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Transfusion of prion-filtered red cells does not increase the rate of alloimmunization or transfusion reactions in patients: results of the UK trial of prion-filtered *versus* standard red cells in surgical patients (PRISM A)

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Summary

This study, conducted for the UK Blood Transfusion Services (UKBTS), evaluated the clinical safety of red cells filtered through a CE-marked prion removal filter (P-Capt). Patients requiring blood transfusion for elective procedures in nine UK hospitals were entered into a non-randomized open trial to assess development of red cell antibodies to standard red cell (RCC) or prion-filtered red cell concentrates (PF-RCC) at eight weeks and six months post-transfusion. Patients who received at least 1 unit of PF-RCC were compared with a control cohort given RCC only. About 917 PF-RCC and 1336 RCC units were transfused into 299 and 291 patients respectively. Twenty-six new red cell antibodies were detected post-transfusion in 10 patients in each arm, an overall alloimmunization rate of 4·4%. Neither the treatment arm [odds ratio (OR) 0·93, 95% confidence interval (CI) 0·3, 2·5] nor number of units transfused (OR 0·95, 95% CI 0·8, 1·1) had a significant effect on the proportion of patients who developed new alloantibodies. No pan-reactive antibodies or antibodies specifically against PF-RCC were detected. There was no difference in transfusion reactions between arms, and no novel transfusion-related adverse events clearly attributable to PF-RCC were seen. These data suggest that prion filtration of red cells does not reduce overall transfusion safety. This finding requires confirmation in large populations of transfused patients.

Keywords: variant Creutzfeldt-Jacob disease, prion filtration, blood transfusion, red cell alloimmunization.

The occurrence of three cases of transfusion-transmitted variant Creutzfeldt-Jacob disease (vCJD) and a fourth transmission diagnosed post-mortem raised concerns over the safety of the UK blood supply (Llewelyn *et al*, 2004; Peden *et al*, 2004) because prion transmission by asymptomatic donors could result in a secondary vCJD outbreak (Peden *et al*, 2004; Hewitt *et al*, 2006). In the absence of a screening test that could be applied to blood donors, a number of steps have been implemented over the last 10–15 years to minimize the risk of vCJD transfusion transmission, including steps to increase appropriate blood usage, and leucocyte depletion (LD) of all blood components (http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Healthservicecirculars/DH_4004264 and http://webarchive.nationalarchives.gov.uk+/www.dh.gov.uk/en/Publicationsandstatistics/Pressreleases/DH_4086160). However, animal studies have shown that the current generation of leucocyte reduction filters may not be fully effective in preventing vCJD transmission, removing only about 40% of the total human transmissible spongiform encephalopathy (TSE) infectivity in endogenously infected blood (Gregori *et al*, 2004). As the primary vCJD outbreak declines, secondary transmission via transfusion becomes an increasingly important factor in determining the extent and duration of the overall UK epidemic (Ghani *et al*, 2003; Wilson & Ricketts, 2004; Garske & Ghani, 2010).

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A red cell filter device, P-Capt (Macopharma, Tourcoing, France), incorporating a specific resin designed to remove prions (Gregori *et al*, 2006), the infectious agent in blood thought to cause vCJD, was CE marked in Europe in 2006. P-Capt filtered red blood cell concentrates (PF-RCC) behaved normally in laboratory assays and had a normal antigenic profile (Murphy *et al*, 2009), and a study in 20 patients showed that exposure to 1–2 PF-RCC units did not generate any attributable adverse events (Cahill *et al*, 2010).

Clinical studies are not required for licensing of blood component devices, but given the potential implementation of prion filtration to a wide patient population, the UK Blood Transfusion Services (UKBTS) commissioned this study to ensure that PF-RCC did not cause any side effects in patients. There were two areas of concern. Firstly, the filter binds normal prion protein (PrPc), a constituent of plasma also present at low levels on the red cell membrane. Removal of normal PrPc from the red cell surface by the high affinity ligand could alter the immunological profile of the red cell membrane. This in turn could potentially result in an increased frequency in recipients of alloantibody formation against the recognized minor blood groups, or formation of alloantibodies that react either with all red cell types or specifically against P-Capt filtered red cells. Therefore, red cell alloimmunization was agreed to be the primary trial outcome. Secondly, transfusion of prion-filtered red cells could result in an increase in the occurrence of well-recognized transfusion reactions or cause new side effects. LD filters, used in the UK since 1999, have not caused any major problems, with reaction rates of about 0·2% per transfusion (Uhlmann *et al*, 2001; Ibojie *et al*, 2002). However, atypical reactions, including marked hypotension in patients taking angiotensin-converting-enzyme (ACE) inhibitors, were reported following introduction of a new bedside LD filter (Fried *et al*, 1996; Sweeney *et al*, 1998), whilst batches of another LD filter caused a peculiar red-eye syndrome in the USA, attributed to leaching of material from the filter during manufacturing (Haley *et al*, 1998). Therefore the secondary outcome for the trial was the incidence of transfusion-related side effects, both classical transfusion reactions and other adverse events thought to be attributable to the transfusion.

This study was initially planned as a one-arm safety study in surgical patients having a single transfusion episode, but since there were very limited data in the literature on red cell alloimmunization rates after transfusion of LD red cells in this patient population, the decision was made to collect comparative data in controls. However, alloimmunization rates reported in the pre-LD era in patients following a single transfusion episode were 5–8% (Redman *et al*, 1996; van de Watering *et al*, 2003). This meant that to conduct a randomized trial powered to detect a clinically significant increase in alloimmunization, thousands of patients would have been needed. Such a trial would have taken an unacceptably long time, given that safety data was considered desirable before a national UK policy decision on filtration could be made. Therefore the size of the trial was built around the number of filters available for evaluation, consistent with being large enough to have a chance of detecting antibodies specific for prion filters. To avoid delays while the P-Capt prion filters were being assessed and manufactured, we started by collecting control data, switching trial sites to filtered red cells once the filters become available. We then switched back to recruitment of control patients to complete the numbers. This sandwich design had the effect of minimizing the impact of patient baseline characteristics or clinical care changing with time.

Our study therefore provides data on rates of red cell antibody formation (primary outcome) and classical transfusion reactions/transfusion related adverse events (secondary outcome) following PF-RCC transfusion to a cohort of patients receiving one-off transfusion support, compared with a control group.

Patients and methods

Patient recruitment

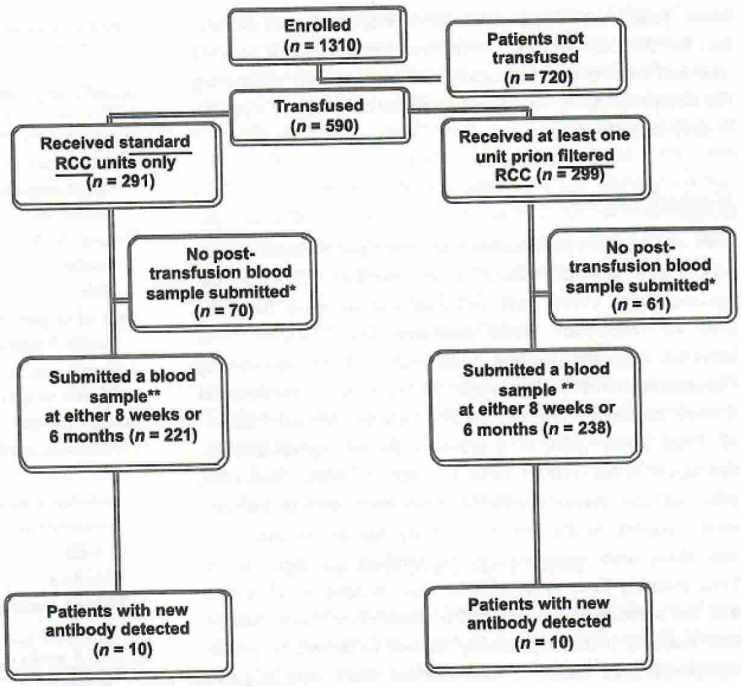
The study was a multi-centre, non-randomized, open, controlled trial in surgical and medical patients. About 270 patients were assigned to each arm. A pragmatic approach to assigning patients to the study groups was used. Across all centres, participants were assigned to receive red cell concentrates (RCC) until P-Capt filtered red cells (PF-RCC) were available, at which point assignment was switched to PF-RCC. Once the target numbers of participants receiving PF-RCC had been achieved, subsequent participants received RCC until data on a similar sized control group had been collected.

Patients were recruited between August 2007 and March 2011. Patients, aged ≥ 18 years and who required elective transfusion support, mainly during elective surgery, were allocated to receive either RCC or PF-RCC for all transfusions from time of admission until discharge from hospital. Pregnant women, patients requiring regular transfusion support and patients with pre-existing red cell antibodies for whom obtaining suitably matched blood urgently would be difficult, were excluded.

The trial was approved by local research ethics committees and was performed according to Good Clinical Practice guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1996). All patients gave written informed consent. About 299 patients received at least one unit of PF-RCC and 291 patients received RCC only (Fig 1).

Preparation of standard and prion-filtered red cells

Patients recruited to the standard arm received RCC manufactured to the UKBTS standard component specification, namely red cells in additive solution (sodium, adenine, glucose and mannitol – SAG-M), LD by filtration, and with a shelf life of 35 days (National Blood Service, 2005). Prion filtered units were prepared at two blood centres, one in England and one in



n denotes number of patients in each case.
*Patients who did not provide any post-transfusion blood samples for antibody screening were excluded from the per protocol analysis of the primary outcome.
**See Table I for details of blood samples tested at 8 weeks and 6 months. RCC, red cell concentrate.

Fig 1. PRISM Study A: CONSORT Diagram

Scotland, by a second filtration step of LD SAG-M red cells using the Macopharma prion filter (PSE 3080xb P-Capt Prion Removal Pack; P-Capt, Macopharma, Tourcoing, France). The procedure was performed at room temperature according to the manufacturer's instructions within 36 h of donation. Filtration was considered complete when the P-Capt filter was flat and the edges began to clear of red cells; on average, the process took 30–60 min. The shelf life of the prion filtered units was unaltered by this process.

Transfused product characteristics

Red cell concentrates transfused to patients were obtained from routine hospital blood bank stock; volumes and haemoglobin (Hb) levels of these units were not recorded but were confirmed by NHSBT Quality Monitoring (QM) data collated over the study period to be within the requirements of UK Blood Transfusion Services. Volume and Hb were recorded for all PF-RCC as the filter is known to retain red cells resulting in lower Hb levels (Wiltshire *et al*, 2010). Selection of larger units for filtration kept the final volume and Hb values within UKBTS requirements.

Investigations

Tests for red cell alloantibodies (primary outcome) were conducted at trial entry and at 8 weeks and 6 months following the transfusion episode. Antibody screening and identification were performed at a single laboratory using UK standard methodology (National Blood Service, 2005). The clinical effects of the transfusion episode were assessed by pre-transfusion Hb concentration, next day Hb concentration, number of red cell units transfused, and total and mean volume of red cells transfused.

Statistical methods

Patients were considered 'on trial' once they had been transfused. A per protocol analysis comparing patients who received at least one unit of PF-RCC to patients who received only RCC was done on the primary outcome, the proportion of patients who developed new red cell antibodies. As this was a safety study, which could not be powered on the incidence of all red cell alloimmunization, stopping rules were devised so that the trial would stop if antibodies to P-Capt filtered red cells were detected in a single patient after transfusion of PF-RCC. It was assumed that the frequency of antibodies to PF-RCC pre-transfusion would be zero. With 270 patients receiving PF-RCC, detection of one patient with antibodies to P-Capt filtered red cells would be significantly different from zero at the 5% level, using a one-sided test.

An exact logistic regression analysis adjusting for the number of units transfused was performed for the primary out-

come (proportion of patients who developed new antibodies) and for the main secondary outcome (proportion of patients who had transfusion reactions). Additionally, tests comparing the two proportions were performed on the primary and secondary outcomes.

Monitoring of outcomes

Data on red cell alloimmunization, transfusion reactions and serious adverse events (SAEs), as per standard ICH GCP definitions (ICH, 1996), were collected and recorded from the time of transfusion until discharge from hospital, and reported regularly to the Independent Data Monitoring Committee (IDMC) for review. All transfusion reactions, as defined by the UK haemovigilance scheme Serious Hazards of Transfusion (SHOT; http://www.shotuk.org/wp-content/uploads/2011/03/SHOT-Categories-2010-v13.pdf), including other adverse events temporally associated with transfusion were reported. At the end of the study, but before data analysis, these were reviewed by independent members of the Trial Steering Committee (TSC), who decided which events met the secondary end-point of a classically defined transfusion reaction (with imputability classed as definitely, probably, possibly, or unlikely), and whether there were any new types of adverse events that could be attributed to the transfusions. Both the IDMC and the TSC included different cardiac anaesthetists and immunohaematologists.

Results

Patient characteristics

From 2088 patients screened (68% consented to the standard arm and 58% to the filtered arm), 1310 patients were enrolled. About 720 patients did not receive a transfusion during hospitalization and were not included in the study. About 590 patients were transfused and their data evaluated for safety. The recruitment periods were: first cohort of control patients (14 August 2007–23 June 2008), filter cohort (24 June 2008–7 July 2010), remaining control patients (8 July 2010–1 March 2011). The baseline characteristics of these patients, which showed no differences between trial arms, are summarized in Table I. A total of 917 units of PF-RCC and 1336 units of RCC were transfused (Table II). Following transfusion, 86 patients (14·6%) withdrew from providing follow-up antibody samples, and 45 patients (7·6%) died during the course of the study (19 standard arm and 26 filtered arm). Three deaths occurred on the day of surgery and 16 within 30 days of surgery. Post-transfusion samples for antibody testing were obtained at either 8 weeks or 6 months from 221/291 (76%) patients in the standard arm and from 238/299 (80%) of patients receiving one or more prion filtered units (Table I).

The majority of transfused patients (66·3%) received 1–3 units of red cells, 26·9% received 4–9 units of red cells and 6·8% received 10 or more units of red cells (Table II).

Table I. Summary of transfused patients.

Number of patients	Standard RCC arm	PF-RCC arm	Overall
Transfused patients, *N*	291	299	590
Baseline characteristics			
Age at surgery, years mean (SD)	70·9 (10·3)	71·2 (10·6)	71·1 (10·4)
Gender, *N* (%)			
Female	134 (46·1)	119 (39·8)	253 (42·9)
Male	157 (53·9)	180 (60·2)	337 (57·1)
Type of surgery, *N* (%)			
Cardiac surgery	246 (84·5)	261 (87·3)	507 (85·9)
Vascular surgery	4 (1·4)	9 (3·0)	13 (2·2)
General surgery*	40 (13·8)	26 (8·7)	66 (11·2)
Medical patients, *N* (%)	1 (0·3)	3 (1·0)	4 (0·7)
Pre-transfusion Hb (g/l), mean (SD)	130 (16)	130 (17)	130 (16)
Transfusion information			
Transfused and provided follow-up blood samples at *N* (%)			
8 weeks	195 (67·0)	215 (71·9)	410 (69·5)
6 months	194 (66·7)	217 (72·6)	411 (69·7)
Either 8 weeks or 6 months	221 (75·9)	238 (79·6)	459 (77·8)
Both 8 weeks & 6 months	168 (57·7)	194 (64·9)	362 (61·4)
Transfused and withdrawn, *N* (%)	44 (15·1)	42 (14·0)	86 (14·6)
Patient decision	39 (13·4)	40 (13·4)	79 (13·4)
Clinical decision	5 (1·7)	2 (0·7)	7 (1·2)
Died, *N* (%)	19 (6·5)	26 (8·7)	45 (7·6)

RCC, red cell concentrate; PF-RCC, prion-filtered red cell concentrates.

*Includes endocrine, colorectal, orthopaedic, urological, and gynaecological surgery.

These proportions were similar across both study arms. Sixty-one (20·4%) patients assigned to the filter arm also received standard RCC following massive blood loss or due to unavailability of filtered units in the blood bank when surgery was rescheduled at short notice. These 61 patients were transfused a total of 242 RCC units and 262 PF-RCC units. About 13 of these patients (21·3%) received 1–3 units of red cells, 28 (45·9%) required 4–9 units and 20 (32·8%) were transfused 10 or more units of red cells, confirming that urgent requirement for transfusions was the reason for the use of unfiltered red cells.

Red cell antibodies

None of the patients was transfused with red cell units other than those recorded for the study before the follow-up antibody samples were taken. Eight patients had antibodies at baseline, one of whom developed a further anti-Jka antibody, detected in the 6-month sample (Table III).

A total of 26 new red cell antibodies were detected in a total of 20 patients (10 standard arm and 10 filter arm), with

Table II. Red cell transfusion and outcome.

	Standard RCC arm	PF-RCC arm	Overall
Patients, *N*	291	299	590
Patients receiving standard and prion filtered units, *N*	0	61*	61
Total number of units used	1068	1185	2253
PF-RCC units	0	917	917
Standard RCC Units	1068	268	1336
Next day Hb following the first transfusion, g/l†	95 (11)	93 (10)	94 (10)
Units transfused, *N* (%)			
1–3 units	197 (67·7)	194 (64·9)	391 (66·3)
4–9 units	76 (26·1)	83 (27·8)	159 (26·9)
>10 units	18 (6·2)	22 (7·4)	40 (6·8)
Total	291 (100)	299 (100)	590 (100)

*Sixty-one patients required transfusion of red cell concentrates (RCC) following transfusion of prion-filtered red cell concentrates (PF-RCC). This was allowed in the study protocol for logistical and safety reasons, largely in massive blood loss situations. About 13 (21·3%) of these patients required 1–3 units of blood, 28 (45·9%) patients required 4–9 units of blood and 20 (32·8%) patients required 10 or more units of blood.

†The next day Hb is shown for the first transfusion only.

an overall alloimmunization rate of 4·4% (Table IV). An exact logistic regression analysis showed that neither the treatment arm nor the number of units received had a significant effect on the proportion of patients who developed new clinically significant antibodies, with odds ratio (ORs) of 0·93 [95% confidence interval (CI) 0·3, 2·5] and 0·95 (95% CI 0·8, 1·1), respectively. An additional test showed no significant difference in the proportion of patients developing alloimmunization between the two study arms [4·5% standard arm vs. 4·2% filtered arm, difference in proportions 0·3%, (95% CI −3·4, 4·1), $P = 0·865$].

Samples from two patients (Patients 7 and 19) were positive for anti-Kpa and anti-Cw when tested with standard screening cells, but negative against the filtered screening cells (Table III). This was an artefact caused by the standard panel expressing Kpa and Cw antigens, whilst the filtered panel did not. Both samples were negative when re-tested against standard panels negative for Kpa and Cw.

Transfusion reactions and adverse events

A total of 26 reactions/adverse events, suspected as being related to the transfusion (seven standard arm and 19 filtered arm), were reported by the trial sites (Table V). After independent clinical review, eight adverse events were deemed to be unrelated to transfusion, all in the filter arm. This final assessment was in agreement with the original opinion of the local principal investigators. These were: respiratory distress and hypertension - thought due to severe chest infection, fluid

Table III. Positive antibodies at 8 week and 6 month follow up samples.

Patient	Gender	Transfusionhistory	Screening sample	8-week sample	6-month sample	Clinically significant
PF-RCC arm						
1	Male	No	No antibody	anti-E	anti-E	Yes
2	Male	No	No antibody	No antibody	anti-E	Yes
3	Male	No	No antibody	anti-E	No antibody	Yes
4	Female	No	No antibody	No antibody	anti-E	Yes
5	Female	N/A	No antibody	anti-E	anti-E, anti-c	Yes
6	Male	No	No antibody	anti-D	N/A	Yes
7	Male	No	No antibody	No antibody	anti-Kpa	Yes
8	Male	No	No antibody	No antibody	anti-K	Yes
9	Male	No	anti-c	anti-c	anti-c, anti-Jka	Yes
10	Female	No	No antibody	No antibody	anti-S, anti-Jkb	Yes
Standard RCC arm						
11	Male	No	No antibody	anti-E	anti-E	Yes
12	Female	No	No antibody	N/A	anti-E	Yes
13	Male	No	No antibody	No antibody	anti-E	Yes
14	Female	No	No antibody	No antibody	anti-E	Yes
15	Male	No	No antibody	anti-E	anti-E, anti-c	Yes
16	Male	Yes	No antibody	N/A	anti-E anti-c	Yes
17	Female	No	No antibody	No antibody	anti-E anti-K	Yes
18	Male	N/A	No antibody	No antibody	anti-Fya	Yes
19	Female	No	No antibody	anti-Cw (eluate negative)	anti-C	Unlikely
20	Male	Yes	No antibody	anti-K, anti- Kpa	Not detected	Yes

N/A, not available; RCC, red cell concentrate; PF-RCC, prion-filtered red cell concentrate.

Table IV. Antibody formation in patients from whom at least one follow-up sample was tested.

	Standard RCC arm	PF-RCC arm	Overall
Patients, *N*	291	299	590
Screening samples tested, *N* (%)	288 (99·0)	296 (99·0)	584 (99·0)*
8-week samples tested, *N* (%)	195 (67·0)	215 (71·9)	410 (69·5)
6-month samples tested, *N* (%)	194 (66·7)	217 (72·6)	411 (69·7)
Samples tested at both 8 weeks & 6 months, *N* (%)	168 (57·7)	194 (64·9)	362 (61·4)
Samples tested at either 8 weeks and/or 6 months, *N* (%)	221 (75·9)	238 (79·6)	459 (77·8)
Patients with new antibody formation, *N* (%)†	10 (4·5)	10 (4·2)	20 (4·4)
Patients with antibodies specific for prion filtered red cells, *N* (%)†	0 (0·0)	0 (0·0)	0 (0·0)
Patients with pan-reacting red cell antibodies, *N* (%)†	0 (0·0)	0 (0·0)	0 (0·0)
Patients with alloimmunization to clinically significant red cell antigens, *N* (%)†	10 (4·5)	10 (4·2)	20 (4·4)

RCC, red cell concentrate; PF-RCC, prion-filtered red cell concentrate.

*This figure is not 100% as a few screening samples were not provided.

†Percentage was calculated using number of patients who gave at least one blood sample at either 8 weeks or 6 months as denominator.

Table V. Categories of suspected transfusion reactions reported and their imputability to transfusion, after review by the Data Management Committee and independent members of the Trial Steering Committee.

Category	Standard RCC arm	PF-RCC arm	Overall
Haemodynamic instability			
Definitely	0	0	13
Probably	0	0	
Possibly	1	3	
Unlikely	1	3	
Not related	0	4	
Haemorrhage	0	0	2
Definitely	0	0	
Probably	0	0	
Possibly	0	0	
Unlikely	0	0	
Not related	0	2	
Febrile			
Definitely	0	0	10
Probably	1	0	
Possibly	2	2	
Unlikely	1	2	
Not related	0	2	
Allergic reaction			
Definitely	0	0	1
Probably	0	0	
Possibly	1	0	
Unlikely	0	0	
Not related	0	0	
Total reported	7	19	26
Not related to transfusion after expert review	0	8	8
At least possibly related to transfusion	7	11	18

RCC, red cell concentrate; PF-RCC, prion-filtered red cell concentrate.

balance excluded transfusion associated circulatory overload (TACO) (1); fever plus hypotension associated with bleeding (1); hypotension, pulse unchanged, endotracheal tube pressing on vagus nerve (1); drop in blood pressure, which had been elevated and fell to normal (1); bleeding from wound drain post-surgery (1); temperature rise from sub-normal to normal, coming off cardio-pulmonary by-pass (1); atrial fibrillation related to ischaemic heart disease and cardiac surgery (1); bleeding from left inter-costal vessel post-surgery (1).

Because the onset of a transfusion reaction may not be immediate, no attempt was made to attribute the reaction to the type of red cells transfused in patients who received both standard and filtered red cells. No patient had more than one transfusion reaction.

Analysis by exact logistic regression on the proportion of patients with transfusion reactions/adverse events showed that neither the arm nor the number of units transfused had a significant effect on transfusion reactions, (OR 1·5, 95% CI 0·5, 4·6) and (OR 1·0, 95% CI 1·0, 1·1), respectively. Comparing the proportion of patients with transfusion reactions (that were definitely, probably, possibly or unlikely to be related) between the two arms showed a difference of −1·3 (95% CI −4·0, −1·5) and a *P*-value of 0·369, which was not significant. Including the eight reported transfusion reactions that were deemed not related to the transfusion in this analysis also yielded a non-significant result with a difference of −3·2 (95% CI −6·8, 0·4) and *P*-value of 0·099.

Serious adverse events

29·7% (175/590) of transfused patients experienced an SAE (30·9% standard arm; 28·4% filtered arm) (Table VI). These SAEs were all judged by the investigators and the IDMC to be clinically expected for the clinical situation and unrelated to the transfusion.

Discussion

Although not powered for the primary outcome, this is the largest safety study of prion-filtered blood components performed to date. In line with a number of smaller studies (Murphy *et al*, 2009; Cancelas *et al*, 2011) we found that transfusion of PF-RCC did not result in increased immunogenicity or other significant complications in patients. In addition, we demonstrated that alloimmunization rates in surgical patients, irrespective of study arm, were similar to previous reports (Redman *et al*, 1996). Whether repeated transfusion of this product to transfusion-dependent patients would result in increased alloimmunization rates has not been addressed in this study.

It is accepted that the open label, non-randomized design of this study could have led to a confounding of the results by changes in patient mix or care over the study period, however the baseline demographics of the two groups at the end of the study period, which spanned 42 months, were comparable by age, gender and type of surgery (Table I). As this study could not be powered on the incidence of all red cell alloimmunization, stopping rules were devised so that the trial would stop if antibodies to P-Capt filtered red cells were detected in a single patient after transfusion of PF-RCC. The rate of red cell alloimmunization and formation of pan-reactive antibodies were monitored by an IDMC.

The prion filtration process results in reduced Hb levels due to red cell trapping within the filter (Wiltshire *et al*, 2010) and further dilution of the product with SAG-M to make the volume up to standard requirements (National Blood Service, 2005), therefore high volume units were selected for manufacture of the prion-filtered units transfused in this study. Quality management data collected at three time points during the study period showed that the mean volume and Hb of prion filtered and standard RCC were comparable and were above the minimum UKBTS specification (National Blood Service, 2005; Wiltshire *et al*, 2010). This suggests that prion filtration for selected patient groups could be implemented without compromising the Hb content of the component. Standardizing the Hb content of the product in the two arms allowed comparison of post-transfusion haemoglobin values and the rates of repeat transfusion in the two arms. No differences were seen to suggest either reduced red cell recovery or shortened intra-vascular survival.

Our primary endpoint, red cell antibody formation following transfusion, required rigorous collection of follow-up samples, which proved to be a significant logistical challenge largely due to the age and frailty of the patient population undergoing cardiac surgery. In addition, the majority of patients lived a significant distance away from the hospital where the surgery took place, resulting in a very wide geographical area over which patients needed to be followed-up. Despite these limitations, the study team managed to collect at least one post-transfusion blood sample in almost 80% of patients.

The use of a central laboratory and designated operator for antibody screening tests was implemented to eliminate variations in testing technique and interpretation of results. Although the manufactured prion-filtered screening panel cells were frozen in aliquots at the study's initiation and used throughout the study period, this method of standardization was not applied to the standard screening panel, as the panel available in the NHSBT laboratory at the time each batch of samples was tested was used. This resulted in variation in additional expressed antigens not normally required for standard screening and resulted in positive antibody screens against the standard panel in three sets of samples, which were found to be negative against the prion-filtered panel cells. Further testing confirmed that these antibodies were reactive against Kpa and Cw antigens, which are not normally expressed in standard screening panels, and the prion-filtered screening panels were negative for these antigens.

The study was designed to report all transfusion reactions, both classically defined ones (as reportable to SHOT) and any adverse events possibly related to the transfusion. At the end of the study period but before data analysis, the reported reactions were subjected to review by independent members of the TSC (including a cardiac anaesthetist), following which, eight of the 26 reported events were considered unrelated to the transfusion episode as they all had other plausible explanations. It is noted, however, that all of the events deemed unrelated occurred in the prion filtered arm, a possible explanation being reporting bias by investigators, an unavoidable consequence of the open-label nature

Table VI. Summary of severe adverse events by clinical category.

	Standard RCC arm	PF-RCC arm	Overall
Patients with SAEs, N	90	85	175
SAE events, total, N:	134	114	248
Central nervous system	6	6	12
Cardiovascular	29	29	58
Respiratory	10	5	15
Renal	10	13	23
Haematology	4	3	7
Surgical	7	2	9
Haemorrhage	34	27	61
Required surgery	30	24	54
Did not require surgery	3	2	5
Coagulopathy with bleeding	1	1	2
Sepsis	25	24	49
Local	9	10	19
Systemic	3	4	7
Chest	13	10	23
Other	9	5	14

RCC, red cell concentrate; PF-RCC, prion-filtered red cell concentrate; SAE, severe adverse event.

of the study. The choice of cardiac surgery patients for a transfusion safety study is not ideal, given the high background rate of SAEs. However, since the drive to reduce surgical blood usage in the UK, an alternative surgical population could not be identified with a high enough transfusion rate combined with a low incidence of background adverse events.

In conclusion, our findings suggest that transfusion of red cells filtered through the P-Capt filter does not appear to reduce the overall safety of transfusion. These data require to be confirmed in larger patient populations, and in the multi-transfused, either by further trials or, more feasibly, through post-marketing surveillance.

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Author's contribution

All authors contributed extensively to the work presented in this paper. M.O.E, L.W, and L.M jointly conceived and designed the study with C.L and S.M; M.O.E, L.C, A.M and C.M wrote the manuscript. L.C performed the statistical analysis; T.R assembled the data; V.H and CC prepared the prion filtered red cells; S.P performed the antibody screening; M.O.E, A.M, C.L, C.M, M.M, L.M, A.D and L.W were part of the study management team; C.L, A.D, S.M, L.M and L.W commented on the manuscript at all stages. All authors discussed the results and implications.

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