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A Randomised Controlled Trial and Economic Evaluation of Intra-Operative Cell Salvage during Caesarean Section in Women at Risk of Haemorrhage: The SALVO Trial (cell SALVage in Obstetrics)

Roberts, Tracy; McLoughlin, Carol; Daniels, Jane; Gao Smith, Fang; Jackson, Louise

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1 ***A Randomised Controlled Trial and***
2 ***Economic Evaluation of Intra-Operative***
3 ***Cell Salvage during Caesarean Section***
4 ***in Women at Risk of Haemorrhage: The***
5 ***SALVO Trial (cell SALVage in Obstetrics)***

6 Khalid S. Khan,^{1*} Philip Moore,² Matthew Wilson,³ Richard Hooper,⁴ Shubha Allard,⁵ Ian
7 Wrench,⁶ Tracy Roberts,⁷ Carol McLoughlin,⁷ Lee Beresford,⁴ James Geoghegan,² Jane
8 Daniels,⁸ Sue Catling,⁹ Vicki A. Clark,¹⁰ Paul Ayuk,¹¹ Stephen Robson,¹² Fang Gao-Smith,¹³
9 Matthew Hogg,¹⁴ Louise Jackson,⁷ Doris Lanz,¹ Julie Dodds,¹ on behalf of the SALVO study
10 group

11 ¹ Women's Health Research Unit, Barts and the London School of Medicine and Dentistry,
12 Queen Mary University of London, UK

13 ² Birmingham Women's Hospital, Birmingham, UK

14 ³ School of Health and Related Research (SchARR), University of Sheffield, UK

15 ⁴ Pragmatic Clinical Trials Unit, Centre for Primary Care and Public Health, Queen Mary
16 University of London, UK

17 ⁵ NHS Blood and Transplant, London, UK

18 ⁶ Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

19 ⁷ Health Economics Unit, University of Birmingham, UK

20 ⁸ Birmingham Clinical Trials Unit, University of Birmingham, UK

21 ⁹ Singleton Hospital, Swansea, UK

22 ¹⁰ Simpson Centre for Reproductive Health, Royal Infirmary, Edinburgh, UK

23 ¹¹ Royal Victoria Infirmary, Newcastle-upon-Tyne, UK

24 ¹² Institute of Cellular Medicine, University of Newcastle, UK

25 ¹³ Perioperative, Critical Care and Trauma Trials Group, University of Birmingham, UK

26 ¹⁴ Royal London Hospital, Barts Health NHS Trust, London, UK

27 * Corresponding author. Professor Khalid S. Khan, Women's Health Research Unit, Centre
28 for Primary Care and Public Health, Barts and the London School of Medicine and Dentistry,
29 Queen Mary University of London, Yvonne Carter Building, 58 Turner Street, London,
30 E1 2AB, United Kingdom; k.s.khan@qmul.ac.uk

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32 Keywords: Cell Salvage, Caesarean Section, Obstetrics.

1 **Abstract**

2 **Background:** Caesarean section is associated with blood loss and maternal morbidity.
3 Excessive blood loss requires transfusion of donor (allogeneic) blood, a finite resource. Cell
4 salvage returns blood lost during surgery to the mother. It may avoid the need for donor
5 blood transfusion, but reliable evidence of its effects is lacking.

6 **Objectives:** To determine if routine use of cell salvage during caesarean section, in mothers
7 at risk of haemorrhage, reduces the rates of blood transfusion and postpartum maternal
8 morbidity, and is cost-effective, in comparison to standard practice without routine salvage
9 use.

10 **Design:** Individually randomised controlled, multicentre trial with cost-effectiveness analysis.
11 Treatment was not blinded.

12 **Setting:** 26 UK obstetric units.

13 **Participants:** Of 3054 women recruited between June 2013 and April 2016, we randomly
14 assigned 3028 women at risk of haemorrhage to cell salvage or routine care. Randomisation
15 was stratified, using random permuted blocks of variable sizes. Of these, 1672 had
16 emergency and 1356 elective caesareans. We excluded women for whom cell salvage or
17 donor blood transfusion was contraindicated.

18 **Interventions:** Cell salvage (intervention) versus routine care without salvage (control). In
19 the intervention group, salvage was set up in 95.6% of the women and, of these, 50.8% had
20 salvaged blood returned. In the control group, 3.9% had salvage deployed.

21 **Main outcome measures:** Primary: donor blood transfusion. Secondary: units of donor blood
22 transfused; time to mobilisation; length of hospitalisation; mean fall in haemoglobin;
23 fetomaternal haemorrhage measured by Kleihauer test; maternal fatigue. Analyses were
24 adjusted for stratification factors and other factors believed to be prognostic a priori. Cost-
25 effectiveness outcomes: costs of resources and service provision taking the UK National
26 Health Service perspective.

27 **Results:** We analysed 1498 and 1492 participants in the intervention and control groups,
28 respectively. Overall, the transfusion rate was 2.5% in the intervention group versus 3.5% in

1 control (adjusted odds ratio [OR] 0.65, 95% confidence interval [CI] 0.42 to 1.01, p=0.056).
2 In a planned subgroup analysis, the transfusion rate was 3.0% in intervention versus 4.6% in
3 control among emergency caesareans (adjusted OR 0.58, 95% CI 0.34 to 0.99), whereas it
4 was 1.8% versus 2.2% among elective caesareans (adjusted OR 0.83, 95% CI 0.38 to 1.83)
5 (interaction p=0.46, suggesting that the difference in effect between subgroups was not
6 statistically significant). Secondary outcomes did not differ between groups, except
7 fetomaternal haemorrhage was higher under salvage in Rhesus D-negative women with D-
8 positive babies (25.6% vs. 10.5% adjusted OR 5.63, 95% CI 1.43 to 22.14, p=0.013). No case
9 of amniotic fluid embolism was observed. The additional cost of routine cell salvage during
10 caesarean was estimated, on average, at £8,110 per donor blood transfusion avoided.

11 **Limitations:** We are unable to comment on long-term antibody sensitisation effects.

12 **Conclusions:** The modest evidence for an effect of routine use of cell salvage during
13 caesarean section on rates of donor blood transfusion was associated with increased
14 fetomaternal haemorrhage, which emphasises the need for adherence to guidance on anti-D
15 prophylaxis. Based on the findings of this trial, cell salvage is unlikely to be considered cost-
16 effective.

17 **Future work:** Research into risk of alloimmunisation among women exposed to cell salvage
18 is needed.

19 **Study Registration:** ISRCTN66118656.

20 **Funding Details:** This project was funded by the NIHR Health Technology Assessment
21 programme, project reference number 10/57/32.

22 *[526 words]*

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2 **List of abbreviations**

3	AE	Adverse Event
4	AFE	Amniotic Fluid Embolism
5	CC	Complication and Comorbidity
6	CEAC	Cost-effectiveness acceptability curves
7	CI	Confidence Interval
8	CONSORT	Consolidated Standards of Reporting Trials
9	CRF	Case Report Form
10	DMC	Data Monitoring Committee
11	HDFN	Haemolytic Disease of the Fetus and Newborn
12	HLC	Higher Level of Care
13	HR	Hazard Ratio
14	HTA	NIHR Health Technology Assessment programme
15	FMH	Fetomaternal haemorrhage (maternal exposure to fetal blood)
16	ICER	Incremental Cost-Effectiveness Ratio
17	IQR	Interquartile Range
18	ISRCTN	International Standard Randomised Controlled Trial Number
19	ITT	Intention To Treat
20	LDF	Leukocyte Depletion Filter
21	MD	Mean Difference
22	MFI	Multidimensional Fatigue Inventory
23	NCT	National Childbirth Trust
24	NHS	(UK) National Health Service
25	NHSBT	NHS Blood and Transplant
26	NICE	National Institute for Health and Care Excellence
27	NIHR	National Institute for Health Research
28	ODP	Operating Department Practitioner
29	OR	Odds Ratio
30	PBM	Patient Blood Management
31	PCTU	Pragmatic Clinical Trials Unit
32	PIS	Patient Information Sheet
33	PP	Per Protocol
34	PPH	Postpartum haemorrhage
35	PSA	Probabilistic Sensitivity Analysis
36	PSSRU	Personal Social Services Research Unit
37	QA	Quality Assurance
38	QALY	Quality-Adjusted Life Year
39	QMUL	Queen Mary University of London
40	RBC	Red Blood Cells

1	RCOG	Royal College of Obstetricians and Gynaecologists
2	RCT	Randomised Controlled Trial
3	REC	Research Ethics Committee
4	RR	Relative Risk
5	SAE	Serious Adverse Event
6	SALVO	Cell SALVage in Obstetrics
7	SD	Standard Deviation
8	SHOT	Serious Hazard of Transfusion
9	TMG	Trial Management Group
10	TSC	Trial Steering Committee

1 ***Plain English summary***

2 Mothers delivering by caesarean section bleed heavily at times. In this situation, unless they
3 get a donor blood transfusion their life is put at risk. Donor blood for transfusion is a limited
4 resource, and despite many advances, people who receive donor blood can sometimes
5 experience adverse reactions. Blood transfusions should only be given when absolutely
6 necessary, and alternatives should be used wherever available.

7 Nowadays, it is possible to use cell salvage. This is a process where blood a patient loses at
8 surgery is collected by a machine, cleaned, and returned to them. In women who have
9 caesarean sections, this might avoid the need for donor blood, reduce the risk of
10 complications and potentially cut costs. We conducted this study to evaluate the effects of
11 routine use of cell salvage in caesarean section, compared to standard care where this is not
12 routinely done.

13 This study included over 3,000 mothers giving birth by caesarean section. Half of these were
14 randomly selected to receive cell salvage, meaning that the cell salvage was set up to collect
15 blood lost. Cell salvage was found to be safe. It slightly reduced the use of blood
16 transfusions. For every 100 mothers given cell salvage, one avoided donor blood transfusion.
17 If the blood groups of the mother and the baby were mismatched, mothers with a negative
18 blood group needed additional treatment to avoid complications in future pregnancies. This
19 can be easily monitored and provided as part of routine care. Based on the results of this
20 study, cell salvage is unlikely to be considered cost-effective.

1 **Scientific summary**

2 **Background**

3 Excessive blood loss (haemorrhage) in childbirth is an important direct cause of maternal
4 death and has a profound impact on survivors. It is responsible for the majority of emergency
5 hysterectomies and maternal critical care admissions. Haemorrhage is more common in
6 women undergoing a caesarean section, particularly in the presence of placental
7 abnormalities (placenta praevia/accreta), pre-eclampsia, antepartum haemorrhage, a history
8 of previous caesarean section(s), or emergency caesarean for any indication. Approximately
9 166,000 caesarean sections (26% of all deliveries) are performed annually in England, around
10 60% of which are emergency procedures. It is the most frequent major surgery conducted by
11 the UK National Health Service. Major haemorrhage can occur without warning during
12 caesarean section with rapid unanticipated deterioration requiring urgent response.

13 The treatment for major haemorrhage involves donor blood transfusion when the operative
14 loss is life threatening or when the mother has severe anaemia following arrest of the
15 haemorrhage. Red cell concentrate is a limited resource in demand by many clinical services.
16 The high frequency of caesarean sections has a major impact on blood transfusion services
17 (with £7M direct cost for donor blood components alone used in the obstetric setting per
18 year), placing a constant challenge to the delivery of high quality health care at all points of
19 need simultaneously. There has also been a major shift to more restrictive clinical transfusion
20 practice aligned to the principles of patient blood management, which include using
21 transfusion alternatives where feasible and harnessing the patient's own reserves.
22 Accordingly, donor blood is used sparingly in the healthy obstetric population. This can
23 result in anaemia postnatally, which is potentially associated with longer recovery, increasing
24 hospitalisation costs and wound infection rates.

25 Intraoperative cell salvage collects the woman's own blood lost during caesarean, processes it
26 and returns it to her circulation. It reduces the infectious and allergenic risks associated with
27 donor blood transfusion. It can be used routinely for moderate blood loss, which is an
28 expected feature of uncomplicated caesarean sections, returning all salvaged blood to
29 minimise postoperative anaemia and its consequences, including reduction in maternal life
30 quality. Cell salvage has been shown to reduce the amount of donor blood given in other
31 operations from a wide spectrum of surgical disciplines, but has hitherto been considered

1 relatively contraindicated for use in obstetrics, as a result of theoretical concerns around the
2 risk of contamination of salvaged blood with amniotic fluid, the potential for provoking
3 maternal amniotic fluid embolism and the possibility of increasing exposure of the mother to
4 fetal blood. These concerns have proven unfounded, as research has not only shown that
5 modern equipment effectively removes amniotic fluid from the salvaged blood, but also that
6 transfer of amniotic fluid into the maternal circulation is a common event during birth which
7 usually does not cause any adverse effects. Cell salvage has begun to enter use in caesarean
8 section, but opinion about its value is not yet evidence-based.

9 **Objectives**

10 The primary objective of the trial was to determine whether the routine use of cell salvage
11 during caesarean section in women at risk of haemorrhage safely reduced the need for donor
12 blood transfusion, in comparison to standard practice where salvage is not routinely used. In
13 addition, we sought to assess the consistency of the effect of cell salvage across subgroups
14 defined by indication for caesarean, and to determine the effect of cell salvage on secondary
15 outcomes including the units of donor blood transfused, fall in perioperative haemoglobin
16 concentration, any resulting morbidity, maternal exposure to fetal blood, as well as its cost-
17 effectiveness.

18 **Methods**

19 The SALVO study was designed as a multicentre individually randomised controlled trial
20 (registered as ISRCTN66118656) with cost-effectiveness analysis. Following the necessary
21 approvals (UK ethical approval number 12/NW/0513), the study was conducted in 26
22 obstetric units across the UK, aiming to recruit 3,050 women to give 80% power to detect a
23 2% difference in the transfusion rate (control event rate of 5%). Our sample consisted of
24 women who were admitted to the labour ward for delivery by emergency (Category 1 to 3:
25 with an element of maternal or fetal compromise) or elective (Category 4: no maternal or
26 fetal compromise) caesarean section, with an identifiable increased risk of haemorrhage, who
27 were at least 16 years of age and able to understand written and spoken English. We excluded
28 women undergoing an elective first caesarean due to either maternal request or known breech
29 presentation, as the risk of severe haemorrhage is very low in these groups. We also excluded
30 women for whom either cell salvage or donor blood transfusion was contraindicated,
31 including sickle cell disease or trait, active malignancy such as abdominal cancer, religious or

1 other beliefs precluding blood transfusion, or significant maternal antibodies making it
2 difficult to find cross-matched blood compatible for transfusion.

3 For all women undergoing elective caesarean section, information about the study was
4 provided at least one day before the surgery, usually at the time of booking the caesarean
5 section; written informed consent for the study was then obtained before the surgery. For
6 women undergoing emergency caesarean section, either written informed consent was
7 obtained before the surgery if there was sufficient time for discussion and reflection, or
8 otherwise verbal consent was taken immediately before the surgery with written consent
9 obtained after the operation usually on the postnatal ward. In either case, in order for consent
10 to be properly informed, the woman either had to have a) received information antenatally
11 before the onset of labour, and previously stated her willingness to take part in the study, or
12 b) following a substantial amendment to the protocol, had sufficient time, and was not too
13 distressed to receive study information after admission to the labour ward; this was deemed to
14 be the case if the woman was comfortable with effective epidural analgesia in situ, or not yet
15 in established first stage of labour, and had at least one hour to come to a decision after
16 receiving the information and prior to giving verbal consent. Participating women were
17 randomised by entry into an online system, to either caesarean section with cell salvage
18 (intervention group), with cell saver set-up and collection of shed blood from the outset of
19 surgery, and return of any processed blood obtained; or to caesarean section without cell
20 salvage (control group), with transfusion of donor blood according to local guidelines.

21 The primary outcome was the proportion of women receiving donor blood transfusion due to
22 haemorrhage. Trial groups were compared according to this outcome on an intention-to-treat-
23 basis estimating the effect using odds ratio (OR) and 95% confidence intervals (CI). Two pre-
24 specified subgroup analyses were planned, including analysis of treatment effect by
25 indication for caesarean section (elective or emergency) and by treatment centre. The first of
26 these was analysed by statistically testing for an interaction between indication for caesarean
27 section and treatment. The second was analysed by testing for a random regression
28 coefficient for the effect of treatment at different centres, in addition to a random intercept.
29 In order to account for women in the control group who received cell salvage due to a clinical
30 decision, an additional sensitivity analysis was planned which would assume that all
31 instances of return of salvaged blood in the control group would have been instances of donor
32 blood transfusion had the cell salvage machine not been present. Analyses were adjusted for a

1 random effect of treatment centre and fixed effects of stratification variables and other
2 baseline characteristics believed to be associated with the outcome measure of haemorrhage a
3 priori.

4 Secondary outcomes included: units of blood transfused; time to first mobilisation; length of
5 hospital stay; pre- and postoperative serum haemoglobin, maternal exposure to fetal blood as
6 measured by a Kleihauer test, maternal fatigue; adverse events (including transfusion
7 reactions); resources used intra- and postoperatively; costs of staff training; and process
8 outcomes (including volume of salvaged blood returned, and technical failure of cell
9 salvage).

10 A cost-effectiveness analysis was carried out from the NHS perspective based on the
11 principal clinical outcome of the trial with the results expressed as cost to avoid donor blood
12 transfusion. A decision tree model was used which collated all the relevant resource use, cost,
13 and outcome data collected prospectively during the trial to compare the overall cost-
14 effectiveness of cell salvage with standard care. The resource use for both groups of the trial
15 was estimated by evaluating the individual components of these procedures (bottom-up
16 costing). Unit cost data were then attached to the resource use. A probabilistic sensitivity
17 analysis was carried out to explore the effects of the inherent uncertainty in parameter
18 estimates on model results.

19 **Results**

20 Between June 2013 and April 2016, 3054 participants requiring caesarean section from 26
21 participating hospitals were initially recruited for randomisation. After 26 exclusions for
22 eligibility and consent issues, 3028 participants were randomly allocated to either control
23 (n=1511) or intervention (n=1517). Of these 3028 participants, 1672 were scheduled for
24 emergency and 1356 for elective caesarean section. A further 35 participants had to be
25 excluded after randomisation due to vaginal delivery or transfer to another site. We analysed
26 data from 1492 participants in the control group and 1498 participants in the cell salvage
27 group, after these exclusions for eligibility and loss to follow-up. Adherence to assigned
28 intervention was 95.6% in the cell salvage group and 96.1% in the control group. Among the
29 women treated with cell salvage in the intervention group, 50.8% had salvaged blood
30 returned, with an average volume of 259.9ml.

1 Overall, the transfusion rate was 2.5% in the group assigned to cell salvage versus 3.5% in
2 control (adjusted OR 0.65, 95% CI 0.42 to 1.01, $p=0.056$). In the planned subgroup analysis,
3 the transfusion rate was 3.0% in women assigned to salvage versus 4.6% in control among
4 emergency caesareans (adjusted OR 0.58, 95% CI 0.34 to 0.99), whereas it was 1.8% versus
5 2.2% among elective caesareans (adjusted OR 0.83, 95% CI 0.38 to 1.83) (interaction
6 $p=0.46$, suggesting that the difference in effect between subgroups was not statistically
7 significant). In an additional, exploratory subgroup analysis, the transfusion rate was 1.9% in
8 women assigned to salvage versus 2.9% in control among caesareans with normal
9 placentation (adjusted OR 0.56, 95% CI 0.34 to 0.94), whereas it was 9.6% versus 8.9%
10 among caesareans with abnormal placentation (adjusted OR 0.83, 95% CI 0.38 to 1.83)
11 (interaction $p=0.28$). As a sensitivity analysis assuming that donor blood transfusion would
12 have been required had cell salvage not been deployed in the control group showed a
13 reduction in the proportion of participants requiring donor blood transfusion (5.6% vs. 2.5%,
14 adjusted OR 0.39, 95% CI 0.26 to 0.59, $p<0.001$).

15 There were small differences between groups for time to mobilisation (median 0.74 vs. 0.72
16 days, adjusted hazard ratio [HR] 1.11, 95% CI 1.03 to 1.19, $p=0.006$) and length of hospital
17 stay (2.131 vs. 2.126 days, adjusted HR 1.08, 95% CI 1.00 to 1.16, $p=0.050$). Mothers
18 assigned to cell salvage had greater exposure to fetal blood (25.6% vs. 10.5%, adjusted OR
19 5.63, 95% CI 1.43 to 22.14, $p=0.013$). There were no differences between groups in other
20 secondary outcomes. There was no case of amniotic fluid embolism observed in any
21 instances of cell salvage use.

22 The results of the economic evaluation suggested that routine cell salvage is more costly than
23 standard care with the average cost per patient estimated at £1,327 compared to £1,244. The
24 incremental cost-effectiveness ratio (ICER) representing the average additional cost of
25 routine cell salvage during caesarean section in women at risk of haemorrhage compared to
26 standard care was estimated to be approximately £8,110 to avoid a donor blood transfusion.
27 This estimate was shown to be robust in sensitivity analyses.

28 **Conclusions**

29 There was modest evidence for an effect of routine use of cell salvage during caesarean
30 section on the need for donor blood transfusion, particularly among emergency procedures. In
31 women with RhD-negative blood groups who gave birth to RhD-positive babies, cell salvage
32 was associated with increased maternal exposure to fetal blood, which needs to be matched

1 with higher doses of anti-D if cell salvage is to be deployed during caesarean sections among
2 RhD-negative mothers. Our finding highlights the need to adhere to guidelines on anti-D
3 prophylaxis and the need for vigilance also with respect to the potential sensitisation to other,
4 rarer antibodies. The health economic analysis could not demonstrate that cell salvage was
5 more cost-effective than standard care. Recommendations for future research include:

- 6 1. Investigate the impact of non-Rhesus antibody sensitisation with long-term follow-up
7 of mothers exposed to cell salvage during caesarean section.
- 8 2. Investigate the need for greater amounts of routine anti-D administration where cell
9 salvage has been used.
- 10 3. Investigate factors, e.g. swab washing or number of suckers used, that increase the
11 likelihood of returning blood during use of cell salvage.
- 12 4. Investigate the effectiveness of cell salvage in specific sub-groups e.g. placenta
13 accreta.
- 14 5. Investigate the role of cell salvage in low-middle income countries where caesarean
15 rates are rising and blood transfusion services are not well developed.
- 16 6. If new, cheaper or more efficient cell salvage technology becomes available, the
17 conclusions of SALVO may need to be revisited. The same is true if donor blood
18 shortages should become extreme and acute.

19 ***Trial registration***

20 This study was prospectively registered as ISRCTN66118656.

21 [2170 words.]

1 **Chapter 1 Introduction**

2 **Background and rationale**

3 **Haemorrhage and caesarean section**

4 Haemorrhage (excessive blood loss) is an important direct cause of maternal death¹. Life
5 threatening blood loss is the primary indication for 95.6% of emergency hysterectomies in
6 labour.² Haemorrhage is the commonest cause for maternal critical care admission³⁻⁵ and
7 places a profound health burden on the childbearing population during an important life
8 event. Haemorrhage is more common in women who have caesarean sections,⁶ particularly
9 when indicated for conditions such as placenta praevia (low lying placenta) or when an
10 emergency caesarean section is required.⁷

11 Approximately 166,000 caesarean sections are performed annually in England. Almost two
12 thirds of these are performed as emergency procedures, and the numbers of operations have
13 been ever increasing.⁸ Caesarean section currently accounts for 26.2% of deliveries (2013-14)
14 and it is the most frequent major operation conducted by the NHS with over 400 performed
15 per day in England alone. Major haemorrhage can occur without warning during caesarean
16 section, and the woman's condition can quickly deteriorate during attempts to arrest blood
17 loss. Rates of major obstetric haemorrhage vary in the literature according to the definition
18 used; postpartum haemorrhage occurs with a frequency of 2.93%,⁶ but severe PPH of 2.5l or
19 more is much less common with a frequency of around 0.5-0.6%.⁹ The likelihood of
20 haemorrhage is increased by risk factors including previous caesarean section, low-lying or
21 morbidly adherent placenta, emergency caesarean section for any indication, antepartum
22 haemorrhage and pre-eclampsia.^{6,9}

23 **Donor blood transfusion in obstetrics**

24 The treatment for major haemorrhage involves allogeneic (donor) blood transfusion when the
25 operative loss is life threatening or when the mother has severe anaemia following arrest of
26 the haemorrhage. Approximately 66,000 units of blood (known as Packed Red Cells) are
27 given annually in the UK maternity setting.¹⁰ This equates to £7M per year¹¹ without
28 considering additional healthcare costs involved in the administration of blood or the

1 financial consequences of maternal acute illness. Thus any reduction in the amount of blood
2 required for obstetrics could significantly reduce the cost of blood transfusions.

3 Donor blood is a limited resource which needs to be used judiciously. Although national
4 blood services are constantly improving their capacity to guarantee availability of blood for
5 transfusion across all clinical requirements,¹² it remains an expensive service to recruit and
6 retain blood donors to minimise the risks of shortages, and new infective risks may pose risks
7 in future. The availability of donor blood is an essential prerequisite for major procedures
8 including joint replacement, cardiac surgery, organ transplantation, cancer care, obstetric
9 emergencies and the management of trauma. This wide range of demands provides
10 significant challenges to the NHS in the delivery of high quality health care to all points of
11 need simultaneously. All NHS hospitals are required to have policies for blood shortages,
12 including cancellation of elective surgery which may require transfusion.

13 There is an increasing focus on Patient Blood Management (PBM), an international initiative
14 promoting the use of transfusion alternatives including cell salvage where feasible and
15 limiting the use of donor transfusion where avoidable.^{13, 14} Transfusion sparing strategies
16 successful in other surgical populations, such as pre-donation and acute normovolaemic
17 haemodilution, cannot be employed in caesarean section. The role of permissive anaemia and
18 high transfusion threshold is potentially limited by maternal symptoms in the post-natal
19 period (see below).

20 Additionally, there are major risks associated with donor blood transfusion, including death
21 from transfusion error, acute transfusion reaction, fatal lung injury and infection
22 transmission.¹⁵ These risks are monitored by the UK Haemovigilance scheme Serious
23 Hazards of Transfusion (SHOT) with feedback of results via annual reports.¹⁶ Despite
24 improved safety mechanisms, these rates persist, although serious events are very rare, with
25 mortality rates of 1 in 100,000.¹⁷ Nevertheless, minimising unnecessary transfusion is an
26 important strand in promoting patient safety.

27 ***Postnatal anaemia and its consequences***

28 Concerns regarding transfusion safety together with changes in clinical practice as
29 highlighted above have led to a more overall restrictive approach to transfusion. The
30 application of these principles to the obstetric setting with higher transfusion thresholds can
31 result in significant postnatal maternal anaemia.

1 In addition to fatigue as a direct consequence, postoperative maternal anaemia has also been
2 associated with longer hospitalisation, increased wound infection rates and delayed time to
3 mobility.¹⁸ Anaemia prolongs hospital stay by a third, with an overall 50% higher cost per
4 hospitalisation.¹⁹ The economic consequences of anaemia resulting from obstetric
5 haemorrhage are therefore profound and any intervention which could reduce maternal
6 morbidity and mortality is worthy of scrutiny.

7 Maternal morbidity resulting from anaemia crucially affects the mother's capacity to provide
8 care for the newborn. An intervention to relieve maternal anaemia is therefore highly relevant
9 for the quality of life of this young, generally healthy population and that of their offspring.

10 ***Intraoperative cell salvage***

11 Intraoperative cell salvage collects the patient's own blood lost during an operation,
12 processes it and returns it to their circulation. This way, cell salvage allows re-transfusion of
13 the patient's own blood that would otherwise have been wasted.

14 Its use has been shown to reduce the amount of donor blood given in other operations: A
15 Cochrane review and other meta-analyses of the use of cell salvage in non-obstetric settings
16 demonstrated a significant reduction in patient exposure to donor blood.²⁰ An HTA report put
17 the relative risk of exposure to donor blood at 0.59 (95% CI 0.48 to 0.73) for pooled trials of
18 cell salvage.²¹ However, this evidence did not include any trials examining caesarean section.

19 Given that cell salvage may reduce the need for a standard donor blood transfusion, there
20 should be fewer transfusion reactions and infections that may be associated with donor blood.

21 One potential complication associated with cell salvage in the non-obstetric setting arises due
22 to the use of leukocyte depletion filters (LDFs) during the return of salvaged blood.^{16, 22-25}

23 LDFs are used in the re-transfusion of salvaged blood with the aim of filtering out foreign
24 cells such as squamous cells contained within amniotic fluid. They have been the subject of
25 scrutiny in the medical literature: There are some reports of unexplained hypotension
26 associated with blood return and filters have been implicated as a potential source of most
27 anaphylactoid responses (although this remains a contentious issue, and in rare cases
28 hypotension has been associated with cell salvage even when no LDF was used).¹⁶ Moreover,
29 the addition of a filter may restrict the rapid re-infusion of blood in the context of massive
30 haemorrhage, by slowing down the blood flow rate. Therefore, these filters are routinely
31 omitted at the discretion of clinicians when rapid blood return is imperative.

1 Overall, cell salvage is a technology that may simultaneously reduce the need for donor blood
2 transfusion and prevent anaemia. It could therefore avoid the serious morbidity associated
3 with haemorrhage as well as achieve a significant reduction in costs. In recent years, cell
4 salvage machines have been refined and have entered routine use in cardiac, orthopaedic,
5 liver and vascular surgery where there is a risk of major haemorrhage. Their use in caesarean
6 section has not yet been adequately examined.

7 ***Cell salvage in caesarean section***

8 Moderate blood loss is a normal expectation during uncomplicated caesarean section. By
9 salvaging this blood, it may be returned to the patient, even when donor blood transfusion
10 would not normally be considered for the reasons already discussed. This might further serve
11 to reduce post-natal anaemia and its associated morbidity, thus benefiting mothers who only
12 lose a moderate amount of blood during caesarean section, and who would not normally be
13 considered for a donor blood transfusion.

14 The use of cell salvage in the obstetric setting had previously been considered contraindicated
15 as a result of theoretical concerns regarding the risk of amniotic fluid embolism (AFE), a
16 serious but extremely rare (about 1 in 20,000) complication of pregnancy and childbirth. Its
17 pathophysiology is more similar to anaphylaxis than to embolism. AFE is usually diagnosed
18 at autopsy when fetal squamous cells are found in the maternal lungs, but fetal cells are also
19 found in the circulation of labouring women who do not develop the typical clinical features
20 of AFE. Even though the term is controversial, the complications of AFE are attributed to
21 multi-organ failure and maternal fatality. Studies examining the quality of blood that would
22 be returned to the mother, had cell salvage been used at caesarean section, have shown that
23 there is no safety concern with modern equipment since amniotic fluid is effectively and
24 completely removed by cell salvage processing.^{26, 27} Despite concerns about AFE as a
25 consequence of cell salvage having proven unfounded in research thus far,^{26, 27} and evidence
26 that transfer of amniotic fluid into the maternal circulation is a common event which does not
27 necessarily cause adverse effects,²⁸⁻³¹ this issue remains of concern to clinicians.

28 Another potential risk associated with cell salvage in the obstetric setting is sensitization to
29 red cell antigens leading to haemolytic disease of the fetus and newborn (HDFN).^{32, 33} This
30 occurs when there is an incompatibility between antigens carried on red blood cells of a
31 woman and her infant, with the RhD antigen being one of the most important. In a D-negative
32 woman carrying a D-positive baby, fetal red cells entering the maternal circulation may

1 provoke an immune response in the maternal immune system. These antibodies can then
2 result in severe fetal and neonatal haemolytic disease in future pregnancies. All RhD-negative
3 unsensitised women delivering a D-positive baby should be routinely offered a standard dose
4 of anti-D immunoglobulin (at least 500IU) as prophylaxis to minimise this risk of
5 sensitization.

6 A test for fetomaternal haemorrhage (FMH) is recommended to quantify the volume of fetal
7 red cells that have entered the maternal circulation and determine if additional doses of anti-D
8 immunoglobulin are indicated. The Kleihauer test is a manual test undertaken in hospital
9 transfusion laboratories as an initial screen to assess the volume of FMH. Since this test is
10 associated with a high coefficient of variation, referral for more specialist testing with flow
11 cytometry is recommended for accurate confirmation if the FMH is estimated to be ≥ 2 ml by
12 the Kleihauer test.

13 The volume of fetal red cells in maternal blood following cell salvage is variable but can be
14 relatively large. Accordingly, updated UK guidelines from the British Society of
15 Haematology published in 2014³³ recommend a minimum anti-D Ig dose of 1500 IU to be
16 administered after reinfusion of salvaged red cells. FMH testing as above should guide if any
17 additional doses of anti-D Ig are required. Antibodies to other red cell antigens are also
18 implicated in causing HDFN.³⁴ These may have consequences for future pregnancies or long-
19 term blood transfusion. While there is no evidence to suggest that cell salvage increases the
20 risk of sensitization, this topic has not been specifically addressed in studies to date,^{35, 36} but
21 merits further scrutiny.

22 The National Institute for Health and Care Excellence (NICE) currently only recommends
23 cell salvage for obstetrics in the emergency management of massive haemorrhage in
24 caesarean section, but has called for robust evidence from clinical trials to support its wider,
25 routine use.³⁷ The guideline states that the technology may be of benefit with careful patient
26 selection, for example caesarean or vaginal delivery in cases with known placenta praevia or
27 placenta accreta. Selective use of cell salvage in obstetrics is also recommended by obstetric
28 and anaesthetic professional bodies.^{38, 39}

29 Cell salvage is beginning to enter routine use in caesarean section in some hospitals, with the
30 aim of realising some of the benefits known from other settings. A national survey 2005-6
31 reported that 38% of UK maternity units had access to cell salvage and 12% included it in

1 their major obstetric haemorrhage protocol.⁴⁰ By 2011, this had increased to 49% of UK
2 maternity units having access to cell salvage.⁴¹ However, use in this context remains
3 unproven and is not supported by evidence for its clinical or economic effectiveness. Opinion
4 had not yet solidified in the clinical community, and clinicians engaged in preparation for the
5 SALVO trial showed that the need to launch a large multicentre randomised controlled trial
6 to generate reliable, valid evidence was recognised.

7 ***Cost considerations***

8 Caesarean section is a frequently performed operation and the cost per patient of
9 consumables used in routine cell salvage is approximately the same as a single unit of blood.
10 This must be set against the cost of blood transfusion, the care costs of prolonged hospital
11 stay and the expense of treating adverse events associated with transfusion. Cell salvage
12 could realise the dual economic goals of earlier hospital discharge and enhanced maternal
13 quality of life.

14 ***Existing evidence***

15 We published⁴² and updated³⁵ a systematic review which identified one small controlled trial
16 of cell salvage in caesarean section in Italy, with 34 participants in each group, which
17 reported a significant reduction in the number of participants requiring transfusion in the cell
18 salvage group.⁴³ However, there were flaws in trial design and conduct, including no
19 explanation of the randomisation method. Furthermore, the control group transfusion rate of
20 23.5% was at least four times greater than normal practice in the UK. The methodology
21 employed in other studies, including a retrospective review,⁴⁴ case series and isolated case
22 reports,⁴⁵⁻⁵³ precluded definitive conclusions but supported the safety of cell salvage in
23 obstetrics.

24 The abovementioned NICE review of cell salvage³⁷ focused on the lack of high quality
25 research and called for randomised controlled trials. The Royal College of Obstetricians and
26 Gynaecologists (RCOG) Guidelines (12/2007)³⁹ recognised that "cell salvage in obstetrics
27 remains controversial". The evidence was graded C as a result of the absence of robust trials
28 on which to base recommendations.

29 An economic model, drawn from primary cost studies and randomised trials, concluded that
30 cell salvage had lower costs and higher quality-adjusted life years compared with all other

1 alternative transfusion strategies except acute normovolaemic haemodilution.²¹ However, this
2 model did not include caesarean section, limiting generalisability to the obstetric setting.

3 A pilot randomised controlled trial of cell salvage in elective (planned) caesarean section was
4 performed at one prospective SALVO participating centre⁵⁴ to help refine the trial processes
5 and assess feasibility. At closure, 57 women undergoing elective caesarean section had been
6 randomised. The consent rate was 71% of women approached. The primary outcome data
7 were collected for 100% of randomised women. The use of cell salvage was feasible and
8 acceptable to staff and to women randomised. Blood salvage and return was technically
9 unproblematic requiring minimal additional resource. Of 30 women randomised to cell
10 salvage, it was set up and deployed in 28 (93%), with sufficient blood collected to enable
11 return of an average of 284 ± 113 ml of blood to five women. Adherence to the
12 randomisation strategy was high with 1 case of use of cell salvage in the control group,
13 following intraoperative haemorrhage due to undiagnosed placenta accreta. No woman in the
14 cell salvage group required allogeneic transfusion compared to 1 woman (3.7%) in the
15 routine treatment group, with an undiagnosed placenta accreta, who received two units of
16 allogeneic blood.

17 **Objectives**

18 The primary objective of the SALVO trial was to determine if the routine use of cell salvage
19 during both elective and emergency caesarean section, in women at risk of haemorrhage,
20 reduced the need for donor blood transfusion in comparison to current practice where salvage
21 is not routinely used. In addition, we sought to assess the consistency of the effect across
22 subgroups defined by indication for caesarean, and to determine the effect on secondary
23 outcomes including the number of units of donor blood transfused, fall in haemoglobin level,
24 maternal morbidity resulting from postoperative anaemia (time to first mobilisation, duration
25 of hospital stay, and postnatal fatigue), maternal exposure to fetal blood, and its cost-
26 effectiveness in comparison to current practice.

27

1 **Chapter 2 Methods**

2 **Trial design**

3 The SALVO trial was a multicentre individually randomised controlled trial with cost-
4 effectiveness analysis.

5 **Setting**

6 The trial was conducted in 26 hospitals with large obstetric units, in 23 NHS Trusts in
7 England, Wales and Scotland (see Appendix 1 for a list of sites). These units each cared for
8 between 3800 and 8000 births annually and performed between 900 and 2000 caesarean
9 sections per year.

10 **Participants**

11 **Eligibility criteria**

12 Inclusion criteria:

13 Women who were admitted to a participating labour ward and who fulfilled all of the
14 following inclusion criteria were eligible to be randomised:

- 15 • 16 years of age or older
- 16 • Ability to provide informed consent
- 17 • Delivery by caesarean section with an identifiable increased risk of haemorrhage,
18 defined as all emergency caesarean sections, and elective caesarean section for all
19 indications other than maternal request or breech presentation.

20 A number of systems for classifying the urgency of caesarean section have been suggested,⁵⁵
21 both to improve communication between healthcare professionals, and to assign maximum
22 time intervals for audit purposes between decision for performing caesarean section and
23 actually carrying out the delivery.^{56, 57} The classification system recommended by the Royal

1 College of Obstetricians and Gynaecologists⁵⁶ was in use in the UK hospitals during SALVO.
2 For stratification purposes, the important distinction for our purposes was between elective
3 (Category 4: No maternal or fetal compromise and timing to suit the woman and maternity
4 services), which has a lower incidence of haemorrhage and transfusion, and emergency
5 categories. We use the term emergency to mean caesareans distinct from the elective
6 category, in that early delivery was mandated clinically. In this category, the immediacy of
7 threat to life of woman or fetus varies and accordingly the urgency to deliver varies too
8 (Category 1: immediate threat and timing immediate; Categories 2 and 3: No immediate
9 threat and timing flexible depending of assessment of maternal or fetal compromise). We
10 have avoided the use of words such as crash, urgent and scheduled, as these have different
11 meanings in different classification systems.

12 Abnormality of placentation was based on the degree of abnormal myometrial invasion
13 (placenta accreta, increta and percreta) and the localisation of its insertion within the lower
14 uterine segment (placenta praevia major or minor) as assessed by antenatal ultrasound
15 examination. In these circumstances, current guidelines suggest that cell salvage may be
16 considered in women at high risk of massive haemorrhage, especially in women who would
17 refuse donor blood. Routine use in these cases is not recommended.

18 Exclusion criteria:

- 19 • Elective first caesarean section for maternal request or breech presentation, with no
20 additional prognostic factor for haemorrhage. Maternal request included women with
21 personal reasons for wishing to avoid vaginal delivery, such as previous traumatic
22 delivery, or psychiatric or psychological problems. These indications do not put the
23 mother at increased risk of haemorrhage. All other indications for caesarean sections,
24 including all emergency cases, were considered an identifiable increased risk of
25 haemorrhage.
- 26 • Sickle cell disease or trait. Use of cell salvage may lead to the presence of abnormal
27 red blood cells, which can deform and block the microscopic blood vessels in the
28 body, leading to a sickle cell "crisis". Even if only the trait form, there is an increased
29 chance that this "sickling" may occur while the blood is in the cell salvage collection
30 reservoir awaiting processing due to the low oxygen levels, and thus a risk that a
31 sickle cell crisis could be precipitated if this blood is returned to the woman.

- 1 • Active malignancy contraindicated to caesarean section, especially cancer in the
2 abdominal region, as there is a theoretical risk of spreading the cancer should cell
3 salvage be used.
- 4 • Cultural or religious beliefs contraindicating blood transfusion (e.g. Jehovah's
5 Witnesses), since donor red blood cell transfusion was the primary study outcome.
- 6 • Significant antibodies making it difficult to find cross-matched blood for transfusion.
7 This is because allogeneic blood for this group of patients is likely to be scarce or
8 unavailable. We considered it appropriate to give these patients cell salvage from the
9 start of their case.
- 10 • Inability to understand written and spoken English.

11 In some circumstances, some of the participating sites applied clinical judgment not to recruit
12 patients with a high risk of haemorrhage and instead preferred to use cell salvage a priori,
13 outside the study.

14 ***Screening and consent procedures***

15 *Screening and antenatal information*

16 In addition to patient information sheets and informed consent forms, we provided sites with
17 short patient pamphlets (which were used to provide information about the study during the
18 antenatal period) as well as posters. All patient recruitment materials were approved by the
19 REC prior to use.

20 Information about the study was distributed to as many women as possible, "booked" to
21 deliver at participating centres during their pregnancy and again on admission to delivery
22 suite, whether they were intending a normal (vaginal) delivery or an elective caesarean
23 section. This process was individualised at each participating centre depending on their
24 routine practice to ensure that the maximum number of women were offered information well
25 in advance of delivery. In some centres, women were provided with information about the
26 trial at their routine anomaly scan appointment, at 18-22 weeks' gestation. The provision of
27 study information was documented in the woman's medical record or handheld notes, and a
28 sticker applied to indicate whether they were or were not interested in taking part in the
29 study. It was also documented at this point whether in an emergency situation they would still
30 be interested in taking part in the study. Written informed consent was obtained by a trained
31 health professional (obstetrician, anaesthetist or midwife) with delegated authority from the

1 Principal Investigator. All women were assessed to ensure that they had the capacity to
2 provide consent. The process and timing for obtaining written consent varied according to
3 clinical urgency (see below and Figure 1).

4 Recruiting women undergoing elective caesarean section

5 Eligible women requiring elective caesarean section were provided with further information
6 and the opportunity to ask questions at the time the operation was booked, and approached
7 for written consent at pre-operative assessment clinic or on the day of surgery.
8 Randomisation took place on the day of surgery.

9 Recruiting women undergoing emergency caesarean section

10 Women booked for delivery received information regarding the trial during their pregnancy,
11 so there was sufficient time to consider participation in the trial should an emergency
12 caesarean section be required. On admission to delivery suite, women's notes were checked
13 to ensure this information had been supplied, and the opportunity for further discussion
14 provided.

15 After recruitment of half the required target sample, a substantial protocol amendment was
16 submitted and approved in order to facilitate recruitment of women undergoing emergency
17 caesarean section. This allowed women to be approached for the first time on delivery suite if
18 they were found to be in the latent stage of labour (i.e. not yet in established first stage of
19 labour according to NICE guidelines^{24, 25}) or were comfortable with epidural analgesia,
20 provided that all of the following criteria were fulfilled:

- 21 • They were willing to receive the trial information and were subsequently willing to
22 discuss the PIS and have any questions answered if desired.
- 23 • They had either 0-3cm cervical dilation, not contracting regularly (i.e. a maximum of
24 one contraction in ten minutes, with contraction lasting less than 30 seconds), or were
25 comfortable with effective epidural analgesia in place.
- 26 • They were given at least one hour to decide whether they would be interested in
27 taking part, should they require a caesarean section. If their situation changed (i.e.
28 labour became established during that hour or they were no longer comfortable under
29 epidural analgesia, or required a caesarean section before the hour elapsed), they were
30 not approached for inclusion. After an hour, the women were approached for further
31 discussion and the opportunity for questions about the study. If the women had a

1 contraction during the discussion, the health professional involved would pause and
2 wait for the contraction to finish. Permission to continue with the discussion was then
3 sought.

4 Women in established labour (i.e. 4 cm cervical dilation and regular painful contractions), or
5 who were not comfortable with epidural analgesia, were not approached for the first time on
6 delivery suite. Women who were distressed and not in a position to absorb the information on
7 the patient leaflet were not approached for the first time on delivery suite.

8 Consent was obtained if a decision for caesarean section was made (see below).

9 Documenting written informed consent

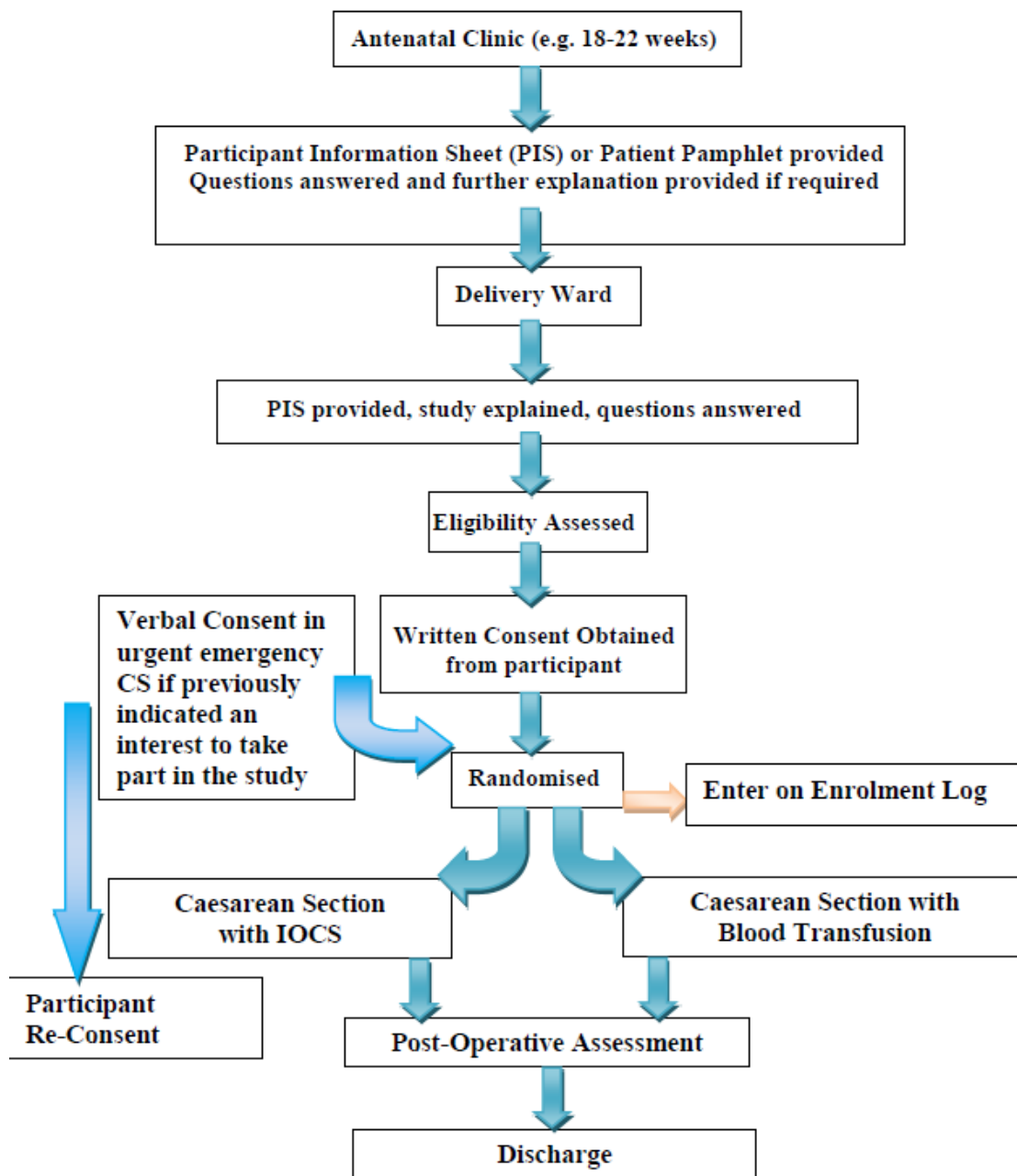
10 Consent comprised a dated signature from the woman and the dated signature of the person
11 who obtained informed consent. It was clearly stated that the participant was free to withdraw
12 from the trial at any time, for any reason, without prejudice to future care and with no
13 obligation to give the reason for withdrawal. A copy of the signed informed consent
14 document was given to the woman. One copy was retained in the woman's medical notes,
15 and another by the Principal Investigator in the investigator site file.

16 Verbal consent and timing of written informed consent

17 All participants undergoing elective caesarean section gave written informed consent before
18 the intervention. Likewise, the majority of emergency caesarean sections in the absence of
19 acute fetal distress were conducted in a controlled manner with ample time for regional
20 anaesthesia to be established, and written consent was obtained at this stage once the decision
21 for caesarean section had been made.

22 In some emergency situations, the urgency meant that there would be insufficient time for
23 written consent to be obtained prior to the emergency caesarean section. Under these
24 circumstances, if the woman had the capacity to consent and had previously indicated an
25 interest in taking part in the trial, verbal consent was obtained by an authorised health
26 professional as described above, and documented on the randomisation checklist. Written
27 consent was then sought once the urgency of the situation was over and the caesarean section
28 complete.

1 Figure 1 Consent procedure flowchart



2 Abbreviations: CS = Caesarean Section; IOCS = Intra-Operative Cell Salvage; PIS = Patient Information Sheet.

1 ***Intervention***

2 All staff were sufficiently trained and familiar in the use of the cell salvage machine, in
3 accordance with local procedures and requirements. The majority of sites used conventional
4 cell saver machines with separate set-up for collection and processing of shed blood, whereas
5 some sites used continuous transfusion systems. To confirm eligibility for randomisation,
6 investigators needed to verify that women met the inclusion/exclusion criteria for the trial as
7 well as gaining informed consent. An eligibility checklist was completed prior to
8 randomisation.

9 Women were randomly allocated to either:

- 10 1. Caesarean section with cell salvage (intervention group), set up routinely with collection of
11 shed blood from the outset of surgery, and return of any processed blood obtained.
- 12 2. Caesarean section without cell salvage (control group), with transfusion of donor blood
13 according to standard local guidelines.

14 The intervention group was treated as follows: Blood was aspirated from the surgical field;
15 the red cell component isolated by centrifugation and re-transfused after washing and
16 filtration. The ability to return salvaged blood is dependent on sufficient volume being
17 collected and processed. Blood was uniformly returned to women in the cell salvage group if
18 this volume threshold was reached, and it was a protocol requirement that cell saver machines
19 were fully set up for both collection and processing upfront at commencement of surgery and
20 that all available processed blood was re-transfused regardless of volume. The use of a
21 leukocyte depletion filter for transfusion of salvaged blood was not mandated as part of the
22 study intervention protocol, but left up to local guidance. We monitored any reports of
23 severe, unanticipated hypotension and their potential association with the presence of
24 leukocyte depletion filters. Likewise, the use of one versus two suction devices, the latter
25 having one dedicated to amniotic fluid only at uterotomy as well as salvage machine “bowl
26 size” was at the discretion of the participating site. Swab washing was encouraged, as it was
27 thought to increase the volume of blood available for processing and thus for re-transfusion,⁵⁸
28 but was ultimately also left to the local investigator’s discretion.

29 The control group was treated as follows: participants received standard current practice
30 (without cell salvage), with allogeneic donor blood transfusion as standard treatment if

1 required. In life threatening acute haemorrhage, women were managed at the discretion of
2 attending clinicians in line with the standard of care for such an emergency,^{1, 39} potentially
3 including the use of cell salvage in the control group.

4 ***Follow-up***

5 Participants were followed up until discharge or transfer from the participating hospital only.
6 Postnatal investigations included assessment of postoperative haemoglobin levels, collection
7 of Multidimensional Fatigue Inventory (MFI)⁵⁹ questionnaires completed by patients (with
8 any missed MFI questionnaires followed up for completion up to two weeks after discharge),
9 documentation of adverse events, mobilisation and discharge times, and for RhD-negative
10 women with RhD-positive babies, assessment of exposure to fetal blood by Kleihauer tests
11 and anti-D given.

12 We took the opportunity to undertake an observational study of practice around anti-D
13 prophylaxis in RhD-negative women who gave birth to a RhD-positive baby. There are UK
14 guidelines stating that all RhD-negative women giving birth to a RhD-positive baby should
15 receive a minimum of 500IU anti-D Ig as a standard dose following delivery to minimise the
16 risk of RhD allo-immunisation. These guidelines published in 2014 also recommend that
17 after cell salvage the minimum standard dose should be higher at 1500IU anti-D. The
18 maternal sample should be tested after delivery to assess the level of fetomaternal
19 haemorrhage (FMH) to guide if additional anti-D doses are needed following the standard
20 dose. In the majority of centres the Kleihauer test is undertaken as an initial screening test but
21 since this is a manual test with a high coefficient of variation the guidelines also make further
22 recommendations. Given the crudeness of Kleihauer results, these guidelines recommend
23 flow cytometry tests to be performed for Kleihauer results $\geq 2\text{ml}$, and repeat administrations
24 and repeat testing after 72 hours for any Kleihauer results $> 4\text{ml}$.⁶⁰ All centres participating in
25 the SALVO trial would have been expected to have local guidelines on anti-D prophylaxis.
26 We aimed to collect data around anti-D prophylaxis and FMH testing in all D-negative
27 women recruited to this study to assess current practice. We did not attempt to collect follow-
28 up data on the development of red cell sensitisation either to the RhD or indeed other red cell
29 antigens in either group since this was outside the scope of this particular study.

1 **Outcomes**

2 The primary outcome was the use of donor blood transfusion. Reducing the proportion of
3 women with this outcome should lead to fewer transfusion-related complications.

4 **Primary outcome**

5 The primary outcome was the proportion of women receiving donor blood transfusion to deal
6 with haemorrhage and its consequences, either during caesarean section, or between surgery
7 and discharge.

8 **Secondary outcomes**

9 The secondary outcomes analysed included: Severity of events (quantified as units of donor
10 blood transfused); time to first mobilisation after caesarean section (calculated as the time
11 from delivery until documented first mobilisation, i.e. ability of the woman to walk
12 unassisted); length of hospital stay (calculated as time from delivery until discharge of the
13 mother); pre- and postoperative serum haemoglobin, mean fall in haemoglobin level;
14 maternal exposure to fetal blood, defined as fetomaternal haemorrhage as quantified by
15 Kleihauer test and defined as Kleihauer $\geq 2\text{ml}$, and administration of anti-D antibody;
16 maternal fatigue measured with the MFI,⁵⁹ a 20-item self-report questionnaire, covering five
17 different dimensions of fatigue (general fatigue, physical fatigue, mental fatigue, reduced
18 motivation, and reduced activity; each question is scored between 1 and 5, with each of the
19 five fatigue dimensions yielding a maximum score of 20); resources used intra- and
20 postoperatively (including cell salvage consumables and donor blood transfusions); adverse
21 and serious adverse events, including proportion of transfusion reactions associated with
22 allogeneic blood transfusion; and costs of staff training, service procurement and provision of
23 care, collected alongside clinical outcomes (for full details on health economics methods, see
24 Chapter 4). Additionally, we collected process outcomes including the volume of blood
25 returned in cell salvage, the proportion of transfusion reaction associated with allogeneic
26 donor blood transfusion and any episodes of technical failure of cell salvage.

27 **Safety considerations**

28 Adverse events (AE) were defined as any untoward medical occurrence in a participant
29 receiving trial intervention, including occurrences which were not necessarily caused by or

1 related to that intervention. An AE was therefore defined as any unfavourable and unintended
2 sign (including an abnormal laboratory finding), symptom or disease temporarily associated
3 with study activities.

4 A Serious Adverse Event (SAE) was defined as an adverse event that fulfilled at least one of
5 the following criteria: fatal; life-threatening; required prolongation of hospitalisation beyond
6 7 nights after caesarean section for maternal reasons; resulted in persistent or significant
7 disability; was a congenital anomaly or birth defect; or was otherwise considered medically
8 significant by the investigator.

9 AEs and SAEs were documented if they occurred between randomisation and discharge.
10 They were only reported if they related to the mother, except for SAEs that fulfilled the
11 criteria of congenital anomaly above. The local principal investigator responsible for the care
12 of the participant, or in his or her absence an authorised medic within the research team, was
13 responsible for assessing the severity, causality and expectedness of an adverse event, and for
14 assessing whether the event was serious according to the definitions given above.

15 If an AE was not defined as serious, the AE was documented in the participants' medical
16 notes (where appropriate) and on the Case Report Form. All reported adverse events were
17 subject to a central medical review and coded and grouped by a clinician member of the trial
18 team.

19 All SAEs occurring during the trial observed by the investigator or reported by the
20 participant, whether or not attributed to the trial, were documented in the participants'
21 medical notes (where appropriate) and reported to the trials office within 24 hours of the site
22 becoming aware of the event. All SAEs were followed up until resolution or the event being
23 considered stable. The chief investigator or a delegated clinical co-applicant reviewed all
24 SAE reports within 24 hours, and raised any queries to be addressed to the sites. Locally, all
25 serious incidents (such as maternal deaths) occurring at a UK NHS site were subject to Root
26 Cause Analyses.⁶¹

27 Any SAEs considered both related to the intervention and unexpected were reported to the
28 sponsor and the PCTU QA manager within 24 hours, and to the main REC within 15 days.
29 Although there were some known or theoretical potential risks associated with the trial
30 (including maternal exposure to fetal blood, amniotic fluid embolism, severe hypotension and
31 transfusion reaction), none were considered to fulfil the criteria of being 'expected'.

1 Therefore, any serious adverse events that were at least possibly related to the trial
2 intervention were reported as unexpected SAEs.

3 If applicable, it was the chief investigator's responsibility to take any urgent safety measures
4 to ensure the safety and protection of the clinical trial participants from any immediate hazard
5 to their health and safety, in which case the REC was informed immediately by telephone,
6 and in writing within 3 days.

7 Annual progress reports to the REC included a listing of all related and unexpected SAEs. All
8 SAEs were reported to the Data Monitoring Committee (DMC) and Trial Steering Committee
9 (TSC) on the occasion of their meetings, i.e. every 6-12 months. The DMC viewed data with
10 knowledge of treatment. In the event of a participant dying as a result of the study protocol or
11 study interventions, any post-mortem findings were to be provided to the chief investigator,
12 who would report the findings to the DMC for continuous safety review.

13 ***Data collection and quality assurance***

14 The SALVO study met the requirements of the Data Protection Act 1998⁶², NHS Caldicott
15 principles⁶³, the Research Governance Framework for Health and Social Care⁶⁴ and Research
16 Ethics Committee approval. Identifiable information collected from participants, including
17 name, date of birth, hospital number and contact details, was considered confidential and
18 collected and stored only at the local NHS site. Study data was collected using paper Case
19 Report Forms, with all data being pseudonymised using a unique participant number, and
20 transmitted to the trials office by secure NHS e-mail transmission or post.

21 The following data were collected through Case Report Forms (CRF):

- 22 • Before surgery: eligibility, obstetric history, indication for caesarean section,
23 prognostic factors for haemorrhage, demographics, due dates and labour data, pre-
24 operative haemoglobin and platelet count.
- 25 • During surgery: time of delivery, time into and out of theatre, transfusion of donor
26 blood products, set-up of cell salvage machine (if applicable), including consumables
27 used and volume of blood returned, reasons for no return of salvaged blood,
28 documentation of any technical failure of cell salvage, additional staff required in
29 theatre due to cell salvage.

- Between surgery and discharge: transfusion of donor blood products, postoperative haemoglobin, fetomaternal haemorrhage measured by Kleihauer test, anti-D administration, flow cytometry for Kleihauer results >2ml, repeat Kleihauer and anti-D administration for initial Kleihauer results >4ml, time of mobilisation and discharge, MFI, adverse events including admission to higher level of care.

CRF data were verified by the trials office and queries raised with individual sites for discrepancies identified. Data were input at the trials office by delegated staff into a bespoke Oracle database with a Java user interface, set up and managed by the PCTU. Data quality was monitored through source data verification on samples of patient records during on-site monitoring and during remote self-monitoring activities, and through central statistical monitoring with discrepancies raised from database extracts, highlighting outliers and discrepancies. On-site and self-monitoring activities also included verification of eligibility, informed consent and completeness of local trial documents according to a predefined trial monitoring plan.

On 69 occasions, stratification factors were found to be entered incorrectly during the randomisation procedure, but these were corrected to the true values in the analysis, which adjusted for stratification factors.

Additional quality control measures undertaken included a cross-check of primary outcome data against local transfusion laboratory records, upon recommendation of the Trial Steering Committee. Manual data entry was also subject to quality control procedures according to predefined procedures, with 100% of primary outcome data being checked, and 10% of all other data being checked with an allowable error threshold of 2% for non-primary outcome data.

Sample size

Establishing a baseline rate for the primary outcome was not straightforward, since estimates in the published literature for blood transfusion in caesarean section varied widely (1.8% to 23.5%).^{43, 65} Factors influencing this figure include country of origin, indication for caesarean section (emergency or elective) and local transfusion policy. Our audits in two centres conducted at the time of study planning put transfusion rates for an unselected caesarean section population at around 5%: A detailed audit of donor blood use at the Royal

1 Hallamshire Hospital Sheffield 2009-10, without cell salvage in routine use, was performed
2 by cross-reference of perioperative records, blood bank data and electronic records stored in
3 cell salvage machines. It reported that in a recent series of 1647 caesarean section over 10
4 months, 89 women were transfused with donor blood, giving a rate of 5.4% (I. Wrench,
5 personal communication). A similar audit at Birmingham Women's Hospital of all caesarean
6 section carried out in 2006, showed that of 1674 women, 83 (5.0%) received a transfusion.⁴²
7 Both auditing units delivered approximately 7300 women per year with a comparable
8 caesarean section rate and could thus be considered representative of UK tertiary obstetric
9 unit practice. Our pilot sample⁵⁴ was too small to assist in providing reliable information on
10 sample size calculations. In the light of reported contemporary observations and audited data
11 on transfusion rates, the assumption of a 5% event rate was used to base the main sample size
12 calculation on.

13 The expected effect estimate was informed by the literature. Our systematic review⁴² and its
14 most recent update³⁵ showed only one small trial published in 1998,⁴³ which randomised a
15 total of 68 participants to either cell salvage or standard care. The transfusion rate in the
16 control group was 23.5% and 2.9% in the cell salvage group. The control event rate was
17 considerably higher than that observed in current UK practice and inconsistent with literature
18 from other sources. This was likely due to a sample at exceptionally high risk of
19 haemorrhage. Weaknesses that raise the risk of bias (e.g. inadequate concealment of
20 randomisation) precluded reliance on it alone to inform our calculations. Non-obstetric
21 literature evaluating cell salvage in interventions with a moderate to high risk of transfusion
22 had two high quality systematic reviews: an HTA report citing a RR of exposure to
23 allogeneic blood of 0.59 (95% CI 0.48-0.73) with salvage,²¹ and a Cochrane review reporting
24 a RR of 0.62 (95% CI 0.50-0.70) for transfusion with salvage compared with normal
25 practice.²⁰ Detecting a smaller effect size would have been possible but the larger sample size
26 required had to be balanced against the cost and practicability of undertaking such a trial.
27 From the current best literature we assumed an intervention effect at or around 0.6 (at a
28 control event rate of 5%, the intervention group would have a transfusion rate of 3%).

29 Therefore, the planned sample size was a total of 3,050 women (1,525 per group), to detect
30 an absolute difference in the transfusion rate of 2% and given a power of 80% for a 2-sided
31 test, a type I error rate of 5% and event rate of 5% in the control group. Our sample size
32 allowed for primary outcome data and follow-up loss of 1% of randomised cases.

1 The planned trial sample was also to represent an even split between elective and emergency
2 caesarean sections, the rationale for which was as follows: The primary event rate in the
3 control group was based on data representing caesarean section across ‘all-comers’ in
4 obstetric units, including both emergencies and elective cases. It included all indications at
5 increased risk of haemorrhage. Ideally, this distribution would be faithfully and
6 proportionally represented in the trial population, but there was good reason to suspect that
7 clinicians would find it much more difficult or be more reticent to recruit those patients at
8 higher risk of haemorrhage, such as emergency indications or in cases of placental
9 abnormality. Equally, a decision to limit recruitment to these high risk groups alone, whilst
10 desirable to maximize the primary outcome event rate and reduce sample size, was likely to
11 result in reticence to take part in the study at all. Adoption of such narrow eligibility criteria
12 may have restricted sites from ever gaining a sufficient rate of recruitment to become
13 confident in the trial processes and rendered the conduct of the trial unviable. Additionally, at
14 the time the study was designed, there was an increasing trend for obstetric units to have
15 started utilizing cell salvage in the routine, uncomplicated elective caesarean section
16 population to facilitate the generation of an effective skill-base among clinical staff to support
17 the deployment of the technology when deemed necessary, even though the majority of these
18 would not suffer significant blood loss. A pragmatic compromise to these conflicting
19 requirements was therefore to exclude those elective cases with the very lowest risk of
20 haemorrhage (elective first caesarean section for breech or maternal request) while at the
21 same time pre-specifying a desired equal distribution across elective and emergency cases.

22 Between June 2013 and March 2014, the majority of the elective patient population was
23 recruited relatively rapidly, exceeding our projected target accrual. The emergency patient
24 population was recruited more slowly, along with high risk elective cases (See Appendix 2,
25 Figure 11). Although sites adapted to the more challenging recruitment of these participants,
26 particularly once the changes to the consenting procedures, introduced through a substantial
27 protocol amendment, had started to take effect, an extension of the projected recruitment
28 duration by 11 months was necessary to allow completion of the target sample size.

29 ***Interim analyses***

30 There were no planned interim analyses for this trial. In the lead up to the recruitment
31 extension request, the funding body recommended an interim futility analysis be presented to
32 the unblinded DMC to assess the probability of achieving a significant result, should the trial

1 be allowed to recruit to completion. This was performed in March 2015, but the DMC did not
2 feel as though it was within their remit to make a decision on the future of the trial based on
3 said analysis. The DMC made their recommendation without the use of the futility analysis
4 results.

5 **Randomisation**

6 Randomisation to the allocated intervention (allocation ratio 1:1) was done using a bespoke
7 web-based randomisation system hosted by the University of Bristol. Randomisation of
8 participants was done on the delivery ward by local study staff. The randomisation used
9 random permuted blocks of variable sizes to ensure that trial staff conducting randomisation
10 could not reliably predict the next allocation. Randomisation was stratified by four criteria:
11 Centre; type of caesarean section (emergency versus elective); presence of abnormal
12 placentation versus normal placentation; and multiple pregnancy (twins or more) versus
13 singleton pregnancy.

14 **Blinding**

15 Allocation concealment with third party randomisation helped minimise selection bias.
16 However, given the nature of the intervention, it was not possible to blind local treatment
17 staff and data entry staff to the allocation. Performance bias may lead transfusion rates to
18 vary. This risk was minimised by ensuring that each centre had an intraoperative transfusion
19 protocol for use in theatre and recovery to standardise operative transfusion triggers across
20 both study groups in each centre. Some centres adopted an agreed haemoglobin threshold for
21 transfusion, which was to be applied equally to both groups.

22 Sites were encouraged to blind postnatal carers to group allocation after caesarean section.
23 The allocation was not recorded in routine case notes, but this did not represent formal
24 blinding as theatre notes were available. The carers on postnatal wards were a different group
25 of staff to the carers on labour wards and operating theatres, and it was on the postnatal wards
26 where the decisions for postoperative donor blood transfusions were made, based on the
27 postoperative haemoglobin level and maternal symptoms. In the event of the need for a donor
28 blood transfusion, serum haemoglobin was measured by blood sample, and pre and post-
29 transfusion and results recorded. This allowed monitoring of numeric transfusion thresholds

1 between units and groups. In the event that between group variations in haemoglobin
2 transfusion triggers were indeed evident, consideration was given for adjusting for such
3 differences in the final analysis.

4 The study statistician remained blinded until completion of data collection and sign-off of the
5 statistical analysis plan so as not to bias the analysis, and the chief investigator remained
6 blinded until completion of the analysis. For interim reporting purposes to the Data
7 Monitoring Committee (DMC) during the running of the trial, an independent statistician
8 employed by the PCTU produced summaries of unblinded data for a closed report to the
9 DMC.

10 ***Statistical methods***

11 ***General considerations***

12 A detailed analysis plan was developed and agreed by the Trial Steering Committee and the
13 Data Monitoring Committee, prior to unblinding and data analysis. All coding and analyses
14 were performed using Stata version 12.⁶⁶ All analyses were intention-to-treat. Where
15 baseline covariates were missing, we used mean imputation of the covariate in adjusted
16 analyses (note that epidemiological arguments against the use of a missing indicator do not
17 apply in randomised trials).⁶⁷ An intention-to-treat approach does not dictate that all outcome
18 data must have been collected,⁶⁸ though pilot work for this trial suggested that all or close to
19 all of the primary outcome data would be obtained. Where outcome data were missing we
20 analysed those who did have outcome data, adjusting for baseline covariates. This approach
21 is unbiased if missingness for the outcome is related to observed covariates ("missing at
22 random"). If missingness in the primary outcome had been >5% then a sensitivity analysis
23 was to be conducted to explore the missing at random assumption. In this case, a
24 pattern/mixture model estimated by a mean score approach would have been adopted.⁶⁸

25 ***Post-randomisation exclusions***

26 Although analysis was by intention to treat, certain exclusions were made post-
27 randomisation. These included all women who were enrolled in error (e.g. who did not meet
28 all eligibility criteria) or did not provide valid written informed consent.

1 Women who withdrew their consent were still analysed unless they specified that their data
2 were not to be used, in which case the data were safely destroyed and excluded from the trial
3 analysis. We also excluded women who experienced a vaginal delivery, as this was not
4 applicable to the outcomes analyses in the sense of the trial, although their baseline
5 characteristics remained available.

6 Post-randomisation exclusions were not replaced during the recruitment phase, as they were
7 considered part of the 1% anticipated loss to follow-up (see section “Sample size” above).

8 ***Evaluation of Demographics, Baseline Covariates and Implementation of*** 9 ***Intervention***

10 Demographic factors and clinical characteristics were summarised with counts (percentages)
11 for categorical variables, mean with standard deviation (SD) for normally distributed
12 continuous variables or median with interquartile (IQR) for other continuous variables. The
13 number of participants who were eligible, recruited and followed up were recorded in a
14 CONSORT flowchart. We also included summaries detailing implementation of the
15 intervention, for example whether swabs were washed.

16 ***Primary Analysis***

17 For the primary outcome measure of patient requirement of peripartum transfusion,
18 differences in treatment effect between treatment groups were assessed using logistic
19 regression. Univariate and multivariable logistic regression models were used to estimate
20 crude and adjusted odds ratios with 95% confidence intervals. A two-sided p-value was
21 reported in each case. The primary analysis was adjusted.

22 Adjusted analysis adjusts for a random effect of treatment centre and fixed effects of
23 stratification variables and other baseline characteristics believed to be associated with the
24 outcome measure of haemorrhage. The latter are factors deemed to be associated antenatally
25 with a substantial increase in the incidence of postpartum haemorrhage, according to Royal
26 College of Obstetricians and Gynaecologists (RCOG) guidelines:⁶⁹ Known placenta praevia
27 and pre-eclampsia/gestational hypertension.

28 Another factor believed to substantially increase risk of postpartum haemorrhage is placental
29 abruption.³¹ As the number of individuals observed with this event was likely to be low, it
30 was decided a priori that this covariate would not be adjusted for in the primary analysis.

1 Instead, the analysis was redone excluding those who experienced placental abruption, as a
2 sensitivity analysis.

3 ***Analysis of Primary Outcome – Subgroup Analysis***

4 The following subgroup analyses were pre-specified for the primary outcome:

- 5 • Analysis of treatment effect by indication for caesarean section.
- 6 • Analysis of treatment effect by recruitment centre.

7 The first of these was analysed by statistically testing for an interaction term between
8 treatment and indication for caesarean section; the second was analysed by testing for a
9 random slope for the effect of treatment at different treatment centres in addition to a random
10 intercept.

11 ***Analysis of Primary Outcome – Sensitivity Analysis***

12 The trial groups were compared according to this outcome on an intention-to-treat basis.
13 However, because clinicians managing women in the control group had access to a cell
14 salvage machine, it was anticipated that some women in the control group might receive cell
15 salvage in place of a donor blood transfusion. As a sensitivity analysis, we therefore analysed
16 the primary outcome assuming that all instances of the return of cell salvaged blood in the
17 control group would have been instances of donor blood transfusion had the cell salvage
18 machine not been present.

19 As mentioned above, the primary analysis was redone excluding those participants who
20 experienced placental abruption as an additional sensitivity analysis.

21 ***Analysis of other outcomes***

22 Secondary outcome measures were compared between groups using appropriate methods.
23 Linear regression was used to analyse quantitative outcomes where a symmetric unimodal
24 distribution is expected (number of units transfused, postoperative serum haemoglobin, mean
25 fall in serum haemoglobin level, and multidimensional fatigue inventory scales). We
26 analysed 5 scales of fatigue (each the total score of 4 items from the 20 statements pertaining
27 to a specific type of fatigue). The analysis of serum haemoglobin allowed for change from
28 baseline by including the pre-operative level as an additional covariate.

1 Time to event variables (time to first mobilisation, length of hospital stay) were analysed with
2 Cox proportional hazard regression.

3 Fetomaternal haemorrhage was dichotomised into a Kleihauer test measurement of <2ml
4 versus ≥ 2 ml and analysed using logistic regression. Other measures detailing fetomaternal
5 haemorrhage, such as dose of anti-D prophylaxis were summarised accordingly. In the
6 analysis of fetomaternal haemorrhage, we used a cut-off of a Kleihauer result of ≥ 2 ml to
7 dichotomise the measurement into a binary variable⁶⁰. However, due to the phrasing of our
8 CRFs, certain measures, such as flow cytometry or repeat Kleihauer tests, were only taken in
9 the event that the initial Kleihauer test results were >2ml or >4ml, in accordance with
10 guidelines.³³ In addition, any results reported as e.g. <4ml could not be dichotomised as
11 described above and was therefore classified as missing data.

12 Adverse events were analysed using logistic regression. Transfusion reaction associated with
13 donor blood transfusion was not analysed as we only saw one event.

14 Crude and adjusted estimates of treatment effect were obtained for each outcome, using
15 univariate and multivariable analyses with the same covariates as in the primary analysis.

16 ***Further exploratory analyses***

17 Further to the pre-specified subgroup analyses, an analysis of treatment effect on donor blood
18 transfusion by abnormal placentation was undertaken for exploratory purposes. We also
19 conducted further analysis to test for consistency of treatment effect in secondary outcomes
20 across subgroups of elective and emergency caesarean section.

21 We conducted a further sensitivity analysis assuming that a donor blood transfusion would
22 have been required, had salvaged blood not been returned in the control when the cell salvage
23 machine was set up in an emergency situation only (as opposed to all cases of salvaged blood
24 return in the control group). We included this further analysis as an amendment to our
25 original pre-specified sensitivity analysis as we recognised with hindsight that our
26 assumptions about the erroneous return of salvaged blood in the control group were broad.
27 We therefore only reclassified cases where blood was returned in an emergency as an attempt
28 to more accurately reflect the truth.

1 There was also interest surrounding the effect of swab washing on the effectiveness of the
2 intervention. We compared transfusion rates between participants who did and did not have
3 swabs washed, within participants who had the cell salvage machine set up.

4 ***Governance and oversight***

5 The SALVO trial was undertaken following clinical trials database registration (ISRCTN
6 registry number 66118656) and the required regulatory approvals and local NHS permissions
7 (UK research ethics committee North West – Haydock, reference number 12/NW/0513). The
8 study was funded by the National Institute for Health Research as part of the Health
9 Technology Assessment programme (HTA reference number: 10/57/32).

10 A trial management group (TMG) was responsible for the day-to-day running of the trial,
11 with support from the Pragmatic Clinical Trials Unit (PCTU) at Queen Mary University of
12 London. The TMG reported to the Trial Steering Committee (TSC), which was composed of
13 an obstetrician, an independent statistician and a consumer representative, and which
14 convened every 6 to 12 months and provided overall supervision of the trial. This included
15 giving advice on trial protocol and changes thereof, resolving problems brought to it by the
16 TMG, monitoring the progress of the trial, protocol adherence and patient safety, considering
17 new information and recommendations of the Data Monitoring Committee (DMC) and other
18 authorities, and approving reports and papers for publication.

19 The DMC consisted of an independent statistician, obstetrician and anaesthetist. The DMC
20 met approximately every 12 months during the running of the trial and reviewed accruing
21 trial data, in order to assess whether there were any ethical or safety issues why the trial
22 should not continue. Interim reports were supplied to the DMC in strict confidence and
23 included unblinded data provided by a PCTU statistician independent of the trial. The DMC
24 formulated recommendations for the attention of the TSC. Both committees also monitored
25 the pooled primary outcome event rate (i.e. across both arms) and formulated
26 recommendations to encourage recruitment of the full spectrum of patients likely to benefit
27 from the intervention.

28 ***Patient and public involvement***

1 Working with organised consumer groups capable of identifying research priorities and
2 introducing their ideas into research programmes was a crucial part of our activities leading
3 to the trial. The National Childbirth Trust (NCT) significantly strengthened the project, being
4 well placed to reflect on their experience in relation to avoiding the need for donor blood
5 transfusion and to encourage participation. A volunteer for the NCT collaborated with the
6 project from its inception, advised on the pilot protocol and agreed to provide representation
7 on the TSC. An additional patient and public representative was identified through “Katie’s
8 Team”, the QMUL women’s health research advisory group, and included in the project at a
9 later stage, who participated in TSC and clinical investigator group meetings, reviewed the
10 plain English summary for this report, and advised on dissemination strategies.

11 In preparation for the trial, a survey was conducted among women who received cell salvage,
12 showing that they perceived the intervention as reassuring, safe, and preferable to donor
13 blood transfusion (our primary outcome).

14 ***Summary of changes to the project protocol***

15 No changes were made to the objectives, outcomes, eligibility criteria, sample size or
16 statistical parameters during the course of the trial. Three substantial and four minor
17 amendments to the protocol were implemented during the trial; they concerned changes to
18 recruitment materials and strategies, clarifications and administrative changes to the protocol,
19 and an extension of the overall recruitment period.

1 **Chapter 3 Results**

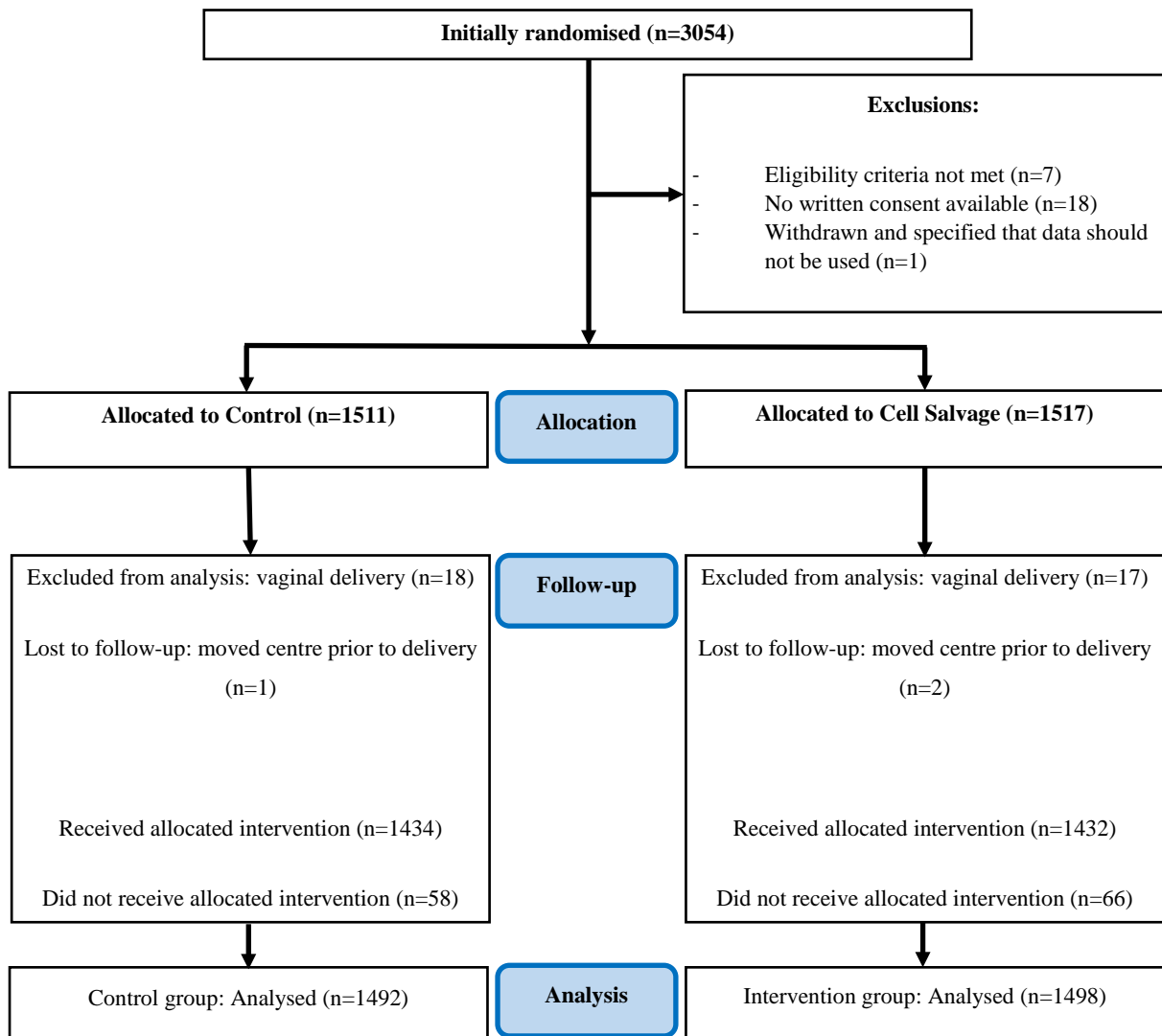
2 **Participants**

3 Between June 2013 and April 2016, 3054 participants requiring caesarean section from 26
4 participating hospitals were recruited (Figure 2). Of these, 26 participants had to be excluded
5 due to issues surrounding consent or eligibility as follows:

- 6 • 9 participants gave verbal consent as per protocol, but written consent could not be
7 obtained postoperatively
- 8 • 4 participants gave written informed consent, but the consent form was destroyed or
9 missing and consent could not be re-obtained
- 10 • 4 participants had not given consent and were randomised in error, but were not
11 exposed to any trial intervention
- 12 • 1 participant was found to have given invalid consent, due to language issues
- 13 • 1 participant gave verbal consent but withdrew consent after surgery
- 14 • 7 participants were found not to have met the eligibility criteria

15 Therefore 1517 participants were assigned to cell salvage (intervention) and 1511 to usual
16 care (control). Pregnancies resulting in vaginal delivery after assignment (n=17 in the cell
17 salvage group and n=18 in the control group) were excluded from the analysis, as were
18 patients who were transferred to a different hospital prior to delivery (n=2 in the cell salvage
19 group and n=1 in the control group) and who were therefore lost to follow-up; the baseline
20 characteristics for these 38 patients are however included in the tables of baseline
21 characteristics. For the analysis, this left 2990 participants (n=1498 in the cell salvage and
22 n=1492 in the control group, respectively).

1 **Figure 2 Participant enrolment and follow-up**



1 ***Baseline data***

2 The main characteristics of participants were similar at baseline (Table 1). The distribution of
3 participants across the different sites is summarised in Table 2.

Table 1 Characteristics of participants at baseline

	Control (n=1511) ^(a)	Cell Salvage (n=1517) ^(a)
Age at Randomisation	31.8 (5.8)	31.6 (5.7)
Pre-operative Haemoglobin (g/l)^(b)	118.1 (11.5) [19]	118.4 (11.3) [11]
Type of Caesarean		
Elective	687 (45.5%)	669 (44.1%)
Emergency	824 (54.5%)	848 (55.9%)
Multiple Births		
Singleton	1428 (94.5%)	1428 (94.1%)
Twins or multiple	83 (5.5%)	89 (5.9%)
Placentation		
Abnormal^(c)	135 (8.9%)	136 (9.0%)
Normal	1376 (91.1%)	1381 (91.0%)
Placenta Praevia	130 (8.6%)	133 (8.8%)
Placenta Accreta	8 (0.5%)	4 (0.3%)
Pre-Eclampsia	74 (4.9%)	69 (4.5%)
Previous Emergency Caesarean	602 (39.8%)	633 (41.7%)
Previous Elective Caesarean	241 (15.9%)	231 (15.2%)
Placental Abruption	3 (0.2%)	2 (0.1%)
Ethnicity		
White	1213 (80.3%)	1219 (80.4%)
Mixed	23 (1.5%)	14 (0.9%)
Asian or Asian British	158 (10.5%)	173 (11.4%)
Black or Black British	67 (4.4%)	71 (4.7%)
Other	50 (3.3%)	40 (2.6%)
Parity		
0	571 (37.8%)	583 (38.4%)
1	556 (36.8%)	562 (37.0%)
2	240 (15.9%)	238 (15.7%)
3+	144 (9.5%)	134 (8.8%)
Gravidity		
1	420 (27.8%)	441 (29.1%)
2	467 (30.9%)	465 (30.6%)
3+	624 (41.3%)	611 (40.3%)
Data presented are n (%) or mean (sd) [n missing]		
(a) Denominator includes 38 patients lost to follow-up due to vaginal delivery or transfer.		
(b) Haemoglobin <105 (g/l): Control group: n=159 (10.7%), Cell Salvage group: n=150 (10.0%)		
(c) Placenta Praevia and / or Placenta Accreta		

Table 2 Participants recruited per site

	Control (n=1511) ^(a)	Cell Salvage (n=1517) ^(a)
Centre		
Birmingham Heartlands Hospital	41 (2.7%)	44 (2.9%)
Birmingham Women's Hospital	7 (0.5%)	6 (0.4%)
Croydon University Hospital	48 (3.2%)	48 (3.2%)
Derriford Hospital Plymouth	57 (3.8%)	59 (3.9%)
Hinchingbrooke Hospital	83 (5.5%)	84 (5.5%)
James Cook University Hospital	109 (7.2%)	108 (7.1%)
Leicester General Hospital	5 (0.3%)	4 (0.3%)
Leicester Royal Infirmary	78 (5.2%)	75 (4.9%)
Norfolk and Norwich University Hospital	5 (0.3%)	5 (0.3%)
Northwick Park Hospital	13 (0.9%)	15 (1.0%)
Nottingham City Hospital	15 (1.0%)	16 (1.0%)
Queens Hospital Romford	60 (4.0%)	58 (3.8%)
Queens Medical Centre Nottingham	15 (1.0%)	13 (0.9%)
Royal Hallamshire Hospital Sheffield	138 (9.1%)	139 (9.2%)
Royal London Hospital	84 (5.6%)	87 (5.7%)
Royal Stoke University Hospital, Stoke-on-Trent	72 (4.8%)	73 (4.8%)
Royal United Hospital Bath	88 (5.8%)	87 (5.7%)
Royal Victoria Infirmary Newcastle	119 (7.9%)	116 (7.7%)
Simpson Centre Edinburgh	47 (3.1%)	51 (3.4%)
Singleton Hospital Swansea	84 (5.6%)	88 (5.8%)
St. Michaels Hospital Bristol	26 (1.7%)	21 (1.4%)
Sunderland Royal Hospital	192 (12.7%)	190 (12.5%)
Torbay Hospital	28 (1.9%)	30 (2.0%)
West Middlesex University Hospital	49 (3.2%)	52 (3.4%)
Whipps Cross University Hospital	29 (1.9%)	27 (1.8%)
Whiston Hospital	19 (1.3%)	21 (1.4%)

Data presented are n (%)

(a) Denominator includes 38 patients lost to follow-up due to vaginal delivery or transfer.

1 **Implementation of cell salvage**

2 In the intervention group, 1432 (95.6%) participants received their allocated treatment with
3 the cell salvage machine set up. There were 24 cases (1.6%) where the cell salvage machine
4 was unavailable or out of order and 42 cases (2.8%) where the machine was simply not set up
5 in deviation of the protocol. In the group receiving salvage, 50.8% had salvaged blood
6 returned averaging 259.9 ml (Table 3). In the control group, 1434 (96.1%) participants

1 received their assigned intervention without the cell salvage machine set up. In 15 cases
 2 (1.0%) the cell salvage machine was used in an emergency and in 43 cases (2.9%) it was set
 3 up from the start of the operation, in deviation of the protocol.

Table 3 Detail regarding cell salvage use

	Control (n=1492)	Cell Salvage (n=1498)
Cell Salvage Machine Set Up		
Set up	43 (2.9%)	1432 (95.6%)
Emergency use	15 (1.0%)	0 (0.0%)
Not set up	1434 (96.1%)	42 (2.8%)
Unavailable/out of order	0 (0.0%)	24 (1.6%)
Received Allocated Treatment	1434 (96.1%)	1432 (95.6%)
If Cell Salvage Set Up (Including Emergency Use) (n=1490)		
Suckers Used		
1	27 (48.2%)	829 (58.1%)
2	29 (51.8%)	598 (41.9%)
Missing ^(a)	2	5
Swabs Washed	21 (36.8%) [1]	781 (54.8%) [6]
Size of Centrifuge Bowl Used (ml)^(b)	183.2 (59.2) [2]	177.1 (59.8) [37]
Leukocyte Depletion Filter Used	25 (43.9%) [1]	782 (54.9%) [7]
Salvaged Blood Returned	35 (60.3%) [0]	726 (50.8%) [3]
If Blood Returned During Cell Salvage (n=761)		
Volume of Blood Returned to Mother (ml)	288.4 (198.3)	259.9 (149.7)
If No Blood Returned During Cell Salvage (n=726)		
Reason For No Return		
No blood produced	14 (63.6%)	575 (88.9%)
Technical error	0 (0.0%)	25 (3.9%)
Other ^(c)	8 (36.4%)	47 (7.3%)
Missing	1	56

Data presented are n (%) or mean (sd) [n missing]

(a) Missing observations are not included in percentage calculations. Where variables are categorical, missing values are listed in a separate row, but are similarly not included in percentage calculations.

(b) Measure not applicable for sites with a continuous transfusion machine only (Control group: n=22, Cell Salvage group: n=180)

(c) Other reasons include 'Clinical decision' (n=7), 'Human error' (n=5), 'Meconium, infection risk or contamination' (n=12), 'Minimal processed blood' (n=25), 'Patient declined' (n=2), 'Tubing trapped next to centrifuge bowl' (n=1), 'Unclear' (n=3)

1 **Primary outcome**

2 Overall, the donor blood transfusion rate was 2.5% in the group assigned to cell salvage
3 versus 3.5% in control, though this result did not reach statistical significance (adjusted OR
4 0.65, 95% CI 0.42 to 1.01, $p=0.056$, Table 4). In a subgroup analysis exploring the
5 consistency of treatment effects in procedures undertaken at different levels of urgency, the
6 transfusion rate was 3.0% in women assigned to salvage versus 4.6% in control among
7 emergency caesareans (adjusted OR 0.58, 95% CI 0.34 to 0.99), whereas it was 1.8% versus
8 2.2% among elective caesareans (adjusted OR 0.83, 95% CI 0.38 to 1.83), though the
9 interaction was not statistically significant ($p=0.46$, Table 4).

10 There was no significant difference in the effectiveness of the intervention between centres
11 (p -value for random slope= 0.091). In a pre-specified sensitivity analysis assuming that a
12 donor blood transfusion would have been required, had salvaged blood not been returned in
13 the control group ($n=31$), the effect of cell salvage was significant (5.6% vs. 2.5%, adjusted
14 OR 0.39, 95% CI 0.26 to 0.59, $p<0.001$, Table 4). When excluding cases of placental
15 abruption from the primary analysis, little difference in the results was seen, with 1
16 transfusion excluded in the control group as a result (3.4% vs. 2.5%, adjusted OR 0.67, 95%
17 CI 0.43 to 1.03, $p=0.071$, Table 4).

18 We also reviewed primary outcome events against available transfusion guidelines, in order
19 to determine whether the lack of blinding introduced bias. Where specific haemoglobin
20 thresholds were defined in local guidelines, we compared these to participants' reported
21 postoperative haemoglobin values. We found 25 instances (14 cell salvage group, 11 control
22 group) where donor blood was administered post-operatively without locally defined
23 haemoglobin thresholds having been reached. The trial management group did not deem the
24 difference between intervention groups a cause for concern, also accounting for the fact that
25 other less quantifiable factors may also be taken into account when deciding on donor blood
26 transfusion. We therefore did not adjust our analysis accordingly.

Table 4 Effect of intervention on donor blood transfusion

	Control (n=1492)	Cell Salvage (n=1498)	Crude Risk Difference % (95% CI)	Crude Intervention Odds Ratio (95% CI)	P Value - Crude Analysis	Adjusted ^(a) Intervention Odds Ratio (95% CI)	P Value - Adjusted Analysis
Primary analysis							
Overall	52 (3.5%)	37 (2.5%)	-1.0 (-2.2, 0.2)	0.70 (0.46, 1.08)	0.10	0.65 (0.42, 1.01)	0.056
Sub-group analysis							
Emergency caesarean (n=1641)	37 (4.6%)	25 (3.0%)				0.58 (0.34, 0.99)	
Elective caesarean (n=1349)	15 (2.2%)	12 (1.8%)				0.83 (0.38, 1.83)	
P value for interaction							0.46
Sensitivity analysis							
Assumption: return of cell salvaged blood in the control group avoided transfusions	83 (5.6%)	37 (2.5%)	-3.1 (-4.5, -1.7)	0.43 (0.29, 0.64)	<0.001	0.39 (0.26, 0.59)	<0.001
Excluding participants with placental abruption (Cell Salvage group: n=2, Control group: n=3)	51 (3.4%)	37 (2.5%)	-1.0 (-2.2, 0.3)	0.72 (0.47, 1.10)	0.13	0.67 (0.43, 1.03)	0.071

CI: Confidence Interval

(a) Adjusted for stratification factors (elective vs. emergency caesarean section, presence of abnormal placentation, singleton vs. twins or multiple births, recruitment centre (as a random effect)) and other factors believed to be prognostic a-priori (known placenta praevia, pre-eclampsia)

1 **Secondary outcomes**

2 Allocation to cell salvage did not have an effect on the units of donor blood transfused
3 (adjusted MD -0.12, 95% CI -0.8 to 0.57, p=0.74, **Error! Reference source not found.**).

4 A small difference was detected between cell salvage and control groups for time to
5 mobilisation (median 0.74 vs. 0.72 days, adjusted HR 1.11, 95% CI 1.03 to 1.19, p=0.006,
6 **Error! Reference source not found.**); this represented a shorter absolute median time to
7 mobilisation of 0.02 days, i.e. around half an hour. A small difference was also observed in
8 length of hospital stay (median 2.131 vs. 2.126 days adjusted HR 1.08, 95% CI 1.00 to 1.16,
9 p=0.050, **Error! Reference source not found.**); this represented a shorter absolute median
10 hospital stay by 0.005 days or around 10 minutes.

11 Analysis of postoperative haemoglobin levels showed no difference between cell salvage and
12 control groups (adjusted MD 0.63, 95% CI -0.09 to 1.35, p=0.085, **Error! Reference source**
13 **not found.**) and this was also the case for fall in haemoglobin level from baseline (adjusted
14 MD -0.68, 95% CI -1.40 to 0.04, p=0.066, **Error! Reference source not found.**).

15 Among RhD-negative women giving birth to RhD-positive babies, allocation to cell salvage
16 was associated with greater fetomaternal haemorrhage, defined as Kleihauer testing ≥ 2 ml
17 (10.5% vs. 25.6%, adjusted OR 5.63, 95% CI 1.43 to 22.14, p=0.013, Table 5). It should be
18 noted that for 67 patients, Kleihauer testing was done but results could not be classified as
19 they were reported as “<4ml” or similar estimations, according to local guidelines; these
20 results are therefore not available for analysis. Anti-D was routinely administered in the vast
21 majority of RhD-negative mothers with RhD-positive babies (99.2% cases in control group,
22 98.6% cases in cell salvage group, **Error! Reference source not found.**), although a total of
23 3 women across both groups did not seem to have received a minimum standard dose of anti-
24 D following delivery, with a risk of RhD allo-immunisation. The dose of anti-D that was
25 administered is summarised in **Error! Reference source not found.**, with further detail on
26 management of large FMH detailed in Table 7. Of the 140 RhD-negative mothers in the cell
27 salvage group, only 40.6% received a dose of 1500 IU, with 56.5% receiving 500 IU. It is
28 worth noting that the updated guidance³³ recommending a higher standard anti-D dose of
29 1500 IU after cell salvage was published in 2014, so practice in some centres with doses of
30 500 IU may predate publication of these guidelines.

Table 5 Analysis of secondary outcomes

		Control (n=1492)	Cell Salvage (n=1498)	Crude Intervention Odds Ratio / Mean Difference / Hazard Ratio (95% CI)	P Value - Crude Analysis	Adjusted ^(a) Intervention Odds Ratio / Mean Difference / Hazard Ratio (95% CI)	P Value - Adjusted Analysis
Secondary Outcomes							
Units of Blood Transfused^(b)	mean (sd)	2.65 (1.66)	2.70 (1.70)	0.05 (-0.67, 0.76)	0.89	-0.12 (-0.80, 0.57)	0.74
Time to Mobilisation (days)^{(c)(g)}	median (IQR) [n missing]	0.74 (0.45) [49]	0.72 (0.45) [61]	1.07 (0.99, 1.15)	0.079	1.11 (1.03, 1.19)	0.006
Length of Hospital Stay (days)^{(c)(h)}	median (IQR) [n missing]	2.13 (1.41) [24]	2.13 (1.37) [12]	1.04 (0.97, 1.12)	0.26	1.08 (1.00, 1.16)	0.050
Safety Outcomes							
Postoperative Haemoglobin Level (g/l)^(d)	mean (sd) [n missing]	103.1 (12.1) [47]	103.8 (12.2) [61]	0.74 (-0.15, 1.63)	0.10	0.63 (-0.09, 1.35)	0.085
Fall in Haemoglobin Level (g/l)^(d)	mean (sd) [n missing]	15.0 (11.2) [65]	14.5 (11.1) [72]	-0.49 (-1.31, 0.33)	0.24	-0.68 (-1.40, 0.04)	0.066
Any Adverse Event Experienced	n (%) [n missing ^(e)]	191 (12.8%) [0]	199 (13.3%) [1]	1.04 (0.84, 1.29)	0.69	1.02 (0.81, 1.29)	0.84
Fetomaternal haemorrhage^(f)	n (%) [n missing]	9 (10.5%) [33]	21 (25.6%) [51]	2.95 (1.26, 6.89)	0.013	5.63 (1.43, 22.14)	0.013

Note: Analysis of transfusion reaction associated with allogeneic donor blood omitted due to observing only one event (Control group)

CI: Confidence Interval; sd: Standard Deviation; IQR: Inter-quartile Range

(a) Adjusted for stratification factors (elective vs. emergency caesarean section, presence of abnormal placentation, singleton vs. twins or multiple births, recruitment centre (as a random effect)) and other factors believed to be prognostic a-priori (known placenta praevia, pre-eclampsia)

(b) Analysis within the subgroup of participants who received donor blood

(c) Taken from time of delivery

(d) Adjusted analysis also adjusts for pre-operative measurement, as well as time postoperative measurement was taken after delivery (log transformed), with mean imputation of missing values for both covariates. Please note that the decision to adjust for the latter was made by blinded members of the trial team after the signing off of the Statistical Analysis Plan. Haemoglobin post-operatively <105 (g/l): Control group: n=787 (54.5%), Cell Salvage group: n=750 (52.2%)

(e) Missing observations are not included in percentage calculations

(f) Measured by Kleihauer test and dichotomised into a result of <2ml vs. ≥2ml. Analysis within the subgroup of participants who had a Kleihauer test. Measure set to missing where results are not categorisable, e.g. Kleihauer result reported as <4ml (Control group: n=25; Cell Salvage group: n=42)

(g) Test of proportional hazards assumption crude analysis P=0.67, adjusted analysis P=0.18

(h) Test of proportional hazards assumption crude analysis P=0.57, adjusted analysis P=0.39

Table 6 Results concerning maternal RhD status

		Control (n=1492)	Cell Salvage (n=1498)
RhD-Negative Mother With RhD-Positive Baby	n (%)	130 (8.7%)	140 (9.3%)
If Mother Negative and Baby Positive (n=270)			
Anti-D Prophylaxis Administered?	n (%)	129 (99.2%)	138 (98.6%)
Anti-D Prophylaxis Dose (IU)			
500	n (%)	59 (46.1%)	78 (56.5%)
1500	n (%)	67 (52.3%)	56 (40.6%)
Other ^(a)	n (%)	2 (1.6%)	4 (2.9%)
Missing ^(b)	n	1	0
Kleihauer Test Performed?	n (%) [n missing]	119 (92.2%) [1]	133 (95.0%) [0]
Fetomaternal haemorrhage (Kleihauer test ≥2ml)	n (%) [n missing ^(c)]	9 (10.5%) [33]	21 (25.6%) [51]
Sample Sent For Flow Cytometry^(d)	n (%)	1 (33.3%)	9 (75.0%)
Repeat Kleihauer Test Performed?^(e)	n (%)	1 (50.0%)	6 (100.0%)
Further Anti-D Prophylaxis Administered?^(e)	n (%) [n missing]	1 (100.0%) [1]	1 (16.7%) [0]
Further Anti-D Prophylaxis Dose (IU)			
250	n (%)	0 (0.0%)	1 (100.0%)
1500	n (%)	1 (100.0%)	0 (0.0%)

(a) Other doses include Control group: 1250, 4000; Cell Salvage group: 1000, 1000, 4500, 5000. See Table 7 for details.

(b) Missing observations are not included in percentage calculations. Where variables are categorical, missing values are listed in a separate row, but are similarly not included in percentage calculations

(c) Measure set to missing where results are not categorisable, e.g. Kleihauer result reported as <4ml (Control group: n=25; Cell Salvage group: n=42)

(d) Measure only collected for participants with Kleihauer >2ml (Control group: n = 3, Cell Salvage group n = 12)

(e) Measure only collected for participants with Kleihauer >4ml (Control group: n=2, Cell Salvage group: n=6). Kleihauer results >4ml are Control group: >4ml, =37ml; Cell Salvage group: =5ml, =6ml, =6ml, =10ml, =11ml, =26ml. See Table 7 for details.

Table 7 Management of RhD-negative women with fetomaternal haemorrhage \geq 2mls by Kleihauer

FMH by Kleihauer (ml)	Anti-D dose (IU)	Flow cytometry undertaken ^(a)	Flow cytometry result (ml)	Repeat Kleihauer undertaken ^(b)	Blood returned during cell salvage?
Cell salvage group (n=21)					
26	4500	Yes	26	Yes	Yes
11	1500	Yes	9	Yes	Yes
10	1500	Yes	10	Yes	Yes
6	1000	Yes	5	Yes	No
6	1000	Yes	6	Yes	Yes
5	1500	Yes	12	Yes ^(c)	Yes
4	5000	No	-		No
4	500	Yes	2		No
3	500	No	-		Yes
3	None	No	-		No
>2	500	Yes	2		Yes
>2	1500	Yes	7		Yes
2	1500				Yes
2	1500				No
2	1500				Yes
2	500				Yes
2	500				Yes
2	500				Yes
2	500				Yes
2	500				Yes
2	500				No
Control group (n=9)					
37	4000	Yes	37	Yes ^(c)	Not set up
>4	1500	No	-	No	Not set up
3	500	No	-		Not set up
2	500				Not set up
5pts with 2	1500				Not set up

FMH: Fetomaternal haemorrhage.

(a) Flow cytometry data was only collected for Kleihauer > 2ml.

(b) Repeat Kleihauer data was only collected for Kleihauer > 4ml.

(c) Repeat anti-D also administered.

Kleihauer tests were undertaken on the majority of RhD-negative participants in both groups (92.2% cases in control group, 95.0% cases in cell salvage group, **Error! Reference source not found.**). Five per cent of women in cell salvage group and 7.8% women in the control group did not have Kleihauer tests undertaken following delivery. It should be noted that a

dose of 500IU of anti-D covers an FMH of 4mls, and while a 1500 IU anti-D dose covers an FMH of ~12mls, a small proportion of women may have had an even higher fetomaternal bleed. A Kleihauer test is therefore recommended to determine if additional doses of anti-D are needed in addition to the standard dose.

Repeat Kleihauer tests were undertaken 72 hours post anti-D administration for the majority of applicable participants and further anti-D was administered for 2 participants (Table 6 **Error! Reference source not found.**). Overall 8 women (n=2 in the control group and n=6 in the intervention group) had larger instances of fetomaternal haemorrhage with >4ml Kleihauer results. Of the two in the control group, one woman had the largest observed FMH on the study, with 37ml. She was managed as per guidelines with flow cytometry for confirmation of the FMH volume, additional anti-D dose administered and repeat Kleihauer test undertaken. The other had an initial Kleihauer result of >4ml, was administered 1500IU of anti-D but had no flow cytometry undertaken. Neither of these two women in the control group received cell salvage. Of the 6 women in the intervention group, five had received cell salvaged blood back. All 6 women had confirmatory flow cytometry done and repeat Kleihauer tests undertaken.

Breakdowns of fetomaternal haemorrhage by sucker use and return of salvaged blood were also summarised (see Table 8). On a descriptive level, sucker use appeared to have little effect on the proportion of participants experiencing fetomaternal haemorrhage (28.3% when one sucker was used versus 25.0% when two suckers were used). Return of salvaged blood appeared to increase fetomaternal haemorrhage (13.0% in cases of no salvaged blood returned versus 48.4% in cases where salvaged blood was returned).

Table 8 Fetomaternal haemorrhage by sucker use and by return of salvaged blood

	One Sucker Used (n=53)	Two Suckers Used (n=24)
Fetomaternal Haemorrhage ^(a)	15 (28.3%)	6 (25.0%)
	No Blood Returned (n=46)	Blood Returned (n=31)
Fetomaternal Haemorrhage ^(b)	6 (13.0%)	15 (48.4%)

Data presented are n (%)

(a) Measured by Kleihauer test and dichotomised into a result of <2ml vs. ≥2ml. Summaries within participants who had the cell salvage machine set up (including Emergency use), for those with complete data on fetomaternal haemorrhage and sucker use

(b) Summaries within participants who had the cell salvage machine set up (including emergency use), for those with complete data on fetomaternal haemorrhage and return of blood during cell salvage

Administration of other donor products (namely Fresh Frozen Plasma, Platelets and Cryoprecipitate) is summarised in Table 9 below.

Table 9 Detail of Administration of Donor Products

		Control (n=1492)	Cell Salvage (n=1498)
Intraoperative			
Donor Blood Given	n (%)	20 (1.3%)	12 (0.8%)
Units^(a) of Blood	mean (sd)	2.60 (1.27)	2.08 (0.51)
FFP Given	n (%)	9 (0.6%)	3 (0.2%)
Units of FFP	mean (sd)	2.11 (0.33)	3.00 (1.00)
Platelets Given	n (%)	2 (0.1%)	0 (0.0%)
Units of Platelets	mean (sd)	1.50 (0.71)	-
Cryoprecipitate Given	n (%)	2 (0.1%)	0 (0.0%)
Units of Cryoprecipitate	mean (sd)	2.00 (0.00)	-
Postnatal			
Donor Blood Given	n (%)	36 (2.4%)	30 (2.0%)
Units of Blood	mean (sd)	2.39 (1.57)	2.50 (1.68)
FFP Given	n (%)	8 (0.5%)	7 (0.5%)
Units of FFP	mean (sd)	3.25 (2.19)	3.29 (0.95)
Platelets Given	n (%)	2 (0.1%)	1 (0.1%)
Units of Platelets	mean (sd)	1.00 (0.00)	1.00 (-)
Cryoprecipitate Given	n (%)	3 (0.2%)	0 (0.0%)
Units of Cryoprecipitate	mean (sd)	2.00 (0.00)	-

sd: Standard Deviation; FFP: Fresh Frozen Plasma

(a) Unit summaries considered within participants who received the specified blood product

The multidimensional fatigue inventory questionnaire was completed for 2408 (80.5%) of participants. Analysis of multidimensional fatigue inventory statement scores showed no significant differences between allocation groups for the fatigue categories of ‘General Fatigue’, ‘Physical Fatigue’, ‘Reduced Motivation’ or ‘Reduced Activity’. There was a modest difference between cell salvage and control group for ‘Mental Fatigue’ (adjusted MD -0.30, 95% CI -0.59 to -0.01, p=0.043, Table 10**Error! Reference source not found.**).

Table 10 Analysis of Multidimensional Fatigue Inventory

	Control (n=1187)	Cell Salvage (n=1221)	Crude Mean Difference (95% CI)	P Value - Crude Analysis	Adjusted ^(a) Mean Difference (95% CI)	P Value - Adjusted Analysis
MFI Groups^(b)						
General Fatigue	12.7 (3.6) [52]	12.5 (3.6) [39]	-0.18 (-0.47, 0.12)	0.24	-0.18 (-0.47, 0.11)	0.22
Physical Fatigue	12.3 (3.9) [22]	12.3 (3.9) [31]	-0.05 (-0.36, 0.26)	0.75	-0.06 (-0.37, 0.25)	0.69
Reduced Motivation	9.6 (3.3) [36]	9.8 (3.4) [46]	0.12 (-0.15, 0.40)	0.37	0.13 (-0.14, 0.40)	0.36
Reduced Activity	11.3 (3.8) [42]	11.4 (3.6) [47]	0.12 (-0.18, 0.43)	0.44	0.12 (-0.18, 0.41)	0.45
Mental Fatigue	8.7 (3.6) [19]	8.4 (3.6) [41]	-0.28 (-0.57, 0.01)	0.061	-0.30 (-0.59, -0.01)	0.043

Data presented are mean (sd) [n missing]

sd: Standard Deviation; CI: Confidence Interval; MFI: Multidimensional Fatigue Inventory

(a) Adjusted for stratification factors (elective vs. emergency caesarean section, presence of abnormal placentation, singleton vs. twins or multiple births, recruitment centre (as a random effect)) and other factors believed to be prognostic a-priori (known placenta praevia, pre-eclampsia)

(b) Sum of MFI statement scores (where participants indicate agreement within a statement between 1 and 5) within fatigue categories. Higher scores indicate increased fatigue.

1 As for process outcomes, the cell salvage machine was set up for 1490 participants across
 2 both groups and salvaged blood was processed and returned for a total of 761 participants (35
 3 [60.3%] in the control group and 726 [50.8%] in the cell salvage group). Volume of salvaged
 4 blood was recorded and summarised and reasoning behind no return of salvaged blood was
 5 also denoted, with the most common reason being that no blood was produced by the cell
 6 salvage machine. Further measures detailing implementation of the intervention, such as
 7 machine settings and equipment use, are summarised in Table 11.

8 **Table 11 Other Details Regarding Cell Salvage Use**

	Control (n=1492)	Cell Salvage (n=1498)
If Cell Salvage Set Up (Including Emergency Use) (n=1490)		
Collection Sets Used^(a)		
0	0 (0.0%)	1 (0.1%)
1	36 (100.0%)	1240 (99.3%)
2	0 (0.0%)	7 (0.6%)
3	0 (0.0%)	1 (0.1%)
Missing ^(b)	0	3
Processing Packs Used^(a)		
0	2 (5.7%)	50 (4.0%)
1	32 (91.4%)	1179 (94.5%)
2	1 (2.9%)	13 (1.0%)
3	0 (0.0%)	4 (0.3%)
4	0 (0.0%)	2 (0.2%)
Missing	1	4
Default Settings Used	54 (94.7%) [1]	1287 (90.3%) [6]

Data presented are n (%) [n missing]

sd: Standard Deviation

(a) Measure not applicable for sites with a continuous transfusion machine only (Cell Salvage group: n=180, Control group: n=22)

(b) Missing observations are not included in percentage calculations. Where variables are categorical, missing values are listed in a separate row, but are similarly not included in percentage calculations

1 **Adverse events**

2 There were 453 adverse events reported in total across both groups, with 191 participants
 3 experiencing 220 adverse events in total in the control group and 199 participants
 4 experiencing a total of 233 adverse events in the cell salvage group. There was no significant
 5 difference between allocation groups for experiencing an adverse event (adjusted OR 1.02,
 6 95% CI 0.81 to 1.29, p=0.84, see Table 5). See Table 12 for details and descriptions of
 7 adverse events. One case of transfusion reaction associated with allogeneic donor blood was
 8 observed in the control group. There was no case of amniotic fluid embolism observed, with
 9 or without use of leukocyte depletion filter.

Table 12 Detail of Adverse Event

	Control (n=1492)	Cell Salvage (n=1498)
Any Adverse Event Experienced	191 (12.8%) [0]	199 (13.3%) [1]
Total Adverse Events	220	233
Breakdowns Per Adverse Event (n=453)		
Adverse Event Severity		
Mild	89 (40.5%)	101 (43.3%)
Moderate	88 (40.0%)	92 (39.5%)
Severe	34 (15.4%)	35 (15.0%)
Life threatening	9 (4.1%)	4 (1.7%)
Fatal	0 (0.0%)	1 (0.4%)
Adverse Event Relatedness To Intervention (If Cell Salvage Set Up (Including Emergency Use) (n=238))		
Unrelated	8 (57.1%)	160 (71.4%)
Unlikely	5 (35.7%)	47 (21.0%)
Possible ^(a)	1 (7.1%)	14 (6.3%)
Probable ^(a)	0 (0.0%)	2 (0.9%)
Definite ^(a)	0 (0.0%)	1 (0.4%)
Is the Adverse Event Serious^(b)	20 (9.1%)	15 (6.4%)
Adverse Event Descriptions^(c) by System Organ Class		
Blood and lymphatic system disorders		
Thrombocytopenia	0 (0.0%)	3 (1.3%)
Anaemia	2 (0.9%)	6 (2.6%)
Cardiac disorders		
Sinus tachycardia	0 (0.0%)	5 (2.2%)

	Control (n=1492)	Cell Salvage (n=1498)
Hypotension	2 (0.9%)	2 (0.9%)
Supraventricular tachycardia	1 (0.5%)	1 (0.4%)
Gastrointestinal disorders		
Diarrhoea	0 (0.0%)	1 (0.4%)
Ileus	4 (1.8%)	3 (1.3%)
Incontinence	0 (0.0%)	1 (0.4%)
General disorders and administration site conditions		
Pain	4 (1.8%)	3 (1.3%)
Non-cardiac chest pain	1 (0.5%)	0 (0.0%)
Immune system disorders		
Reaction to cell salvaged blood	0 (0.0%)	5 (2.2%)
Reaction to donor blood	1 (0.5%)	0 (0.0%)
Allergic reaction	1 (0.5%)	0 (0.0%)
Infections and infestations		
Lung infection	2 (0.9%)	0 (0.0%)
Wound infection	5 (2.3%)	6 (2.6%)
Uterine infection	1 (0.5%)	2 (0.9%)
Sepsis	11 (5.0%)	11 (4.7%)
Unknown source	12 (5.5%)	21 (9.0%)
Injury, poisoning and procedural complications		
Wound dehiscence	1 (0.5%)	2 (0.9%)
Metabolism and nutrition disorders		
Hyperglycaemia	0 (0.0%)	1 (0.4%)
Musculoskeletal and connective tissue disorders		
Pain in extremity	0 (0.0%)	2 (0.9%)
Back pain	1 (0.5%)	0 (0.0%)
Nervous system disorders		
Presyncope	2 (0.9%)	3 (1.3%)
Seizure	2 (0.9%)	1 (0.4%)
Limb weakness	0 (0.0%)	1 (0.4%)
Pregnancy, puerperium and perinatal conditions - Other		
Hypertensive disease of pregnancy	32 (14.6%)	34 (14.6%)
Uterine atony	1 (0.5%)	0 (0.0%)
Placental abnormality	2 (0.9%)	1 (0.4%)
Maternal exposure to fetal blood	1 (0.5%)	0 (0.0%)
Renal and urinary disorders		
Urinary retention	3 (1.4%)	2 (0.9%)
Oliguria	3 (1.4%)	0 (0.0%)
Chronic kidney disease	0 (0.0%)	1 (0.4%)
Prolonged catheterisation	1 (0.5%)	3 (1.3%)
Proteinuria	1 (0.5%)	1 (0.4%)
Hematuria	1 (0.5%)	1 (0.4%)
Reproductive system and breast disorders		
Fibroids	1 (0.5%)	0 (0.0%)

	Control (n=1492)	Cell Salvage (n=1498)
Uterine haemorrhage	106 (48.4%)	93 (39.9%)
Respiratory, thoracic and mediastinal disorders		
Cough	0 (0.0%)	1 (0.4%)
Dyspnea	1 (0.5%)	0 (0.0%)
Hypoxia	1 (0.5%)	1 (0.4%)
Pulmonary edema	0 (0.0%)	1 (0.4%)
Sleep apnea	1 (0.5%)	0 (0.0%)
Skin and subcutaneous tissue disorders		
Pruritus	0 (0.0%)	1 (0.4%)
Surgical and medical procedures - Other		
Anaesthetic complication	3 (1.4%)	1 (0.4%)
Surgical complication	5 (2.3%)	2 (0.9%)
Wound haematoma	1 (0.5%)	5 (2.2%)
Vascular disorders		
Venous eczema	0 (0.0%)	1 (0.4%)
Hypertension	1 (0.5%)	3 (1.3%)
Thromboembolic event	1 (0.5%)	1 (0.4%)
Missing^(d)	1	0

Data presented are n (%) [n missing]

(a) For further detail see Table 13

(b) For further detail see Table 14

(c) Descriptions are coded by the trial team

(d) Missing observations are not included in percentage calculations. Where variables are categorical, missing values are listed in a separate row, but are similarly not included in percentage calculations

1 In 18 cases adverse events were considered to be related to cell salvage, with 15 events
2 possibly related, 2 events probably related and 1 event definitely related to the intervention.
3 See Table 13 for details of related adverse events. Of the 18 adverse events classed as related
4 to cell salvage, the majority (n=16) were also in the context of the use of a leukocyte
5 depletion filter. These included transient episodes of hypotension which might have been
6 related to the return of cell salvaged blood, as well as haemorrhagic and infective
7 complications; as cell salvage removes clotting factors and platelets, it can theoretically lead
8 to coagulopathy unless coagulation products are simultaneously given, and there is also a
9 potential risk of returning infective agents such as bacteria in the salvaged blood. The
10 ultimate judgement on whether these complications might have been caused by cell salvage
11 lay with the local principal investigator.

Table 13 Further Detail for Events Potentially Related to Cell Salvage

Adverse Event Relatedness to Intervention	Allocation	System Organ Class of Adverse Event	Adverse Event Description
Possible	Control	Reproductive system and breast disorders	Uterine haemorrhage
Possible	Cell Salvage	Cardiac disorders	Hypotension
Possible	Cell Salvage	Immune system disorders	Reaction to cell salvaged blood
Possible	Cell Salvage	Immune system disorders	Reaction to cell salvaged blood
Possible	Cell Salvage	Infections and infestations	Sepsis
Possible	Cell Salvage	Infections and infestations	Unknown source
Possible	Cell Salvage	Infections and infestations	Unknown source
Possible	Cell Salvage	Infections and infestations	Unknown source
Possible	Cell Salvage	Infections and infestations	Unknown source
Possible	Cell Salvage	Infections and infestations	Unknown source
Possible	Cell Salvage	Reproductive system and breast disorders	Uterine haemorrhage
Possible	Cell Salvage	Reproductive system and breast disorders	Uterine haemorrhage
Possible	Cell Salvage	Surgical and medical procedures - Other	Wound haematoma
Possible	Cell Salvage	Infections and infestations	Wound infection
Probable	Cell Salvage	Immune system disorders	Reaction to cell salvaged blood
Probable	Cell Salvage	Immune system disorders	Reaction to cell salvaged blood
Definite	Cell Salvage	Immune system disorders	Reaction to cell salvaged blood

1 There were 36 Serious Adverse Events (SAEs) reported during the SALVO trial. Of these, 32
2 are included in the adverse event table (Table 14), with one SAE having 3 adverse events
3 pertaining to it. There were 4 additional serious adverse events concerning the offspring (such
4 as congenital anomalies), which did not require reporting for the main adverse event analysis.
5 One fatal event was observed among trial participants. It was considered unrelated to the
6 intervention. This maternal death occurred in a patient who died on the sixth day following
7 her delivery.

8 Two serious adverse reactions were reported in this trial, i.e. SAEs which were considered
9 related to the intervention. The first was reported as a reaction to salvaged blood. The patient
10 became tachycardic, flushed and had difficulty breathing, starting shortly after the start of the
11 re-transfusion and resolving completely once the transfusion was stopped. The event was
12 classed by the local investigator as life-threatening, and as most likely due to the use of a
13 leukocyte depletion filter. The second event was a sudden onset of hypotension, after re-
14 transfusion of 600ml of cell salvaged blood; the patient recovered fully. The event was also
15 reported as life-threatening, and as most likely secondary to the use of a leukocyte depletion
16 filter.

Table 14 Further Detail for Serious Adverse Events

Description ^(a) of Serious Adverse Event	Allocation	Reason for Seriousness	Serious Adverse Event Relatedness to Intervention
Bladder damage during surgery ^(b)	Control	Hospitalisation > 7 days	Unrelated
Concealed obstetric haemorrhage	Control	Life-threatening	Unrelated
HELLP Syndrome	Control	Other	Unrelated
Infection of unknown origin	Control	Hospitalisation > 7 days	Unrelated
Massive obstetric haemorrhage	Control	Life-threatening	Unrelated
Massive obstetric haemorrhage	Control	Life-threatening	Unlikely
Massive obstetric haemorrhage	Control	Life-threatening	Unrelated
Massive obstetric haemorrhage	Control	Life-threatening	Unrelated
Massive obstetric haemorrhage	Control	Life-threatening	Unrelated
Massive obstetric haemorrhage	Control	Life-threatening	Unrelated
Massive obstetric haemorrhage	Control	Life-threatening	Unrelated
Pneumonia	Control	Hospitalisation > 7 days	Unrelated
Pre-eclampsia	Control	Hospitalisation > 7 days	Unrelated
Pre-eclampsia	Control	Hospitalisation > 7 days	Unrelated
Pulmonary embolism and obstetric haemorrhage	Control	Life-threatening	Unrelated
Sepsis	Control	Hospitalisation > 7 days	Unrelated
Vertebral disc prolapse	Control	Disability/incapacity	Unlikely
Wound complication	Control	Hospitalisation > 7 days	Unrelated
Bowel obstruction, caecal gangrene	Cell Salvage	Hospitalisation > 7 days	Unrelated
Bowel perforation, sepsis, multi-organ failure	Cell Salvage	Fatal	Unrelated
Fetal congenital abnormality ^(c)	Cell Salvage	Congenital abnormality / birth defect	Unrelated
Fetal congenital abnormality ^(c)	Cell Salvage	Congenital abnormality / birth defect	Unrelated
Fetal epidermolysis bullosa ^(c)	Cell Salvage	Congenital abnormality / birth defect	Unrelated
Hypertension	Cell Salvage	Hospitalisation > 7 days	Unrelated
Massive obstetric haemorrhage	Cell Salvage	Life-threatening	Unlikely
Massive obstetric haemorrhage	Cell Salvage	Life-threatening	Unrelated
Palpitations and shortness of breath. Post-partum echocardiogram suggested mild left ventricular systolic dysfunction	Cell Salvage	Hospitalisation > 7 days	Unlikely
Pre-eclampsia	Cell Salvage	Hospitalisation > 7 days	Unrelated
Pre-eclampsia	Cell Salvage	Hospitalisation > 7 days	Unrelated
Pre-existing atrial fibrillation and wound complication	Cell Salvage	Hospitalisation > 7 days	Unrelated

Description ^(a) of Serious Adverse Event	Allocation	Reason for Seriousness	Serious Adverse Event Relatedness to Intervention
Reaction to salvaged blood or leukocyte depletion filter (hypotension)	Cell Salvage	Life-threatening	Probably
Reaction to salvaged blood or leukocyte depletion filter (tachycardia, dyspnoea)	Cell Salvage	Life-threatening	Definitely
Sepsis	Cell Salvage	Hospitalisation > 7 days	Unlikely
Sepsis	Cell Salvage	Hospitalisation > 7 days	Unlikely
Stillbirth ^(c)	Cell Salvage	Congenital abnormality / birth defect	Unrelated
Wound complication	Cell Salvage	Hospitalisation > 7 days	Unrelated
Wound complication	Cell Salvage	Hospitalisation > 7 days	Unrelated

(a) Descriptions are coded by the trial team

(b) Participant had 3 adverse events which were ticked as serious, all falling under the serious adverse event described

(c) Serious adverse events not included in **Error! Reference source not found.** as they concern the baby, not the mother

1 ***Further exploratory analyses***

2 There was no significant difference in the effectiveness of cell salvage on secondary
3 outcomes between elective and emergency caesarean section (Table 15), or in the effect of
4 cell salvage on reducing donor blood transfusion between participants with normal and
5 abnormal placentation (p-value for interaction term=0.28, Table 16).

6 In a sensitivity analysis assuming that a donor blood transfusion would have been required,
7 had salvaged blood not been returned in the control when the cell salvage machine was set up
8 in an emergency (n=8), the effect of cell salvage on donor blood transfusion was significant
9 (4.0% vs. 2.5%, adjusted OR 0.56, 95% CI 0.36 to 0.86, p=0.008, Table 17).

10 We observed that swab washing greatly increased the proportion of participants who received
11 salvaged blood (16.0% when swabs were not washed vs. 81.3% when swabs were washed)
12 and that the volume of blood returned was higher when swabs were washed (mean (sd) =
13 32.8 (100.5) when swabs were not washed vs. 219.3 (169.8) when swabs were washed)
14 (Table 18). In a comparison between participants who did and did not have swabs washed
15 within those who had the cell salvage machine set up, no significant difference in the
16 transfusion rates was observed (adjusted OR 0.79, 95% CI 0.39 to 1.57, p=0.50, Table 19).

Table 15 Analysis of Secondary Outcomes: Further Exploratory Subgroup Analysis

		Elective caesarean section (n=1349)			Emergency caesarean section (n=1641)			P Value For Interaction Term
		Control (n=684)	Cell Salvage (n=665)	Adjusted ^(a) Intervention Odds Ratio / Mean Difference / Hazard Ratio (95% CI)	Control (n=808)	Cell Salvage (n=833)	Adjusted Intervention Odds Ratio / Mean Difference / Hazard Ratio (95% CI)	
Units of Blood Transfused^(b)	mean (sd)	3.33 (2.53)	2.92 (2.35)	-0.20 (-1.42, 1.02)	2.38 (1.06)	2.60 (1.32)	-0.08 (-0.92, 0.77)	0.87
Time to Mobilisation (days)^(c)	median (IQR) [n missing]	0.79 (0.43) [30]	0.79 (0.46) [29]	1.03 (0.92, 1.15)	0.69 (0.45) [19]	0.66 (0.43) [32]	1.18 (1.07, 1.30)	0.083
Length of Hospital Stay (days)^(c)	median (IQR) [n missing]	2.10 (1.21) [19]	2.08 (1.00) [10]	1.06 (0.95, 1.18)	2.20 (1.81) [5]	2.18 (1.49) [2]	1.09 (0.99, 1.20)	0.70
Postoperative Haemoglobin Level (g/l)^(d)	mean (sd) [n missing]	104.28 (11.19) [17]	106.18 (12.05) [25]	1.19 (0.12, 2.25)	102.03 (12.78) [30]	101.91 (12.03) [36]	0.17 (-0.80, 1.14)	0.17
Fall in Haemoglobin Level (g/l)^(e)	mean (sd) [n missing]	12.37 (9.41) [21]	11.66 (9.92) [27]	-1.18 (-2.24, -0.11)	17.32 (12.17) [44]	16.86 (11.53) [45]	-0.26 (-1.23, 0.72)	0.21
Any Adverse Event Experienced	n (%) [n missing ⁽⁵⁾]	48 (7.0) [0]	48 (7.2) [0]	1.08 (0.70, 1.66)	143 (17.7) [0]	151 (18.1) [1]	1.00 (0.77, 1.31)	0.78
Fetomaternal haemorrhage^(f)	n (%) [n missing]	4 (10.3) [13]	9 (26.5) [17]	9.71 (1.11, 85.11)	5 (10.6) [20]	12 (25.0) [34]	4.08 (0.81, 20.51)	0.51

*Analysis of Transfusion Reaction Associated with Allogeneic Donor Blood omitted due to observing only one event (Control group)

CI: Confidence Interval; sd: Standard Deviation; IQR: Inter-quartile Range

(a) Adjusted for stratification factors (elective vs. emergency caesarean section, presence of abnormal placentation, singleton vs. twins or multiple births, recruitment centre (as a random effect)) and other factors believed to be prognostic a-priori (known placenta praevia, pre-eclampsia)

(b) Analysis within the subgroup of participants who received donor blood

(c) Taken from time of delivery

(d) Adjusted analysis also adjusts for pre-operative measurement, as well as time postoperative measurement was taken after delivery (log transformed), with mean imputation of missing values for both covariates. Please note that the decision to adjust for the latter was made by blinded members of the trial team after the signing off of the Statistical Analysis Plan

(e) Missing observations are not included in percentage calculations

(f) Measured by Kleihauer test and dichotomised into a result of <2 vs. ≥2ml. Analysis within the subgroup of participants who had a Kleihauer test

Table 16 Analysis of Primary Outcome: Further Exploratory Subgroup Analysis; placentation

	Normal Placentation (n=2720)			Abnormal Placentation (n=270)			P Value For Interaction Term
	Control (n=1357)	Cell Salvage (n=1363)	Adjusted ^(a) Intervention Odds Ratio (95% CI)	Control (n=135)	Cell Salvage (n=135)	Adjusted Intervention Odds Ratio (95% CI)	
Donor Blood Transfusion	40 (2.9%)	24 (1.8%)	0.56 (0.34, 0.94)	12 (8.9%)	13 (9.6%)	0.98 (0.42, 2.32)	0.28

CI: Confidence Interval

(a) Adjusted for stratification factors (elective vs. emergency caesarean section, presence of abnormal placentation, singleton vs. twins or multiple births, recruitment centre (as a random effect)) and other factors believed to be prognostic a-priori (known placenta praevia, pre-eclampsia)

Table 17 Analysis of Primary Outcome: Further Exploratory Sensitivity Analysis

	Control (n=1492)	Cell Salvage (n=1498)	Crude Risk Difference % (95% CI)	Crude Intervention Odds Ratio (95% CI)	P Value - Crude Analysis	Adjusted ^(a) Intervention Odds Ratio (95% CI)	P Value - Adjusted Analysis	
Donor Blood Transfusion: Sensitivity Analysis 3^(b)	n (%)	60 (4.0%)	37 (2.5%)	-1.6 (-2.8, -0.3)	0.60 (0.40, 0.92)	0.018	0.56 (0.36, 0.86)	0.008

CI: Confidence Interval

(a) Adjusted for stratification factors (elective vs. emergency caesarean section, presence of abnormal placentation, singleton vs. twins or multiple births, recruitment centre (as a random effect)) and other factors believed to be prognostic a-priori (known placenta praevia, pre-eclampsia)

(b) Assuming all instances of blood returned using cell salvage set up in an emergency in the control group would have been transfusions had the cell salvage machine not been present

Table 18 Summaries Specific to Swab Washing

		Swabs Not Washed (n=681)	Swabs Washed (n=802)
Salvaged Blood Returned	n (%) [n missing ^(a)]	109 (16.0%) [1]	651 (81.3%) [1]
Volume of Blood Returned to Mother (ml)	mean (sd)	32.8 (100.5)	219.3 (169.8)

sd: Standard Deviation

(a) Missing observations are not included in percentage calculations

Table 19 Analysis of Primary Outcome: Further Exploratory Analysis by Swab Washing

		Swabs Not Washed (n=681)	Swabs Washed (n=802)	Crude Odds Ratio (95% CI)	P Value - Crude Analysis	Adjusted ^(a) Odds Ratio (95% CI)	P Value - Adjusted Analysis
Donor Blood Transfusion^(b)	n (%)	18 (2.6%)	18 (2.2%)	0.85 (0.44, 1.64)	0.62	0.79 (0.39, 1.57)	0.50

CI: Confidence Interval

(a) Adjusted for stratification factors (elective vs. emergency caesarean section, presence of abnormal placentation, singleton vs. twins or multiple births, recruitment centre (as a random effect)) and other factors believed to be prognostic a-priori (known placenta praevia, pre-eclampsia)

(b) Analysis within participants who had the cell salvage machine set up (including Emergency use), for those with complete swab washing data

1 **Chapter 4 Health Economic Evaluation**

2 **Introduction**

3 This chapter reports the economic evaluation carried out alongside the SALVO trial. The
4 primary objective of the study was to determine whether the routine use of cell salvage
5 during caesarean section, in women at risk of haemorrhage, reduced the need for donor blood
6 transfusion compared to standard care.

7 **Methods**

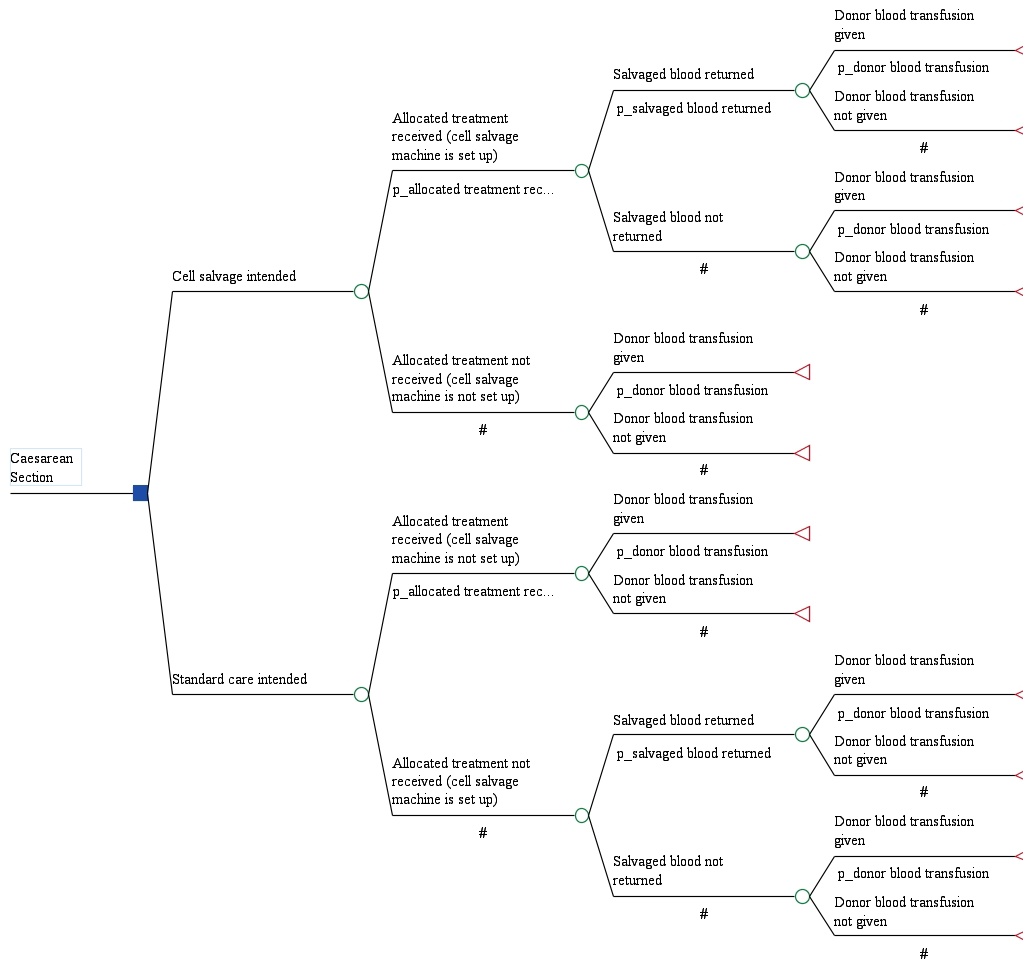
8 To compare the costs and outcomes of cell salvage and standard care in the SALVO trial, a
9 decision analytic model was deemed the most suitable method of presenting the alternative
10 pathways and collating the data for analysis and sensitivity analysis. In a decision analytic
11 model, consequences are expressed as probabilities, weighted against costs and outcomes to
12 derive an expected value for each alternative option.⁷⁰ The economic evaluation took the
13 form of a cost-effectiveness analysis (CEA) from the perspective of the healthcare provider
14 based on the principal clinical outcome of the trial. The main comparison is the use of cell
15 salvage versus standard care. The results are reported in terms of the additional cost per donor
16 blood transfusion avoided by using cell salvage compared to standard care. Standard care is
17 defined for the purposes of the trial as “transfusion of donor blood according to standard local
18 guidelines”. Costs were calculated in 2014-2015 UK pounds (£). Given the objectives of the
19 trial and the duration of follow-up, only a within trial economic analysis was carried out and
20 outcomes beyond this point were not considered relevant.

21 **Model Structure**

22 A decision tree model was developed in TreeAge Pro 2016 (TreeAge Software, Inc.,
23 Williamstown, MA, USA). The structure was informed by the objectives of the study and the
24 pathways indicated by the clinical data. The model pathways (Figure 3) represent that of the
25 trial in which patients undergoing a caesarean section were randomised to receive either cell
26 salvage or standard care. Square boxes represent decision nodes, where there is a choice to be
27 made between strategies. Circles represent chance nodes, where there are a number of

1 subsequent events that could happen and each event is assigned a probability that it will
 2 occur. Triangles represent terminal nodes, signifying the last stage in the model.

3 **Figure 3 Decision tree structure**



4 Figure 3 shows the model starts with the choice of transfusion strategies considered in the
 5 SALVO trial:

- 6 • Cell salvage
- 7 • Standard care

8
 9 Women allocated to either transfusion strategy have a possibility of receiving the treatment to
 10 which they were allocated or not. In both pathways, if the cell salvage machine was switched
 11 on, women have a possibility of receiving cell salvage, either on its own or in combination

1 with donor blood transfusion. There is also a possibility that the woman may not require a
2 transfusion.

3 The pathways of the model represent, as far as possible, the clinical procedures carried out in
4 the study. The model combines the probability of a woman following a particular path and
5 the associated costs. Probabilities, detailed in Table 20, were obtained from the trial and
6 attached to each pathway. The cost and outcome measures that were incorporated into the
7 model were collected prospectively during the SALVO trial using forms filled out at the pre-,
8 intra-, and postoperative phase and at the time of discharge from hospital. Intraoperative
9 resource use and costs were estimated as the mean cost per caesarean section procedure
10 conducted for each treatment pathway in the model and postoperative resource use and costs
11 were estimated as the mean cost per patient in both treatment strategies represented in the
12 model.

13 **Table 20 Probabilities used in the model**

	Trial data	Probability	Distribution
Cell salvage intended			
<i>Cell salvage intended → allocated treatment received (machine was on)</i>	1432 / 1498	0.96	Beta
Allocated treatment received → salvaged blood returned	726/1432	0.51	Beta
Allocated treatment received → salvaged blood not returned	703/1432	0.49	Beta
Salvaged blood returned → donor blood transfusion given	22/726	0.03	Beta
Salvaged blood returned → donor blood transfusion not given	704 /726	0.97	Beta
Salvaged blood not returned → donor blood transfusion given	9/703	0.01	Beta
Salvaged blood not returned → donor blood transfusion not given	697 / 703	0.99	Beta
<i>Cell salvage intended → allocated treatment not received (machine was off)</i>	66/1498	0.04	Beta
Allocated treatment not received → donor blood transfusion given	6/66	0.09	Beta
Allocated treatment not received → donor blood transfusion not given	60/66	0.91	Beta
Standard care intended			
<i>Standard care intended → allocated treatment received (machine was off)</i>	1434/1492	0.96	Beta
Allocated treatment received → donor blood transfusion given	47/1434	0.03	Beta
Allocated treatment received → donor blood transfusion not given	1387 / 1434	0.97	Beta
<i>Standard care intended → allocated treatment not received (machine was on)</i>	58/1492	0.04	Beta
Allocated treatment not received → salvaged blood returned	35/58	0.60	Beta
Allocated treatment not received → salvaged blood not returned	23/58	0.40	Beta
Salvaged blood returned → donor blood transfusion given	4/35	0.11	Beta
Salvaged blood returned → donor blood transfusion not given	31/35	0.89	Beta
Salvaged blood not returned → donor blood transfusion given	1/23	0.04	Beta

1 **Data**

2 Resource use and costs

3 The resource use for both groups of the trial was estimated by evaluating the individual
4 components of these procedures (bottom-up costing). Unit cost data was then attached to the
5 resource use. Data were collected on all major NHS resource use for each patient using the
6 trial case report forms. The main resource use monitored included:

7 ***Intraoperative:***

- 8 • Equipment and disposables required for the cell salvage procedure
- 9 • Additional staff called into theatre solely for the purposes of cell salvage
- 10 • Drugs used in the caesarean section procedure
- 11 • The use of donor blood transfusion to deal with haemorrhage and its consequences
- 12 • The use of salvaged blood transfusion to deal with haemorrhage and its consequences

13 ***Postoperative:***

- 14 • Length and type of hospital inpatient stay including additional treatment required
15 attributed to the caesarean section procedure.
- 16 • The use of donor blood transfusion to deal with haemorrhage and its consequences

17 Intraoperative resource use and costs

18 For the analysis intraoperative resource use data were obtained from the SALVO trial. Costs
19 were estimated for each item to arrive at a mean cost per caesarean section procedure
20 conducted for each treatment pathway in the model. To estimate the cost of a caesarean
21 section procedure some costs were calculated at the patient level (e.g. swab washing) and
22 some at the procedural level (e.g. drugs used in the caesarean section procedure). This is
23 outlined in Table 21 **Error! Reference source not found.** and further detail is provided
24 below.

1 Table 21 Intraoperative resource use and costs per procedure

Item	Resource Use		Unit Cost	Mean cost per procedure		Assumption / Working	Source
	Cell salvage (n=1498)	Control (n=1492)		Cell salvage (n=1498)	Control (n=1492)		
Running costs	1432	58	£6.14	£6.14	£6.14	Based on annual maintenance costs for Haemonetics Cell Saver 5 machine and estimated annual usage	UHB, personal communication (Aug 2016) NICE costing statement blood transfusion (Nov2015) ¹¹
Collection Set	1	1	£41.71	£41.71	£41.71	Based on the assumption that one collection set is used per procedure	NHS Supply Chain Catalogue (accessed Aug 2016): Autotransfusion reservoir 3 litre ⁷¹
Processing Pack	1	1	£77	£77	£77	Based on the assumption that one processing pack is used per procedure	NHS Supply Chain Catalogue (accessed August 2016): Intraoperative autologous blood system cell saver 5+ bowl set 125ml ⁷¹
Leukocyte depletion filter	782	25	n/a	n/a	n/a	Cost not included in the analysis as leukocyte depletion filter included in the collection set for Haemonetics Cell Saver 5 machine	NHS Supply Chain Catalogue (accessed August 2016): Autotransfusion reservoir 3 litre ⁷¹
Additional sucker	598	29	£15.41	£6.43	£7.70	Mean cost based on the number of additional suckers used in each treatment group / total number of patients who received cell salvage	NHS Supply Chain Catalogue (accessed August 2016): Aspiration & anticoagulation line Cell Saver. £308.02 for 20 ⁷¹
Swab washing	781	21	£0.80	£0.44	£0.29	Mean cost based on the number of times swabs were washed in each treatment group / total number of patients who received cell salvage	ICS Factsheet 1 Swab Washing March 2015, ⁷² based on the cost of 1L of sodium chloride 0.9%, BNF ⁷³
Staff			£0.72 (min)	£11.57	£12.03	Based on the staff type most frequently called into theatre.	Unit cost for hospital based nurse, band 5, PSSRU unit costs 2015 (costs include qualifications) ⁷⁴
Saline (litres)	2	2	£0.80	£1.60	£1.60	Based on the assumption that 2 litres of saline would be administered to all patients undergoing cell salvage prior to collection ¹¹	Based on the cost of 1L of sodium chloride 0.9%, BNF ⁷³
Heparin sodium (30,000 IU)	2	2	£10.60	£21.20	£21.20	Based on the assumption that 60,000 iu heparin would be administered to all patients undergoing cell salvage prior to collection ¹¹	Based on the cost of 1ml amp of heparin sodium 25,000 iu/ml and 1ml amp of heparin sodium 5,000 iu/ml, BNF ⁷³
Anti-D (500 IU)	1	1	£33.75	£3.04	£3.04	Based on the assumption that all D negative women delivering a D positive baby receive at least 500 IU of anti-D. ³³ Mean cost per procedure based on the probability of a woman requiring anti-D in each treatment group (0.09)	Based on the cost of 500-unit vial of anti-D immunoglobulin, BNF ⁷³
Anti-D (1500 IU)	1	1	£58	£5.22	£5.22	Based on the assumption that women who receive cell salvage are offered 1500 IU of anti-D. ³³ Mean cost per procedure based on the probability of a woman requiring anti-D in each treatment group (0.09)	Based on the cost of 1,500-unit vial of anti-D immunoglobulin, BNF ⁷³
RBC transfusion (units)	3	3	First unit: £194 Subsequent units: £166	£520	£520	Based on the assumption that all units transfused in each treatment group were RBC ¹¹	NICE costing statement for blood transfusion (November 2015). ¹¹ Unit cost for RBC obtained from NHSBT 2016/17 ⁷⁵

1 ***Equipment and disposables required for the cell salvage procedure***

2 Many centres reported that their cell salvage machines were obtained on lease and as such
3 only the running costs and cost of consumables would be incurred. Therefore the acquisition
4 costs for a cell salvage machine were not included in the analysis but the addition of this cost
5 was explored in a sensitivity analysis. The costs of materials used by participating centres
6 varied. The acquisition cost and annual maintenance cost for a Haemonetics® Cell Saver® 5
7 machine was obtained from one centre. Costs for consumables were sourced from the NHS
8 Supply Chain Catalogue (August 2016)⁷¹ and correspond to the consumables used with this
9 machine. The annual number of procedures that would use the cell salvage machine was
10 based on the NICE costing statement for blood transfusion published in November 2015.¹¹

11 The Haemonetics Cell Saver 5 machine uses two separate kits of consumables for collection
12 and re-infusion. In the SALVO trial, some centres (n=202 participants treated; see Table 11)
13 used a continuous-transfusion cell saver machine that required the use of different
14 consumables. However, for this analysis it was assumed that each centre used one set of
15 consumables for collection and reinfusion. This was tested in a sensitivity analysis. The cost
16 of a collection set and processing pack (used for reinfusion) with a 125ml bowl for a
17 Haemonetics Cell Saver 5 machine was obtained from the NHS Supply Chain Catalogue
18 (August 2016).⁷¹ For some cell salvage procedures in the study (n=807), a leukocyte
19 depletion filter was used, while this was not used for the remaining procedures. As this item
20 is included in the collection set, no additional cost was incurred. Contained in the processing
21 pack is one aspiration and anticoagulation line (sucker). For some caesarean section
22 procedures in the study (n=627), an additional sucker was used and this additional cost was
23 apportioned across all caesarean section procedures where cell salvage was conducted. The
24 cost of an additional sucker was obtained from the NHS Supply Chain Catalogue (August
25 2016)⁷¹ and the total cost based on usage was divided by the number of patients in each
26 group of the trial that set up the cell saver machine to arrive at a mean cost of the procedure
27 per patient in each group.

28 Blood loss can also be removed from the operative site by swabs. By washing swabs, the
29 blood that is normally discarded can be collected and the overall efficiency of red cell
30 recovery improved.⁵⁸ Swab washing occurred in 802 procedures in the SALVO trial, 781
31 procedures in the cell salvage group and 21 procedures in the control group. The UK Cell
32 Salvage Action Group recommends that swabs are washed in one litre of saline.⁷² The cost of

1 saline (0.9% Sodium Chloride) was obtained from the British National Formulary.⁷³ The total
2 cost of swab washing in each group of the trial was apportioned by the number of patients
3 who received cell salvage in that group of the trial.

4 ***Additional staff called into theatre solely for the purposes of cell salvage***

5 The amount of time additional staff, called into theatre solely for the purposes of cell salvage,
6 spent in the operating theatre was recorded in the SALVO trial. Staff grade was identified at a
7 broad level (Nurse, ODP, and Doctor) and job band distinction was not recorded, though it
8 was frequently included in the notes if a midwife was called into theatre. The analysis is
9 based on the staff type most frequently called into theatre (ODP in both groups) and assumed
10 the lowest possible cost within this job grade (Hospital based nurse, band 5). Staff unit costs
11 were obtained from the PSSRU unit costs (2015).⁷⁴ The total cost of additional staff required
12 for cell salvage was distributed by the number of times the cell salvage machine was set up in
13 both groups of the trial.

14 ***Drugs used in the caesarean section procedure***

15 Typically saline and an anticoagulant (for example heparin) would be used for people
16 undergoing cell salvage. The saline is required for collection of the blood (separate to saline
17 used for swab washing) and the heparin to stop the collected blood clotting.¹¹ It was assumed,
18 as per the NICE costing statement, that 2 litres of saline and 60,000 IU heparin (30,000 IU
19 per litre of saline) would be used for collection in any caesarean section procedure where the
20 cell salvage machine was turned on. The cost of saline (0.9% Sodium Chloride) and heparin
21 were obtained from the British National Formulary.⁷³ These costs were added to the average
22 cost of the cell salvage procedure.

23 Guidelines suggest that all D-negative unsensitised women delivering a RhD-positive baby
24 should be routinely offered a standard dose of anti-D immunoglobulin (at least 500 IU) as
25 prophylaxis, to minimise this risk of sensitisation, and all women who receive cell salvage
26 should be offered a higher dose (1,500 IU).³³ The probability of a woman requiring
27 administration of anti-D i.e. a rhesus D-negative mother with rhesus D-positive baby was
28 0.09 in both groups of the SALVO trial. The cost of anti-D (RH0) immunoglobulin was
29 obtained from the British National Formulary⁷³ and the total cost based on usage was divided
30 by the number of women in each arm of the model to arrive at a mean cost per patient in each
31 treatment pathway.

1 ***Donor blood transfusion***

2 The cost of donor blood transfusion used in the model was based on the costing methodology
3 employed by NICE in which the resource use and costs for both blood bank and ward
4 procedures were split to reflect the cost of transfusing the first unit and the cost of transfusing
5 subsequent units.¹¹ For simplicity, the cost of transfusion of red blood cells (RBC) is used in
6 the model. RBC made up the largest proportion of the blood products transfused in the
7 SALVO trial. Adjusting the cost of transfusion to reflect the different proportions of different
8 blood products transfused is complex and unlikely to result in a significant cost difference.
9 This approach is supported by NICE.¹¹ The unit cost of RBC was taken from NHS Blood
10 and Transfusion list price for 2016/2017.⁷⁵ The mean number of units transfused per patient
11 in each group of the trial was obtained and rounded up to represent the fact that any
12 remaining blood in a unit would be disposed. The following approach was taken to calculate
13 the mean cost: $\text{CostTransfusion} = \text{CostFirstUnit} + \text{CostSubsequentUnits}$.

14 All patients in the model required blood grouping and antibody screening, even if they did
15 not end up requiring a donor blood transfusion. The cost of these procedures was obtained
16 from the NICE costing statement¹¹ and applied *once* to people in the model that did not
17 receive a donor blood transfusion. Note that for those that did receive a donor blood
18 transfusion this cost is incorporated into the cost of the first unit of blood.

19 **Postoperative resource use and costs**

20 For the analysis, postoperative resource use data were obtained from the SALVO trial. Costs
21 were estimated for each item based on their occurrence in each branch of the model to arrive
22 at a mean cost per patient for each branch. This is outlined in Table 22**Error! Reference**
23 **source not found.** and further detail is provided below.

Table 22 Postoperative resource use and costs

Item	Resource Use		Unit Cost	Mean cost per patient		Assumption / Working	Source
	Cell salvage (n=1498)	Control (n=1492)		Cell salvage (n=1498)	Control (n=1492)		
Inpatient stay (normal days)	3,734.5	3,852	£431.45	£1,074	£1,113	See Table 23 and Table 25	NHS reference costs 2014/15 ⁷⁶
Inpatient stay (HLC)	189.5	136	See Table 24	£78	£56	See Table 24 and Table 25	NHS reference costs 2015/15 ⁷⁶ National tariff payment system 2016/17 ⁷⁷
Adverse events	3	0	n/a	n/a	n/a	Based on the assumption that transfusion would be discontinued in the event of an adverse reaction	BCSH guidelines ⁷⁸
Hospital transfer	2	2	£99	£0.13	£0.13	n/a	PSSRU 2015 ⁷⁴
Investigations	6	10	See Table 27	£0.42	£0.70	n/a	NHS reference costs 2014/15 ⁷⁶
Additional surgery	11	8	See Table 28 Error! Reference source not found.	£13	£9	See Table 34	NHS reference costs 2014/15 ⁷⁶
RBC transfusion (units)	3	3	First unit: £190 Subsequent units: £165	£13	£17	Based on the assumption that all units transfused in each treatment group were RBC	NICE costing statement for blood transfusion (November 2015). ¹¹ Unit cost for RBC obtained from NHSBT 2016/17 ⁷⁵
Total cost of postnatal care per patient				£1,178.55	£1,195.83		

1 ***Length and type of hospital inpatient stay***

2 Total time in hospital was recorded for each participant in the SALVO trial (cell salvage
 3 group mean = 2.64 days, standard care group mean = 2.72 days). Within the trial a higher
 4 level of care (HLC) form was completed for 212 patients. This form indicated the number of
 5 days or partial days the patient received level 0, 1, 2 and 3 care. For this study a partial day
 6 was costed as half a full day. Level 0 care is defined in the trial literature as “patients whose
 7 needs can be met through general ward care”. Admission to HLC where level 0 care was
 8 administered was therefore costed as normal care. The total number of days spent receiving
 9 HLC (level 1-3) was deducted from the total time spent in hospital to arrive at the total
 10 number of days in normal care for each group. The weighted average cost per inpatient day
 11 was obtained from NHS reference costs 2014/2015⁷⁶ (Table 23) and was applied to arrive at a
 12 mean cost per patient of normal care.

Table 23 Cost per inpatient day of normal care

Currency code	Currency description	Activity	National average unit cost
Elective inpatient excess bed days			
NZ50A	Planned Caesarean Section with CC Score 4+	11	£99.22
NZ50B	Planned Caesarean Section with CC Score 2-3	46	£415.20
NZ50C	Planned Caesarean Section with CC Score 0-1	116	£740.07
NZ51A	Emergency Caesarean Section with CC Score 4+	12	£358.93
NZ51B	Emergency Caesarean Section with CC Score 2-3	83	£231.87
NZ51C	Emergency Caesarean Section with CC Score 0-1	93	£311.29
Non-elective inpatient excess bed days			
NZ50A	Planned Caesarean Section with CC Score 4+	2,316	£412.57
NZ50B	Planned Caesarean Section with CC Score 2-3	7,670	£438.31
NZ50C	Planned Caesarean Section with CC Score 0-1	6,022	£437.22
NZ51A	Emergency Caesarean Section with CC Score 4+	2,840	£408.49
NZ51B	Emergency Caesarean Section with CC Score 2-3	5,388	£417.82
NZ51C	Emergency Caesarean Section with CC Score 0-1	9,806	£440.84
Weighted average cost per inpatient day			£431

13 The cost for a day receiving level 3 care was obtained from the National tariff payment
 14 system 2016/17 – maternity pathway⁷⁷ which gives costs for a day of intensive care.
 15 Information on the cost per day at level 1 and 2 was not available. For the purposes of this
 16 study it was assumed that level 1 care was 25% more expensive per day than level 0 care and

1 level 2 care was 25% more expensive than level 1 care (Table 24). The following approach
 2 was taken to calculate the mean cost per patient in each arm of the model (Table 25):
 3 $\text{CostHLC} = (\text{TotalCostLevel1Care} + \text{TotalCostLevel2Care} + \text{TotalCostLevel3Care}) /$
 4 npatients .

Table 24 Level of care

Level of care	Cost per day	Assumption/working	Source
0	£431	See Table 23	NHS reference costs 2014/15 ⁷⁶
1	£539	Based on the assumption that level 1 care is 25% more expensive than level 0 care	n/a
2	£674	Based on the assumption that level 2 care is 25% more expensive than level 1 care	n/a
3	£848	n/a	National tariff payment system 2016/17 ⁷⁷

Table 25 Inpatient stay resource use and costs

Item	Source / working	Cell salvage (n=1498)	Control (n=1492)
Normal days in hospital			
Total days in hospital	Trial data	3,924	3,988
Total days in HLC	Trial data (level 1-3)	189.5	136
Total normal days	Total days in hospital less total days in HLC	3,734.5	3,852
Cost per normal day	See Table 23	£431	£431
Total cost for normal days in hospital	Total normal days x cost per day	£1,609,354	£1,660,212
Cost per patient	Total cost / n in trial group	£1,074	£1,113
HLC days in hospital			
Total days spent at level 1 care	Trial data	96.5	67.5
Cost per day at level 1 care	See Table 24	£539	£539
Total cost per treatment arm	Total days x cost per day	£52,014	£36,383
Total days spent at level 2 care	Trial data	84.5	67
Cost per day at level 2 care	National tariff payment system 2016/17 ⁷⁷	£674	£674
Total cost per treatment arm	Total days x cost per day	£56,953	£45,158
Total days spent at level 3 care	Trial data	8.5	1.5
Cost per day at level 3 care	National tariff payment system 2016/17 ⁷⁷	£848	£848
Total cost per treatment arm	Total days x cost per day	£7,208	£1,272
Total cost of HLC per treatment arm	Total cost level 1 + 2 + 3	£116,175	£82,813

Cost per patient	Total cost / n in trial group	£78	£56
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1 **Adverse events**

2 Although the occurrence of all adverse events deemed relevant to the procedure were
3 recorded as a categorical outcome (yes/no), only clinically defined serious adverse events that
4 occurred within the trial and were deemed relevant to the procedure were considered
5 potentially relevant to this analysis (n=2). This is based on the assumption that non serious
6 adverse events deemed relevant to the procedure would have limited or zero resource impact.
7 The two adverse events considered potentially relevant to this analysis were recorded in the
8 trial as life-threatening acute transfusion reactions. Guidelines recommend that for life-
9 threatening acute transfusion reactions the correct procedure is to discontinue transfusion.⁷⁸
10 Therefore, no additional costs were incurred and the occurrence of adverse events is not
11 included in this analysis.

12 **Hospital transfer**

13 Costs for hospital transfer were obtained from PSSRU (2015).⁷⁴ The following approach was
14 taken to calculate the mean cost per patient in each arm of the model (Table 26):
15 $Cost_{HospitalTransfer} = TotalCost_{HospitalTransfer} * Probability_{HospitalTransfer}$.

Table 26 Hospital transfer resource use and costs

Item	Source / working	Cell salvage (n=1498)	Control (n=1492)
Resource use	Trial data	2	2
Unit cost	Based on cost per ambulance service. PSSRU 2015 ⁷⁴	£99	£99
Total cost	Resource use x unit cost	£198	£198
n patients requiring hospital transfer	Trial data	2	2
Probability of hospital transfer	n patients requiring hospital transfer / n in trial group	0.0013	0.0013
Cost per patient	Total cost per patient * probability	£0.13	£0.13

16 **Investigations**

17 Data on the number of x-rays, CT scans and MRI scans were recorded in the SALVO trial.
18 As stated in NHS reference costs 2014/2015, plain film x-rays that are part of an admission or
19 outpatient attendance are not reported separately due to their high volume and low cost.⁷⁶ The
20 occurrence of x-rays is therefore not included in this analysis. Costs for CT scans and MRI
21 scans were obtained from NHS reference costs 2014/2015.⁷⁶ The following approach was

- 1 taken to calculate the mean cost per patient in each arm of the model (Table 27):
 2 $CostInvestigations = TotalCostInvestigations * ProbabilityInvestigations.$

Table 27 Investigations resource use and costs

Item	Source / working	Cell salvage (n=1498)	Control (n=1492)
CT Scan			
Resource use	Trial data	6	9
Unit cost	NHS reference costs 2014/2015 ⁷⁶	£94	£94
Total cost	Resource use x unit cost	£564	£846
MRI Scan			
Resource use	Trial data	0	1
Unit cost	NHS reference costs 2014/2015 ⁷⁶	n/a	£138
Total cost	Resource use x unit cost	n/a	£138
Total cost investigations	Total cost CT + Total cost MRI	£564	£984
n patients requiring investigations	Trial data	4	7
Probability of requiring investigations	n patients requiring investigations / n in trial group	0.003	0.005
Cost per patient	Total cost per patient * probability	£0.42	£0.70

3 *Additional surgery*

- 4 24 additional surgeries were recorded in the SALVO trial (Cell salvage group n=15, control
 5 group n=9). The cost for each additional surgery was obtained from NHS reference costs
 6 (2015).⁷⁶ The cost for time spent in hospital as a result of the additional surgery was
 7 subtracted from the NHS reference cost on the assumption that these costs would have been
 8 incorporated in the cost of hospital inpatient stay. The following approach was taken to
 9 calculate the mean cost per patient in each arm of the model (Table 28**Error! Reference**
 10 **source not found.**): $CostAdditionalSurgery = TotalCostAdditionalSurgery * ProbabilityAdditionalSurgery.$
 11

Table 28 Additional surgeries resource use and costs

Item	Resource Use		Unit Cost	Total Cost		Source
	Cell salvage (n=1498)	Control (n=1492)		Cell salvage (n=1498)	Control (n=1492)	
Sutures	2	2	£2,991	£5,982	£5,982	NHS reference costs 2014/15 ⁷⁶
Hysterectomy	3	2	£1,621	£4,863	£3,242	NHS reference costs 2014/15. See Table 29 Error! Reference source not found.
Laparotomy	3	2	£690	£2,070	£1,380	NHS reference costs 2014/15. See Table 30
Evacuation	2	2	£1,042	£2,084	£2,084	NHS reference costs 2014/15. See Table 31
Colon procedure	2	0	£1,088	£2,176	n/a	NHS reference costs 2014/15. See Table 32
Bowel procedure	0	1	£399	n/a	£399	NHS reference costs 2014/15. See Table 33
Drainage	3	0	£690	£2,070	n/a	NHS reference costs 2014/15
Total cost additional surgery				£19,245	£13,087	
n patients requiring additional surgery	11	8				
Probability of requiring additional surgery	0.0073	0.0054				
Cost per patient				£13	£9	

Table 29 Hysterectomy procedure cost

Currency code	Currency description	Activity	National average unit cost	Average length of stay	
				elective	non-elective
MA07E	Major open upper genital tract procedures with CC score 5+	578	£5,909.25	5.37	11
MA07F	Major open upper genital tract procedures with CC score 3-4	1,780	£4,387.14	3.49	6
MA07G	Major open upper genital tract procedures with CC score 0-2	24,190	£3,511.27	2.49	3
MA08A	Major, laparoscopic or endoscopic, upper genital tract procedures with CC score 2+	3,076	£3,445.44	1.86	3
MA08B	Major, laparoscopic or endoscopic, upper genital tract procedures with CC score 0-1	16,845	£2,889.92	1.47	2
Weighted average cost per procedure		£3,345			
Average length of stay		4			
Cost per day of care (level 0)		£431			
Total cost of hospital stay		£1,724			
Average cost per procedure excluding cost of hospital stay		£1,621			

Table 30 Laparotomy procedure cost

Currency code	Currency description	Activity	National average unit cost	Average length of stay	
				elective	non-elective
(ii) Laparotomy procedure cost					
MA10Z	Minor, laparoscopic or endoscopic, upper genital tract procedures	17,787	£1,341.48	1.02	2
Average cost per procedure		£1,341			
Average length of stay		1.51			
Cost per day of care (level 0)		£431			
Total cost of hospital stay		£651			
Average cost per procedure excluding cost of hospital stay		£690			

Table 31 Evacuation procedure cost

Currency code	Currency description	Activity	National average unit cost	Average length of stay	
				elective	non-elective
MA17D	Dilation and evacuation, 14 to 20 weeks gestation	763	£2,011.19	1.60	3
Average cost per procedure		£2,011			
Average length of stay		2.25			
Cost per day of care (level 0)		£431			
Total cost of hospital stay		£969			
Average cost per procedure excluding cost of hospital stay		£1,042			

Table 32 Colon procedure cost

Currency code	Currency description	Activity	National average unit cost	Average length of stay	
				elective	non-elective
FZ75C	Proximal colon procedures, 19 years and over, with CC score 6+	809	£8,952.50	11.26	16
FZ75D	Proximal colon procedures, 19 years and over, with CC score 3-5	2,139	£6,751.80	7.18	11
FZ75E	Proximal colon procedures, 19 years and over, with CC score 0-2	6,430	£5,795.71	5.28	8
Weighted average cost per procedure		£6,286			
Average length of stay		10			
Cost per day of care (level 0)		£431			
Total cost of hospital stay		£5198			
Average cost per procedure excluding cost of hospital stay		£1,088			

Table 33 Small bowel procedure cost

Currency code	Currency description	Activity	National average unit cost	Average length of stay	
				elective	non-elective
FZ67C	Major small intestine procedures, 19 years and over, with CC score 7+	860	£9,719.99	15.84	21
FZ67D	Major small intestine procedures, 19 years and over, with CC score 4-6	1,476	£7,127.58	8.86	14
FZ67E	Major small intestine procedures, 19 years and over, with CC score 2-3	2,751	£5,164.47	5.83	10
FZ67F	Major small intestine procedures, 19 years and over, with CC score 0-1	4,662	£3,561.35	4.66	7
Weighted average cost per procedure		£5,097			
Average length of stay		11			
Cost per day of care (level 0)		£431			
Total cost of hospital stay		£4,703			
Average cost per procedure excluding cost of hospital stay		£399			

1 ***Donor blood transfusion***

2 The cost of donor blood transfusion received postnatally is based on the same costs as those
3 used for transfusion received intraoperatively in this model. For simplicity, the cost of
4 transfusion of RBC is used. The mean number of units transfused to each patient in each
5 group of the trial was obtained and rounded up to represent the fact that any remaining blood
6 in a unit would be disposed of. The following approach was taken to calculate the mean cost
7 per patient in each arm of the model (Table 34): $\text{CostTransfusion} = (\text{CostFirstUnit} +$
8 $\text{CostSubsequentUnits}) * \text{ProbabilityTransfusion_PostOp}$.

Item	Source / working	Cell salvage (n=1498)	Control (n=1492)
Resource use (mean units transfused)	Trial data	3	3
Unit cost 1 st unit	NHSBT 2016 ⁷⁵ , NICE costing statement for blood transfusion ¹¹	£190	£190
Unit cost subsequent units	NHSBT 2016 ⁷⁵ , NICE costing statement for blood transfusion ¹¹	£165	£165
Total cost	Resource use x unit cost	£520	£520
n patients requiring transfusion	Trial data	38	49
Probability of transfusion	n patients requiring transfusion / n in trial group	0.025	0.033
Cost per patient	Total cost per patient * probability	£13	£17

Table 34 Blood transfusion resource use and costs

1 **Outcomes**

2 The outcome of interest in the trial was the use of donor blood transfusion in response to
3 haemorrhage and its consequences.

4 **Assumptions**

5 It was necessary to make the following pragmatic assumptions before the analysis could be
6 carried out:

7 (i) Trial Centres

8 All of the centres involved in the trial were assumed to have the same expertise and to have
9 followed similar protocols in the management of patients.

10 (ii) Equipment and disposables required for the cell salvage procedure

11 It was assumed that all centres performing cell salvage used consumables and that one
12 collection set and one processing pack were used per cell salvage procedure. Costs for
13 equipment and disposables were obtained for a Haemonetics Cell Saver 5 machine. Variance
14 in costs was explored in sensitivity analysis. Where swab washing occurred, it was assumed
15 that the swabs were washed in one litre of saline.⁷²

16 (iii) Use of cell salvage machine

1 Where the cell salvage machine was switched on it was assumed that running costs would be
2 incurred and a collection set would be used even if no salvaged blood was returned to the
3 patient. It was also assumed that heparin and saline would be used prior to collection.¹¹

4 (iv) Additional staff called into theatre solely for the purposes of cell salvage
5 We based our analysis on the staff type most frequently called into theatre in the trial and
6 assumed the lowest possible cost within this job band distinction. Staff cost variance was
7 explored through sensitivity analysis.

8 (v) Salvaged Blood

9 The threshold setting on a cell salvage machine to process can be set to engage for salvaged
10 blood above a certain volume and in this study trial centres displayed variance in the
11 minimum volume threshold they selected. Trial guidance given to participating centres stated
12 that all processed blood produced by the machines should be returned to the patient. This
13 analysis assumed that all minimum threshold settings were disengaged. The cost of collection
14 of all shed blood was considered, regardless of whether that blood was subsequently returned
15 to the patient.

16 (vi) Donor Blood

17 All units transfused were assumed to be RBC.¹¹ The mean number of units transfused per
18 patient was rounded up to account for the fact that any remaining blood in a bag would be
19 disposed of.

20 (vii) Length and type of inpatient stay

21 Where patients received level 0 care when admitted to HLC it was assumed that their needs
22 could be met through general ward care. It was assumed that level 1 care was 25% more
23 expensive per day than level 0 care and level 2 care was 25% more expensive than level 1
24 care.

25 (viii) Additional surgeries

26 Additional surgeries were included in this analysis with the cost of inpatient bed days
27 excluded to avoid double counting. Inpatient bed days were assumed to be the equivalent of
28 level 0 care.

29 (ix) Adverse events

1 It was assumed that non serious adverse events deemed relevant to the procedure would have
2 limited or zero resource impact. It was assumed that in the case of an acute transfusion
3 reaction, the transfusion would be discontinued.¹⁰

4 (x) Infant health

5 In this study the health of the infant was not considered relevant to the intervention.
6 Information relating to the clinical status and care of the infant was therefore not included in
7 the analysis.

8 **Analysis**

9 Given the objectives of the trial and the duration of follow-up, a within trial economic
10 analysis was carried out. The analysis took the perspective of the NHS following current
11 recommendations from NICE.⁷⁹ The main economic analysis was a cost-effectiveness
12 analysis with results expressed as cost per donor transfusion avoided.

13 We carried out three main analyses on the trial data. In Analysis 1 the base-case was based on
14 the intention-to-treat (ITT) principle. In this method, patients are compared within the
15 treatment groups to which they were originally randomised irrespective of the treatment
16 received.⁸⁰ This method of analysis allows the estimates to follow real-life scenarios in which
17 patients may not always receive the planned treatment. Not using ITT analysis can often
18 exaggerate the benefits of a given intervention.⁸⁰

19 Analysis 2 was based on the treatment received by patients irrespective of randomisation (the
20 'per protocol' (PP) analysis). Within the SALVO trial, equal numbers of patients were
21 randomised to either cell salvage or control. However, because some clinicians managing
22 women in the control group had access to a cell salvage machine, it was possible that women
23 in the control group could receive cell salvage in place of a donor blood transfusion. A PP
24 analysis was carried out to look at the effect of treatment received on the outcome estimates.
25 Therefore, in analysis 2 all patients who received cell salvage were compared with those who
26 received standard care, irrespective of the treatment to which they were randomised.

27 Analysis 3 considered only patients who underwent an emergency caesarean section. This
28 analysis was considered necessary as the SALVO trial found that numerically, there was a
29 greater reduction in rate of transfusion within the emergency patient group compared to the

1 elective patient group. This analysis followed the same methodology as analyses 1 and 2.
2 Probabilities were obtained from the trial and attached to each pathway in the existing model.
3 For the analysis, intra- and post-operative resource use data were obtained from the SALVO
4 trial. Intraoperative costs were estimated for each item to arrive at a mean cost per caesarean
5 section procedure for each treatment pathway in the model. Postoperative costs were
6 estimated for each item based on their occurrence in each branch of the model to arrive at a

Trial data	Probability	Distribution
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7 mean cost per patient for each branch (See Tables 35 to 37 below).

Table 35 Probabilities used in the emergency caesarean section model

Cell salvage intended			
<i>Cell salvage intended → allocated treatment received (machine was on)</i>	794 / 833	0.953	Beta
Allocated treatment received → salvaged blood returned	390/794	0.491	Beta
Allocated treatment received → salvaged blood not returned	401/794	0.509	Beta
Salvaged blood returned → donor blood transfusion given	5/390	0.013	Beta
Salvaged blood returned → donor blood transfusion not given	385/390	0.987	Beta
Salvaged blood not returned → donor blood transfusion given	2/401	0.005	Beta
Salvaged blood not returned → donor blood transfusion not given	399/401	0.995	Beta
<i>Cell salvage intended → allocated treatment not received (machine was off)</i>	39/833	0.047	Beta
Allocated treatment not received → donor blood transfusion given	1/39	0.026	Beta
Allocated treatment not received → donor blood transfusion not given	38/39	0.974	Beta
Standard care intended			
<i>Standard care intended → allocated treatment received (machine was off)</i>	780/808	0.965	Beta
Allocated treatment received → donor blood transfusion given	9/780	0.012	Beta
Allocated treatment received → donor blood transfusion not given	771/780	0.988	Beta
<i>Standard care intended → allocated treatment not received (machine was on)</i>	28/808	0.035	Beta
Allocated treatment not received → salvaged blood returned	14/28	0.5	Beta
Allocated treatment not received → salvaged blood not returned	14/28	0.5	Beta
Salvaged blood returned → donor blood transfusion given	1/14	0.071	Beta
Salvaged blood returned → donor blood transfusion not given	13/14	0.929	Beta
Salvaged blood not returned → donor blood transfusion given	0/14	0	Beta
Salvaged blood not returned → donor blood transfusion not given	14/14	1	Beta

Table 36 Emergency caesarean section intraoperative resource use and costs per procedure

Item	Resource Use		Unit Cost	Mean cost per procedure		Assumption / Working	Source
	Cell salvage (n=833)	Control (n=808)		Cell salvage (n=833)	Control (n=808)		
Running costs			£6.14	£6.14	£6.14	Based on annual maintenance costs for Haemonetics Cell Saver 5 machine and estimated annual usage	UHB, personal communication (Aug 2016) NICE costing statement blood transfusion (Nov2015)
Collection Set	1	1	£41.71	£41.71	£41.71	Based on the assumption that one collection set is used per procedure	NHS Supply Chain Catalogue (accessed Aug 2016): Autotransfusion reservoir 3 litre
Processing Pack	1	1	£77.00	£77.00	£77.00	Based on the assumption that one processing pack is used per procedure	NHS Supply Chain Catalogue (accessed August 2016): Intraoperative autologous blood system cell saver 5+ bowl set 125ml
Filter	n/a	n/a	n/a	n/a	n/a	No usage of leukocyte depletion filter recorded in the trial	n/a
Additional sucker	321	14	£15.41	£6.23	£7.70	Mean cost based on the number of additional suckers used in each treatment arm / total number of patients who received cell salvage	NHS Supply Chain Catalogue (accessed August 2016): Aspiration & anticoagulation line Cell Saver. £308.02 for 20
Swab washing	444	11	£0.80	£0.45	£0.31	Mean cost based on the number of times swabs were washed in each treatment arm / total number of patients who received cell salvage	ICS Factsheet 1 Swab Washing March 2015, based on the cost of 1L of sodium chloride 0.9%, BNF
Staff	82.21 (min)	30 (min)	£0.72 (min)	£11.70	£1.54	Based on the staff type most frequently called into theatre.	Unit cost for hospital based nurse, band 5, PSSRU unit costs 2015 (costs include qualifications)
Saline (litres)	2	2	£0.80	£1.60	£1.60	Based on the assumption that 2 litres of saline would be administered to all patients undergoing cell salvage prior to collection	Based on the cost of 1L of sodium chloride 0.9%, BNF
Heparin sodium (30,000 IU)	2	2	£10.60	£21.20	£21.20	Based on the assumption that 60,000 iu heparin would be administered to all patients undergoing cell salvage prior to collection	Based on the cost of 1ml amp of heparin sodium 25,000 iu/ml and 1ml amp of heparin sodium 5,000 iu/ml, BNF
Anti-D (500 IU)	1	1	£33.75	£3.04	£3.04	Based on the assumption that all D negative women delivering a D positive baby receive at least 500 IU of anti-D. Mean cost per procedure based on the probability of a woman requiring anti-D in each treatment arm (0.09)	Based on the cost of 500-unit vial of anti-D immunoglobulin, BNF
Anti-D (1500 IU)	1	1	£58.00	£5.22	£5.22	Based on the assumption that women who receive cell salvage are offered 1500 IU of anti-D. Mean cost per procedure based on the probability of a woman requiring anti-D in each treatment arm (0.09)	Based on the cost of 1,500-unit vial of anti-D immunoglobulin, BNF
RBC transfusion (units)	2	3	First unit: £190 Subsequent	£355	£520	Based on the assumption that all units transfused in each treatment arm were RBC	NICE costing statement for blood transfusion (November 2015). Unit cost for RBC obtained from NHSBT 2016/17

units: £165

Table 37 Emergency caesarean postoperative resource use and costs per patient

1

Item	Resource Use		Unit Cost	Mean cost per patient		Assumption / Working	Source
	Cell salvage (n=833)	Control (n=808)		Cell salvage (n=833)	Control (n=808)		
Inpatient stay (normal days)	2,212	2,246	£431	£1,147	£1,205	See Table 23 & 25	NHS reference costs 2014/15
Inpatient stay (HLC)	135	99.5	See Table 24	£100	£78	See Table 24 & 25	NHS reference costs 2015/15 National tariff payment system 2016/17
Adverse events	n/a	n/a	n/a	n/a	n/a	No adverse events recorded in the trial	
Hospital transfer	1	2	£99	£0.12	£0.25	n/a	PSSRU 2015
Investigations	2	6	See Table 27	£0.23	£0.75	n/a	NHS reference costs 2014/15
Additional surgery	8	3	See Error! Reference source not found.	£11	£3	See Table 34	NHS reference costs 2014/15
RBC transfusion (units)	3	3	First unit: £190 Subsequent units: £165	£13	£19	Based on the assumption that all units transfused in each treatment arm were RBC	NICE costing statement for blood transfusion (November 2015). Unit cost for RBC obtained from NHSBT 2016/17
Total cost of postnatal care per patient				£1,271	£1,306		

1 ***Sensitivity analysis***

2 Deterministic and probabilistic sensitivity analyses (PSAs) were carried out for each analysis
3 to explore the effects of the inherent uncertainty in parameter estimates on model results.
4 Deterministic sensitivity analysis involves varying one or more parameters while keeping the
5 others at their baseline value. Although deterministic sensitivity analyses can be helpful to
6 identify which model inputs are important in driving a decision or to identify threshold
7 values, comprehensive representation can be obtained by undertaking a PSA, in which the
8 uncertainty around a parameter is represented with a probability distribution. Monte Carlo
9 simulation was used to sample from these distributions to allow the effect of parameter
10 uncertainty to be evaluated. This involved 1000 repeated random draws from the distributions
11 to indicate how variation in the model parameters would affect the results and hence illustrate
12 the decision uncertainty. Beta distributions were used for probability data and Gamma
13 distributions for costs.^{81, 82}

14 The results of the analyses are presented in terms of incremental cost-effectiveness ratios
15 (ICERs), which reflect the additional cost per donor blood transfusion avoided of cell salvage
16 compared with standard care. The results of the cost-effectiveness analysis are presented
17 using scatterplots and cost-effectiveness acceptability curves (CEACs) to reflect sampling
18 variation and uncertainties in the appropriate threshold cost-effectiveness value.

19 ***Deterministic sensitivity analyses***

20 A number of deterministic sensitivity analyses were conducted in each analysis:

21 (i) Equipment and disposables required for the cell salvage procedure

22 The main analyses used costs for consumables based on a particular model of cell saver
23 machine. To assess the difference that variation in these estimates would make, the unit costs
24 were replaced with unit costs obtained from the NICE costing statement for blood
25 transfusion.¹¹ We then explored the impact of the inclusion of acquisition costs for a cell
26 salvage machine and the impact of using a continuous-transfusion cell salvage machine that
27 requires a suction set and reservoir (prices sourced from participating unit) where the
28 machine is only set up for processing in patients having blood returned and where swab
29 washing was not conducted..

1 (ii) Staff

2 The main analyses used the mean length of time additional staff were present in theatre in
3 each group solely for the purposes of cell salvage. We explored the impact of not calling an
4 additional member of staff into theatre.

5 (iii) Donor blood

6 To facilitate robust evaluation in cost-effectiveness analyses relating to donor blood, a
7 comprehensive estimate for the cost of a unit of donor blood is required. The NHS Blood and
8 Transplant Authority have valued the cost of RBC to be £120 per unit based on direct costs to
9 the healthcare services.⁷⁵ However, there is significant uncertainty surrounding this figure.
10 We conducted a study (submitted for publication) parallel to the SALVO trial that aimed to
11 dissect the current price of blood. We explored what elements are contributing to the current
12 cost of blood and what elements are missing. Our study concluded that the current costing
13 approach of assuming there will always be an adequate supply of donor blood must be
14 replaced with including provisions for the continued shrinking of the donor pool and the
15 impact that future shocks to the blood supply system could have. The sensitivity analysis
16 assessed the difference that variation in the estimated cost of blood made to the overall cost-
17 effectiveness of cell salvage.

18 **Results**

19 ***Analysis 1: Intention-to-treat***

20 The results of the analysis are shown in Table 38. The strategy in which standard care was
21 intended was the least costly, with the average cost per patient estimated at £1,244. However
22 the cell salvage intended group was only slightly more expensive with the average cost per
23 patient estimated at £1,327. The cell salvage intended strategy was the most effective at
24 avoiding a transfusion. The estimated ICER for the cell salvage intended strategy compared
25 with standard care was £8,110 per donor blood transfusion avoided. This means that it would
26 cost an additional £8,110 to avoid a donor blood transfusion through cell salvage compared to
27 standard care.

1 The scatterplot (Figure 4) shows the modelled uncertainty in the cost and effectiveness of the
 2 cell salvage intended strategy compared with the standard care intended strategy from 1,000
 3 Monte Carlo simulations. In this, the ICER of each simulation is plotted on the cost-
 4 effectiveness plane providing information about the joint density of the differences in cost
 5 and effectiveness between the two strategies. From Figure 4, it is evident that although cell
 6 salvage is a more effective transfusion strategy, it is uncertain whether it is less or more
 7 costly than standard care. The CEAC (Figure 5) shows that the probability that cell salvage is
 8 cost-effective increases as the willingness to pay for a donor blood transfusion avoided
 9 increases. Given that there is not a pre-specified threshold of willingness to pay for a blood
 10 transfusion avoided, as in the case of quality adjusted life years where £20,000 to £30,000 are
 11 the recommended cut-off points by NICE, the identification of the probability of cell salvage
 12 being cost-effective is less straightforward. However, the CEAC shows that if the maximum
 13 willingness to pay for a donor blood transfusion avoided was, for example, £50,000, the
 14 probability of cell salvage being cost-effective would be 62%.

Table 38 Results for the base-case analysis

Transfusion Strategy	Average cost per patient (£)	Effectiveness Donor Blood Transfusion Avoided	ICER (£)
Standard care intended	1,244	0.965	
Cell salvage intended	1,327	0.975	8,110

Figure 4 Incremental cost-effectiveness scatterplot for donor blood transfusion avoided (ITT)

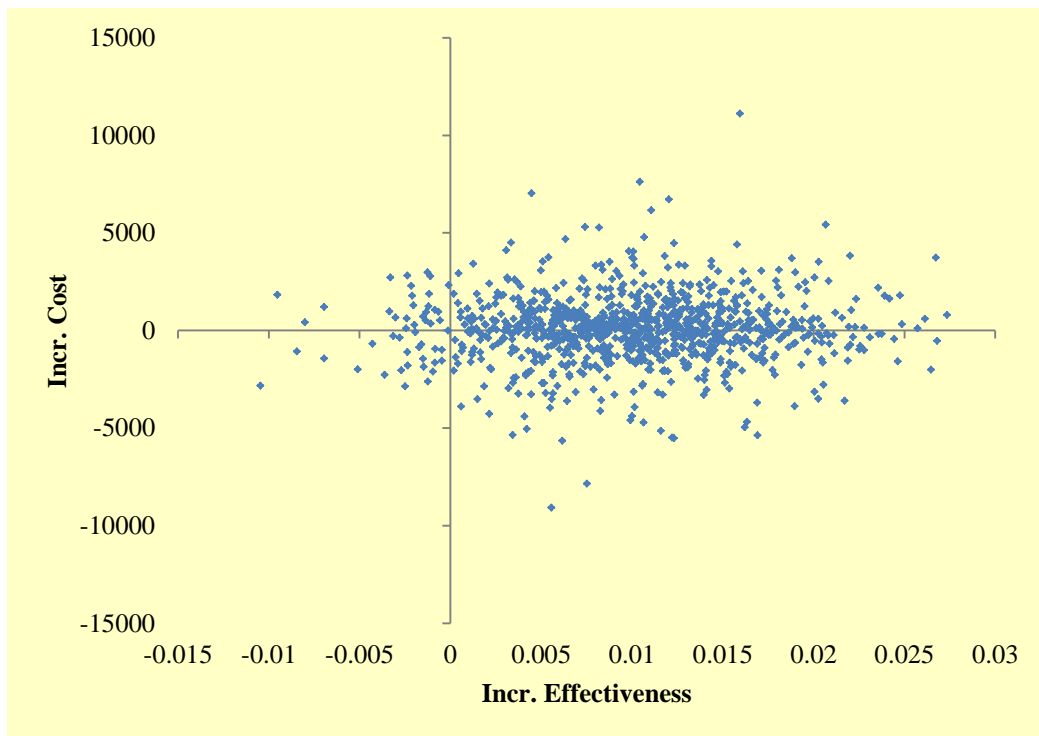
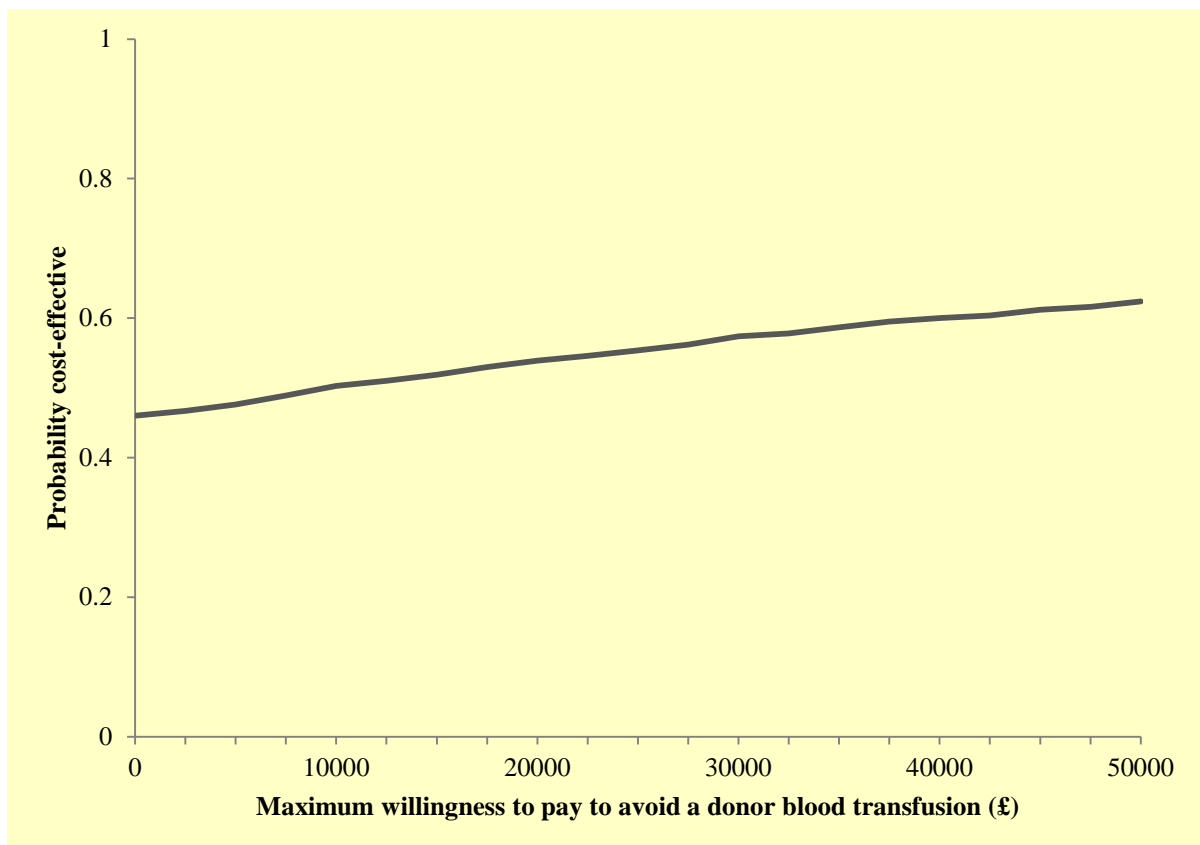


Figure 5 Cost-effectiveness acceptability curve for donor blood transfusion avoided (ITT)



1 **Analysis 2: Per-protocol**

2 The results of the analysis are shown in Table 39. In terms of cost, standard care is again the
3 least costly strategy with mean cost per patient estimated at £1,238. The cell salvage strategy
4 was the most effective at avoiding a transfusion. The estimated ICER for the cell salvage
5 strategy compared with standard care was £8,252 per donor blood transfusion avoided.

6 The scatterplot (Figure 6) shows that although cell salvage is a more effective transfusion
7 strategy, it is again uncertain whether it is less or more costly than standard care. This
8 uncertainty has been graphed in the CEAC (Figure 7). The graph shows that if the maximum
9 willingness to pay for a donor blood transfusion avoided was £50,000, the probability that
10 cell salvage was cost-effective would be 63%.

Table 39 Results for the per-protocol analysis

Transfusion strategy	Average cost per patient (£)	Effectiveness Donor Blood Transfusion Avoided	ICER (£)
Standard care	1,238	0.967	
Cell salvage	1,330	0.978	8,252

Figure 6 Incremental cost-effectiveness scatterplot for donor blood transfusion avoided (per protocol)

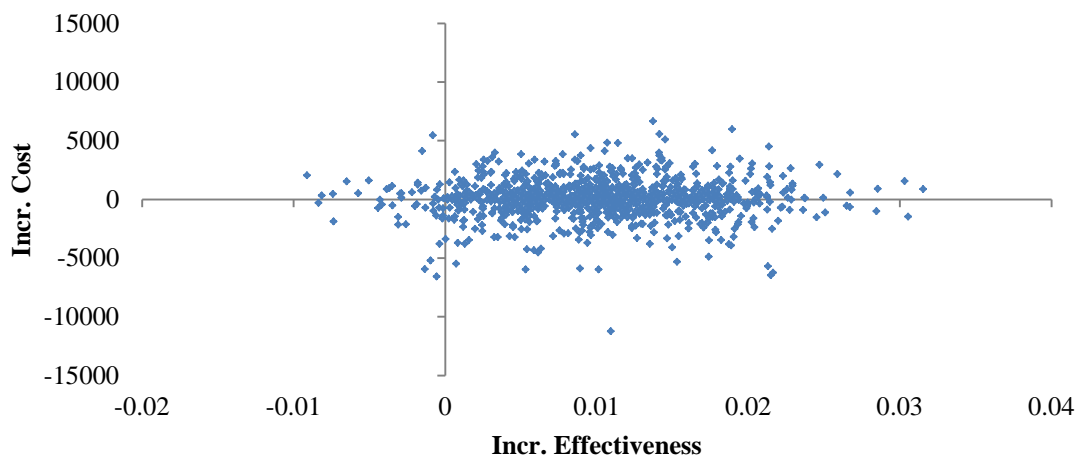
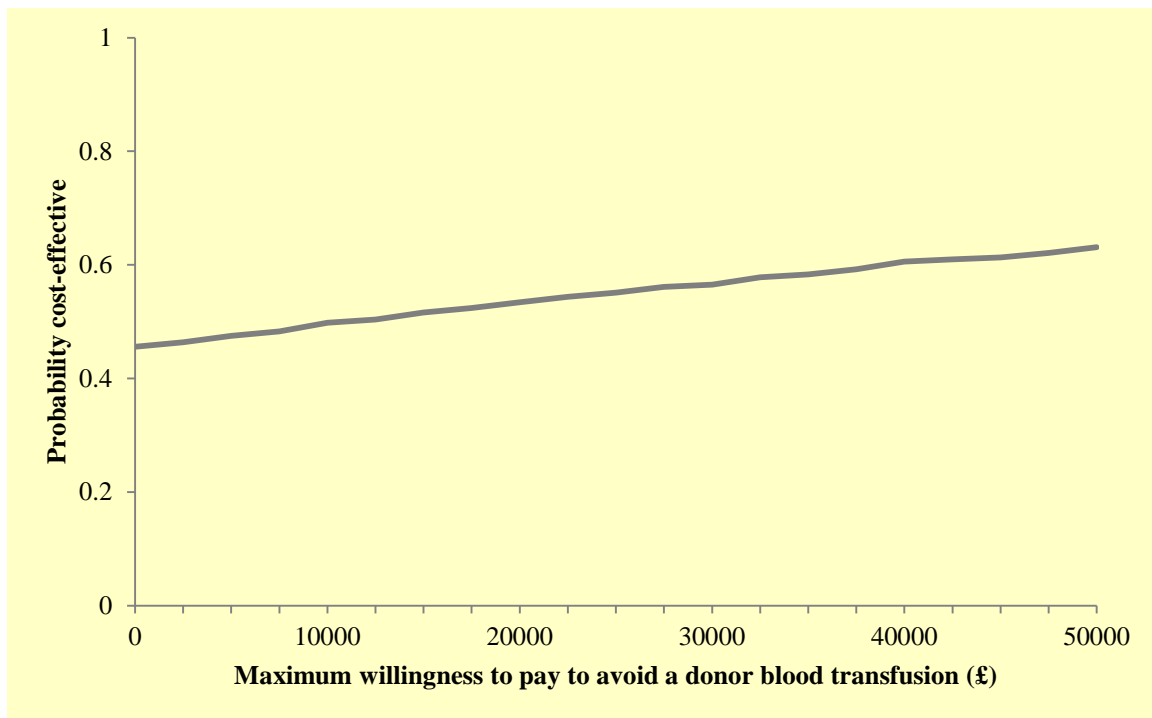


Figure 7 Cost-effectiveness acceptability curve for donor blood transfusion avoided (per protocol)



1 **Analysis 3: Emergency caesarean**

2 The results of the analysis are shown in Table 40. The strategy in which standard care was
 3 followed remains the least costly, though higher in comparison to the previous two analyses,
 4 with the average cost per patient estimated at £1,352. The cell salvage group had an average
 5 cost per patient estimated at £1,407, also slightly higher than the previous analyses. The cell
 6 salvage strategy continues to be the most effective at avoiding a transfusion. The estimated
 7 ICER for the cell salvage strategy compared with standard care was £13,713 per donor blood
 8 transfusion avoided.

9 The scatterplot (Figure 8) shows again that although cell salvage is a more effective
 10 transfusion strategy, it remains uncertain whether it is less or more costly than standard care.
 11 The CEAC (Figure 9) shows that the probability that cell salvage is cost-effective remains
 12 between 47% and 55% as the willingness to pay for a donor blood transfusion avoided
 13 increases.

Table 40 Results for the emergency caesarean analysis

Transfusion strategy	Average cost per patient (£)	Effectiveness Donor Blood Transfusion Avoided	ICER (£)
Standard care	1,352	0.986	

Figure 8 Incremental cost-effectiveness scatterplot for donor blood transfusion avoided (emergency only)

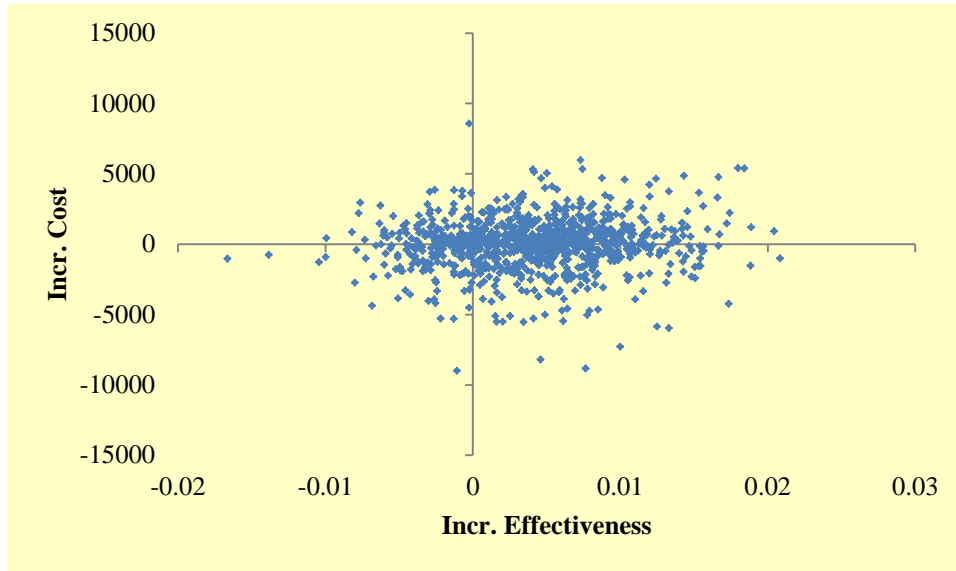
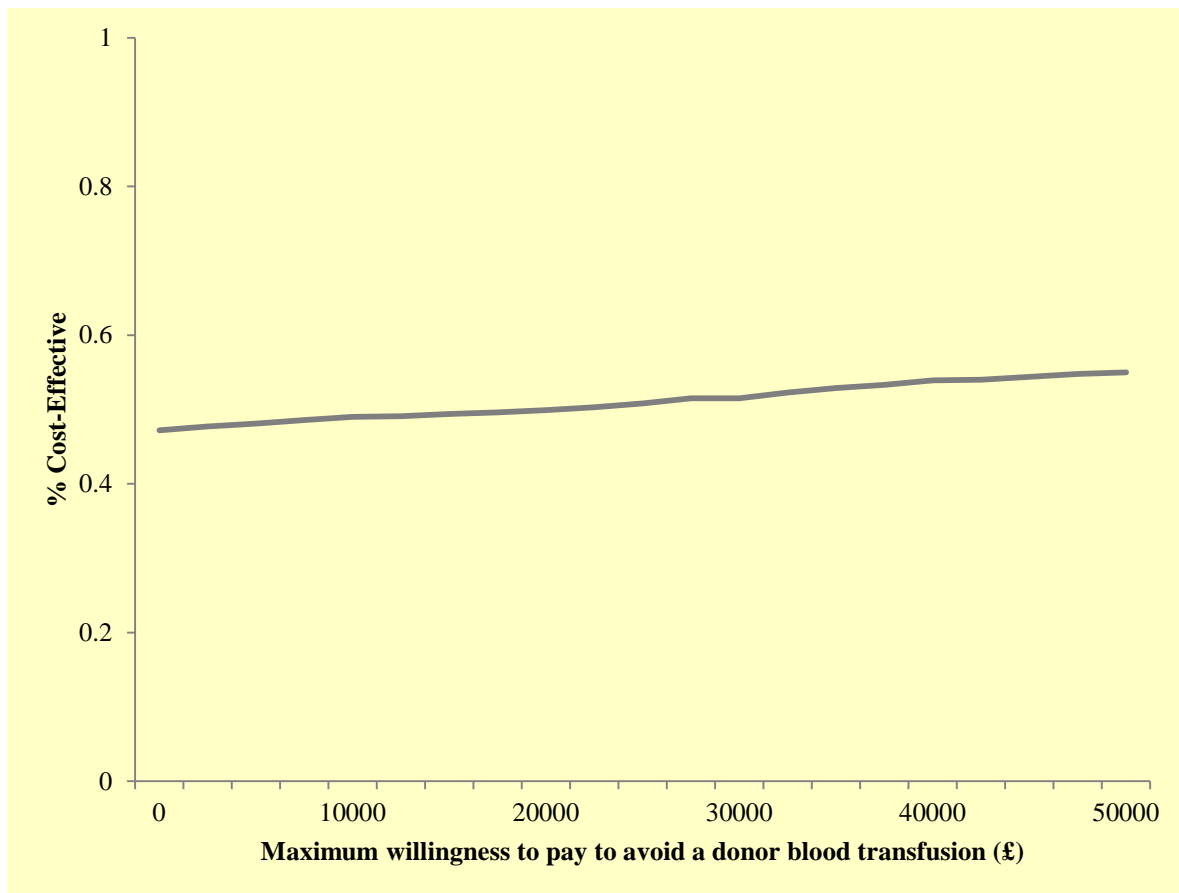


Figure 9 Cost-effectiveness acceptability curve for donor blood transfusion avoided (emergency only)



1 **Sensitivity Analysis**

2 Deterministic sensitivity analysis

3 As demonstrated in

4

1 Table 41, the results of the deterministic sensitivity analysis were as follows:

- 2 (i) Varying the cost of consumables to those used by NICE had a marginal impact on
3 the ICER in each analysis. Similarly, including acquisition costs in the analysis
4 had only a minimal impact on the ICER. In the trial 202 centres used a
5 continuous-transfusion cell saver machine which required different consumables
6 to the ones included in the main analyses. The impact of including costs for the
7 consumables used by this machine, where the machine is only set up for
8 processing in patients having blood returned and where swab washing is not
9 conducted resulted in an ICER of £1,022 in analysis 1, £1,184 in analysis 2 and a
10 dominant ICER in analysis 3 i.e. cell salvage was considered less costly and more
11 effective compared to standard care.
- 12 (ii) In this sensitivity analysis the cost of additional staff called into theatre solely for
13 the purposes of cell salvage was removed. This reduced the ICER to £7,065 in the
14 ITT analysis, £7,210 in the PP analysis, and £10,932 in the emergency caesareans
15 analysis.
- 16 (iii) Raising the cost of a three unit transfusion of RBC to £1,500 reduced the ICER by
17 £974 in both analysis 1 and 2 and it reduced the ICER by over £1,000 in analysis
18 3. Threshold analysis showed that for cell salvage to be considered cost-effective,
19 the cost of a transfusion would have to be £8,637 in analysis 1, £8,778 in analysis
20 2, and £13,186 in analysis 3.

	Original value		Revised value		Original result	
	Cost per donor blood transfusion avoided					
			Analysis 1	Analysis 2	Analysis 3	
			£8,110	£8,252	£13,713	
	Revised result					
(i) Equipment and disposables required for the cell salvage procedure						
Applying the cost of consumables (collection set + processing pack) used by NICE	£118.71		£119.75	£8,205	£8,346	£13,952
Including acquisition costs based on Haemonetics Cell Saver machine	-		£22.13	£10,114	£10,246	£18,805
Using a continuous-transfusion cell saver where the machine is only set up for processing in patients having blood returned and swab washing is not conducted	Cell salvage	Control	£34.73	£1,022	£1,184	Dominates
	£125.14	£126.40				
(ii) Staff						
No additional member of staff being called into theatre solely for the purposes of cell salvage	Cell salvage	Control	£0	£7,065	£7,210	£10,932
	£11.57	£12.03				
(iii) Donor blood						
Variation in the estimate of the cost of a 3 unit RBC transfusion	£520		£750	£7,886	£8,028	£13,330
			£1,000	£7,636	£7,778	£13,080
			£1,250	£7,386	£7,528	£12,830
			£1,500	£7,136	£7,278	£12,580
For cell salvage to be considered cost-effective in this model the price of a 3 unit RBC transfusion would have to be:				£8,637	£8,778	£13,186

Table 41 Deterministic sensitivity analysis

1 Discussion

2 Principal findings

3 The results of this economic evaluation suggest that routine cell salvage is more costly than
4 standard care with the average cost per patient estimated at £1,327 compared to £1,244. The
5 ICER of this strategy compared with standard care is approximately £8,110 to avoid a donor
6 blood transfusion. The PSA suggests that at a willingness to pay threshold of £50,000, the
7 probability of routine cell salvage being cost-effective is 62%. The results of this analysis
8 were shown to be robust for the majority of deterministic sensitivity analyses with one

1 exception; using a cell salvage machine that required different consumables to those included
2 in the main analyses where the machine is only set up for processing in patients having blood
3 returned and where swab washing is not conducted resulted in a significant effect on the
4 ICER, reducing it to £1,022 per donor blood transfusion avoided.

5 A per protocol analysis produced an ICER of £8,252 per transfusion avoided, but this result
6 should be considered with caution as the population in this analysis is a subset of the ITT
7 population who completed the study without any major protocol violations.⁸⁰ In clinical
8 practice uptake of cell salvage is unlikely to be “per-protocol”. In a third analysis, looking at
9 emergency caesareans only, cell salvage appears to be more effective than standard care for
10 avoiding a donor blood transfusion but the resulting ICER of £13,713 is driven by the
11 increased probability that these patients will require a higher level of postoperative care.

12 ***Strengths and limitations of the economic evaluation***

13 The strength of this model based economic evaluation is that it was based on a rigorously
14 conducted RCT. The cost and outcome data measures that were incorporated into the model
15 were collected prospectively during the RCT using forms filled out at the pre-, intra-, and
16 postoperative phase and at the time of discharge from hospital. In addition the economic
17 evaluation benefitted from significant clinical and statistical input throughout its design and
18 development. All assumptions used in the model were agreed with the trial team before the
19 analysis was carried out and without knowledge of how these assumptions would affect the
20 results.

21 In terms of limitations, not all potential outcomes have been included, because of the limited
22 time scale in our model and the lack of long-term data, for example we could not account for
23 long-term implications relating to fetomaternal haemorrhage as data relating to this was not
24 available from the trial. In addition, information relating to the clinical status and care of the
25 infant was not included in the analysis. A further limitation of the evaluation is that
26 outcomes were expressed in terms of clinical effectiveness rather than in terms of a standard
27 unit of benefit, the quality-adjusted life-year (QALY). Finally, the use of platelets and other
28 blood products has not been included in the evaluation. However, the results of the sensitivity
29 and threshold analyses demonstrated that including these costs would not have impacted on
30 the cost-effectiveness results.

31 ***Strengths and weaknesses in relation to other studies***

1 To date, there has only been one, small, RCT looking at the elective use of cell salvage at
2 caesarean section⁴³ and this study did not include an economic element. A Cochrane review
3 of cell salvage in adult elective surgery assessed the clinical and cost-effectiveness of cell
4 salvage and other autologous transfusion strategies in elective surgery.²¹ It suggested that cell
5 salvage may be an 'effective and cost-effective alternative to the allogeneic blood transfusion
6 strategy'. However, no obstetric papers were identified for this review.

7 ***Meaning of the economic evaluation***

8 The results of the economic evaluation suggest that while cell salvage is a marginally more
9 effective strategy than standard care in avoiding a donor blood transfusion, it is unlikely that
10 cell salvage would be considered cost-effective. However, the results in natural units of cost
11 per transfusion avoided are difficult to interpret and are very subjective. They will vary
12 depending on the context. The lack of long term data on the health and quality of life of
13 patients in both groups of the trial means that further research is needed to fully understand
14 the cost implications of both strategies. For patients undergoing an emergency caesarean
15 section, where cell salvage is performed using a continuous-transfusion cell saver machine,
16 the machine is only set up for processing in patients having blood returned and where swab
17 washing is not conducted, cell salvage would be considered less costly and more effective
18 compared to standard care. However, this scenario is not necessarily generalisable; therefore
19 this result should be interpreted with caution.

20 ***Unanswered questions and future research***

21 The current evaluation has used data from a large, multicentre randomised trial which
22 demonstrated modest evidence that routine use of cell salvage during caesarean section
23 reduced the need for donor blood transfusion. The main cause of uncertainty regards the cost
24 implications of adopting cell salvage in routine practice. Future studies should explore the
25 long-term health and economic impacts associated with both transfusion strategies. Also,
26 evidence on the preferences of women needs to be considered. For example hospitals may
27 wish to have the option of cell salvage available for Jehovah's Witness patients where there is
28 no option to use donor blood.

29 Finally, and related, the issue of donor blood as a limited resource needs to be considered. It
30 is important to remember that transfusion with cell salvage can always exist. We have not
31 considered this in our evaluation. While there is an expectation that donor blood will always

1 be there when needed, transfusion using donor blood cannot be guaranteed. In such a
2 scenario, where the option of donor blood is limited or not available, the routine use of cell
3 salvage would dominate (less costly and more effective) compared to standard care.

4 The routine use of cell salvage during caesarean section reduces, to some extent, the need for
5 donor blood. Whether this treatment strategy is also cost-effective will on one hand depend
6 on the cost of a donor blood transfusion and on the other hand the operating cost of the cell
7 salvage procedure. Implementation and more efficient operation of cell salvage machines in
8 routine care could reduce the associated costs; at the current price level of donor blood and
9 operating costs of cell salvage, cell salvage appears to be a more costly strategy to reduce the
10 use of donor blood; and only when the price of a blood transfusion increases to levels beyond
11 £8,637, cell salvage might become a cost-effective strategy.

1 **Chapter 5 Discussion**

2 **Aim and overview**

3 The provision of a reliable donor blood transfusion service has critical implications for
4 maternal health; in healthcare systems where this is available, maternal mortality due to
5 haemorrhage is almost a thousand fold less than in those where it is not.^{83, 84} Donor blood
6 transfusion is a safe intervention with remarkably few associated adverse effects, although
7 these may be serious and even rarely fatal. In the face of such a proven clinical intervention,
8 any new technique seeking to further reduce mortality would have to be extremely effective,
9 and require an unfeasibly large trial in order to demonstrate it. Despite these limitations to
10 evaluation of a new technology, for many clinicians, this would be intuitively considered the
11 aim of introducing cell salvage into obstetric clinical practice. More realistically, cell salvage
12 might reduce reliance on donor blood, the production and delivery of which remains
13 relatively expensive (£120 per unit⁷⁵) and while representing a “pooled” national resource,
14 may suffer from local hospital shortages when consumption is increased by a case of
15 unexpected severe haemorrhage. However, cell salvage is a technology with its own costs
16 and therefore, it was clear from the outset of the SALVO trial that the health economic
17 evaluation would be a crucial aspect of the SALVO trial, in order to show a worthwhile
18 reduction in spend on donor blood units which was greater than the cost of the intervention.
19 With an increasing reluctance to transfuse donor blood to even quite substantially anaemic
20 women, due to the possible adverse effects, cell salvage offered the possibility of safely
21 increasing postoperative haemoglobin levels, leading to additional savings in patient care and
22 hospital stay. These again, required rigorous health economic evaluation to provide
23 meaningful conclusions, particularly as other clinical interventions⁸⁵ for optimising pre-
24 operative haemoglobin levels (e.g. iron therapy) or reducing intraoperative blood loss (e.g.
25 tranexamic acid or interventional radiology) may be cheaper and more efficacious.

26 A number of endpoints were considered as candidates for a primary outcome. The selection
27 of transfusion rate was ultimately a pragmatic one, based on objectiveness, ease of collection
28 and the existence of pre-existing data. Additionally, a patient questionnaire given to women
29 who had undergone the procedure highlighted the reassuring nature of receiving one’s own
30 blood instead of donor blood (see original SALVO protocol).

1 **Main findings**

2 This large, multicentre randomised trial demonstrated modest evidence that routine,
3 prophylactic use of cell salvage during caesarean section reduced the need for donor blood
4 transfusion. It was associated with increased maternal exposure to fetal blood among Rh-
5 negative mothers. Small differences were observed between groups for time to mobilisation
6 and length of hospital stay but not in other secondary outcomes. Although numerically there
7 appeared to be a greater effect in the emergency group, compared with the elective group, the
8 difference in effect between subgroups was not statistically significant. Exploratory analysis
9 did not suggest a subgroup benefit in women with abnormal placentation. Although it
10 appeared to increase the volume of salvaged blood returned, the use of “swab washing” when
11 conducting cell salvage did not appear to effect the need for donor blood transfusion.

12 Health economic analysis demonstrated that it would cost £8,110 to avoid a blood transfusion
13 with the use of cell salvage as used in the study. This cost could potentially be reduced by
14 varying both the indication for cell salvage in caesarean section, and by changing the
15 technique used. Set-up for a continuous cell saver machine, with “collection” only, until
16 sufficient volume was obtained for processing could save the cost of the processing
17 consumables. Swab washing could be relinquished as a technique, since it did not appear to
18 have any effect on donor blood transfusion rate.

19 **Strengths and limitations of the trial**

20 To our knowledge, SALVO is the largest multicentre evaluation of cell salvage in caesarean
21 section to date. The randomised trial was prospectively registered, robustly conducted,
22 independently monitored, rigorously analysed, and transparently reported (see Figure 2). This
23 should provide for confidence in validity and reliability of the findings. The study sample
24 was diverse, spread across more than 20 UK centres. Only two indications for caesarean
25 section were considered exclusions; first elective caesarean section for either breech or
26 maternal request. The very low probability that these cases might require donor blood meant
27 that excluding them left only women with a recognisable increased risk of haemorrhage and
28 thus potential need for transfusion, increasing the power of the study to detect a difference.
29 This broad base for inclusion adds to the generalisability of the findings.

1 The trial recruited to target, had comparability at baseline and compliance with assignment,
2 minimal loss on follow-up and primary outcome. A substantial challenge to the conduct of an
3 individually randomised trial is obtaining consent from women in labour who require
4 emergency caesarean.^{86, 87} Therefore, meeting the target for recruitment in a challenging
5 clinical context was a major achievement. We considered this group to be the one most likely
6 to derive specific benefit from this health technology. Another challenge was the promotion
7 of equipoise among participating clinicians, who were keen to adopt the technology, without
8 robust evidence in cases where anxiety for life threatening haemorrhage was high,
9 particularly for cases of abnormal placentation.

10 Due to the nature of the intervention and the fact that mothers are usually awake for
11 caesarean section, it was considered impractical to formally blind either clinicians or patients
12 to the group allocation. In view of this and the local variation in transfusion practices, the trial
13 collected transfusion policies from each unit, and then reviewed transfusion decisions in light
14 of these. Although clinicians were found to commonly give donor blood in deviation to local
15 policy, no difference was found in the rate with which this non-adherence to local policy
16 occurred between intervention and control groups.

17 A criticism of sample size and power with presumption of likelihood of type II error could
18 risk erroneous conclusions. We highlight that a p-value that is in the region of a 0.05,
19 regardless of the side of the threshold in which it lies, deserves careful consideration with
20 respect to use of the evidence for guiding practice. The failure to achieve statistical
21 significance cannot be attributed to insufficient data when the study is completed to the
22 planned size with independent monitoring. We would like to propose the following
23 considerations in interpretation of our main finding: (a) addition of new data does not
24 guarantee that the p-value threshold for significance will be reached;⁸⁸ and (b) the point
25 estimate is the most plausible estimate of the true effect. This being the case we believe that
26 our main finding meets the criteria for accurate decision making.

27 From the outset we were aware that we were investigating the effect of an intervention in a
28 heterogeneous population in terms of baseline risk. This heterogeneity is principally derived
29 from the indication for caesarean section. This situation guided the use of covariate-adjusted
30 and subgroup analyses as an integral part of trial planning, analysis and inference. The
31 credibility of findings in subgroup analysis depends on a number of factors. We planned
32 these a priori and limited the number of subgroup analyses to the bare minimum in order to

1 limit the risk of spurious significance associated with multiple hypothesis testing. Caution
2 must be exercised in the conduct and interpretation of evidence derived from subgroup
3 analysis, however not investigating or ignoring results of subgroup analyses could also lead
4 to incorrect inferences. Although interaction proved statistically insignificant, suggesting no
5 evidence for an inconsistent effect of cell salvage between elective and emergency cases,
6 taking into account the observed point estimates and confidence intervals from subgroup
7 analyses for the primary outcome measure, we believe that our findings concerning the effect
8 in emergency caesareans merits consideration.

9 The role of our sensitivity analysis was to evaluate the integrity of the primary analysis
10 conducted based on the intention-to-treat principle. The design and analysis was predicated
11 on adherence to assignment, whether control or cell salvage. We sought for consistency
12 between the results of primary analysis and the results of sensitivity analysis to examine the
13 credibility of the main finding. We planned a priori to assess if the erroneous return of cell
14 salvaged blood in the control group could potentially avert the use of donor transfusion. In
15 the throes of a developing surgical emergency, it may be thought a useful intervention to deal
16 with ongoing haemorrhage by clinicians handling cases in the control group. We could not
17 prevent such a clinical intervention in an ethically consistent trial policy. We therefore
18 proposed to reclassify such cases as having experienced the primary outcome. Study
19 structures and team members strove to promote adherence to assignment but protocol
20 deviations are common in pragmatic trials and several cases assigned to the control group did
21 indeed receive salvage, even in the absence of such an acute emergency situation. One
22 proposal to handle this problem could include alternative trial designs, such as cluster
23 randomisation, but this approach does not necessarily guarantee avoidance of performance
24 bias and generally reduces statistical power. Our approach to sensitivity analysis maintained
25 the intention-to-treat principle, avoiding per protocol and as treated analyses that have a
26 tendency to produce spurious significance. Our sensitivity analyses confirmed the main
27 finding for the primary outcome.

28 SALVO studied both emergency and elective (planned) caesarean sections, despite the fact
29 that due to a higher incidence of haemorrhage in the former, a significant result might be
30 more likely to be detected if the trial had excluded electives. There were two reasons for this.
31 First, some centres were known to have already commenced using cell salvage routinely for
32 elective cases in the absence of any evidence, so the question of evaluating effectiveness in

1 this group remained pertinent. Second, emergencies represented a population much more
2 challenging to recruit. The elective sample gave centres the opportunity to deploy and prove
3 the trial processes in a much more straightforward population. Despite this, two groups of
4 electives were known to have extremely low rates of haemorrhage and were therefore
5 excluded (first caesareans for either breech or maternal request). The effect of cell salvage in
6 the emergency group, whilst non-significant with regards to interaction with the elective
7 group, will be interesting to clinicians. On the other hand, the finding of no effect in the
8 placental abnormalities subgroup is less relevant for policy as guidance already exists for use
9 of salvage in these high risk cases.³⁹

10 At the time SALVO was conceived and designed, cell salvage techniques used in obstetrics
11 was markedly heterogeneous and dependent on local attitudes and expertise. It was clear from
12 the outset that a robust trial would require close to optimal use of the intervention in order for
13 the results to be accepted by the clinical community. Optimal use in this context, maximises
14 the volume of salvaged blood returned to the mother. Therefore a number of technical aspects
15 of the machine use were made mandatory for trial patients to achieve this aim. Some other
16 aspects which might increase blood return, were left to local preference, as it was felt that it
17 would be difficult to commission enough recruiting centres to complete the study if these
18 technical elements of cell salvage management were made mandatory. Subgroup analysis of
19 swab washing failed to show any effect on the primary outcome. We conclude that there are
20 no other identifiable mechanisms, utilising current cell salvage technology, which might
21 significantly increase the return of salvaged blood to the patient compared to trial practices
22 capable of casting any doubt on the validity of our results.

23 ***External validity and generalisability***

24 We consider the external validity of the SALVO trial to be very robust; it was conducted in a
25 broad group of obstetric units, including large, tertiary teaching hospitals to small district
26 general hospitals. It recruited from a diverse range of indications for caesarean section, with
27 few exclusion criteria. The nature of the intervention was maintained as pragmatic as
28 possible, consistent with efficacy and adequate recruitment, yet delivered in a predictable
29 manner which is easy to emulate outside the context of a trial. The adherence to protocol was
30 higher than expected for an intervention which had already begun to enter routine practice
31 with a consequent potential loss of equipoise when the trial commenced.

1 **Red cell immunisation**

2 The UK Serious Hazards of Transfusion (SHOT) haemovigilance scheme has repeatedly
3 highlighted suboptimal practice in relation to the management of anti-D prophylaxis in cases
4 of caesarean section with Rhesus incompatibility. They have stressed the need for improved
5 awareness of national guidelines, supported by education and training amongst all healthcare
6 professional involved (www.shotuk.org). We had the novel opportunity to observe practice
7 around anti-D prophylaxis in particular in relation to cell salvage.

8 Whilst total omissions of anti-D prophylaxis after delivery occurred only a small number of
9 cases in either group (total n=3), there are many other opportunities for improved adherence
10 to national guidelines, in particular regarding the recommended minimum anti-D dose of
11 1500IU following cell salvage³³ and the need for fetomaternal haemorrhage (FMH) testing to
12 assess if further anti-D is needed beyond the standard dose. This highlights a need for close
13 communication between clinicians and laboratory teams, to ensure relevant testing
14 undertaken followed by subsequent appropriate management to minimise the risk of RhD
15 sensitisation.

16 Whilst secondary analysis indicated a significantly higher risk of FMH ≥ 2 mls based on
17 Kleihauer testing in the cell salvage group, the clinical implications of this result are unclear.
18 We have incomplete data on flow cytometry results to confirm FMH volumes. Further
19 analysis where results were available indicate that the majority of women with bleeds >4 mls
20 did receive appropriate doses of anti-D with further follow-up testing to check for fetal red
21 cell clearance as per guidelines, though there were some omissions. We are unable to
22 comment on the overall efficacy of anti-D prophylaxis and the subsequent risk of RhD
23 sensitisation. The SHOT scheme is currently collecting data on all pregnant women who have
24 produced immune anti-D detected for the first time, to better understand the reasons
25 underlying RhD sensitisation.

26 Although we are unable to comment on the risk of alloimmunisation to other red cell
27 antibodies following cell salvage as opposed to standard care, our data support the assertion
28 that the use of cell salvage significantly increases the risk of fetomaternal haemorrhage.
29 When just the women receiving cell salvaged blood are considered, the rate of FMH based on
30 the definition used in the study, is more than 4 times that of the control group. The
31 implications of this may go beyond the increased cost of a larger anti-D dose required in

1 women receiving cell salvaged blood. Although we did not specifically study other red cell
2 antigens, it is plausible and likely that this increased fetomaternal haemorrhage would cause
3 increased rates of introduction into the maternal circulation as well. As no anti-D equivalent
4 is available for these antigens, maternal antibody formation will not be avoided, and these
5 antibodies (e.g. anti-Kell) may make cross matching blood for these women significantly
6 more difficult in the future, incurring additional healthcare costs. As the rate and severity of
7 these potential complications is completely unknown, we were unable incorporate it into our
8 health economic analysis.

9 ***Adverse and Serious Adverse Events***

10 Adverse and serious adverse events were spread evenly across the two groups. An increase in
11 the rate of amniotic fluid embolism (AFE) has long been considered a potential adverse effect
12 of returning cell salvaged blood at caesarean section, even though research indicates it is
13 removed by the cell saver. It is reassuring that we did not observe any cases of AFE in either
14 group, but particularly not in the sub-group who actually received salvaged blood back,
15 whether or not a leukocyte depletion filter was used. It is notable that all the adverse events
16 definitely or probably related to cell salvage occurred when a leukocyte depletion filter was
17 in use, consisting of acute haemodynamic and respiratory reactions to the return of salvaged
18 blood. These reactions have been well reported in the literature, and are thought to be due to
19 an effect the filter induces on the salvaged blood, rather than due to the blood per se. We did
20 not observe any definitely or probably cell salvage related adverse events when a filter was
21 not used. Of 15 possibly related adverse events, a filter had been used in 13. These included a
22 range of adverse events, including infective and haemorrhagic complications which could
23 easily have been unrelated to the use of cell salvage; ultimately, it was for the local principal
24 investigator to make this judgement on relatedness. There was one case of reaction to donor
25 blood in the control group, from which the mother made a full recovery. This is in keeping
26 with the known rates of reaction.¹⁷ One maternal death occurred in a trial participant, who
27 had been allocated to the cell salvage intervention group. A local case review was carried out
28 by the Trust involved, and did not find any link to the use of cell salvage.

29 Adverse events from donor blood transfusion are potentially serious, but are also very rare,
30 with an incidence of 1 in 16,000.¹⁷ Mortality associated with donor blood transfusion is even
31 more uncommon, with an incidence of 1 in 100,000.¹⁷ We have demonstrated that the cost to

1 avoid a transfusion event when routinely using cell salvage in caesarean section is £8,110.
2 When considered with the observed increase in fetomaternal haemorrhage (see below) and
3 potential long term effects of this, which currently remain uncharacterised, it remains unclear
4 whether cell salvage is beneficial in this patient group. The exception to this is in cases such
5 as for Jehovah's Witnesses, where donor blood cannot be used, and cell salvage represents
6 the only therapeutic option. We are also unable to comment on the specific benefit in the
7 group at high risk of torrential haemorrhage such as placenta accreta, since we had
8 insufficient recruits in this group to come to any meaningful conclusions.

9 **Conclusions**

10 **Implications for healthcare service**

- 11 • Cell salvage may reduce the need for donor blood transfusion. It is unlikely to be
12 considered cost-effective when routinely set up for use in caesarean section. The cost-
13 effectiveness varies by indication for caesarean section and cost of cell saver
14 technique used.
- 15 • In RhD-negative mothers having RhD-positive babies, there appears to be an
16 increased chance of fetomaternal haemorrhage when cell salvaged blood is returned to
17 the mother, which needs to be taken into consideration with regards to applying and
18 updating guidance on the use of anti-D prophylaxis. Our findings highlight the need
19 for increased vigilance and appropriate prevention of the risk of RhD-
20 isoimmunisation among RhD-negative mothers.
- 21 • If cell salvage continues to be used in groups such as Jehovah's Witnesses and
22 placenta accreta, women should be counselled about the balance of risks in using cell
23 salvage.

24 **Recommendations for further research**

- 25 • The effect of increased fetomaternal haemorrhage associated with cell salvage on the
26 incidence of rarer, non-RhD red cell antigens needs to be characterised and quantified
27 in the long term.
- 28 • Investigation is needed to determine if greater amounts of routine anti-D
29 administration are required where cell salvage has been used on RhD-negative
30 mothers.

- 1 • Additional factors, e.g. swab washing or number of suckers used, which may increase
2 the likelihood of blood return during use of cell salvage, should be investigated.
- 3 • The effectiveness of cell salvage in specific sub-groups, such as placenta accreta,
4 remains to be investigated.
- 5 • The role of cell salvage in low-middle income countries where caesarean rates are
6 rising and blood transfusion services are not well developed should be investigated.
- 7 • If new, cheaper or more efficient cell salvage technology becomes available, the
8 conclusions of SALVO may need to be revisited. The same is true if donor blood
9 shortages should become extreme and acute.
- 10 • Recent and ongoing research into the use of tranexamic acid and other strategies to
11 prevent or manage maternal anaemia to make caesarean safer will merit consideration
12 in practice and future research alongside our findings.⁸⁵

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1 **Contributions of authors**

2 **Khalid S. Khan** (Professor, Women's Health, QMUL) was the chief investigator. He
3 contributed to the study design and protocol writing, study management, oversight of study
4 conduct and the initial writing and final editing of the report.

5 **Philip Moore** (Consultant Anaesthetist) was a co-applicant, contributed to study design and
6 writing the protocol, provided day-to-day clinical advice, oversight as a member of the trial
7 management group, medical review of clinical study data, contributed to study management
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24 **Carol McLoughlin** (Health economist) contributed to the health economic analysis plan,
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26 **Lee Beresford** (Statistician) wrote the statistical analysis plan, provided statistical support,
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25 ***Data sharing and accessibility***

1 We shall make data available to the scientific community with as few restrictions as feasible,
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3 reasonable requests to the corresponding author. We will, however, retain exclusive use of
4 the data until the publication of major outputs.

5 [30,080 words]

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Appendices

Appendix 1 List of participating sites and SALVO research staff

- Barts Health Trust, London:
 - Royal London Hospital
 - Whipps Cross University HospitalMatthew Hogg (principal investigator), Sajith Philip, Sarah Weist, Felipe Castro Cardona, Heike Bojahr, Lilith Loncke, Prudence Jones.
- Royal United Hospitals Bath NHS Foundation Trust:
 - Royal United Hospital, BathChris Marsh (principal investigator), Sara Burnard, Wendy Duberry, Elly Doyle, Karen Patrick, Catherine Bressington, Jenny Pullen, Mel Rich, Jess Withers, Amy Lloyd.
- Heart of England NHS Foundation Trust:
 - Birmingham Heartlands HospitalNicky Osborn (principal investigator), Ahmed Mesbah, Katie Trowman, Linda Bradley, Katie Atterbury, Teresa Melody.
- Birmingham Women's NHS Foundation Trust:
 - Birmingham Women's HospitalJames Geoghegan (principal investigator), Philip Moore, Chloe O'Hara, Elizabeth Ewer.
- University Hospitals Bristol NHS Foundation Trust
 - St Michael's Hospital, BristolIsobel Gardner (principal investigator), Carole Shahin, Alison Kirby, Mariethel Gudaca, Eirini Troupkou, Colleen Hunt, Claire Dowse, Nicola Harvey, Nicolas Wharton, Mark Scrutton
- Chelsea and Westminster Hospital NHS Foundation Trust:
 - West Middlesex University Hospital, IsleworthDominika Dabrowska (principal investigator), Marie O'Connell, Bernadette Tilley, Catherine Sheehan, Philip Barclay, Christine Adamson, Mehari Teklay, Sherif Omran, Sujatha Vishvanath, Amanpreet Sarna, Sheldon Zhang, Rafiu Ojo, Lisa Takab, Tina Brough, Emma Fox, Sarah Barker, Ano Rathambegoda, Edward Twumasi, Jacob Sheen, Belinda White, Wilky Ian Nunal, Emmanuel Espiritu.
- Croydon Health Services NHS Trust:
 - Croydon University HospitalBini Ajay (principal investigator), Dhileepan Srinivasan, Temilola Doherty, Valerie Fuller, Tony Hewitt, Ramandeep Sharma, Ajeet Kumar, Rebecca Byrne, Vana Wardley.

- 1 • NHS Lothian:
- 2 ○ Simpson Centre for Reproductive Health, Edinburgh
- 3 Vicki Clark, Arlene Wise (principal investigators), Ida Hassing, Karen Edgar.
- 4 • Hinchingsbrooke Health Care NHS Trust:
- 5 ○ Hinchingsbrooke Hospital
- 6 Sangeeta Pathak (principal investigator), Tara Pauley, Charlotte Clayton, Aarti
- 7 Bahirat.
- 8 • Leicester University Hospitals NHS Trust
- 9 ○ Leicester Royal Infirmary
- 10 ○ Leicester General Hospital
- 11 Tommy Mousa (principal investigator), Molly Patterson, Sharon Bates, Jo
- 12 Dickens, Katie Peck, Anna Muggleton, Claire Dodd, Asma Rabab, Tina
- 13 Evans, Tracey Bryan, Magda Kierzenkowska, Margaret Weston, Sarah Clarke,
- 14 Katie Warwick, C Elton, P Sharpe, A Morris, P Ramasamy, E Hart, R
- 15 Leighton, O Navti, O Joseph.
- 16 • South Tees Hospitals NHS Foundation Trust:
- 17 ○ James Cook University Hospital, Middlesbrough
- 18 Sanjay Rao (principal investigator), Aethele Khunda and the research team,
- 19 Hazel Alexander, Sarah Croft, Obstetric Consultants and Anaesthetists,
- 20 Speciality Trainees, Labour Ward Midwifery team, Theatre team.
- 21 • The Newcastle upon Tyne Hospitals NHS Foundation Trust:
- 22 ○ Royal Victoria Infirmary, Newcastle
- 23 Paul Ayuk (principal investigator), Sophia Webster, Jill Sturt, Celia McKee,
- 24 Angela Yulia, Andrea Fenn, Michelle Perkins, MaCassie Galeon, Jill Riches,
- 25 Cat Rowney, Erica Del Prete, Sue Harbertson, Terri Brosnan, Sharon Chilton,
- 26 Victoria Murtha, Jenna Wall, Emma Schultz, Alison Bates, Nicola King.
- 27 • Norfolk and Norwich University Hospitals NHS Foundation Trust:
- 28 ○ Norfolk and Norwich University Hospital
- 29 Maria del Rocio Ochoa-Ferraro (principal investigator), Elizabeth Turner,
- 30 Jonathon Francis, David Thornton, Carole Winstanley, Jeremy Corfe, Rachel
- 31 Appleton.
- 32 • London North West Healthcare NHS Trust:
- 33 ○ Northwick Park Hospital
- 34 Parijat Bhattacharjee (principal investigator).
- 35 • Nottingham University Hospitals NHS Trust:
- 36 ○ Queens Medical Centre, Nottingham
- 37 ○ Nottingham City Hospital
- 38 Lesley Woods (principal investigator), Jim Thornton, George Bugg, Sujata
- 39 Handa, Arani Pillai, Yvette Davis, Yvonne Toomassi, Yvette Gunn, Denise
- 40 Lochrie, Carys Smith.

- 1 • Plymouth Hospitals NHS Trust:
- 2 ○ Derriford Hospital, Plymouth
- 3 Darryl Thorp-Jones (principal investigator), Heidi Hollands, Jocelyn Watson,
- 4 Alison Stolton, Amanda Carney.
- 5 • Barking, Havering and Redbridge University Hospitals NHS Trust:
- 6 ○ Queen's Hospital, Romford
- 7 Vinod Patil (principal investigator), Annemarie McGregor, Rebecca Murray,
- 8 Dorothy Sutton, Theresa McCluskey, Julie Wright, Molly Murwira, Sue
- 9 Rogers, Mark Beaufond.
- 10 • Sheffield Teaching Hospitals NHS Foundation Trust:
- 11 ○ Royal Hallamshire Hospital, Sheffield
- 12 Ian Wrench (principal investigator), Siobhan Gillespie, Carolyn Clark, Emma
- 13 Steel, Sarah Senbeto, Paula Woodcock, Tessa Bonnett, Nicola Cawley,
- 14 Hannah Yeeles.
- 15 • University Hospitals of North Midlands NHS Trust:
- 16 ○ Royal Stoke University Hospital, Stoke-on-Trent
- 17 Jules Allt (principal investigator), Charlotte Howell, Siby Sebastian, A
- 18 Rajashanker, Angela Rooney, Sara Mountford, Suzanne Jerreat, Amanda
- 19 Redford, Anna Fleming, Donna Brayford, Wendy Dudley, Sarah Elson,
- 20 Rachel Sparkes, Andrea Vickers, Chris Hollins, N Butler, S Scally, Theresa
- 21 Webbon, Susan Bell, Andrea Morgan, Brett Beasley, MJ Newton.
- 22 • City Hospitals Sunderland NHS Foundation Trust:
- 23 ○ Sunderland Royal Hospital
- 24 Aarti Ullal (principal investigator), Kim Hinshaw, Helen Cameron, Kirsten
- 25 Herdman, Eileen Walton, Gill Campbell, Lesley Hewitt, Deborah Bonney,
- 26 Kathleen Hubbard, Karen Armstrong, Judith Ormonde, Joanne Knight,
- 27 Kathryn Witte, Dawn Edmundson, Sonia Thompson, Denise Mace, Sharon
- 28 Morrell, Suzanne Stelling, Marion Collings, Julie Harris, Amanda Bargh,
- 29 Judith Holland, Chris Field, Catherine Parkinson.
- 30 • Abertawe Bro Morgannwg University Health Board:
- 31 ○ Singleton Hospital, Swansea
- 32 Susan Williams (principal investigator), Sue Catling, Sharon Jones, Trudy
- 33 Smith, Helen Worrell, Sarah Fox.
- 34 • Torbay and South Devon NHS Foundation Trust:
- 35 ○ Torbay Hospital
- 36 David Portch (principal investigator), Richard Hughes, Shakila Sudhaker,
- 37 Jeremy Ackers, Pauline Fitzell, Janet Palmer.
- 38 • St Helens and Knowsley Teaching Hospitals NHS Trust:
- 39 Whiston Hospital, Prescot
- 40 Peter Yoxall (principal investigator), Zoe Grindley.

Appendix 2 Recruitment graphs

Figure 10 Overall recruitment graph

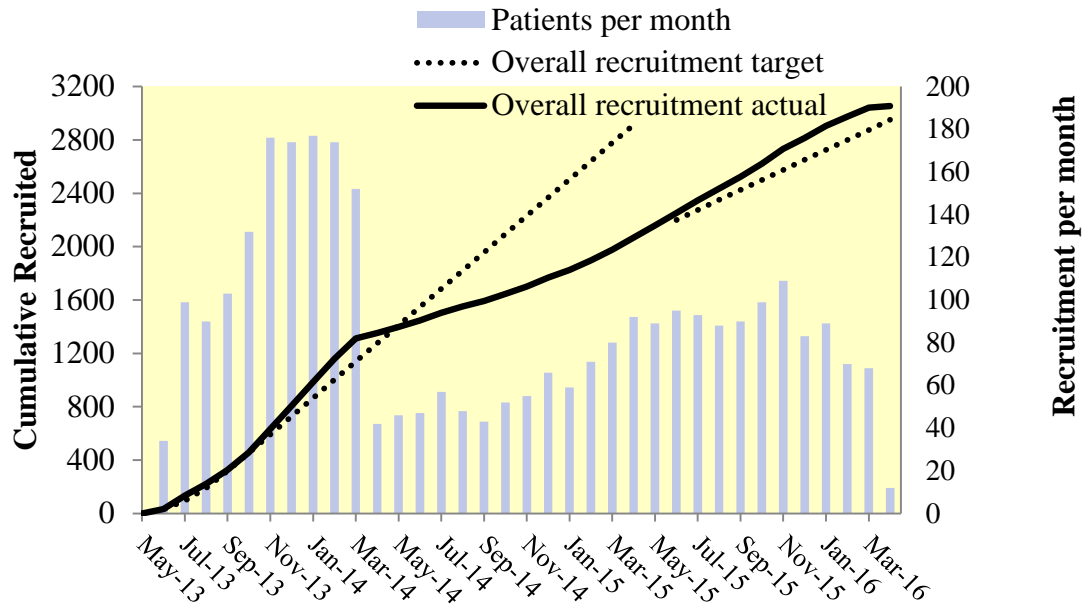


Figure 11 Recruitment graph by caesarean section type

