet in addition to the platelet pool itself. As the shelf life of red cells is longer than platelets, however, there is more likelihood that recalled red cells will not have yet been issued to hospitals at the time of an initial reactive, whereas platelets will have been, which will reduce the impact of the recall on hospitals.

Component recall involves additional work for Blood Service Issues departments in initiating the recall, and additional work for hospitals locating and returning the component. If the component has already been transfused the recipient will require assessment and explanation. Blood Services' Bacteriology Laboratories will perform confirmatory testing on the samples and residual and associated components as outlined above. The NHSBT/PHE Epidemiology Unit collates the clinical data and results of investigations and produces reports. A considerable amount of resource is therefore put into this activity both in hospitals and Blood Services.

Cumulative results from NHSBT on the rate of positive screens are as follows (source NHSBT/HPE Epidemiology Unit, Feb 2001 – June 2013):

Table A2: NHSBT cumulative bacterial screening initial reactive and confirmed positive rates

	No. screened	No. initial reactive	% initial reactive	No. confirmed positive	% confirmed positive
Apheresis	498,801	2,485	0.5	87	0.02
Pooled	93,051	341	0.37	72	0.08
Total	**591,852**	**2,826**	**0.48**	**159**	**0.03**

It is noted that a higher proportion of apheresis platelets are initial reactive than pooled, although the confirmed positive rate is higher for pools.

The following table estimates how many components will require recall at different proportions of apheresis collection, using the assumptions as follows:

- each initial reactive of an apheresis platelet will lead to 2.14 units being recalled (from 2012 NHSBT apheresis production performance data)
- each initial reactive of a pooled platelet will lead to 4 units of red cells and one pooled platelet being recalled
- initial reactive rates as given in table A2
- number of units produced per year = 272,100

Table A3: Estimated component recalls at different % of platelets collected by apheresis

	Recalls per year			
% Apheresis	**80%**	**50%**	**35%**	**20%**
Platelet units	2,530	1,959	1,673	1,388
Red cell units	805	2,013	2,617	3,222
Total units	3,335	3,972	4,290	4,610

For decreasing percentage of apheresis units produced, fewer platelet units will require recall from hospitals. An increasing number of red cells units will require recall – as explained above these are less likely to have been issued to hospitals so this will be less of a burden for hospitals, but these units will be removed from stock and investigated so will not be available for transfusion.

In 2012 there were 23 cases of suspected transfusion transmitted bacterial infection reported to the NHSBT National Bacteriology Laboratory for investigation after transfusion of apheresis platelets, compared to 5 cases after transfusion of pooled platelets (none were confirmed positive). This reflects the current split of 80% of platelets being derived from apheresis.

4. Adverse events

In a UK study comparing the incidence of febrile non-haemolytic transfusion reactions (FNHTR) to platelets in patients with haematological malignancy, there was no difference between reaction rates following leucodepleted apheresis (3.1%) and BC pooled platelets (3.8%) [7]. There was no difference in reactions between apheresis and pooled platelets in the TRAP study [4] or in the systematic review performed by Heddle [3].

There is no reported difference in the rate of alloimmunisation between apheresis and pooled platelets so long as the products are leucodepleted [3,4,8].

A systematic review of pooled vs. apheresis platelets found that the risk of TRALI secondary to platelets appeared to be equal when the two types of component were compared [9].

The risk of transfusion-transmitted viral infection is very low when exposure to a single donor is considered – residual risk in the UK 2010-11 has been calculated as 0.76 per million for HBV, 0.036 per million for HCV, and 0.125 per million for HIV [10]. Increasing the number of donors contributing to a transfusion will increase this small risk. Vamvakas in his systematic review estimated the increase in risk to be equivalent to 1.2 – 3.9 additional infections of HIV or HCV in the USA per annum, and 9.0 – 27.1 for HBV. For a newly emerging virus (e.g. HIV-like) he estimated the risk to be greater at 252 – 757 additional infections [9].

5. Impact on red cell components

Whole blood donations which are used for manufacture of buffy coats to contribute to platelet pools are bled into different packs known as Bottom and Top (BAT) packs; those which are destined to make red cell +/- FFP components alone are bled into Top and Top (TAT) packs. When BAT packs are processed, some red cells are retained within the buffy coat layer therefore QM data shows a reduction in the red cell and Hb content of red cell components made from these donations.

Table A4: Hb content of SAGM red cells with and without buffy coat manufacture

	Hb (g/unit) (mean)
TAT (no BC)	58.1
BAT (plus BC)	45.2
All methods	54.3
Specification	> 40

There is a lower Hb content and volume in the BAT red cells, although all meet specification. This is likely only to be a concern for regularly transfused patients.

It has been estimated that approximately 50,000 units of red cells are required in the UK per annum for transfusion to patients with sickle cell disease and thalassaemia. 311,737 units of platelets were issued in the UK in 2012 (source Annual SHOT Report 2012). If the proportion of pooled platelets was increased to 80%, then almost 1 million units of BAT red cells would be produced, compared to 250,000 if 80% of platelets were from apheresis. The total number of red cells issued in 2012 was 2.15 million, therefore even if the proportion of donations collected into BAT packs increases, there will still be sufficient numbers collected into TAT to support such patients.

6. Impact on donors

Whole blood donation and apheresis platelet donation can both give rise to donor complications such as bruises, nerve injury and faints. Reports have suggested that the rate is lower in apheresis donors compared to whole blood [11]. In addition, donating by apheresis has additional complications of citrate reactions, and there is also concern about potential long term complications in frequent apheresis donors of reduction in bone density secondary to citrate, although this has not been conclusively proven.

Reduction in the number of apheresis components collected, however, would not increase the number of whole blood collections made in order to provide an increased proportion of pooled platelets as the drive for whole blood donation would still be manufacture of red cells and additional donations specifically for pooled platelets would not be required. There would therefore be a reduction in the number of donations made, and hence a reduction in the number of adverse events seen.

Introduction of platelet additive solution (PAS) – additional considerations

1. Background

There are a number of PAS that are licensed for storage of platelets. The current generation of PAS that are widely used include Composol, PASIII (also marketed as Intersol), and modified PASIII (PASIIIM, marketed as SSP+ or T PAS+). A further generation of PAS are in development that include glucose with or without bicarbonate, these are not discussed further here.

Currently systems that are CE marked for pathogen inactivation of platelets can only be used to day 7 of storage if platelets are suspended in approximately 65% PASIII or PASIIIM. Therefore, if PAS were to be implemented without pathogen inactivation, it would be likely that PASIII or PASIIIM would be used as it would facilitate a transition to pathogen inactivation at a later date, should a recommendation to do so be made. For that reason, review of data below has been restricted to those PAS.

2. Laboratory data

A summary of their composition is given in the table below. The only difference between PASIII and PASIIIM solutions is the inclusion of potassium and magnesium in the latter. This has been shown to reduce platelet activation during platelet storage when added to platelet storage media [12].

For either buffy coat derived or apheresis platelets, glucose consumption in PASIII is similar to that for PC stored in plasma but is lower in those stored in PASIIIM. Platelet activation, as assessed by expression of CD62P, is similar for PC stored in plasma or PASIIIM, but is higher in PC stored in PASIII [13,14]. There is now a body of evidence accumulating to suggest platelet function in vitro is improved in PASIIIM compared with PASIII (this is not reviewed at length here).

Table A5: Platelet additive solution composition (mmol/l of additive solution not platelet unit)

	PASIII	PASIIIM
Manufacturer	Fenwal (as Intersol)	Macopharma & Terumo (as SSP+ or T PAS+)
CE Marked?	YES 7 days	YES 7 days
FDA approved	Yes for 35% plasma to d5 for Amicus PC only	NO
CE marked for 7d storage with PI systems	YES	YES
Recommended plasma carry over	30-47% for PI	>20% 30-47% for PI
Sodium Chloride	77.3	69.3
Tri-sodium citrate	10.8	10.8
Sodium acetate	32.3	32.3
Sodium phosphate	28.2	28.2
Potassium chloride	-	5
Magnesium Chloride/sulphate	-	1.5

Composition taken from Nogawa et al 2013 [15].

3. Clinical data

a) Recovery and survival

Two studies have assessed PASIIIM in healthy volunteers. One on buffy coat platelets showed similar recovery and survival compared with those stored in plasma when stored for 7 days [16]. Another using apheresis platelets to day 7 showed a slightly lower recovery for PASIIIM (53±13%) compared with PASIII (65±11%) [17]. The latter study used paired units stored in either PAS from a given donor, but different isotopes were used for labelling (indium for PC in PASIII and chromium for PC in PASIIIM). The latter might contribute to the observed differences. The data for PASIII and PASIIIM in the latter study are within the range of values reported by others for day 7 storage in plasma.

A further study has assessed apheresis platelet collected by Amicus and stored for 5 days in PASIII [18]. The data meet the criteria set by the FDA that the recovery of stored platelets should be >66% that of fresh and >58% of fresh for survival.

b) In thrombocytopenic patients

In a randomised controlled trial on pathogen inactivated platelets, there was no difference in clinical efficacy of untreated platelets stored in either 100% plasma or 65% PASIII [19]. Furthermore, in the context of pathogen inactivation, suspension of platelets in 65% PASIII appears to provide platelets that are clinically effective [20]. Since laboratory data show that platelet function is better preserved in PASIIIM than PASIII, one would not expect clinical data in PASIIIM to be inferior to that of PASIII.

De Wildt-Eggen and Gulliksson [21] reviewed 8 clinical studies on thrombocytopenic patients comparing platelets in plasma with platelets in PAS and found no significant difference in CCI in 7 of these; in the eighth a significant reduction in the PAS platelets in both the 1 hour (20.7 $\pm$ 8.5 vs 17.1 $\pm$ 6.6) and 24 hour CCI (11.5 $\pm$ 8.0 vs 9.5 $\pm$ 7.0) was noted [22].

Kerkhoffs et al also found a significant decrease in 1 hour and 24 hour CCI for platelets in PASII versus plasma, but there was no difference in transfusion interval, or number of platelet and red cell units transfused [23].

c) Summary

The available data suggests that platelets stored in 65% PASIII or PASIIIM will be of acceptable quality. Intersol, SSP+ and T PAS+ are CE marked for this purpose, and some blood centres in the EU store platelets in them routinely, with or without pathogen inactivation.

There are limited data on neonatal split platelets, and data may need to be generated on these should implementation be recommended. In the Netherlands, although approximately 30% of platelets are in PASIII, these are not yet used for neonates because of lack of data on split packs. PAS platelets are in use for neonates in other countries however – one centre in Austria has used SSP+ platelets since 2011 including for neonates, and Belgium uses SSP+ for almost 100% of their platelets including for neonates (personal communication, Macopharma).

Platelets in additive solution and plasma already exist as a specified component in the Red Book.

4. Transfusion reactions

Non-haemolytic febrile transfusion reactions (NHFTRs) can be caused by cytokines derived from contaminating leucocytes (reduced by leucodepletion) but allergic reactions are generally caused by reactions to plasma proteins and might be expected to reduce if the amount of plasma transfused is less. Three studies demonstrate significant reduction of the incidence of transfusion reactions to platelets in PSM compared with platelets in plasma, albeit with markedly differing rates between studies: 78% vs 23% (PAS-1) [24], 12% vs 5.3% (PAS-II) [22] and 5.5% vs 2.4% (PAS-II) [23]. A further study did not find a significant difference in transfusion reaction rates between platelets in plasma, platelets in PASIII and pathogen inactivated platelets in PASIII, though number were small [19].

A reduction in the rate of transfusion reactions is better for patients, and reduces resource requirements for following up and investigating the cause by both hospitals and blood services.

5. Increased availability of plasma from male donors for manufacture of FFP

If male plasma is not required to resuspend pooled platelets, (with PAS being used instead) then there will be increased availability of male plasma for manufacture into clinical FFP.

6. Infectious complications

All four UK Blood Services use the BacT/Alert system for screening platelets for bacteria. In a study which investigated the effect of PAS on the growth dynamics of contaminating bacteria, it was demonstrated that use of PAS did not affect detection of some bacteria in the system, and for others the likelihood of early bacterial detection may be improved [25].

With regard to vCJD infectivity, PASIIIM does not appear to alter platelet activation and alpha granule release. It is possible that there may be some release of PRPc into the additive solution but that is not considered to be a significant concern (personal communication Prof. D. Anstee).

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ANNEX C: PLATELET DONORS AND RECIPIENTS IDENTIFIED THROUGH THE TRANSFUSION MEDICINE EPIDEMIOLOGY REVIEW (TMER)

DONORS – vCJD cases who donated platelets in the past

Only three vCJD cases reported as donors (out of 18 vCJD donors whose component were issued for hospital use) had donated platelets.

a) Apheresis platelet donors, n=0

b) Whole blood donors contributing to platelet pool, n=3

TMER No	Platelet component donated	Year of Transfusion	Donor contribution to Pool?	Recipient ID	Interval from Tx to recipient death (years)
396	Platelets pooled	1996	buffy coat (and probably 25% plasma)	238	8 yrs, 3 months
448	Platelets pooled	1997	buffy coat and 25% of plasma*	102	2 yrs, 9 months
476	Platelets pooled, LD	2002	buffy coat, but not plasma	125	1 yr, 11 months
476	Platelets pooled, LD	2004	buffy coat (not known if donor plasma used for pool)	129	1 yr, 6 months

* note from centre to say pre 2002 platelet pools prepared by "wet buffy coat" method in which equal amounts of plasma pooled from 4 donors to make platelet pool, assume this also applies to other component in table as well.

3/18 whole blood donors who developed vCJD contributed to 4 platelet pools which were issued to hospitals. All four recipients were traced, and are all dead, with interval from transfusion to death ranging from 2-9 years. None of the above platelet pool recipients developed vCJD. However another recipient who received RBC from TMER No 396 in the same year, did develop vCJD 6 years, 6 months after transfusion (this was the first transfusion transmitted vCJD case reported in the Lancet).

RECIPIENTS – vCJD Cases who received platelets in the past

a) Apheresis platelet recipients (n=1)

b) Pooled platelet recipients (n=2)

Only 2/10 vCJD cases who received blood transfusions in the past had received platelet components, from which 29 donors have been traced, none of whom have gone on to develop vCJD.

TMER No	Platelet component transfused	Year of transfusion	No of platelet donations traced	No of platelet donors identified	Interval from transfusion to onset of vCJD
269	2 units pooled platelets*	July 1993	8*	8	4 years, 9 months
269	4 units pooled platelets*	Oct 1993	16*	16	4 years, 6 months
269	1 unit apheresis platelets	Oct 1993	1	1	4 years, 6 months
484	1 unit pooled platelets	1997	4	4	7 years, 10 months

*these are presumed to be pooled platelets, as donations and donors traced in TMER without recording the pooled platelet donation number.

Only one vCJD case above (TMER No 269) definitely received a unit of platelets donated by an apheresis donor. They had received a total of 103 donor exposures from all components transfused in total over two transfusion episodes in 1993, and also undergone a liver transplant.

The other vCJD case (TMER 484) who received a unit of pooled platelets, had also been given 22 units of RBC, one of which was from a donor who developed vCJD, and 22 units of FFP (this was the third case of vCJD transfusion transmitted infection identified)

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