JPAC 17-10 Amended

Joint UKBTS Professional Advisory Committee ([1]) Summary Sheet

1. **Paper for the JPAC meeting on:**	09 March 2017
2. **Date submitted:**	02 February 2017
3. **Title (including version no.):**	Use of plasma from first time donors
4. **Author(s):**	Drs Alan Kitchen, Pat Hewitt, Katy Davison on behalf of the SAC on Transfusion Transmitted Infections
5. **Brief summary:**	SACTTI has been asked to review the current Red Book requirement (Chapter 7, Section 3) which states that for FFP for direct clinical use is not produced from donations from first time donors. This requirement was a recommendation from SACTTI, and approved by MSBT, in 1995, as a safety measure to help minimise any risk of infection from plasma components against a background, at the time, of public anxiety and expectations regarding blood safety, growing media scrutiny and an increasingly litigious patient population. However the minutes of the SACTTI meeting at which this decision was made do make it clear that there was no specific evidence for this at the time, indeed there was a general lack of evidence either way, but that at the time it was felt to be an appropriate safety measure. Now that the sensitivity of the donation screening process has increased significantly with the implementation of molecular screening in addition to serology, and now that there are more data available, including the regular residual risk analysis, SACTTI agreed that it was unlikely that using plasma from first time donors for direct clinical use had any greater risk than using plasma from existing donors.
6. **Action required by the JPAC:** (What do you want JPAC to do in response to this paper?) e.g. • endorse a specific recommendation • advise where there is a choice of possible actions • advise on priorities within the work plan • provide a steer on policy	Endorse SACTTI's decision to now to reverse an earlier SACTTI recommendation, made at a time when the sensitivity of the donation screening process was significantly lower than that today.
7. **Any other relevant information:**	

([1]) **Joint U**nited **K**ingdom **B**lood **T**ransfusion **S**ervices **Professional Advisory Committee**

Removal of the current Red Book requirement for FFP not to be prepared from plasma from first time donors

Background

SACTTI has been asked to review the current Red Book requirement (Chapter 7, Section 3) which states that for FFP for direct clinical use is not produced from donations from first time donors. This requirement was a recommendation from SACTTI, and approved by MSBT, in 1995, as a safety measure to help minimise any risk of infection from plasma components against a background, at the time, of public anxiety and expectations regarding blood safety, growing media scrutiny and an increasingly litigious patient population. The minutes of the special SACTTI meeting called to consider this issue (SACTTI EC 25/95) make it clear, however, that the recommendation was not based on any specific evidence; at that time there was insufficient epidemiological evidence available to provide a definitive scientific basis for the decision.

The relevant paragraph in the SACTTI minutes follows: '*after a lengthy discussion regarding the availability of data on plasma safety it was concluded that while UK FFP is probably relatively safe, there is insufficient epidemiological evidence at present to provide a definitive scientific basis for decisions. Apart from a retrospective study of seroconversions among NLBTC apheresis donors and scattered anecdotal reports from a few other centres, very little data exist*.'

It is fairly certain that an important element of the 1995 decision was the higher number of infections identified in first time donors compared to the numbers found in repeat donors. However, the key issue is not the total number or rate of infections in first-time donors v. repeat donors, but the number of new (incident) infections in donors, since it is the early infections which are more likely to be undetected by screening tests - the window period risk. In first time donors, unless there is clear evidence from laboratory testing and any available history that the infection is recent, the detected infections have to be considered to reflect prevalence rather than incidence, and therefore whether the numbers truly reflect any difference in actual risk can be questioned.

Although SACTTI has not been asked to review the issue of FFP from first time donors since making the recommendation in 1995, it is worth noting that in May 2015 SACTTI was asked by NHSBT if it would be possible to use quarantined FFP from first time donors after those donors had returned and were shown to have negative microbiology screening tests on the subsequent donation (SACTTI 15-18). After discussion, SACTTI agreed that the quarantined FFP from first time donors could be used, and importantly SACTTI also queried the need to quarantine the plasma in the first place, given that molecular screening is now routine. This 2015 response from SACTTI thus supports the current request to remove the requirement to not use plasma from first time donors.

Current situation

The following are the key elements that are relevant to this request:

- The routine screening tests applied to blood donations have changed dramatically since the 1995 decision. Serological tests have improved in sensitivity and specificity, but more importantly molecular screening has been introduced, which has increased significantly the overall sensitivity of the screening programme
- Currently, the estimated residual risks of transmission of viral infections from screened blood is very low (Table 1) and now considered to be due only to donations collected in the window period of infection
- The current risks of transmission of syphilis and HTLV are already low and the risk of transmission of either from FFP is negligible: treponemes are not stable in frozen plasma, HTLV is considered to be predominantly a cell associated virus, and free virus would be at such a low level that HTLV transmission is not considered a risk with cell-free products
- In 2014 SACTTI proposed that the residual risk estimates would in future take account only of window period risk, since, with the level of automation across services, the risk of an error resulting in the release of a screen repeat reactive donation was judged to be negligible, and thus did not influence the overall residual risk estimates. This change was approved by JPAC

Table 1: Estimated risk that a donation entering the UK blood supply is a potentially infectious HBV, HCV or HIV window period donation: 2013-2015

Risk due to window period		HBV[1]	HCV[2]	HIV[3]
Number of potentially infectious window period donations in 1 million donations entering the blood supply (95% CI). This is equal to risk x 1,000,000	All donations	0.79 (0.22 – 1.30)	0.025 (0.01 - 0.04)	0.18 (0.12 - 0.27)
	Donations from new donors	2.07 (0.48 – 4.73)	0.07 (0.01 - 0.42)	0.03 (0.01 - 0.11)
	Donations from repeat donors	0.68 (0.20 – 1.12)	0.02 (0.01 - 0.04)	0.19 (0.10 - 0.25)
Number of donations (millions) entering the blood supply before 1 of those donations can be expected to be a potentially infectious donation. This is equal to 1/(risk x 1,000,000)	All donations	1.3	40.5	5.7
	Donations from new donors	0.48	15.1	31.0
	Donations from repeat donors	1.5	47.6	5.3

[1] HBV testing assumed all donations were tested for markers of HBsAg and HBV DNA using NAT with a window period of 30 days

[2] anti-HCV testing and HCV RNA testing with a window period 4 days

[3] Combined HIV antigen/antibody testing and HIV NAT with a window period 9 days

The risk due to WP amongst all donations was calculated as the weighted average of the risk amongst new and repeat donors, weighted according to the number of donations made from new and repeat donors. **All NAT testing was on pooled samples of 24 donations.**

- Any donation in the window period of an infection by definition reflects a recently acquired infection. Whilst the incidence of infection in repeat donors can be determined from seroconversions (a change from a negative to a positive state) that in first time donors rarely can be determined with any accuracy. In any case, the incidence of infection is only a very imperfect indicator of the number of recent infections, and thus the window period risk.
- Donations which are confirmed RNA/DNA positive and serology screen negative, reflect very recent (and thus potential window period) donations. In the period from 2011-2015 there have been a total of 27 donations detected on the basis of molecular screening alone, 1 HIV, 6 HCV and 20 HBV, although 16 of the HBV pick-ups were occult HBV cases and therefore not recent infections. There is also one known HIV 'RNA only' case in 2016, a total of 28 donations
- Of the 28 known donations picked up by molecular screening and serology screen negative, only 12 (2 HIV, 6 HCV and 4 HBV) can be considered to reflect recent infection. The actual risk of transmission of HBV from a donation from an occult HBV donor is considered to be low (previous discussions between NHSBT and hepatologists)
- Four (33%) of the 12 donations (2 HBV, 1 HCV, 1 HIV) were from first time donors, although only approximately 15% of all donations are from first time donors
- Whilst it is correct to consider the incidence of recent infections to be slightly higher in first time rather than repeat donors and the residual risk figures (Table 1) reflect the increased risk from first time donors, the number of donations from first time donors is significantly lower than the number of donations from repeat donors, and thus any overall increase in the likelihood of a window period donation entering the blood supply if FFP is to be made from first-time donors is very small
- Using the residual risk estimates for 2013-2015 (Table 1), a figure of 2.2 x10^6 donations per year and 15% of those donations coming from first time donors, figures can be derived to estimate the number of WP donations that would enter the blood supply from both first time and repeat donors (Table 2)

Table 2 Estimate of actual number of potentially infectious donations entering the blood supply in any one year

Estimated annual number of donations (n=2.2 x10^6)	HBV		HCV		HIV	
	No. WP donations per 10^6 donations[1]	Absolute No. WP donations per year	No. WP donations per 10^6 donations[1]	Absolute No. WP donations per year	No. WP donations per 10^6 donations[1]	Absolute No. WP donations per year
First time donors (n= 330,000)	1.51	0.498	0.07	0.023	0.03	0.01
Repeat donors (n= 1,870,000)	0.56	1.05	0.019	0.036	0.17	0.318

[1] From Table 1, row 1, number of potentially infectious WP donations, per 10^6 donations, entering the blood supply

- In Table 2 in all cases it can be seen that more of the WP donations estimated to enter the blood supply originate from repeat rather than first time donors
- FFP is only made from a % of donations, thus reducing further any additional risk
- The number of donations collected within NHSBT is falling, and currently (2016) totals 1.8 x 10^6 per year, which will change the risk estimate figures slightly, the decrease in donations collected resulting in a consequent decrease in the actual number of WP donations which could enter the blood supply
- On this basis it can be argued that the contribution from first time donors to the number of WP donations that could potentially enter the blood is less than that from repeat donors
- On this basis, it can be argued that, with current screening regimes, any increased risk from the use of first-time donations for production of FFP is so small as to be negligible

Removal of the requirement

Would removal of the requirement for FFP not to be made from plasma from first time donors increase any microbiological risk associated with components prepared from the plasma?

If it is accepted that :

- the current residual risk is solely due to window period infections
- the overall sensitivity of the screening programme is significantly higher than in 1995
- any increase in risk would be determined by a higher number/rate of incident infections in first time donors, but modified by the proportion of all donations that are collected from first time donors
- the higher risk currently is from repeat donors (Table 2)

then it follows that removing the requirement would be unlikely to lead to any significant increase in the already very low risk of transmission of infection.

Recommendation

SACTTI concludes that removing the requirement not to produce FFP from first time donors would be unlikely to lead to any significant increase in the already very low risk of transmission of infection.

Alan Kitchen, Pat Hewitt, Katy Davison

On behalf of SACTTI

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