Draft for Consultation

Transfusion

Blood transfusion

NICE guideline

Appendices M-N

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Draft for consultation

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Appendix M: Cost-effectiveness analysis: tranexamic acid and cell salvage

M.1 Introduction

A key clinical issue identified by the GDG was which intervention to offer at the time of surgery to reduce the need for allogeneic blood transfusions: cell salvage, tranexamic acid (TXA) or both in combination. They wanted to understand if one intervention was more effective than the other, if the combination of cell salvage and TXA was better than either intervention and if there were specific population groups in which one intervention or combination may be more effective.

Cell salvage is a procedure whereby blood loss during or after surgery is collected and then re-transfused to the patient with the aim of reducing the need of allogeneic blood transfusion. TXA is an antifibrinolytic pharmacological agent administered at the time of surgery with the aim of reducing bleeding and thus reducing the need for allogeneic blood transfusion. Reducing the use of allogeneic blood is of economic importance as it is a scarce and costly resource. In addition, transfusion of allogeneic blood is potentially associated with transfusion-related complications.

The clinical evidence suggested that cell salvage and TXA were both clinically effective compared to placebo. In addition, it suggested that in some patient groups cell salvage in combination with TXA is more effective at reducing the number of people transfused and volume transfused compared to TXA alone. Economic evaluations identified in the systematic literature search indicated that cell salvage and TXA are likely to be cost-effective individually compared to standard treatment (no intervention or placebo) (see Full Guideline, section 6.5). However, uncertainty remained regarding whether one may be more cost-effective than the other (head-to-head comparison) or whether they are more cost-effective when given in combination. As a result this topic was identified by the GDG as the highest economic priority for original economic modelling.

M.2 Methods

M.2.1 Model overview

A cost-utility analysis was undertaken to evaluate whether cell salvage (intra-operative and post-operative), TXA, a combination of both or standard treatment (no cell salvage or TXA) is the most cost-effective option for reducing allogeneic blood transfusion in adults undergoing surgery at moderate or high risk of bleeding. A decision tree-based model was used to estimate lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective. The analysis was conducted in accordance with the NICE reference case unless otherwise stated including discounting at 3.5% for costs and QALYs.

In addition to the cost per QALY analysis, the number of units avoided for interventions to be cost neutral was also evaluated as the GDG felt this was helpful to decision-making given that reducing transfusions is in itself a goal given the scarce nature of blood as a resource in the NHS. Of note, the volume of the standard unit of red blood cells in the NHS is 280ml with a range of 220-340ml.

M.2.1.1 Population

Two population subgroups were analysed in the model:

1. Adults undergoing surgery at moderate risk of bleeding (0.5-1 litres)
2. Adults undergoing surgery at high risk of bleeding (>1 litre).

These subgroups were selected in line with the analysis of the clinical data. Further details regarding the rationale and methodology used for stratification are available in the methods section of the clinical review (see Full Guideline, section 6.4.2). Studies that were categorised as high risk were predominantly RCTs on cardiovascular surgery and those categorised as moderate risk were predominantly orthopaedic surgery.

Adults undergoing surgery at low risk of bleeding (<0.5 litres) were not included in the analysis as they would not be eligible for cell salvage because there would not be sufficient blood loss. Children undergoing surgery were not included in this analysis as insufficient clinical evidence was identified for this population to allow for modelling.

M.2.1.2 Comparators

The comparators for each population subgroup were selected based on the availability of evidence from the clinical review and in discussion with the GDG. It was agreed that only interventions with data on both proportion transfused and volume transfused would be included in the model as the GDG felt that it was not possible to make assumptions for these key outcomes.

Comparators for the high risk of bleeding subgroup:

1. Standard treatment
2. TXA
3. Intra-operative cell salvage
4. Post-operative cell salvage
5. TXA + intra-operative cell salvage

Comparators for the moderate risk of bleeding subgroup:

1. Standard treatment
2. TXA
3. Post-operative cell salvage
4. Intra-operative cell salvage + post-operative cell salvage

Comparators in the clinical review but with insufficient evidence to be included in the model were:

- High risk of bleeding subgroup: intra-operative cell salvage + post-operative cell salvage; post-operative cell salvage + TXA; intra-operative cell salvage + post-operative cell salvage + TXA.
- Moderate risk of bleeding subgroup: intra-operative cell salvage; intra-operative cell salvage + TXA; post-operative cell salvage + TXA; intra-operative cell salvage + post-operative cell salvage + TXA

M.2.1.3 Time horizon

A lifetime horizon was selected for the cost-effectiveness analysis because there was evidence that mortality was impacted with some interventions. Despite these interventions being for short-term use during and/or after surgery, a lifetime horizon is most appropriate to capture the full impact of treatment when mortality is impacted. For example, if treatment prevents death and the patient then goes on to live out their full life expectancy, calculating effects at 30 days will underestimate the QALYs gained.

Although differences in mortality were not incorporated into the moderate risk subgroup model in the base case analysis, a lifetime analysis was retained for comparability between the results of the two subgroups and to allow for sensitivity analyses incorporating mortality.

M.2.1.4 Deviations from NICE reference case

No deviations from the NICE reference case were taken.

M.2.2 Approach to modelling

The populations entering the model were adults undergoing a surgical intervention that were at moderate or high risk of bleeding. The aim of TXA and both intra-operative and post-operative cell salvage is to reduce the need for allogeneic blood transfusion. Key inputs in the model were therefore the proportion of people receiving an allogeneic transfusion and the volume of allogeneic blood transfused (in those that received a transfusion). Differences in proportions of patients transfused and volumes of blood transfused will translate to differences in costs between interventions.

The clinical evidence also suggested a clinically and statistically significant decrease in 30-day mortality with TXA in the high risk group and therefore it was thought important to incorporate mortality into the model.

The GDG also wished to try and incorporate differences between interventions in terms of adverse events as this may impact costs and QALYs. Adverse events could be intervention-related or transfusion-related. This impact was incorporated into the model in terms of differences in length of hospitalisation – this was then associated with a reduced quality of life and additional costs. Although the model did not explicitly model acute transfusion and treatment-related adverse events, the GDG judged length of stay to be a reasonable proxy for these acute events. This is because the ultimate impact of acute adverse event will be to prolong the patient's hospital stay while they are managed. More details are provided in the following paragraphs.

The main potential adverse event for TXA was considered to be thrombotic complications. The clinical evidence review found no evidence of an increased risk of deep vein thrombosis or other thrombotic events for TXA; therefore the GDG decided that it was unnecessary to include this outcome in the model. Epileptic seizures as a result of high doses of TXA have been reported in

the literature[504], however the GDG considered that this was a rare event and therefore this was not explicitly included in the model. However, it was considered that the impact of adverse events would be largely captured by the use of length of stay as a proxy as described above.

For cell salvage, adverse events can occur as a result of operating error or machinery failure. In addition, adverse clinical events can occur during processing and pathological reactions to re-infused blood. In 2013, 12 cases of adverse events were reported by SHOT, however none resulted in major morbidity or mortality.[82] Due to the scarcity of data for these adverse events, the GDG decided not to explicitly include them in the model. However, it was considered that the impact of adverse events would be largely captured by the use of length of stay as a proxy as described above.

Allogeneic transfusion is associated with low risks of serious harm or death. According to the Serious Hazards of Transfusions (SHOT) the risks of major morbidity and mortality based on data from 2013, were 51.8 and 8 per 1,000,000 units issued in 2013, respectively.[82] Adverse events can be broadly categorised into acute events and long-term events. The GDG agreed that the impact of acute events such as acute transfusion reactions, transfusion-related acute lung injury, transfusion-related circulatory overload and haemolytic transfusion reactions would be captured in the 30-day mortality and length of stay. Long-term events include transfusion-transmitted infections which can be viral (for example HIV), bacterial (for example staphylococcus aureus), parasitic (for example malaria) or from prions (for example variant Creutzfeld-Jakob disease). Between 2010 and 2013, SHOT reported two incidents of hepatitis B, two incidents of hepatitis E and one incident Parvovirus B19 in the UK.[82] The GDG acknowledged the severity of these infections, however considered them extremely rare and unlikely to impact on the results of the economic model. As a result it was agreed to not incorporate the risk of transfusion-transmitted infections in the model.

The model inputs for proportion transfused, volume transfused, length of stay and 30-day mortality were taken from the meta-analyses and network meta-analyses included in the clinical evidence in this guideline (see Full Guideline, section 6.5).

Uncertainty was explored through probabilistic analysis and extensive sensitivity analyses.

A number of assumptions were made when developing the model. The key assumptions are outlined below but are also discussed in more detail in subsequent sections of this report:

- People entering the model are eligible for each intervention listed for that subgroup.
- All allogeneic transfusions given in the model were red blood cell transfusions.
- The mortality rate after 30 days was the same for all people entering the model, irrespective of the intervention received or transfusion.
- TXA was administered intravenously.
- Cell salvage technicians were already trained and therefore the cost of training was not incorporated.
- Cell salvage equipment was available on lease via consumable charges.
- Post-operative cell salvage was unwashed.
- ICS and / or PCS were conducted for all people assigned to that intervention.

M.2.2.1 Model structure

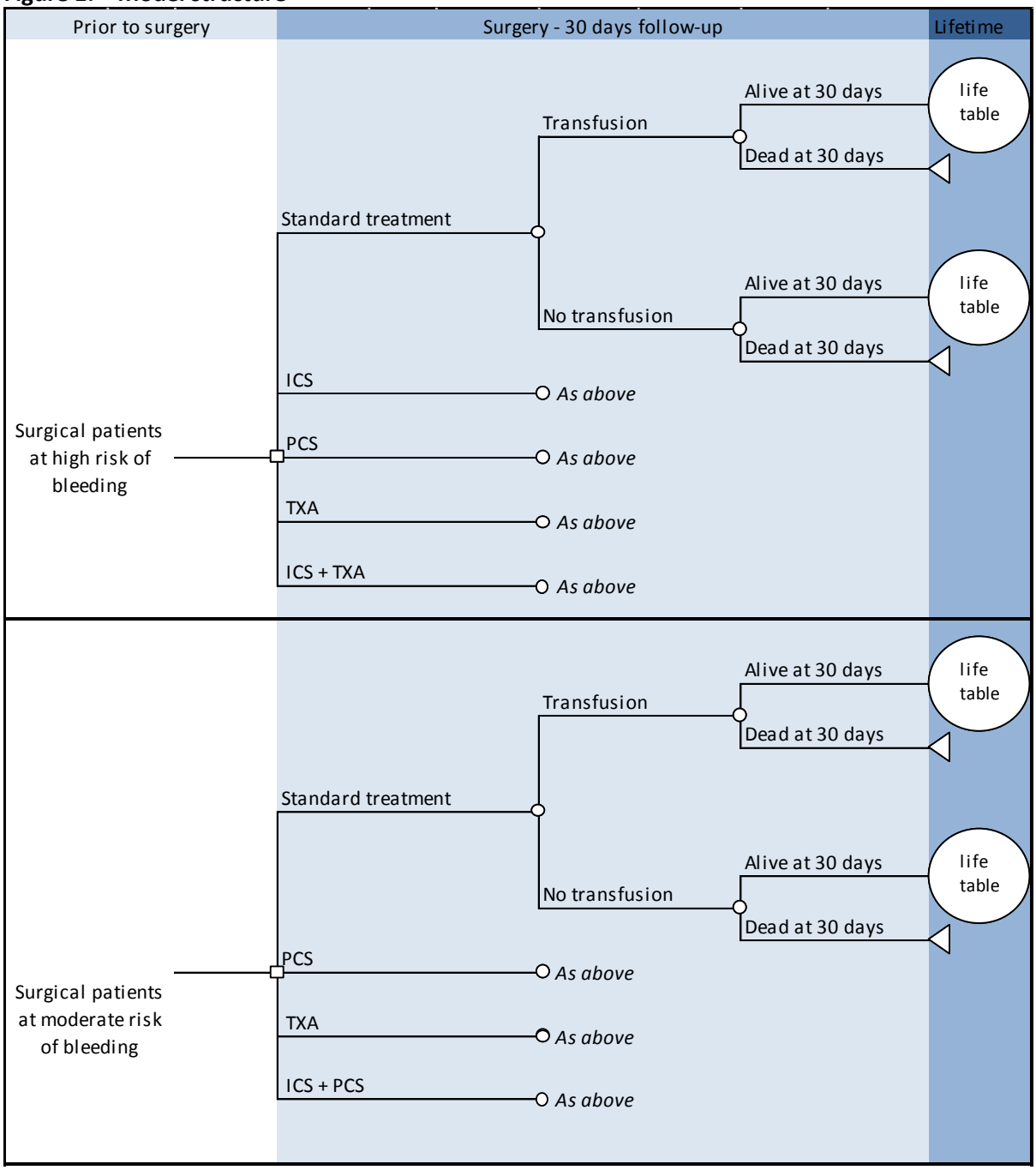
A decision tree was constructed to estimate outcomes over the 30-days post-surgery. Beyond 30 days, a life table was used to extrapolate results to a lifetime perspective. In the decision tree, the population received one of the interventions as detailed in section M.2.1.2. Following this two alternative events were possible: receiving or not receiving an allogeneic blood transfusion, the probability of which depended on the intervention received. In those receiving an allogeneic blood transfusion, the volume of blood transfused was assigned also dependant on the intervention received. In addition, the decision tree incorporated mortality between time of surgery and 30 days follow-up; note that the probability depended on the intervention received, not on whether or not they received a transfusion.

All patients are attributed a length of stay which varies by intervention and the impact of this on both costs and quality of life is captured.

For those who are dead at 30 days in the model, it was assumed they died on average at 15 days – that is, at the half-way point. For those who are alive at 30 days, a life table is used to estimate life years and QALYs. After 30 days, it was assumed in the model that mortality and quality of life was not influenced by surgery, the intervention received or transfusion, and standard age-adjusted UK life expectancies were used to generate lifetime QALYs (see section M.2.3.5 for further detail).

Costs and QALYs were determined by the intervention received, the probability of receiving an allogeneic transfusion, volume transfused, length of hospital stay and mortality. The full model structure is provided in Figure 1 below.

Figure 1: Model structure



Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid. Note that the probability of being dead or alive at 30 days depended on the intervention received, not on whether or not they received a transfusion, despite how pictorially represented above.

M.2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. Probability distributions in the analysis were parameterised using error estimates from data

sources, for example confidence interval around relative risk estimates. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 2,500 times – and results were summarised. We checked for convergence by plotting the incremental net monetary benefit for ICS+TXA versus standard treatment and PCS versus standard treatment on a graph and noted convergence at approximately 1000 iterations. The probabilistic analysis was used for the base case analysis and also selected sensitivity analysis where deterministic results suggested the conclusion of the analysis changed.

The way in which distributions are defined reflects the nature of the data. For example, utilities were given a beta distribution, which is bounded by zero and one, reflecting that a QoL weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Baseline volume transfused Baseline length of stay Mean difference in length of stay Mean difference volume transfused	Normal	Unbounded. Derived from mean or mean difference and its standard error. The standard error was calculated as follows: SE = (upper CI – lower CI)/1.96*2
Utility decrement associated with being in hospital	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: Alpha = $(mean/SE)^2$ Beta = $SE^2/Mean$
Baseline probability transfused Baseline probability 30-day mortality Utility after 30 days	Beta	Bounded between 0 and 1(although utility can technically go below 0 the values being used here are far from 0 and so this was considered reasonable). Derived from mean of total quality of life score /probability and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $mean^2$*[(1−mean)/SE2]−mean Beta = Alpha*[(1−mean)/mean]
Intervention-specific relative risk 30-day mortality Standardised mortality ratio	Lognormal	Bounded at 0, positively skewed. The natural log of the mean was calculated as follows: Mean = ln(mean) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2

Parameter	Type of distribution	Properties of distribution
Probability transfused (intervention-specific)	Normal	We assumed that the log odds ratios associated with each intervention were defined by a multivariate normal distribution. When simulating from a multivariate normal distribution it is important to preserve the correlations between parameters, which can be represented by the variance covariance matrix. We therefore parameterise the treatment specific log odds ratios (δ_i) as follows: $\begin{pmatrix}\delta_1\\ \delta_2\\ \delta_3\\ \delta_4\\ \delta_5\end{pmatrix} \sim MVLN(\boldsymbol{\mu}, \boldsymbol{\Sigma})$ Where: $\boldsymbol{\mu} = \begin{pmatrix}d_1\\ d_2\\ d_3\\ d_4\\ d_5\end{pmatrix}$ is a vector representing the mean log odds ratios for each intervention and $\boldsymbol{\Sigma} = \begin{pmatrix}\boldsymbol{\sigma}_{1,1}^2 & \boldsymbol{\sigma}_{1,2} & \cdots & \dots & \boldsymbol{\sigma}_{1,5}\\ \boldsymbol{\sigma}_{2,1} & \ddots & \ddots & \ddots & \vdots\\ \vdots & \ddots & \ddots & \ddots & \vdots\\ \vdots & \ddots & \ddots & \ddots & \vdots\\ \boldsymbol{\sigma}_{5,1} & \boldsymbol{\sigma}_{5,2} & \dots & \dots & \boldsymbol{\sigma}_{5,5}^2\end{pmatrix}$ is a matrix representing the variances of the log odds ratios for each treatment and the covariance between them. For example $\boldsymbol{\sigma}_{1,5}$ represents the covariance between interventions 1 and 5. Then the treatment specific log odds ratios are sampled using a cholesky decomposition and then transformed into absolute probabilities of response using the methods described in section M.2.6.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- All costs (interventions, transfusion and excess bed days)
- mortality rates after 30-days (from life tables)

Costs of interventions and transfusion were not varied probabilistically as no error estimates from the data sources were available. Deterministic sensitivity analyses were undertaken to explore the robustness of these costs and are described in section M.2.4. The cost of excess bed days from the NHS reference costs and the mortality rates from life tables for England and Wales were not varied probabilistically as they are based on national data and therefore the level of uncertainty in the model inputs was considered to be very low and did not warrant incorporation.

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions, on which intervention should be recommended, would change. The sensitivity analyses that were undertaken are described in section M.2.4.

M.2.3 Model inputs

M.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review and network-meta analyses (NMA) undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 2 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 2: Overview of parameters and parameter distributions used in the model

Parameter description	Data	Source	Distribution and parameters
Population	Adults undergoing surgery at high or moderate risk of bleeding	GDG consensus	n/a
Subgroups	**1)** High risk **2)** Moderate risk	GDG consensus	n/a
Comparators	High risk: **1)** ST **2)** TXA **3)** ICS **4)** PCS **5)** TXA + ICS Moderate risk: **1)** ST **2)** TXA **3)** PCS **4)** ICS+PCS	Data availability & GDG consensus	n/a
Perspective	UK NHS and PSS	NICE reference case[523]	n/a
Time horizon	Lifetime	NICE reference case[523]	n/a
Discount rate	Outcomes: 3.5%	NICE reference case[523]	n/a
Cohort settings			
Start age (years)	High risk: 66 Moderate risk: 69	National Adult Cardiac Surgery Audit 2010-11[521]; National Joint Registry 11th Annual Report 2014[524]	n/a
Male	50%	Assumption	n/a
Baseline risk – high risk subgroup			
Probability transfused	48.21%	Based on synthesized data from standard treatment arms in clinical review (a)	Beta. Mean=0.4821; SE=0.0445
Volume transfused (units)	4.16		Normal. Mean=4.16; SE=0.18
Length of stay (days)	9.75		Normal. Mean=9.75;

Parameter description	Data	Source	Distribution and parameters
			SE=0.35
Probability 30-day mortality	3.43%		Beta. Mean=0.0343; SE=0.0114
Baseline risk – moderate risk subgroup			
Probability transfused	37.43%	Based on synthesized data from standard treatment arms in clinical review (a)	Beta. Mean=0.3743; SE=0.0422
Volume transfused (units)	1.80		Normal. Mean=1.80; SE=0.06
Length of stay (days)	5.70		Normal. Mean=5.70; SE=0.18
Probability 30-day mortality	0.16%		Beta. Mean=0.0016; SE=0.0024
Treatment effects – high risk subgroup			
Probability transfused	TXA=29.62% ICS=36.91% PCS=16.16% TXA+ICS=22.73%	NMA conducted as part of clinical review (b)	Normal. Mean (log-odds ratio), SE. TXA=-0.79, 0.09 ICS=-0.46, 0.21 PCS=-1.58, 0.44 TCA+ICS=-1.15, 0.29
Difference in volume transfused (units)	TXA=-0.87 ICS=-0.84 PCS=-1.02 TXA+ICS=-2.17		Normal. Mean difference, SE. TXA=-0.87, 0.22 ICS=-0.84, 0.39 PCS=-1.02, 0.63 ICS+TXA=-2.17, 0.62
Difference in length of stay (days)	TXA=-0.15 ICS=-0.16 PCS=-7.13 TXA+ICS=0.64		Normal. Mean difference, SE. TXA=-0.15, 0.37 ICS= -0.16, 1.16 PCS= -7.13, 2.55 ICS+TXA= 0.64, 0.99
Relative risk 30-day mortality	TXA=0.52 ICS=1 PCS=1 TXA+ICS=1	TXA from pairwise MA as part of clinical review (b) Others, assumption RR =1 (i.e. no mortality effect vs. standard treatment)	For TXA Lognormal. ln(RR)=-0.65, ln(SE)=0.26 Others fixed.
Treatment effects – moderate risk subgroup			
Probability transfused	TXA=9.65% PCS=19.68% ICS+PCS=22.80%	NMA conducted as part of clinical review (b)	Normal. Mean (log-odds ratio), SE. TXA=-1.72, 0.16 PCS=-0.89, 0.26 ICS+PCS=-0.71, 0.64
Difference in volume transfused (units)	TXA=-0.91 PCS=-0.82	NMA conducted as part of clinical review (b)	Normal. Mean difference, SE.

Parameter description	Data	Source	Distribution and parameters
	ICS+PCS=1.11		TXA=-0.91, 0.24 PCS=-0. 822, 0.27 ICS+PCS=1.11, 0.61
Difference in length of stay (days)	TXA=-0.25 PCS=-0.37 ICS+PCS=0.20		Normal. Mean difference, SE. TXA=-0.25, 0.17 PCS=-0.37, 0.69 ICS+PCS=0.20, 0.20
Relative risk 30-day mortality	TXA=1 PCS=1 ICS+PCS=1	Assumption RR = 1 (i.e. no mortality effect vs. standard treatment)	Fixed
Utilities			
Disutility of being in hospital	-0.248	Difference between utilities for limiting long-standing illness and non-limiting long standing illness, Health Survey for England 2012[599]	Gamma. Mean=0.248; SE=0.008
Utility after 30 days	0.858	Adult general population mean utility, Health Survey for England 2012[599]	Beta. Mean=0.858; SE=0.003
Costs			
ICS	£295	PSSRU 2013[183], NHS Supply Chain Catalogue April 2014[532], BNF 67[359], NICE Clinical Guideline CG174[520], Crotty 2006[179]	Fixed
PCS	£88	PSSRU 2013[183], NHS Supply Chain Catalogue April 2014[532]	Fixed
ICS+PCS	£350	PSSRU 2013[183], NHS Supply Chain Catalogue April 2014[532], BNF 67[359], NICE Clinical Guideline CG174[520], Crotty 2006[179]	Fixed
TXA (high risk subgroup)	£19	Total dose 6000 mg, slow IV injection followed by continuous IV infusion. BNF 67[359], eMIT July 201[4164], NHS Supply Chain Catalogue April 2014[532], NICE Clinical Guideline CG174[520]	Fixed
TXA (moderate risk subgroup)	£9	Total dose 3000 mg slow IV injection. BNF 67[359], eMIT July 2014[164]	Fixed
ICS+TXA	£314	Sum of ICS and TXA (high risk subgroup)	Fixed

Parameter description	Data	Source	Distribution and parameters
No allogeneic transfusion	£22	Agrawal 2006[17], PSSRU 2013[183]	Fixed
First unit transfused	£192	Agrawal 2006[17], NHSBT 2014/15[531], PSSRU 2013[183]	Fixed
Subsequent units transfused	£167	Agrawal 2006[17], NHSBT 2014/15[531], PSSRU 2013[183]	Fixed
Additional hospital day (high risk subgroup)	£372	NHS reference costs 2012/2013[202]	Fixed
Additional hospital day (moderate risk subgroup)	£318	NHS reference costs 2012/2013[202]	Fixed

Abbreviations: BNF = British National Formulary; CI = confidence intervals; eMIT = *Electronic Market Information Tool; ICS = intra-operative cell salvage; MD = mean difference; PSSRU = Personal Social Services Research Unit; PCS = post-operative cell salvage; SE = standard error; ST = standard treatment; TXA = tranexamic acid*

(a) Studies included were those from the meta-analyses or network meta-analyses reported in the clinical review. Details of these studies are available in (see Full Guideline, section 6.5).These were synthesized either by calculating the weighted average or by undertaking a baseline model. Further detail is provided below in Section M.2.3.3.

(b) Studies included were those from the meta-analyses or network meta-analyses reported in the clinical review. Details of these studies are available in (see Full Guideline, section 6.5).

M.2.3.2 Initial cohort settings

The starting age of the model cohort was 69 years for the moderate risk subgroup and 66 years for the high risk subgroup. The age was based on the mean age for recipients of primary hip or knee replacements and CABG surgery, respectively, as reported in national audits on the basis that the majority of evidence of effectiveness came from these populations.[521,524] The population was assumed to be made up of an equal portion of male and female patients. Note that these settings only impact the life table based extrapolation beyond the initial 30-day decision tree.

M.2.3.3 Baseline event rates

Standard treatment (no cell salvage or TXA) was the baseline intervention in the model.

M.2.3.3.1 Proportion transfused

The baseline proportion transfused for standard treatment was modelled using a logistic regression (logit) in WinBUGS, the code and data used can be found in Appendix L. The aim of the logistic regression was to calculate the baseline probability for this outcome by pooling event rates for standard treatment taken from the RCTs. Separate models were conducted for high and moderate risk of bleeding subgroups. The baseline event rates used in the model are summarised in the table below (Table 3).

Table 3: Probability transfused

Probability transfused	Data	Source
High risk	48.21%	NMA conducted as part of clinical review
Moderate risk	37.43%	NMA conducted as part of clinical review

M.2.3.3.2 Volume transfused

The cost of transfusing the first unit is different to the cost of transfusing subsequent units (see section M.2.3.7.5), for this reason it was necessary in the model to calculate the absolute volume transfused for all interventions by combining the baseline volume transfused with the mean differences.

The baseline mean was estimated by calculating a weighted average mean for the standard treatment arms in the trials (note, a WINBUGS model was not used due to this being a continuous outcome).

The data used to calculate the baseline mean volume transfused used in the model are summarised in the table below (Table 4).

Table 4: Volume transfused

Study	Mean volume	Total number of patients	SE
High risk			
BOWLEY2006[86]	11.17	23	1.26
NIRANJAN2006[535]	1.38	40	0.21
GOEL2007[275]	2.4	25	0.26
AGHDAII2012[15]	0.7	25	0.2
ZHAO2003[826]	2.22	30	0.07
ARMELLIN2001[42]	1.93	63	0.16
BLAUHUT1994[78]	2.44	9	0.38
CORBEAU1995[167]	2.83	12	0.42
DALMAU2000[187]	8.38	37	1.01
HORROW1990[329]	0.76	20	0.24
KATOH1997[374]	3.03	31	0.82
SPEEKENBRINK1995[685]	4.27	11	0.95
UOZAKI2001[737]	9.16	6	2.69
YASSEN1993[810]	12.4	10	2.53
ZABEEDA2002[817]	1.68	25	0.20
AHN2012[19]	1.4	38	0.19
MADDALI2007[452]	3.17	111	0.09
SHI2013[646]	6.51	278	0.44
SHI2013A[647]	9.36	59	1.49
WANG2012[772]	1.62	115	0.24
GHAVIDEL2014[22]	1.65	100	0.55
Average volume high risk	**4.16**		**0.18**
Moderate risk			
ATAY2010i[47]	1.68	19	0.33
ATAY2010ii[47]	0.71	21	0.21
SOOSMAN2006[672]	1.9	10	0.22
KIRKOS2006 [391]	1.06	77	0.13

Study	Mean volume	Total number of patients	SE
ALTINEL2007[29]	2.29	16	0.31
TRIPKOVIC2008[729]	1.74	30	0.21
SOOSMAN2014[675]	2.68	54	0.12
HIIPPALA1995[321]	3.58	12	0.45
HIIPPALA1997[322]	3.46	34	0.21
JANSEN1999[350]	2.5	21	0.54
CAGLAR2008[104]	1.6	10	0.21
CHAROENCH2011[135]	1.89	50	0.12
CHAROENCH2012 [134]	1.55	120	0.09
KAZEMI2010[377]	0.84	32	0.16
MACGILLIVRAY2011[449]	1.11	20	0.22
ANTINOLFI2014[38]	2.2	20	0.22
Average volume moderate risk	**1.80**		**0.06**

Abbreviation: SE = standard error

M.2.3.3.3 Length of stay

The baseline mean was estimated by calculating a weighted average mean for the standard treatment arms in the trials (note, a WINBUGS model was not used due to this being a continuous outcome). The data used to calculate the baseline length of stay in the model are summarised in the table below (Table 5).

Table 5: Length of stay

Study	Mean volume	Total number of patients	SE
High risk			
NIRANJAN2006[535]	7.85	40	0.42
SIRVINKAS2007[659]	16.45	49	0.93
MURPHY2004[505]	6.8	97	0.41
MANSOUR2004[459]	6.4	20	0.67
MEHRAEIN2007[474]	4.8	33	0.16
WEI2006[783]	7.3	40	0.19
VERMEIJDEN2015[753]	11.8	177	0.72
Average length of stay high risk	**9.75**		**0.35**
Moderate risk			
SO-OSMAN2006[672]	9	22	0.60
ALTINEL2007[29]	16.5	16	1.73
ABUZAKUK2007[7]	8.3	52	0.39
HORSTMANN2014A[333]	4.3	62	0.13
ELLIS2001[227]	10	10	0.63
ABDELALEEM2013[3]	2	367	0.03

Study	Mean volume	Total number of patients	SE
AGUILERA2013[18]	7.5	42	0.40
BIDOLEGUI2014[71]	3.8	25	1.88
CRESCENTI2011[177]	9	100	0.43
KAZEMI2010[377]	15.5	32	1.32
LEE2013[419]	15.2	34	0.53
SADEGHI2007[616]	5.8	35	0.25
ZOHAR2004[834]	9	20	0.45
YUE2015[815]	4.9	49	0.10
Average length of stay moderate risk	**5.75**		**0.27**

Abbreviation: SE = standard error

M.2.3.3.4 30-day mortality

The baseline mortality rate for standard treatment was modelled using a logistic regression (logit) in WinBUGS, the code for which can be found in Appendix L. The aim of the logistic regression was to calculate baseline probability for this outcome by pooling event rates for standard treatment taken from the RCTs. Separate models were conducted for high and moderate risk of bleeding subgroups. The data used to calculate the baseline mortality rates used in the model and the probability of 30-day mortality calculated from the logistic regression are summarised in the table below (Table 6).

Table 6: Probability 30-day mortality

Study	Event (death)	Total number of patients
High risk		
MERCER2004[477]	1	41
BOWLEY2006[86]	15	23
NIRANJAN2006[535]	1	40
DAMGAARD2006[189]	2	29
PLEYM2005[578]	0	25
MURPHY2004[505]	3	97
ABULAZM2006[6]	4	50
ANDREASEN2004[35]	0	23
BARIC2007[56]	3	96
KARSKI2005[369]	1	165
SANTOS2006[621]	2	31
SHI2013[646]	3	278
SHI2013A[647]	1	59
ARMELLIN2001[42]	3	150
BOYLAN1996[87]	3	20
COFFEY1995[161]	1	14

Study	Event (death)	Total number of patients
DALMAU2000[187]	4	40
DRYDEN1997[216]	4	19
KASPAR1997[371]	0	16
KATOH1997[374]	0	31
KATSAROS1996[375]	2	106
NUTTALL2000[541]	2	45
ESFANDIARI2013[230]	2	75
VERMEIJDEN2015[753]	5	177
Probability 30-day mortality, High risk	**3.43%**	**0.011**
Moderate risk		
HORSTMANN2014A[333]	0	62
HIIPPALA1997[322]	1	38
ALSHRYDA2013[26]	0	78
CRESCENTI2011[177]	0	100
PFIZER2011[574]	0	42
SADEGHI2007[616]	1	35
SEO2013[636]	0	50
WONG2010[799]	0	35
XU2013[803]	0	86
ZUFFEREY2010[835]	0	57
Probability 30-day mortality, Moderate risk	**0.16%**	**0.002**

Abbreviation: SE = standard error

M.2.3.4 Relative treatment effects

Treatment effects for each intervention relative to standard treatment were estimated as part of the clinical review. In the model, these relative treatment effects were applied to baseline event rates for standard treatment in order to generate intervention-specific event rates for each intervention.

M.2.3.4.1 Proportion transfused

The relative proportion transfused for each intervention compared to standard care was based on the NMA conducted for the guideline. To calculate relative treatment effect on proportion transfused, an NMA was conducted in WinBUGS (see Appendix L for full data inputs and NMA code). Full trial details are available in the Full Guideline, section 6.5.

The log odds ratios generated from the NMA are summarised in the table below (Table 7). A summary of the relative risks generated from the NMA can be found in the NMA results in the Full Guideline, section 6.5. The absolute probabilities used in the model as calculated above are summarised in Table 8.

Table 7: Network meta-analysis results – proportion transfused

Treatment	Proportion transfused (log odds ratios compared with standard treatment)[(a)]			
	Mean	Standard deviation	Median	95% Credible interval
High risk				
TXA	-0.794	0.087	-0.793	-0.969, -0.624
ICS	-0.465	0.212	-0.464	-0.887, -0.051
PCS	-1.575	0.444	-1.565	-2.492, -0.737
TXA + ICS	-1.152	0.286	-1.149	-1.723, -0.588
Moderate risk				
TXA	-1.723	0.162	-1.720	-2.052, -1.416
PCS	-0.893	0.262	-0.889	-1.418, -0.387
ICS+PCS	-0.706	0.637	-0.702	-1.977, 0.538

(a) These are the mean, median, SD and percentiles of the posterior distribution for the log odds ratio
Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid

Table 8: Probability transfused

Probability transfused	Data	Source
High risk	TXA = 29.62% ICS = 36.91% PCS = 16.16% TXA + ICS = 22.73%	NMA conducted as part of clinical review
Moderate risk	TXA = 9.65% PCS = 19.68% ICS+PCS = 22.80%	NMA conducted as part of clinical review

Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid

M.2.3.4.2 Difference in volume transfused

The mean difference in volume of allogeneic blood transfused for each intervention compared to standard treatment was based on the NMA conducted for the guideline (see Appendix L for full data inputs and NMA code) in the high and moderate risk groups. Full trial details are available in the Full Guideline, section 6.5. The results of the NMA are summarised in Table 9.

Table 9: Network meta-analysis results – volume transfused

Treatment	Difference in volume transfused (units) compared with standard treatment			
	Mean	Standard deviation	Median	Credible interval
High risk				
TXA	-0.869	0.217	-0.854	-1.343, -0.484
ICS	-0.838	0.390	-0.818	-1.671, -0.115
PCS	-1.021	0.627	-1.021	-2.290, 0.251
TXA + ICS	-2.169	0.625	-2.160	-3.444, -0.944
Moderate risk				
TXA	-0.907	0.242	-0.903	-1.397, -0.437

Treatment	Difference in volume transfused (units) compared with standard treatment			
	Mean	Standard deviation	Median	Credible interval
PCS	-0.822	0.272	-0.822	-1.364, -0.283
ICS+PCS	1.109	0.605	1.110	-0.103, 2.313

Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid

The relative treatment effects used in the model are summarised in the table below (Table 10).

Table 10: Difference in volume transfused compared with standard treatment

Difference in volume transfused (units)	Data	Source
High risk (SE)	TXA = -0.87 (0.22) ICS = -0.84 (0.39) PCS = -1.02 (0.63) TXA + ICS = -2.17 (0.63)	NMA conducted as part of clinical review
Moderate risk (95% CI)	TXA = -0.91 (-1.40, -0.44) PCS = -0.82 (-1.36, -0.28) ICS+PCS = 1.11 (-0.10, 2.31)	NMA conducted as part of clinical review

Abbreviations: CI = confidence intervals; ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid

M.2.3.4.3 Difference in length of stay

The mean difference in length of stay for each intervention compared to standard treatment was based on the NMA conducted for the guideline (see Appendix L for full data inputs and NMA code) in the high risk group. Full trial details are available in the Full Guideline, section 6.5. The results of the NMA are summarised in Table 11. In the moderate risk group, an NMA was not feasible and so the pairwise meta-analysis results from the clinical review were used.

Table 11: Network meta-analysis results – length of stay (high risk)

Treatment	Difference in length of stay (days) compared with standard treatment			
	Mean	Standard deviation	Median	Credible interval
TXA	-0.151	0.369	-0.127	-0.966, 0.494
ICS	-0.163	0.618	-0.167	-1.346, 1.041
PCS	-7.134	1.160	-7.123	-9.394, -4.869
TXA + ICS	0.639	0.993	0.638	-1.306, 2.607

Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid

The relative treatment effects used in the model are summarised in the table below (Table 12).

Table 12: Difference in length of stay

Difference in length of stay (days)	Data	Source
High risk (SE)	TXA = -0.15 (0.37) ICS = -0.16 (0.62) PCS = -7.13 (1.16) TXA + ICS = 0.64 (0.99)	NMA conducted as part of clinical review

Difference in length of stay (days)	Data	Source
Moderate risk (95% CI)	TXA = -0.25 (-0.59, 0.09) PCS = -0.37(-1.73, 0.99) ICS+PCS = 0.20 (-0.20, 0.60)	Pairwise MA as part of clinical review

Abbreviations: CI = confidence intervals; ICS = intra-operative cell salvage; PCS = post-operative cell salvage; SE = standard error; TXA = tranexamic acid

A sensitivity analysis was conducted to explore the impact of excluding length of stay from the analysis.

M.2.3.4.4 30-day mortality

An NMA was not undertaken because there was insufficient data (a combination of low event rates and limited number of studies) for it to be reliable. A series of pairwise meta-analyses was therefore undertaken for this outcome in RevMan for both the high and moderate risk of bleeding subgroups (see Full Guideline, section 6.5). For the high risk subgroup analysis, the GDG concluded that there was a clear mortality benefit for TXA compared to standard treatment, but none of the other interventions demonstrated any clinically significant difference in mortality. In addition there was a great deal of uncertainty around the estimates for other interventions. The GDG decided to incorporate the differential effect of TXA on mortality for the high risk of bleeding subgroup in the model for the base case. For all other interventions in the high risk group, it was assumed there was no mortality difference compared to standard treatment. Sensitivity analyses were conducted to explore the impact of these assumptions regarding 30-day mortality. See section M.2.4.1 for further detail.

In the moderate risk group, 30-day mortality was an outcome reported for TXA versus standard treatment studies and ICS+PCS versus standard treatment. The GDG concluded that no clinically significant differences were reported; therefore it was assumed there was no mortality difference for any of the interventions in this risk group compared to standard treatment. Sensitivity analyses were conducted to explore the impact of these assumptions, see section M.2.4.1 for further detail.

For those who are dead at 30 days in the model, it was assumed they died on average at 15 days – that is, at the half-way point.

The relative treatment effects used in the model are summarised in the table below (Table 13).

Table 13: Relative risk 30-day mortality

Relative risk 30-day mortality	Data	Source
High risk (95% CI)	TXA = 0.52 (0.31, 0.87) ICS = 1 PCS = 1 TXA +ICS = 1	TXA from pairwise meta-analysis as part of clinical review. Others, assumption RR =1 (i.e. no mortality effect vs. standard treatment)
Moderate risk	TXA = 1 PCS = 1 ICS+PCS = 1	Assumption RR = 1 (i.e. no mortality effect vs. standard treatment)

Abbreviations: CI= confidence intervals; ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid

M.2.3.5 Mortality after 30 days

The GDG agreed that surgery-, treatment- and transfusion-related mortality would generally occur within 30 days and therefore be captured by the 30-day mortality rates. For that reason, in the base case, age-dependent mortality was assumed for all people after 30 days. This was based on mortality rates from life tables for England and Wales, 2010-2012.[544] Using these mortality rates the discounted and undiscounted life expectancy for those alive after 30 days was calculated.

For the moderate risk of bleeding subgroup, which is predominantly people undergoing orthopaedic surgery, the GDG felt this was appropriate as age was likely to be the main predictor of mortality. For the high risk group, which was predominantly cardiovascular surgery, the GDG noted that this group encompasses a wide range of conditions and surgeries, making it difficult to adjust mortality without making a number of assumptions, therefore the GDG agreed that for the base case, using age-adjusted mortality rates was acceptable. However, due to the uncertainty regarding the appropriateness of using unadjusted age-dependent mortality in the high risk group, a sensitivity analysis was conducted. See section M.2.4.6 for further detail.

M.2.3.6 Utilities

For economic evaluation, a specific measure of health-related quality of life (HRQoL) known as utility is required to calculate QALYs. Utilities indicate the preference for health states on a scale from 0 (death) to 1 (perfect health). The NICE reference case specifies that the preferred way for this to be assessed is by the EQ-5D instrument.

Utility up to 30 day

It was decided by the GDG that differences in short-term intervention-related and transfusion-related adverse events between interventions in the model would be captured by looking at differences in length of stay (see M.2.2) and that the impact on patients in terms of QALYs would be quantified by attributing a utility (quality of life) decrement to time spent in hospital.

A systematic search using a quality of life filter and transfusion terms (see Appendix G) identified no studies with utility measures relating to receiving an allogeneic transfusion that were relevant to our model.

We reviewed the cost-utility analyses ordered in our health economic systematic search for this guideline to identify any utility values that have been used in other analyses in this area. These analyses have mostly focused on morbidity as a result of long-term transfusion-related infections[176,451,460], which we are not incorporating in this model as outlined in section M.2.2. Two studies were however identified with potentially useful information which are discussed below.[193,710]

One study by Thomas 2001 reported EQ-5D values as part of a randomised controlled trial of cell salvage in total knee replacement surgery where patients either received or didn't receive post-operative cell salvage.[710] Although the trial found improvements in EQ-5D over time, no differences between the two groups were observed at baseline and at 1 week, 1 month and 3 month follow up. In addition, the trial reported no significant difference in length of stay between groups. The author of the paper, a GDG member, explained that the improvements in EQ-5D observed are likely to be primarily due to the alleviation of pain experienced by a patient

receiving this type of surgery and that the impact of the interventions on well-being was likely to be minimal. This study was considered by the GDG and they agreed that this data was not helpful in informing the model. Of note this study was not included in the clinical review of evidence as it was published prior to 2003.

One economic analysis by Davies 2006, used EQ-5D utility values from the 1996 Health Survey for England for health states associated with having a limiting and non-limiting long-standing illness for the period of time from surgery to hospital discharge, and hospital discharge to 30 days, respectively.[193] This approach was taken as the authors noted that when they compared these values with published utility values for transfusion-related adverse events (for example: hepatitis A, B and C and HIV), the latter were either equivalent or higher, thus suggesting that transfusion-related adverse events are likely to have a minimal impact on HRQoL compared with the impact of the underlying reason for surgery, the short-term disutility associated with surgery and hospital admission. After 30 days, for those who experienced no adverse events, they used the EQ-5D value from the 1996 Health Survey for England for health states associated with no long-standing illness. In this study, they did model long-term adverse events (for example: stroke, vCJD, Hepatitis A, B or C, HIV) and for those they either used the EQ-5D value for no long-standing illness or long-standing non-limiting illness dependent on the condition and for stroke they used a condition-specific published EQ-5D value.

Additional ad-hoc searches were also conducted including reviewing the Cost-Effectiveness Analysis registry catalogue of preference scores and two PubMed searches using the following terms: search terms: 'surgery AND Length of stay AND EQ-5D'; 'surgery AND hospitalization AND EQ-5D', which yielded 39 and 57 studies respectively, none of which provided utility values that were relevant for the model.

For our analysis, it was agreed that the utility decrement for being in hospital would be taken from the difference in utility between a limiting long-standing illness (surgery to hospital discharge) and a non-limiting long-standing illness (hospital discharge to 30 days) as done in the published analysis by Davies et al.[193] This utility decrement would be applied to time spent in hospital, so for the standard treatment that would be the mean length of stay and for the other interventions it would be applied to the mean difference in length of stay. This allowed us to estimate the incremental QALYs compared to standard treatment. For those who died within 30 days in the model, it was assumed that the utility decrement was maintained until they died at 15 days. Table 14 summarises the mean utilities associated with long-standing illness from the Health Survey for England 2012[599] and the utility decrement used in the economic model.

Table 14: EQ-5D values associated with long-standing illness

Health state	Mean	SE
Limiting long-standing illness	0.651	0.007
Non-limiting long-standing illness	0.898	0.003
Utility decrement between limiting and non-limiting long-standing illness	*-0.247*	*0.008*

Source: Health Survey for England 2012[599]

Utilities after 30 days

Beyond 30-days we applied the mean EQ-5D value for the adult general population to all people alive in the model. This utility value was taken from the Health Survey for England 2012[599] and is summarised in Table 15.

Table 15: Mean general population EQ-5D value

Population	Mean	SE
Adult general population, England	0.858	0.003

Source: Health Survey for England 2012[599]

Utility sensitivity analyses

A sensitivity analysis was conducted to explore the impact of excluding length of stay from the analysis which results in excluding the utility decrement linked to length of stay. In addition, a further sensitivity analysis was conducted to explore the impact of varying the utility decrement for being in hospital. See section M.2.4.5 for details of the sensitivity analyses undertaken.

M.2.3.7 Resource use and costs

M.2.3.7.1 Tranexamic acid

The total cost of TXA per patient applied in the model was £19.02 for the high risk group and £8.60 for the moderate group. The breakdown of resource use, costs and assumptions is summarised in Table 16. Further detail is outlined below.

Table 16: TXA resource use and cost

Item	Resource use	Unit cost	Cost	Assumptions, sources
TXA resource use and unit cost for high risk of bleeding subgroup				
TXA (500 mg/5 ml ampoules)	12	£1.43	£17.21	Total dose 6000 mg, slow IV injection followed by continuous IV infusion; dose source: BNF 67[359]; cost source eMIT July 2014.[164]
Saline (litres)	1	£0.70	£0.70	NICE clinical guideline CG174.[520]
Administration set	1	£1.11	£1.11	Sendal administration set 160 cm with built in 3 way tap and 120 cm extension line (FKA397), NHS Supply Chain Catalogue April 2014.[532]
Total cost			£19.02	
TXA resource use and unit cost for moderate risk of bleeding subgroup				
TXA (500 mg/5 ml ampoules)	6	£1.43	£8.60	Total dose 3000 mg slow IV injection; dose source: BNF 67[359]; cost source eMIT July 2014.[164]
Total cost			£8.60	

Abbreviations: BNF = British National Formulary; eMIT = Electronic Market Information Tool; PSSRU = Personal Social Services Research Unit; TXA = tranexamic acid.

In current clinical practice the dose and route of administration (oral, intravenous and topical) of TXA varies widely and this was reflected in the studies identified in the clinical review. For the

model, the GDG agreed to cost TXA based on intravenous (IV) administration, as this is the route most commonly reported in the literature. Furthermore, the GDG noted that the dose would be similar for IV and topical administration. The dose used for oral TXA may be different; however this route is less frequently used for moderate and high risk of bleeding surgery.

A number of different doses were considered by the GDG, including doses reported in the BNF, RCTs, and doses they or their colleagues have used in clinical practice. The GDG agreed to base the dosage for the high risk group, which is mostly cardiac surgery, on the dose listed in the BNF for slow IV injection followed by contiunous IV infusion.[359] The listed dose for slow IV injection (general fibrinolysis) is 1 g every 6-8 hours and for continuous IV infusion (local fibrinolysis) it is 25-50 mg/kg over 24 hours. The total dose of TXA using this regimen was 5.6 g, assuming the average patient weight was 70 kg. As one ampoule of TXA contains 500 mg/5 mL, 12 ampoules (6 g) were costed. A total dose of 6 g is supported by the regimen outlined in the BART study[244] which is often followed in clinical practice and supported by GDG expert opinion.

For the moderate risk group, which is predominently orthopaedic surgery, the GDG expert opinion was that TXA would be administered as a slow IV injection (local fibrinolysis) at the start of surgery as opposed to continuous infusion. The dose was therefore based on the total dose for this route of administration (3 g) listed in the BNF[359] and supported by GDG expert opinion.

The unit cost of TXA was obtained from the Electronic Market Information Tool July 2014.[164] This source was used as it is the preferred source for generic drugs prescribed in secondary care.

In the high risk group, the cost of an adminstration set and 1 litre of saline was included for the IV infusion of TXA. The unit cost were obtained from NHS Supply Chain Catalogue (April 2014) and NICE clinical guideline CG174, respectively.[520]

No staff time was included for the administration of TXA. The GDG noted the anaesthetist, who would be present for the duration of surgery, would administer TXA and this would not require any additional time when compared to those not receiving TXA.

M.2.3.7.2 ICS

The cost of ICS applied in the model was £294.64 per patient. The breakdown of resource use, costs and assumptions is outlined below and summarised in Table 17. Note that ICS was only included as an intervention in the high risk group.

Table 17: Intra-operative cell salvage resource use and cost

Item	Resource use	Unit cost	Cost	Assumptions, source
ICS resource use and cost per case				
Staff time (hours)	3.5	£41.00	£143.50	Based on 3 hour surgery duration and 30 minutes clear up time. Unit cost for day ward nurse, Band 5, PSSRU Unit cost 2012/2013 (costs include qualifications).[183]
Cell salvage collection kit	1	£67.42	£67.42	Disposable set for Dideco Electa 745e/125 with 125 ml bowl (or 55 ml, 175 ml, 225 ml - all same price), NHS Supply Chain Catalogue April 2014.[532]
Cell salvage re-infusion	1	£44.73	£44.73	Disposable wash set for Dideco Electa 740e/125 with 125 ml bowl (or 55 ml, 175 ml, 225 ml - all same price),

Item	Resource use	Unit cost	Cost	Assumptions, source
kit				NHS Supply Chain Catalogue April 2014.[532]
40 micron goccia filter	1	£7.60	£7.60	40 micron goccia filter for Xtra, NHS Supply Chain Catalogue April 2014.[532]
Heparin sodium (30,000 iu)	2	£10.60	£21.20	Based on cost of 1mL amp of heparin sodium 25,000 iu/ml and 1 ml amp of heparin sodium 5,000 iu/ml, BNF 67.[359]
Saline (litres)	6	£0.70	£4.20	NICE clinical guideline CG174.[520]
Running costs	1	£6.00	£6.00	Crotty 2006, 2006 £ values inflated to 2012/2013 £.[179,551]
Total cost			**£294.64**	

Abbreviations: BNF = British National Formulary; hrs = hours; iu = international units; ICS = intra-operative cell salvage; PSSRU = Personal Social Services Research Unit.

Staffing

The GDG noted the amount of dedicated staff time varies depending on the amount of blood salvaged. In high risk of bleeding surgical cases, the cell salvage operator would be an additional member of staff to the standard theatre staff and would be required for the duration of surgery time and then an additional 30 minutes to clear up at the end of surgery. This time will include any observations required whilst salvaged blood is being transfused. Although ICS was not included as a comparator for the moderate risk of bleeding group, the GDG noted that in these cases the cell salvage operator is likely to be an existing member of the theatre staff and would have other responsibilities other than operating the cell salvage equipment. The majority of the clinical data in the high risk of bleeding subgroup was in people receiving CABG surgery. Based on GDG experience, the average duration of CABG surgery was assumed to be three hours and this was used in the model. Based on GDG consensus about current practice, it was assumed that this member of staff would be equivalent to a band 5 staff nurse.

Staff unit costs were taken from the PSSRU unit costs 2013.[183]

A trained cell salvage operator is required for ICS. The GDG noted that training can be provided in-house as part of usual training (for examples as e-learning), or provided by the manufacturers of cell salvage equipment. A cell salvage costing study by Crotty 2006 noted that training is available from a number of hospital trusts, including Nottingham University Hospitals NHS Trust.[179] The 2014 cost of Nottingham University Hospitals NHS Trust's 'Advanced Autotransfusion Course' is £95 per person.[727] The GDG discussed that even if there was an additional cost to the NHS for training, when this cost is distributed across each case of cell salvage, the additional cost would be minimal, and therefore it was agreed to not include the cost of training in the analysis.

Equipment and consumables

For ICS a cell salvage machine is needed. Cell salvage machines are either purchased outright or leased with costs covered via consumable charges. The consumables are more expensive if the equipment is procured on lease than if purchased. As the cost of the equipment is not available from national published cost sources, it was assumed that the equipment in the economic

analysis was on lease and only the consumable charges and running costs of the equipment were incurred.

The consumable for ICS is a kit that is made up of two parts. The first part of the kit which allows for the collection of blood is required for all patients. If sufficient blood is collected (approximately one unit of blood) then a second part of the kit is used which allows for the washing and re-infusion of the salvaged blood. In the high risk of bleeding subgroup, it was assumed that all patients would require both parts of the kit (collection and re-infusion). A number of different ICS machines and corresponding kits are available. The cost of the kit was based on the disposable set and disposable wash set for the Dideco Electa 740e/55 with 55 ml bowl as this was the only cost for an ICS kit published in the NHS Supply Chain Catalogue (April 2014).[532] The cost of a 40 micron goccia filter was added to the cost as this is also required.

Of note, the lease agreements often assume a minimum usage of the equipment and therefore a minimum order of consumables. The GDG highlighted that this minimum usage may be an issue for a district general hospital which may have a low expected usage of ICS. However, no adjustment of the consumable costs was feasible as no published information was identified on what this minimum usage may be.

The running costs of the equipment was expected to be minimal as the maintenance of the equipment would be included in the lease agreement. The running costs were based on costs estimated in a UK costing study of cell salvage, this cost was inflated from 2006 GBP to 2012/2013 GBP using 2013 purchasing power parities.[179,551]

Drugs

Typically saline and an anticoagulant (for example heparin) would be administered to people undergoing ICS. The saline is required for collection and washing of the blood and the heparin to stop the collected blood clotting. The volume and amount used would depend on the volume of blood salvaged. This information was not available from the clinical review of the evidence, therefore the GDG recommended the following assumptions for the base case analysis: 2 litres of saline and 60,000 iu heparin (30,000 iu per litre of saline) for collection and then a further 4 litres of saline for washing. The cost of saline (0.9% Sodium Chloride) was taken from the NICE clinical guideline CG174, which obtained costs from the Department of Health Commercial Medicines Unit (CMU) in 2012.[520] The unit cost of heparin was unavailable from the drug tariff, NICE's prefered source for unit costs and so was obtained from the British National Formulary 67.[359]

M.2.3.7.3 PCS

The cost of PCS applied in the model was £88.42 per patient. The breakdown of resource use, costs and assumptions is outlined below and summarised in Table 18.

Table 18: Post-operative cell salvage resource use and cost

Item	Resource use	Unit cost	Cost	Assumptions, source
PCS resource use and cost per case				
Staff time (hrs)	0.67	£41.00	£27.33	Based on 'ward time' for transfusion of RBC (see Table 20). Unit cost for day ward nurse, Band 5, PSSRU Unit cost 2012/2013 (costs include qualifications).[183]

Item	Resource use	Unit cost	Cost	Assumptions, source
Average cost of PCS kit	1	£61.09	£61.09	Average of PCS kits (manufacturers: Astra Tech Sangvia, Bellovac ABT, CellTrans, HandyVac ATS, Redax, Stryker), NHS Supply Chain Catalogue April 2014.[532]
Total cost			**£88.42**	

Abbreviations: PSSRU = Personal Social Services Research Unit; PCS = post-operative cell salvage.

Of note, for PCS, both washed and unwashed PCS techniques exist. For unwashed PCS, a maximum of 1 litre can be salvaged and there is no requirement for equipment, only a disposable kit is used. For washed PCS, there is no limit on the amount of blood salvage and a machine is used in combination with a disposable kit. For the moderate risk group, all PCS trials identified in the clinical review used unwashed PCS and for the high risk group, the studies either used washed or unwashed PCS (50:50 split). The studies that used washed PCS reported volumes of salvaged blood below 1 litre. As a result, the GDG assumed in the model that unwashed PCS was used for both risk groups.

Staffing

For unwashed PCS, the kit is set up by the surgical team in the operating theatre. It was assumed that no additional staff time was required for this set up as the surgical team would be placing drains instead of the kit if PCS was not being done. Once a patient is taken to the ward and the bag is filled, a nurse is required to invert the bag and open the filter and line to start the transfusion. In addition, as with allogeneic transfusions, the nurse would be required to carry out regular observations of the patient during the transfusion. The GDG assumed that the time required for these steps would be equivalent to the time spent on the ward when transfusing a unit of allogeneic blood. The staff time associated with transfusing allogeneic blood has been detailed in section M.2.3.7.5 and Table 20, based on these estimations it takes 40 minutes of band 5 staff nurse time.

Staff unit costs were taken from the PSSRU unit costs 2013.[183]

Equipment and consumables

For unwashed PCS, no machine is required, only a kit. A number of different kits are available from different manufacturers. The cost of the kit is based on the average cost of the kits listed in the NHS Supply Chain Catalogue (April 2014).[532]

Drugs

No drugs are required for PCS.

M.2.3.7.4 ICS+PCS

The cost of ICS and PCS combined applied in the model was £350.33 per patient. The breakdown of resource use, costs and assumptions is outlined below and summarised in Table 19. Of note, the combination of ICS+PCS was only included as an intervention in the moderate risk group.

Staffing

For ICS and PCS combined, the GDG noted that when used in surgeries with moderate risk of bleeding, the cell salvage operator is likely to be an existing member of the theatre staff and would have other responsibilities other than operating the cell salvage equipment and so no additional staff time during surgery would be required. As with unwashed PCS, it was assumed that 40 minutes of band 5 staff nurse time would be required on the ward to start the transfusion and for patient observations.

Staff unit costs were taken from the PSSRU unit costs 2013.[183]

Equipment and consumables

As with ICS, a cell salvage machine is required for the combination of ICS and PCS. It was assumed that the equipment used was the OrthoPAT, which is an integrated system allowing both types of cell salvage to be undertaken. The majority of trials identified in the moderate risk clinical evidence review used this system. The cost of the kit was based on the integrated processing set for OrthoPAT (NHS Supply Chain Catalogue, April 2014).[532] For the moderate risk group, in clinical practice, a proportion of patients may not bleed sufficiently to require ICS and PCS and so although the equipment will be set up, the full cost of the disposable kit may not be incurred. In the model, we have assumed that all patients assigned to ICS+PCS will have cell salvage as this is how the trials were conducted. Therefore the full cost of the disposables was included for all patients.

As with ICS the running costs were based on costs estimated in a UK costing study of cell salvage, this cost was inflated from 2006 GBP to 2012/2013 GBP using 2013 purchasing power parities.[179,551]

Drugs

For the combination of ICS and PCS, the same drugs as ICS are assumed to be required.

Table 19: Intra- and post-operative cell salvage combination resource use and cost

Item	Resource use	Unit cost	Cost	Assumptions, source
ICS+PCS resource use and cost per case				
Staff time (hours)	0.67	£41.00	£27.33	Based on 'ward time' for transfusion of RBC (see Table 20). Unit cost for day ward nurse, Band 5, PSSRU Unit cost 2012/2013 (costs include qualifications).[183]
OrthoPAT kit	1	£291.60	£291.60	Integrated processing set for OrthoPAT, NHS Supply Chain Catalogue April 2014.[532]
Heparin sodium	2	£10.60	£21.20	Based on cost of 1 ml amp of heparin sodium 25,000 iu/ml and 1 ml amp of heparin sodium 5,000

Item	Resource use	Unit cost	Cost	Assumptions, source
(30,000 iu)				iu/ml, BNF 67.[359]
Saline (litres)	6	£0.70	£4.20	NICE clinical guideline CG174.[520]
Running costs	1	£6.00	£6.00	Crotty 2006, 2006 £ values inflated to 2012/2013 £.[179,551]
Total cost			**£350.33**	

Abbreviations: BNF = British National Formulary; iu = international units; ICS= intra-operative cell salvage; PSSRU = Personal Social Services Research Unit; PCS = post-operative cell salvage.

M.2.3.7.5 Allogeneic blood transfusion

The cost of allogeneic transfusion applied in the model was £192.67 for the first unit transfused, and £167.31 per subsequent unit transfused. A cost of £22.02 per person was applied to those who were not transfused in the model; this cost covers the cost blood grouping and antibody screening which is required for all surgical patients. The breakdown of resource use, costs and assumptions is summarised in Table 20. Further detail is outlined below.

Five studies were identified in the systematic review of the health economics literature that provided detailed costing of allogeneic blood transfusion.[17,273,641,745,750] Only one of these studies, Agrawal 2006, provided disaggregated costs, allowing us to easily identify resource use for GDG validation and updating of costs with current published unit costs.[16] This was a study conducted in the haematology and oncology departments of two UK hospitals, one teaching and one district general hospital, using time and motion techniques. Resource use for both blood bank and ward procedures were assessed in this study.

Using the time estimates from Agrawal 2006[16], GDG expert opinion and unit costs from the PSSRU unit costs 2013[183] we were able to estimate staff costs for allogeneic blood transfusion. The GDG validated the staff time estimates with their current clinical practice. For the staff time on the ward, the GDG reduced the estimates from Agrawal 2006 as they judged that these were an overestimate compared to current practice. The GDG estimated, based on their hospital practice, that the staff time on the ward would be 40 minutes (rather than 76 minutes), this would include 15 minutes for blood collection and patient administration and 25 minutes for patient observations (5 observations lasting 5 minutes each). For disposables required in the blood bank and on the ward, the resource use and unit costs were taken directly from Agrawal 2006; costs were inflated from 2004 GBP to 2012/2013 GBP using 2013 purchasing power parities.[179,551]

The GDG agreed that for simplicity, the cost of transfusion of red blood cells (RBC) would be used in the model. RBC would invariably make up the largest proportion of the blood products transfused. Furthermore, the GDG felt that adjusting the cost of transfusion to reflect the different proportions of different blood products transfused would be complex and unlikely to result in a significant cost difference. The unit cost of RBC was taken from NHS Blood and Transfusion list price for 2014/2015.[531] Costs were split to reflect the cost of transfusing the first unit and the cost of transfusing subsequent units. Table 20 provides a detailed summary of the resource use, unit costs and assumptions made to calculate the total cost of transfusing allogeneic blood.

The following approach was taken to calculate the total cost of allogeneic transfusion for each intervention:

If mean volume transfused for intervention X was less than or equal to 1 unit:

$$\text{CostTransfusionX} = \text{VolumeTransfusedX} \times \text{CostFirstUnit}$$

If the mean volume transfused for intervention X was greater than 1 unit:

$$\text{CostTransfusionX} = \text{CostFirstUnit} + ((\text{VolumeTransfusedX} - 1) \times \text{CostSubsequentUnit})$$

The GDG noted that all surgical patients at moderate or high risk of bleeding would require blood grouping and antibody screening, even if they do not end up requiring an allogeneic blood transfusion. The cost of these procedures is detailed in Table 21. This cost is applied once to people in the model that do not receive an allogeneic transfusion. Note that for those that are transfused this cost is incorporated into the cost of the first unit of blood.

Table 20: Allogeneic blood transfusion

Component	Mean time (min)	Staff cost per min (£)	Mean cost 1st unit (£)	Mean cost subsequent unit (£)	Assumptions & sources
Staff time (blood bank)					
Clerical procedures	10.63	£0.78	£8.33	N/A	Staff time from Agrawal 2006.[17] Staff unit cost for blood bank from PSSRU 2013 ('science technical & therapeutic staff' other, qualified, band 6/7, £47/hour) except collection and delivery taken from PSSRU 2013 ('administration and estates staff', band 3, £23/hour).[183] Costs assumed to be incurred once only and so cost not included for subsequent units with the exception of computer issue on the basis of one unit is issued at a time. Time for computer issue taken from teaching hospital which used computer issue.
Blood grouping and antibody screening (incl. antibody identification where necessary)	10.72	£0.78	£8.39	N/A	
Computer issue (incl. blood issue)	5.38	£0.78	£4.22	£4.22	
Blood collection	5.00	£0.38	£1.92	£1.92	
Blood ordering	1.02	£0.78	£0.80	£0.80	
Blood delivery	10.00	£0.38	£3.83	£3.83	
Staff time (ward)					
Collection and patient administration	15.00	£0.68	£10.25	£10.25	Staff time based on GDG expert opinion. Staff unit cost from PSSRU 2013 ('day or 24hr ward nurse', including qualifications, band 5, £41/hour).[183]
Observations	25.00	£0.68	£17.08	£17.08	
Disposables (blood bank)					
Blood bank disposables	N/A	N/A	£3.22	£3.22	From Agrawal 2006 (teaching hospital). Costs were for two units and so have been divided in two. 2004 £ values inflated to 2012-

Component	Mean time (min)	Staff cost per min (£)	Mean cost 1st unit (£)	Mean cost subsequent unit (£)	Assumptions & sources
					2013 £.[17 551]
Disposables (ward)					
Patient assessment	N/A	N/A	£2.55	N/A	From Agrawal 2006 (district general hospital). Costs assumed to be incurred once only and so cost not included for subsequent units. 2004 £ values inflated to 2012-2013 £.[17 551]
Transfusion preparation	N/A	N/A	£1.22	N/A	
Transfusion for 1st unit	N/A	N/A	£4.60	N/A	
Transfusion for subsequent units	N/A	N/A	N/A	£0.24	From Agrawal 2006. Cost only incurred for subsequent units. 2004 £ values inflated to 2012-2013 £.[17 551]
Blood product					
RBC per unit	N/A	N/A	£121.85	£121.85	From NHSBT 2014/2015. Assumed all transfusions in model are RBC.[531]
Wastage per unit	N/A	N/A	£1.83	£1.83	Wastage assumed to be equal to 1.5% of the cost of a unit of RBC, based on reported rate from Agrawal 2006 (district general hospital).[17]
Other costs					
Blood bank machines & IT per unit	N/A	N/A	£2.08	£2.08	From Agrawal 2006. Costs were for two units and so have been divided in two. 2004 £ values inflated to 2012-2013 £.[17 551]
Total cost (1st unit)			**£192.17**		
Total cost (subsequent unit)				**£167.31**	

Abbreviations: hrs = hours; NHSBT = National Health Service Blood and Transplant; PSSRU = Personal Social Services Research Unit.

Table 21: People not transfused in model

Component	Mean time (min)	Staff cost per min (£)	Mean cost (£)	Assumptions & sources
Staff time (blood bank)				
Clerical procedures	10.63	£0.78	£8.33	Staff time from Agrawal 2006.[17] Staff unit cost for blood bank from PSSRU 2013 ('science technical & therapeutic staff' other, qualified, band 6/7, £47/hr)[183]
Blood grouping and antibody screening (incl. antibody identification where necessary)	10.72	£0.78	£8.39	
Disposables (blood bank)				
Blood bank disposables			£3.22	From Agrawal 2006 (teaching hospital). Costs were for two units and so have been divided in two. 2004 £ values inflated to

Component	Mean time (min)	Staff cost per min (£)	Mean cost (£)	Assumptions & sources
				2012-2013 £.[17 551]
Other costs				
Blood bank machines & IT			£2.08	From Agrawal 2006. Costs were for two units and so have been divided in two. 2004 £ values inflated to 2012-2013 £.[17 551]
Total cost			**£22.02**	

Abbreviations: hrs = hours; PSSRU = Personal Social Services Research Unit.

M.2.3.7.6 Length of hospital stay

The incremental cost of length of stay was incorporated into the model using the published 2012-2013 NHS reference costs for excess bed days.[202] For the high risk of bleeding subgroup, the weighted unit cost for a bed day was calculated from NHS reference costs using data for elective inpatient excess bed days for CABG (currency codes: EA14A, EA14B, EA14C, EA14D, EA16A, EA16B, EA16C, EA16D, EA51A, EA51B, EA51C, EA51D). For the moderate risk of bleeding subgroup, the weighted unit cost for a bed day was calculated from NHS reference costs using data for elective inpatient excess bed days for both trauma and non-trauma hip and knee procedures. These are currency codes: HA11A to HA29Z for trauma and HB11A to HB29Z for non-trauma (excluding codes: HB15F, HB15G, HB25G, HB25H and HB25J which relate to patients 18 years and under). The GDG considered these surgeries reflective of the majority of surgeries reported in the clinical evidence for each risk group.

The costs used for length of stay in the model for the high and moderate risk of bleeding subgroups are listed Table 22. In the model, the incremental cost for length of stay was calculated by multiplying the unit cost for an excess bed day by the mean difference in length of stay for each intervention. This would result in a cost saving if the intervention reduced length of stay or an additional cost if it increased length of stay compared to baseline.

Table 22: Excess bed day unit cost

Item	Cost	Assumptions, source
Cost of additional length of stay in high risk of bleeding subgroup	£372.21	Weighted average of elective inpatient excess bed days for CABG (currency codes: EA14A, EA14B, EA14C, EA14D, EA16A, EA16B, EA16C, EA16D, EA51A, EA51B, EA51C, EA51D). 2012-2013 NHS reference costs.[202]
Cost of additional length of stay in moderate risk of bleeding subgroup	£317.66	Weighted average of elective inpatient excess bed days for both trauma and non-trauma hip and knee procedures [currency codes HA11A to HA29Z for trauma and HB11A to HB29Z for non-trauma (excluding codes: HB15F, HB15G, HB25G, HB25H and HB25J which relate to patients 18 years and under)]. 2012-2013 NHS reference costs.[202]

A sensitivity analysis was conducted to explore the impact of excluding length of stay from the analysis.

M.2.4 Sensitivity analyses

M.2.4.1 Vary baseline event rates (SA1, SA2)

Some GDG members highlighted concerns with regards to the baseline event rates from the trials as they felt these were high and did not reflect current practice. The GDG discussed the difficulty in ascertaining the true current transfusion rate due to variation in transfusion protocols across hospitals and differences in mean haemoglobin levels in the patient population. A sensitivity analysis was undertaken where the baseline events of proportion transfused and number of units were reduced by 50%, this was done for both subgroups. This was done in a first sensitivity analysis by only reducing the proportion transfused and keeping all else constant. A second analysis was conducted where both the proportion and number of units transfused were reduced. Note, for the number of units, the proportion reduction applied to both the baseline mean and the treatment effect. The aim of these sensitivity analyses is to allow the GDG to understand whether or not the cost-effectiveness of the interventions changes if the baseline events are lower.

M.2.4.2 Baseline mortality rate (SA3)

The baseline 30-day mortality rate varied widely between the studies used to calculate the mean 30-day mortality rate. This may reflect the different surgery types and practices within each study. As a result, a sensitivity analysis was conducted for each risk group, were the lowest and then the highest baseline 30-day mortality rate was used. The aim of these sensitivity analyses is to allow the GDG to understand whether or not the cost-effectiveness of the interventions changes if the baseline events are lower or higher. The range of baseline mortality rates used in these sensitivity analyses are in summarised in Table 23.

Table 23: Baseline 30-day mortality range

Relative risk 30-day mortality	Range	Source
High risk	0% - 65.22%	KATOH1997, BOWLEY2006
Moderate risk	0% - 2.86%	HORSTMANN2014A, SADEGHI2007

M.2.4.3 Exclude length of stay from analysis (cost and utilities excluded) (SA4)

Due to the uncertainty regarding the length of stay data, a sensitivity analysis was conducted where length of stay was excluded from the economic model. In this analysis neither the impact of length of stay on costs or quality of life would be included.

M.2.4.4 Use proportions for PCS LOS high risk group (SA5)

For the post-operative cell salvage in the high risk group, only one study informed the length of stay outcome. In this study, the baseline length of stay was much longer (16.45 days) than the overall baseline length of stay estimated from all the RCTs (average 9.75 days). A sensitivity analysis was conducted where the mean difference of post-operative cell salvage compared to standard treatment was estimated by calculating the proportion reduction in length of stay as opposed to the mean difference to account for this high baseline. The mean difference used for PCS in this sensitivity analysis was -4.23 days.

M.2.4.5 Utility values (SA6, SA7)

The utility decrement used in the base case was taken from the difference in utility in people with a limiting long-standing illness and a non-limiting long-standing illness and is assumed to approximate the difference between being and not being in hospital. Due to the uncertainty of this assumption, a sensitivity analysis was conducted where this utility decrement applied for being in hospital was increased and decreased by 50%.

M.2.4.6 Adjust mortality and quality of life post 30 days for high risk subgroup (SA8, SA9, SA23, SA24)

Due to the uncertainty regarding the appropriateness of using age-dependent mortality in the high risk group, a sensitivity analysis was conducted, where this group were attributed a higher mortality rate to reflect the increased mortality in this population. This higher mortality rate was implemented by applying a standardised mortality ratios (all-cause mortality) for myocardial infarction and stroke respectively to the age-dependent general population mortality rates (Table 24).The standardised mortality ratio was taken from the Hypertension NICE clinical guideline (CG127) which in turn identified standardised mortality ratio from the literature.[519]

Table 24: Standardised mortality ratio

Condition	Data (95% CI)	Source
MI	2.68 (2.48, 2.91)	Average SMR for men and women. All-cause mortality after first non-fatal MI compared to that expected in general population. Danish population.[97]
Stroke	2.72 (2.59, 2.85)	Average SMRs for men and women. All-cause mortality after first non-fatal stroke compared to that expected in general population. Danish population.[96]

In addition, quality of life weights (EQ-5D) for MI and stroke were applied multiplicatively to the general population weights after 30 days for this subgroup. The values used (Table 25) were from the Hypertension NICE clinical guideline (CG127) which in turn identified them from a comprehensive literature search.[519]

Table 25: Quality of life (EQ-5D) after 30 days high risk subgroup

Condition	Data (SE)	Source
MI	0.760 (0.018)	Goodacre 2004[281]
Stroke	0.629 (0.04)	Tengs 2003[709]

Two additional sensitivity analyses were conducted following these which combined the adjustment of mortality and quality of life for MI and stroke with SA5. SA5 was the sensitivity analysis where the mean difference of post-operative cell salvage compared to standard treatment was estimated by calculating the proportion reduction in length of stay as opposed to the mean difference to account for this high baseline. The mean difference used for PCS in this sensitivity analysis was -4.23 days. This was done as the GDG wanted to explore these results further.

M.2.4.7 Relative risk - mortality at 30 days (SA10, SA11)

A sensitivity analysis was conducted to explore uncertainty around 30-day mortality, where 30-day mortality data from the pairwise meta-analyses was used for all interventions in both the moderate and high risk subgroup models. The data used in this sensitivity analysis is summarised in Table 26. No direct evidence was available for TXA + ICS compared to standard care in the high risk group, therefore two indirect estimates were calculated from evidence comparing this combination to ICS and TXA respectively. No data was available for PCS compared to standard treatment for the moderate risk. Due to the absence of evidence, it was assumed that for this comparator and subgroup, there was no differential impact on mortality compared to standard treatment.

Table 26: Relative risk 30-day mortality

Relative risk 30-day mortality	Data (95% CI)	Source
High risk	TXA = 0.52 (0.31, 0.87) ICS = 0.65 (0.27, 1.59) PCS = 3 (0.13, 70.30) *TXA +ICS = 0.68 (0.04, 11.91)* *TXA + ICS = 4.01 (0.21, 75.06)*	Pairwise MA as part of clinical review. For TXA + ICS, no direct evidence available, indirect estimate calculated from TXA ICS vs. ICS and ICS vs. ST evidence and ICS+TXA vs. TXA and TXA vs. ST evidence (2 sensitivity analyses).
Moderate risk	TXA = 0.73 (0.15, 3.66) PCS = 1 ICS+PCS = 3.32 (0.14, 79.77)	Pairwise MA as part of clinical review. For PCS, assumption RR = 1 as no data available (i.e. no mortality effect vs. standard treatment)

Abbreviations: CI = confidence intervals; ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid

M.2.4.8 Mortality at 30days – ICS+TXA (SA12)

The mortality benefit was only significant for TXA versus standard treatment and for all other interventions, including ICS+TXA we assumed in the base case no difference in mortality compared to standard treatment. However, it was deemed plausible that the benefit of TXA would not be diminished by adding ICS. Therefore, for ICS+TXA, a further sensitivity analysis was conducted where we assumed the same mortality benefit of TXA for the combination of ICS+TXA.

M.2.4.9 Intervention costs (SA13, SA14, SA15)

The GDG were interested in exploring the effect of varying the cost of the disposable kits for cell salvage on the results. A separate sensitivity analysis was conducted for each cell salvage disposable type (ICS, PCS and the ICS+PCS combination). In each sensitivity analysis the cost of the disposable kit was varied in 10% increments (between 10% and 100%), keeping all else constant.

M.2.4.10 Number transfused PCS high risk (SA16)

The relative risks generated from the NMA and pairwise meta-analysis for the proportion transfused for PCS versus standard treatment were very different. A possible reason for this is

that the NMA uses the baseline transfusion rate from all studies in the network, not just the PCS studies.

- Pairwise: 0.60 (0.45, 0.81)
- NMA: 0.3596 (0.1268, 0.8032)

Due to the uncertainty with the NMA estimate, the GDG agreed to conduct a sensitivity analysis where the pairwise estimate was used instead.

M.2.4.11 Discount rate (SA17)

A sensitivity analysis using a discount rate of 1.5% for health benefits was conducted.

M.2.4.12 Exclude PCS from high risk analysis (SA18)

The GDG acknowledged that patients who have extensive bleeding post-operatively may require reoperation to stem the bleeding rather than PCS. When reviewing the clinical evidence for PCS in the high risk subgroup, the GDG noted that studies of PCS were in patients having first time CABG where post-operative bleeding may not be extensive and hence this evidence may not be applicable to all high risk surgeries. Furthermore, one study which had a 100% transfusion rate in the control arm, contributed significantly to the pooled effect size from the meta-analysis – the GDG agreed this did not reflect current practice. Due to the uncertainty of the applicability of the evidence, the GDG wanted to see which intervention was most cost-effective when PCS was excluded from the high risk subgroup analysis.

M.2.4.13 Combination sensitivity analyses (SA19, SA20)

A few additional sensitivity analyses were conducted for the high risk group to bias in favour of ICS+TXA to see if the results altered. In the first, a combination of SA4 and SA12 was conducted, where length of stay was excluded from the analysis and the mortality relative risk for TXA at 30 days is used for ICS+TXA as well. In a second analysis, as well as SA4 and SA12, the cost of the disposable kit for ICS (and ICS+TXA) is reduced by 90%.

M.2.4.14 Blood transfusion cost (SA21, SA22)

To explore the sensitivity of the results to the cost of transfusion, the cost of transfusion was reduced and increased by 50%.

M.2.5 Exploratory threshold analyses

A series of exploratory threshold analyses were conducted. Details of these analyses are explained in the results section.

M.2.6 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation.

The decision tree was used to estimate outcomes over the 30 days post-surgery. At the end of this time point, patients are either dead or alive. Following this, a life table was used to extrapolate results to a lifetime perspective.

Total QALYs for the cohort were calculated by summing the QALYs for the cohort up to 30 days and the QALYs for the cohort after 30 days. Up to 30 days, QALYs for those receiving standard treatment and who survive are calculated as described in the equation below:

$$\boldsymbol{QALYs < 30\ days, Alive\ ST =}$$

$$\boldsymbol{n^{alive} \times [(LoS \times uH) + ((LY30d - LoS) \times uGP)]}$$

Where:
LoS=length of stay
$LY30d$=30 days converted to years
n^{alive}=number alive at 30 days
ST=standard treatment
uGP=utility of general population
uH=utility general population + utility decrement

For all other interventions, the QALYs up to 30 days for those who are alive are calculated using the following equation:

$$\boldsymbol{QALYs\ < 30\ days, Alive\ Other =}$$

$$\boldsymbol{n^{alive} \times [(LoS \times uH) + (QALYs < 30 days\ Alive\ ST)]}$$

Where:
LoS=length of stay
n^{alive}=number alive at 30 days
ST=standard treatment
uH =utility general population + utility decrement

Finally, the QALYs up to 30 days for those who die are calculated as follows for all interventions in the model:

$$\boldsymbol{QALYs\ < 30\ dead = n^{dead} \times LY15d \times (uGP + uH)}$$

Where:
$LY15d$=15 days converted to years
n^{dead}=number dead at 30 days
uGP=utility of general population
uH=utility general population + utility decrement

After 30 days, QALYs for the cohort were calculated by multiplying the number of patients alive at 30 days by the estimated QALYs per person. This was estimated from the life table weighted by the post-30 day utility value. A half-cycle correction was applied, and QALYs were discounted to reflect time preference (discount rate 3.5% per year).

Life expectancy (life years) per person was estimated using the life tables and depended on the age of the cohort. The life table Life years for the cohort were computed each year (cycle). A half-cycle correction was applied. Life years were then discounted to reflect time preference (discount rate 3.5%). Life years during the first year (cycle) were not discounted. The total discounted life years were the sum of the discounted life years per cycle. To calculate undiscounted and discounted QALYs, total undiscounted and discounted life years were weighted by a utility value.

All costs were incurred within the first year and therefore were not discounted.

Discount formula:

$$\boldsymbol{Discounted\ total = \frac{Total}{(1+r)^n}}$$

Where:
r=discount rate per annum
n=time (years)

In the deterministic and probabilistic analyses, the total number of QALYs and costs accrued was recorded. The total cost and QALYs accrued by the cohort was divided by the number of patients in the cohort to calculate the average cost per patient and QALY per patient for each comparator in the analysis.

The model was run separately for each subgroup – high risk and moderate risk of bleeding.

Computations associated with the NMA

To calculate relative treatment effect on proportion transfused, an NMA was conducted in WinBUGS (See M.2). The aim of the NMA was to calculate intervention specific log odds ratios for the proportion transfused, which can be combined with the baseline odds to produce absolute probabilities on the natural scale as follows:

$$\widetilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$ And: $$\boldsymbol{p} = \frac{\boldsymbol{e}^{\tilde{\theta}}}{\mathbf{1} + \boldsymbol{e}^{\tilde{\theta}}}$$	Where: $\widetilde{\mathrm{BO}}$=baseline odds $\tilde{\theta}$=treatment specific odds $\widetilde{\mathrm{OR}}$= treatment specific log odds ratio p=absolute probability

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensure that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

Note the baseline probability transfused was transformed to baseline log odds ratio using the following formula:

$$\widetilde{\boldsymbol{BO}} = \boldsymbol{Ln}\left(\frac{\boldsymbol{p}}{(\mathbf{1}-\boldsymbol{p})}\right)$$	Where: $\widetilde{\mathrm{BO}}$=baseline log odds ratio p=absolute probability

The Cholesky decomposition was used to preserve the correlations between parameters, further detail is provided in Table 1.

M.2.7 Estimation of cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$\boldsymbol{ICER} = \frac{\boldsymbol{Costs}(\boldsymbol{B}) - \boldsymbol{Costs}(\boldsymbol{A})}{\boldsymbol{QALYs}(\boldsymbol{B}) - \boldsymbol{QALYs}(\boldsymbol{A})}$$ *Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A*	Cost-effective if: • ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating

ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of incremental net monetary benefit (INMB) compared to the baseline intervention, standard treatment. This is calculated by multiplying the incremental QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the incremental costs (formula below). The decision rule then applied is that the comparator with the highest INMB is the most cost-effective option at the specified threshold, that is, the option that provides the highest number of QALYs at an acceptable cost.

$$\boldsymbol{Incremental\ Net\ Monetary\ Benefit(X)} = ([\boldsymbol{QALYs(x)} - \boldsymbol{QALYs(B)}]\boldsymbol{x\lambda}) - (\boldsymbol{Costs(X)} - \boldsymbol{Costs(B)})$$ *Where: λ = threshold (£20,000 per QALY gained) and B = baseline intervention*	Cost-effective if: • Highest incremental net benefit

Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For ease of computation, INMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

In addition to presenting the results in terms of incremental net monetary benefit, the GDG wanted to know in terms of blood units how much blood transfusion would need to be reduced for the interventions to be cost neutral. The following approach was taken to calculate the minimum number of units avoided for an intervention X to be cost neutral:

$$\boldsymbol{Minimum\ units\ avoided\ for\ InterventionX\ to\ be\ cost\ neutral} = \boldsymbol{CostInterventionX / CostSubsequentUnits}$$

M.2.8 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[522] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several interventions, we use the INMB to rank the strategies on the basis of their relative cost-effectiveness. The highest INMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

M.2.9 Model validation

The model was developed in consultation with the GDG; the model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second senior health economist from the NCGC; this included systematic checking of the model calculations.

M.3 Results

M.3.1 Base case analysis

M.3.1.1 High risk subgroup

In the base case analysis for the high risk subgroup (treatment options: standard treatment, ICS, PCS, TXA and ICS+TXA), TXA was found to be the most cost-effective option. Results are summarised below in Table 27 in terms of costs, QALYs and cost-effectiveness (incremental net monetary benefit, probability costs effective and ranking) and shown graphically with relevant incremental cost-effectiveness ratios in Figure 2.

TXA produces the highest incremental QALYs versus standard treatment and PCS produces the highest incremental cost savings versus standard treatment. TXA has the highest incremental net monetary benefit at £20,000 per QALY versus standard treatment and is therefore the most cost-effective intervention. Furthermore, the probability of TXA being the most cost-effective option at £20,000 per QALY is 72%. PCS has the second highest incremental net monetary benefit and is ranked second, with a 28% probability of being the most cost-effective intervention. ICS alone and the combination of ICS and TXA produce the highest costs and the lowest QALYs, as a result these interventions are ranked 4th and 5th respectively, behind standard treatment.

Table 27: Base case analysis results (probabilistic analysis), cost-effectiveness, high risk

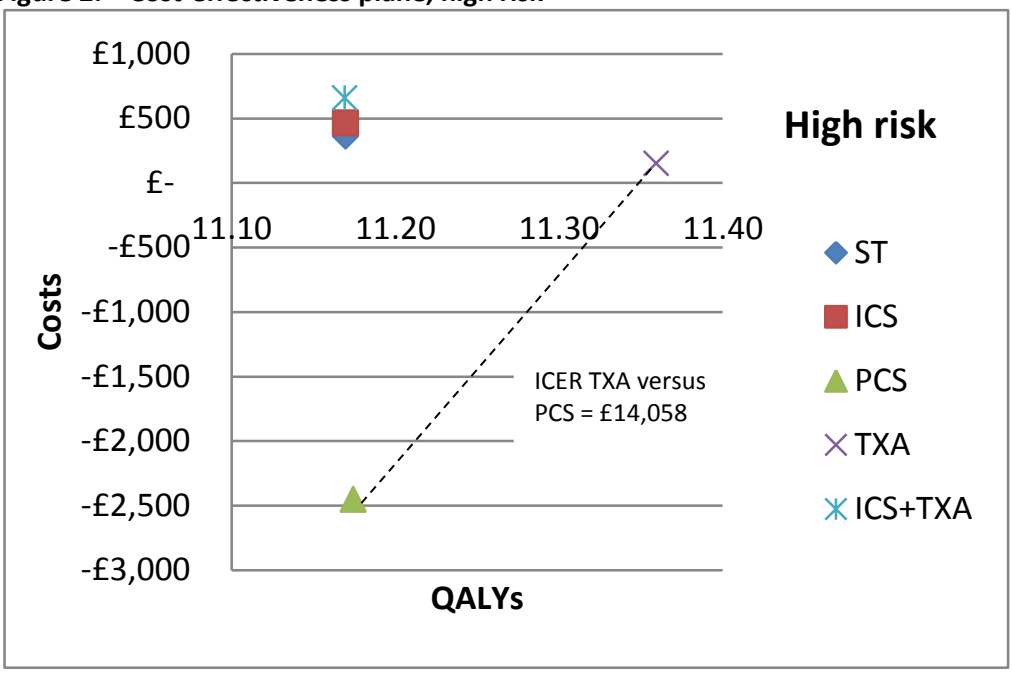
Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K(a)	Probability most CE option	Rank (95% CI)
ST			£0	0%	3 (3, 5)
ICS	0.000	£104	-£102	0%	4 (3, 5)
PCS	0.005	-£2,815	£2,908	28%	2 (1, 2)
TXA	0.190	-£212	£4,009	72%	1 (1, 2)
ICS+TXA	0.000	£295	-£303	0%	5 (3, 5)

Abbreviations: CE = cost-effective; CI = confidence intervals; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALYs = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid.

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cos- effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

The mean costs and QALYs from the probabilistic analysis have also been presented graphically on the cost-effectiveness plane in Figure 2. All interventions with the exception of PCS are dominated by TXA which has both lower costs and greater health benefits. PCS has lower costs than TXA but also lower QALYs. The incremental cost-effectiveness ratio of TXA versus PCS is £14,058 per QALY.

Figure 2: Cost-effectiveness plane, high risk



Abbreviations: ICER = incremental cost-effectiveness ratio; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

The disaggregated costs and health outcomes from the probabilistic base case analysis are summarised in Table 28 and Table 29.

As can be seen in Table 28, the higher QALYs with TXA are largely due to the greater number of life years associated with this treatment. The small differences in QALYs between other treatments, including PCS, are due to the differences in length of stay (that is attributed a lower health-related quality of life).

Table 28: Base case analysis, disaggregated health outcomes, high risk

Intervention	Mean units transfused across all patients	Number transfused per 1,000	Length of stay, days	Life years undiscounted	Life years discounted	Mean QALYs undiscounted	Mean QALYs discounted
ST	2.00	482	9.76	18.202	13.029	15.607	11.169
ICS	1.23	370	-0.16 (MD)	18.202	13.029	15.608	11.170
PCS	0.54	173	-7.14 (MD)	18.202	13.029	15.612	11.174
TXA	0.98	298	-0.16 (MD)	18.512	13.250	15.873	11.359
ICS+TXA	0.46	232	0.65 (MD)	18.202	13.029	15.607	11.169

Abbreviations: ICS = intra-operative cell salvage; MD = mean difference; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

As can be seen in Table 29, the total cost associated with each intervention is a composite of the intervention cost, blood costs and hospital stay costs. PCS has the lowest total costs; this is mostly attributable to the savings from a large reduction in hospital stay in the model. TXA has the second lowest cost due to a combination of a low intervention cost, moderate blood cost and a

small saving due to a reduced length of stay. ICS+TXA had the lowest blood cost however it also had the highest intervention cost and an increase in cost related to length of stay.

Table 29: Base case analysis, disaggregated costs, high risk

Intervention	Intervention cost	Blood cost	Incremental length of stay cost vs ST	Mean total costs(a)
ST	£0	£359	£0	£359
ICS	£295	£229	-£61	£463
PCS	£88	£114	-£2,658	-£2,456
TXA	£19	£187	-£59	£147
ICS+TXA	£314	£100	£241	£654

Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

(a) Total costs = intervention cost + blood costs + difference in cost due to difference in length of stay compared to ST; hence mean total costs can be negative

Finally, the GDG wanted to know in terms of units of blood used, by how much transfusion would need to be reduced, compared to standard treatment, for the interventions to be cost neutral. The minimum number of units an intervention should avoid to be cost neutral is presented in Table 30. Of note, this analysis does not factor in any other costs such as length of stay and is not an incremental analysis. From this analysis it can be seen that when considering only the cost of the interventions and transfusion, in the high risk subgroup PCS and TXA are already cost neutral. The other interventions currently do not save enough units transfused to be cost neutral.

Table 30: Units avoided for interventions to be cost neutral, high risk

Intervention	Total units transfused	Incremental units avoided vs ST	Units avoided to be cost neutral
ST	2.00	n/a	n/a
ICS	1.23	0.77	1.76
PCS	0.54	1.46	0.53
TXA	0.98	1.02	0.11
ICS+TXA	0.46	1.54	1.87

Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

M.3.1.2 Moderate risk subgroup

In the base case analysis for the moderate risk subgroup (treatment options: standard treatment, ICS+PCS, PCS and TXA), TXA was found to be the most cost-effective option. Results are summarised below in Table 31 in terms of costs, QALYs and cost-effectiveness (incremental net monetary benefit, probability costs effective and ranking) and shown graphically with relevant incremental cost-effectiveness ratios in Figure 3.

TXA produces the highest incremental cost savings versus standard treatment. There was no difference in the incremental QALYs versus standard treatment between interventions to the 3rd decimal place. TXA has the highest incremental net monetary benefit at £20,000 per QALY versus standard treatment and is therefore the most cost-effective intervention. Furthermore, the probability of TXA being the most cost-effective option at £20,000 per QALY is 60%. PCS has the

second highest incremental net monetary benefit and is ranked second, with a 40% probability of being the most cost-effective intervention. The combination of ICS and PCS produce the highest costs, as a result this intervention is ranked 4th, behind standard treatment.

Table 31: Base case analysis results (probabilistic analysis), cost-effectiveness, moderate risk

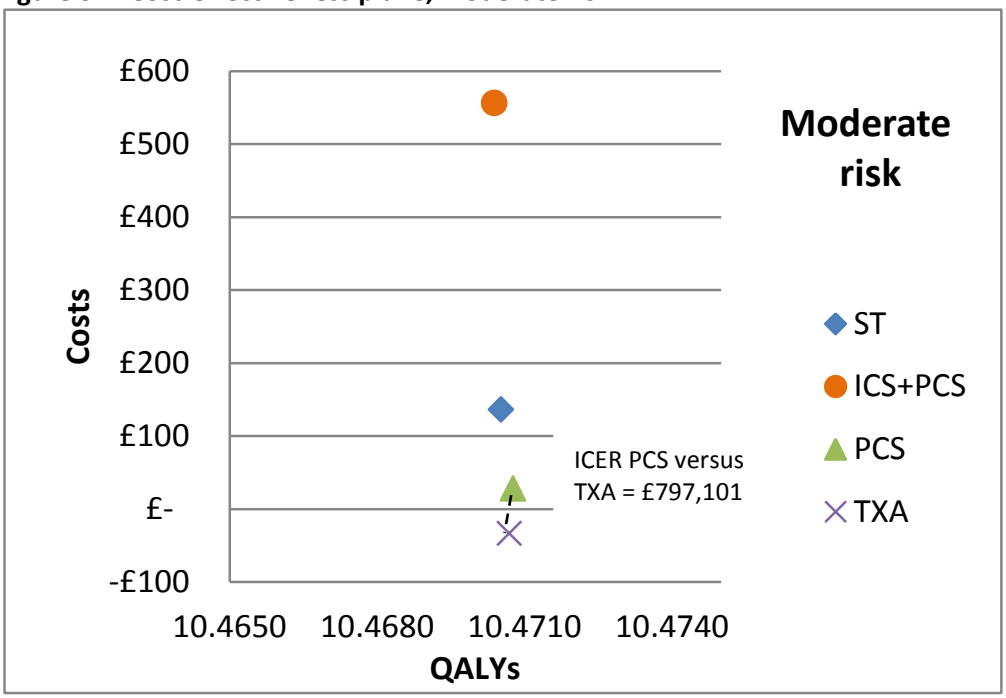
Intervention	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K(a)	Probability most CE option	Rank (95% CI)
ST			£0	0%	3 (2, 3)
ICS+PCS	0.000	£420	-£423	0%	4 (4, 4)
PCS	0.000	-£108	£113	40%	2 (1, 3)
TXA	0.000	-£169	£173	60%	1 (1, 2)

Abbreviations: CE = cost-effective; CI = confidence intervals; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALYs = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost-effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

The mean costs and QALYs from the probabilistic analysis have also been presented graphically on the cost-effectiveness plane in Figure 3. All interventions with the exception of PCS are dominated by TXA which has both lower costs and greater health benefits. PCS has higher costs than TXA but greater QALYs. The incremental cost-effectiveness ratio of PCS versus TXA is £797,101 per QALY.

Figure 3: Cost-effectiveness plane, moderate risk



Abbreviations: ICER = incremental cost-effectiveness ratio; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

The disaggregated costs and health outcomes from the probabilistic base case analysis are summarised in Table 32 and Table 33.

As can be seen in Table 32, the slightly lower QALYs with ICS+PCS are due to the increased length of stay associated with this treatment (that is attributed a lower health-related quality of life). The other treatments did have different length of stay durations, but the impact on QALYs was not apparent to the 3rd decimal point.

Table 32: Base case analysis, disaggregated health outcomes, moderate risk

Intervention	Mean units transfused across all patients	Number transfused per 1,000	Length of stay, days	Life years undiscounted	Life years discounted	Mean QALYs undiscounted	Mean QALYs discounted
ST	0.68	375	5.71	16.468	12.210	14.123	10.471
ICS+PCS	0.71	244	0.20 (MD)	16.468	12.210	14.123	10.470
PCS	0.20	201	-0.36 (MD)	16.468	12.210	14.123	10.471
TXA	0.09	99	-0.25 (MD)	16.468	12.210	14.123	10.471

Abbreviations: ICS = intra-operative cell salvage; MD = mean difference; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

As can be seen in Table 33, the total cost associated with each intervention is a composite of the intervention cost, blood costs and hospital stay costs. TXA has the lowest total costs; this is attributable to a combination of low intervention cost, savings due to a reduction in hospital stay in the model and reduced blood costs. PCS has the second lowest costs due to a combination of a moderately low intervention cost, moderate blood costs and savings due to a reduced length of stay. ICS+PCS had the highest intervention cost, blood costs and an increase in costs related to length of stay.

Table 33: Base case analysis, disaggregated costs, moderate risk

Analysis	Intervention cost	Blood cost	Incremental length of stay cost vs ST	Mean total costs(a)
ST	£0	£136	£0	£136
ICS+PCS	£350	£142	£64	£556
PCS	£88	£55	-£118	£28
TXA	£9	£37	-£78	-£33

Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

(a) Total costs = intervention cost + blood costs + difference in cost due to difference in length of stay compared to ST; hence mean total costs can be negative

The GDG wanted to know in terms of units of blood used, by how much transfusion would need to be reduced, compared to standard treatment, for the interventions to be cost neutral. The minimum number of units an intervention should avoid to be cost neutral is presented in Table 34. Of note this analysis does not factor in any other costs such as length of stay and is not an incremental analysis. From this analysis it can be seen that when considering only the cost of the interventions and transfusion, in the moderate risk subgroup TXA is already cost neutral. The other interventions currently do not save enough units transfused to be cost neutral. Of note, for ICS+PCS the mean total units is greater than standard treatment and therefore the incremental units avoided versus standard treatment is negative in the base case.

Table 34: Units avoided for interventions to be cost neutral, moderate risk

Analysis	Total units transfused (base case)	Incremental units avoided vs ST (base case)	Units avoided to be cost neutral
ST	0.68	n/a	n/a
ICS+PCS	0.71	-0.04	2.09
PCS	0.20	0.48	0.53
TXA	0.09	0.59	0.05

Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

M.3.2 Sensitivity analyses

M.3.2.1 High risk

A number of sensitivity analyses were conducted as described in section M.2.4. The deterministic results of these analyses are summarised in Table 35 and Table 36. The sensitivity analyses that resulted in a change of ranking are discussed in further detail below. For these sensitivity analyses, the results were also generated probabilistically to explore them further, see Table 37.

SA3: Reduce baseline mortality rate at 30 days within range, Lower range

In this sensitivity analysis, the lower range of the baseline mortality rate at 30 days was used in the model (0%). With this baseline mortality rate the mortality benefit from TXA is no longer present. As a result PCS is the most cost-effective option as it has the lowest costs and highest QALYs as a result of the large reduction in length of stay, with a 100% probability of being the most cost-effective option. TXA is ranked second in this sensitivity analysis and all other rankings remain unchanged.

SA4: Exclude length of stay from analysis (both cost and impact on QoL)

When length of stay was excluded from the analysis, the QALYs for all interventions with the exception of TXA, which has a differential mortality effect, are the same. TXA remains the most cost-effective option and the probability of it being the most cost-effective option increased from 72% in the base case to 100% here. The absence of the cost related to the longer length of stay, results in the combination of ICS and TXA changing ranking from 5th to 4th and ICS from 4th to 5th.

SA8 and SA9: Adjust mortality and quality of life post 30 days for high risk subgroup

In these sensitivity analyses SA8 and SA9, a higher mortality rate was implemented after 30 days as well as adjusting the quality of life to reflect that of MI and stoke, respectively. In both the MI (SA8) and stroke (SA9) sensitivity analyses, PCS was the most cost-effective option, with TXA being ranked second and all other rankings remain unchanged. The probability of PCS being the most cost-effective option is 76% for MI and 86% for stroke, compared to 28% in the base case.

The QALY difference between TXA and PCS was reduced in these sensitivity analyses compared to the base case. This is because patients are less well (higher mortality rate and worse quality of life) and therefore they have less to gain from TXA's mortality benefit. In addition, the mean total cost of PCS is lower than TXA as a result of savings associated with the large mean difference in

length of stay for PCS. When combining this smaller QALY difference observed and this large cost difference, PCS becomes the more cost-effective option in these sensitivity analyses.

The GDG have highlighted concerns with the length of stay data for PCS in the high risk group, that is that the length of stay estimate was informed by only one study. This study had an unusually high baseline length of stay which likely accounted for the large difference in length of stay reported. To explore this concern further, SA8 and SA9 were combined with SA5. SA5 was a sensitivity analysis that explored the use of proportions to estimate the PCS difference in length of stay as opposed to the mean difference, to account for the different baseline. When these analyses were combined, SA23 (SA8 & SA5) and SA24 (SA9 & SA5), TXA returned to being the most cost-effective option, thus indicating that the length of stay data for PCS is a key driver.

SA10: Use all clinical data for 30-day mortality - version 1 (using indirect evidence from ICS for high risk)

When the 30-day mortality relative risks for all interventions are used (where the relative risk for ICS+TXA is estimated using indirect evidence from ICS versus ICS+TXA), TXA remains the most cost-effective intervention in the deterministic analysis. The ranking of the other interventions changes compared to the base case results, reflecting the relative risk point estimates used in this sensitivity analysis. In particular, PCS with a 30-day mortality relative risk of 3, ICS of 0.52, and ICS+TXA of 0.68 change rankings from 2nd, 4th and 5th to 5th, 2nd and 3rd respectively.

Due to the wide confidence intervals around the 30-day mortality relative risks for all the interventions (except TXA), when the probabilistic sensitivity analysis was conducted, the confidence intervals around all the ranks become very wide and the probability of TXA being the most cost-effective intervention reduces significantly.

SA11: Use all clinical data for 30-day mortality - version 2 (using indirect evidence from TXA for high risk)

When the 30-day mortality relative risks for all interventions are used (where the relative risk for ICS+TXA is estimated using indirect evidence from TXA versus ICS+TXA), TXA remains the most cost-effective intervention in the deterministic analysis. The ranking of the ICS and PCS change from 4th and 2nd in the base case to 2nd and 4th respectively, reflecting the relative risk point estimates used in this sensitivity analysis.

Due to the wide confidence intervals around the 30-day mortality relative risks for all the interventions (except TXA), when the probabilistic sensitivity analysis was conducted, the confidence intervals around all the ranks become very wide and the probability of TXA being the most cost-effective intervention reduces significantly.

SA12: Assume high risk ICS+TXA mortality rate = mortality rate of TXA

When it was assumed that the 30-day mortality benefit of TXA is maintained when TXA is given in combination with ICS, the ranking of ICS+TXA changed from 5th in the base case to 2nd. This is reflected in the probabilistic sensitivity analysis. In addition, the probability of TXA being the most cost-effective option reduced from 72% to 65% and the probability of ICS+TXA being the most cost-effective option increases from 0% to 7%.

SA18: Exclude PCS as comparator for high risk group

When PCS was not considered a comparator in the high risk group analysis, TXA remains the most cost-effective option, followed by standard treatment, then ICS alone and finally the combination of ICS+TXA. The ranking is reflected in the probabilistic analysis.

SA19: Assume high risk ICS+TXA mortality rate = mortality rate of TXA & exclude LOS from analysis and SA20: SA4, SA12 and SA15 (cost of disposables are 10% cost)

Sensitivity analyses SA19 and SA20 bias in favour of the combination intervention of ICS+TXA. In SA19, both the 30-day mortality relative risk of ICS+TXA was assumed to be equal to that of TXA, and length of stay was excluded from the analysis. In SA20, as well as what was done in SA19, the cost of the ICS disposable was reduced to 10% of its price used in the base case. These analyses resulted in ICS +TXA changing from 5th to 2nd rank. This was reflected in the probabilistic analyses. The probability of TXA being the most cost-effective option increases from 72% to 99% for both SA19 and SA20. The confidence intervals around the rank for ICS+TXA are very tight, indicating that ICS+TXA has a high probability of being the second most cost-effective option.

Table 35: Deterministic sensitivity analyses results, high risk

Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K	Rank
Base case (deterministic)				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.005	-£2,818	£2,912	2
TXA	0.190	-£210	£4,009	1
ICS+TXA	0.000	£291	-£299	5
SA1: Reduce baseline number transfused by 50%				
ST			£0	3
ICS	0.000	£159	-£157	4
PCS	0.005	-£2,703	£2,796	2
TXA	0.190	-£136	£3,935	1
ICS+TXA	0.000	£414	-£422	5
SA2: Reduce baseline number and volume transfused by 50%				
ST			£0	3
ICS	0.000	£196	-£194	4
PCS	0.005	-£2,635	£2,728	2
TXA	0.190	-£87	£3,885	1
ICS+TXA	0.000	£482	-£491	5
SA3: Reduce baseline mortality rate at 30 days within range, Lower range				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.005	-£2,818	£2,915	1
TXA	0.000	-£210	£212	2
ICS+TXA	0.000	£291	-£300	5
SA3: Reduce baseline mortality rate at 30 days within range, Upper range				

Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K	Rank
ST			£0	3
ICS	0.000	£103	-£103	4
PCS	0.002	-£2,818	£2,852	2
TXA	3.613	-£210	£72,462	1
ICS+TXA	0.000	£291	-£294	5
SA4: Exclude length of stay from analysis (both cost and impact on QoL)				
ST			£0	3
ICS	0.000	£164	-£164	5
PCS	0.000	-£163	£163	2
TXA	0.190	-£154	£3,953	1
ICS+TXA	0.000	£53	-£53	4
SA5: Use proportion reduction for length of stay for PCS in high risk group				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.003	-£1,736	£1,792	2
TXA	0.190	-£210	£4,009	1
ICS+TXA	0.000	£291	-£299	5
SA6: Increase utility decrement for being in hospital by 50%				
ST			£0	3
ICS	0.000	£103	-£100	4
PCS	0.007	-£2,818	£2,958	2
TXA	0.190	-£210	£4,010	1
ICS+TXA	-0.001	£291	-£304	5
SA7: Decrease utility decrement for being in hospital by 50%				
ST			£0	3
ICS	0.000	£103	-£102	4
PCS	0.002	-£2,818	£2,865	2
TXA	0.190	-£210	£4,007	1
ICS+TXA	0.000	£291	-£295	5
SA8: Adjust mortality and QoL post 30 days for MI in high risk group				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.005	-£2,818	£2,912	1
TXA	0.104	-£210	£2,297	2
ICS+TXA	0.000	£291	-£299	5
SA9: Adjust mortality and QoL post 30 days for stroke in high risk group				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.005	-£2,818	£2,912	1

Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K	Rank
TXA	0.086	-£210	£1,927	2
ICS+TXA	0.000	£291	-£299	5
SA10: Use all clinical data for 30-day mortality - version 1 (using indirect evidence from ICS for high risk)				
ST			£0	4
ICS	0.139	£103	£2,667	2
PCS	-0.787	-£2,818	-£12,914	5
TXA	0.190	-£210	£4,009	1
ICS+TXA	0.128	£291	£2,263	3
SA11: Use all clinical data for 30-day mortality - version 2 (using indirect evidence from TXA for high risk)				
ST			£0	3
ICS	0.139	£103	£2,667	2
PCS	-0.787	-£2,818	-£12,914	4
TXA	0.190	-£210	£4,009	1
ICS+TXA	-1.191	£291	-£24,106	5
SA12: Assume high risk ICS+TXA mortality rate = mortality rate of TXA				
ST			£0	4
ICS	0.000	£103	-£101	5
PCS	0.005	-£2,818	£2,912	3
TXA	0.190	-£210	£4,009	1
ICS+TXA	0.189	£291	£3,497	2
SA16: Use pairwise data for number transfused PCS in high risk				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.005	-£2,751	£2,844	2
TXA	0.190	-£210	£4,009	1
ICS+TXA	0.000	£291	-£299	5
SA17: Change discounting rate for health effects to 1.5%				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.005	-£2,818	£2,912	2
TXA	0.228	-£210	£4,768	1
ICS+TXA	0.000	£291	-£299	5
SA18: Exclude PCS as comparator for high risk group				
ST			£0	2
ICS	0.000	£103	-£101	3
TXA	0.190	-£210	£4,009	1
ICS+TXA	0.000	£291	-£299	4

Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K	Rank
SA19: Assume high risk ICS+TXA mortality rate = mortality rate of TXA & exclude LOS from analysis				
ST			£0	4
ICS	0.000	£164	-£164	5
PCS	0.000	-£163	£163	3
TXA	0.190	-£154	£3,953	1
ICS+TXA	0.190	£53	£3,746	2
SA20: SA4, SA12 and SA15 (10% cost)				
ST			£0	4
ICS	0.000	£56	-£56	5
PCS	0.000	-£163	£163	3
TXA	0.190	-£154	£3,953	1
ICS+TXA	0.190	-£55	£3,853	2
SA21: Cost of transfusion increased by 50%				
ST			£0	3
ICS	0.000	£38	-£36	4
PCS	0.005	-£2,944	£3,037	2
TXA	0.190	-£297	£4,095	1
ICS+TXA	0.000	£161	-£169	5
SA22: Cost of transfusion decreased by 50%				
ST			£0	3
ICS	0.000	£169	-£167	4
PCS	0.005	-£2,693	£2,786	2
TXA	0.190	-£124	£3,922	1
ICS+TXA	0.000	£421	-£430	5
SA23: SA5 & SA8				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.003	-£1,736	£1,792	2
TXA	0.104	-£210	£2,297	1
ICS+TXA	0.000	£291	-£299	5
SA24: SA5 & SA9				
ST			£0	3
ICS	0.000	£103	-£101	4
PCS	0.003	-£1,736	£1,792	2
TXA	0.086	-£210	£1,927	1
ICS+TXA	0.000	£291	-£299	5

Abbreviations: CI = confidence intervals; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost-effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

Table 36: Deterministic sensitivity analyses results, high risk (SA14, SA15)

	INMB at £20K(a)				Optimal strategy
Analysis	ICS	PCS	TXA	ICS+TXA	
SA14: Adjust cost of cell salvage disposables PCS. 10% increments (10-100%)					
10%	-£101	£2,967	£4,009	-£299	TXA
20%	-£101	£2,961	£4,009	-£299	TXA
30%	-£101	£2,955	£4,009	-£299	TXA
40%	-£101	£2,948	£4,009	-£299	TXA
50%	-£101	£2,942	£4,009	-£299	TXA
60%	-£101	£2,936	£4,009	-£299	TXA
70%	-£101	£2,930	£4,009	-£299	TXA
80%	-£101	£2,924	£4,009	-£299	TXA
90%	-£101	£2,918	£4,009	-£299	TXA
100%	-£101	£2,912	£4,009	-£299	TXA
SA15: Adjust cost of cell salvage disposables ICS (for ICS alone and ICS+TXA). 10% increments (10-100%)					
10%	£6	£2,912	£4,009	-£192	TXA
20%	-£6	£2,912	£4,009	-£204	TXA
30%	-£18	£2,912	£4,009	-£216	TXA
40%	-£30	£2,912	£4,009	-£227	TXA
50%	-£41	£2,912	£4,009	-£239	TXA
60%	-£53	£2,912	£4,009	-£251	TXA
70%	-£65	£2,912	£4,009	-£263	TXA
80%	-£77	£2,912	£4,009	-£275	TXA
90%	-£89	£2,912	£4,009	-£287	TXA
100%	-£101	£2,912	£4,009	-£299	TXA

Abbreviations: ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; ST = standard treatment; TXA = tranexamic acid

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost- effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

Table 37: Probabilistic sensitivity analyses results, high risk

Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K(a)	Probability most CE option	Rank (95% CI)
Base case (probabilistic)					
ST			£0	0%	3 (3, 5)
ICS	0.000	£104	-£102	0%	4 (3, 5)
PCS	0.005	-£2,815	£2,908	28%	2 (1, 2)
TXA	0.190	-£212	£4,009	72%	1 (1, 2)
ICS+TXA	0.000	£295	-£303	0%	5 (3, 5)
SA3: Reduce baseline mortality rate at 30 days within range (lower range)					
ST			£0	0%	3 (2, 5)
ICS	0.000	£101	-£99	0%	4 (2, 5)

Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K(a)	Probability most CE option	Rank (95% CI)
PCS	0.005	-£2,818	£2,914	100%	1 (1, 1)
TXA	0.000	-£206	£207	0%	2 (2, 4)
ICS+TXA	0.000	£304	-£313	0%	5 (2, 5)
SA4: Exclude length of stay from analysis (both cost and impact on QoL)					
ST			£0	0%	3 (3, 4)
ICS	0.000	£166	-£166	0%	5 (5, 5)
PCS	0.000	-£158	£158	0%	2 (2, 2)
TXA	0.189	-£153	£3,932	100%	1 (1, 1)
ICS+TXA	0.000	£55	-£55	0%	4 (3, 4)
SA10: Use all clinical data for 30-day mortality - version 1 (using indirect evidence from ICS for high risk)					
ST			£0	0%	4 (3, 5)
ICS	0.136	£99	£2,623	6%	2 (1, 5)
PCS	-0.837	-£2,803	-£13,928	45%	5 (1, 5)
TXA	0.191	-£208	£4,021	12%	1 (1, 4)
ICS+TXA	0.130	£291	£2,311	36%	3 (1, 5)
SA11: Use all clinical data for 30-day mortality - version 2 (using indirect evidence from TXA for high risk)					
ST			£0	0%	3 (3, 5)
ICS	0.143	£108	£2,748	13%	2 (1, 5)
PCS	-0.829	-£2,815	-£13,760	50%	4 (1, 5)
TXA	0.190	-£217	£4,023	26%	1 (1, 4)
ICS+TXA	-1.233	£305	-£24,972	12%	5 (1, 5)
SA12: Assume high risk ICS+TXA mortality rate = mortality rate of TXA					
ST			£0	0%	4 (4, 5)
ICS	0.0001	£102	-£100	0%	5 (4, 5)
PCS	0.0047	-£2,803	£2,896	28%	3 (1, 3)
TXA	0.1886	-£210	£3,982	65%	1 (1, 3)
ICS+TXA	0.1880	£289	£3,472	7%	2 (1, 3)
SA18: Exclude PCS as comparator for high risk group					
ST			£0	0%	2 (2, 4)
ICS	0.000	£108	-£106	28%	3 (2, 4)
TXA	0.191	-£215	£4,030	72%	1 (1, 1)
ICS+TXA	0.000	£306	-£315	0%	4 (2, 4)
SA19: Assume high risk ICS+TXA mortality rate = mortality rate of TXA & exclude LOS from analysis					
ST			£0	0%	4 (4, 4)
ICS	0.000	£164	-£164	0%	5 (5, 5)
PCS	0.000	-£157	£157	1%	3 (3, 3)
TXA	0.190	-£153	£3,962	99%	1 (1, 1)
ICS+TXA	0.190	£53	£3,756	0%	2 (2, 2)

Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K(a)	Probability most CE option	Rank (95% CI)
SA20: SA4, SA12 and SA15 (10% cost)					
ST			£0	0%	4 (4, 5)
ICS	0.000	£57	-£57	0%	5 (4, 5)
PCS	0.000	-£157	£157	1%	3 (3, 3)
TXA	0.189	-£153	£3,937	99%	1 (1, 1)
ICS+TXA	0.189	-£52	£3,837	0%	2 (2, 2)

Abbreviations: CE = cost-effective; CI = confidence intervals; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; LOS = length of stay; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost-effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cos- effective than this option.

M.3.2.2 Moderate risk

A number of sensitivity analyses were conducted as described in section M.2.4. The deterministic results of these analyses are summarised in Table 38 and Table 39. One sensitivity analysis resulted in a change of ranking (SA4), this is discussed in further detail below. The results were also generated probabilistically to explore it further, see Table 40.

SA4: Exclude length of stay from analysis (both cost and impact on QoL)

When length of stay is excluded from the analysis, the QALYs for all interventions are the same. TXA remains the most cost-effective option and the probability of it being the most cost-effective option increased from 60% in the base case to 100% here. The absence of the cost related to the longer length of stay, results in PCS changing rank from 2nd to 3rd.

Table 38: Deterministic sensitivity analyses results, moderate risk

Analysis	QALYs	Costs	INMB at £20K	Rank
Base case (deterministic)				
ST			£0	3
ICS+PCS	0.000	£412	-£414	4
PCS	0.000	-£110	£115	2
TXA	0.000	-£170	£174	1
SA1: Reduce baseline number transfused by 50%				
ST			£0	3
ICS+PCS	0.000	£407	-£410	4
PCS	0.000	-£72	£77	2
TXA	0.000	-£122	£125	1
SA2: Reduce baseline number and volume transfused by 50%				
ST			£0	3
ICS+PCS	0.000	£411	-£413	4
PCS	0.000	-£51	£56	2
TXA	0.000	-£97	£100	1

Analysis	QALYs	Costs	INMB at £20K	Rank
SA3: Reduce baseline mortality rate at 30 days within range, Lower range				
ST			£0	3
ICS+PCS	0.000	£412	-£414	4
PCS	0.000	-£110	£115	2
TXA	0.000	-£170	£174	1
SA3: Reduce baseline mortality rate at 30 days within range, Upper range				
ST			£0	3
ICS+PCS	0.000	£412	-£414	4
PCS	0.000	-£110	£115	2
TXA	0.000	-£170	£174	1
SA4: Exclude length of stay from analysis (both cost and impact on QoL)				
ST			£0	2
ICS+PCS	0.000	£348	-£348	4
PCS	0.000	£7	-£7	3
TXA	0.000	-£91	£91	1
SA6: Increase utility decrement for being in hospital by 50%				
ST			£0	3
ICS+PCS	0.000	£412	-£416	4
PCS	0.000	-£110	£118	2
TXA	0.000	-£170	£175	1
SA7: Decrease utility decrement for being in hospital by 50%				
ST			£0	3
ICS+PCS	0.000	£412	-£413	4
PCS	0.000	-£110	£113	2
TXA	0.000	-£170	£172	1
SA10: Use all clinical data for 30-day mortality - version 1				
ST			£0	3
ICS+PCS	-0.039	£412	-£1,200	4
PCS	0.000	-£110	£115	2
TXA	0.005	-£170	£265	1
SA17: Change discounting rate for health effects to 1.5%				
ST			£0	3
ICS+PCS	0.000	£412	-£414	4
PCS	0.000	-£110	£115	2
TXA	0.000	-£170	£174	1
SA21: Cost of transfusion increased by 50%				
ST			£0	3
ICS+PCS	0.000	£411	-£413	4
PCS	0.000	-£151	£156	2

Analysis	QALYs	Costs	INMB at £20K	Rank
TXA	0.000	-£220	£223	1
SA22: Cost of transfusion decreased by 50%				
ST			£0	3
ICS+PCS	0.000	£413	-£415	4
PCS	0.000	-£70	£75	2
TXA	0.000	-£121	£124	1

Abbreviations: ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; ST = standard treatment; TXA = tranexamic acid

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost-effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

Table 39: Deterministic sensitivity analyses results, moderate risk (SA13, SA14)

	INMB at £20K(a)			
Analysis	**ICS+PCS**	**PCS**	**TXA**	**Optimal strategy**
SA13: Adjust cost of cell salvage disposables ICS+PCS. 10% increments (10-100%)				
10%	-£152	£115	£174	TXA
20%	-£181	£115	£174	TXA
30%	-£210	£115	£174	TXA
40%	-£239	£115	£174	TXA
50%	-£269	£115	£174	TXA
60%	-£298	£115	£174	TXA
70%	-£327	£115	£174	TXA
80%	-£356	£115	£174	TXA
90%	-£385	£115	£174	TXA
100%	-£414	£115	£174	TXA
SA14: Adjust cost of cell salvage disposables PCS. 10% increments (10-100%)				
10%	-£414	£170	£174	TXA
20%	-£414	£164	£174	TXA
30%	-£414	£158	£174	TXA
40%	-£414	£152	£174	TXA
50%	-£414	£146	£174	TXA
60%	-£414	£140	£174	TXA
70%	-£414	£134	£174	TXA
80%	-£414	£128	£174	TXA
90%	-£414	£121	£174	TXA
100%	-£414	£115	£174	TXA

Abbreviations: CI = confidence intervals; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost-effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

Table 40: Probabilistic sensitivity analyses results, moderate risk

Analysis	Incremental QALYs vs. ST	Incremental costs vs. ST	INMB at £20K(a)	Probability most CE option	Rank (95% CI)
Base case (probabilistic)					
ST			£0	0%	3 (2, 3)
ICS+PCS	0.000	£420	-£423	0%	4 (4, 4)
PCS	0.000	-£108	£113	40%	2 (1, 3)
TXA	0.000	-£169	£173	60%	1 (1, 2)
SA4: Exclude length of stay from analysis (both cost and impact on QoL)					
ST			£0	0%	2 (2, 3)
ICS+PCS	0.000	£357	-£357	0%	4 (4, 4)
PCS	0.000	£7	-£7	0%	3 (2, 3)
TXA	0.000	-£91	£91	100%	1 (1, 1)

Abbreviations: CE = cost-effective; CI = confidence intervals; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; LOS = length of stay; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost-effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

M.3.3 Exploratory threshold analyses

Rationale

The GDG felt that, while TXA alone was found to be the most cost-effective option overall, for certain patients with particularly high blood loss the addition of cell salvage to TXA may still be a cost-effective option on the basis that:

1. The mechanisms of action are different for TXA and cell salvage and so it was considered that the relative benefit of cell salvage over TXA is likely to be greater with increased blood loss:
    a. TXA is an anti-fibrinolytic drug that is administered in advance and reduces the risk of blood loss, therefore reducing the need for allogeneic transfusions
    b. With cell salvage, lost blood is collected and re-transfused to the patient, thus also reducing the need for allogeneic transfusions
    c. The GDG felt that while TXA would help reduce allogeneic transfusion up to a point (due to reducing blood loss), the potential to collect blood lost and re-transfuse it with cell salvage is unlimited – the greater the volume of blood lost the greater the volume that can be salvaged
    d. Due to this it was felt that at very high levels of blood loss the relative benefit of TXA in combination with cell salvage over TXA alone was likely to be greater.
2. The mortality benefit seen with TXA alone was likely to also be achieved with ICS+TXA

It was not possible to explore this within the context of RCT level clinical data. On this basis a series of exploratory threshold analyses were undertaken to quantitatively investigate whether, under circumstances like those described above, the combination of cell salvage to TXA might be the most cost-effective option in some patients.

Methods

For all threshold analysis, the baseline probability transfused and the volume transfused were increased incrementally.

For the first two threshold analyses (TA1 and TA2), the relative probability transfused and relative difference in volume transfused for each intervention was kept constant. For the subsequent two threshold analyses (TA3 and TA4), the relative probability transfused for each intervention was kept constant, however the relative difference in volume transfused was increased for interventions containing cell salvage and kept constant for those without cell salvage.

Due to the uncertainty associated with the reliability of the length of stay data, the analyses were conducted with (TA1 and TA3) and without length of stay (TA2 and TA4).

The baseline and intervention probabilities transfused used in all the exploratory threshold analysis are summarised in Table 41. Included in the table are the odds ratios used to estimate the relative treatment effects, the baseline probabilities transfused (base case and incremental increases) and the corresponding calculated absolute probabilities transfused for each intervention. Of note, due to the programming of the model, we were unable to enter a 100% probability transfused for the baseline risk and therefore had to use 99% instead.

Table 41: Probability transfused for all exploratory threshold analyses (TA1-TA4)

Data	Baseline	TXA	PCS	ICS	ICS+TXA
Odds ratios	n/a	0.452	0.207	0.628	0.316
Base case	48%	30%	16%	37%	23%
Increments for threshold analysis	50%	31%	17%	39%	24%
	60%	40%	24%	49%	32%
	70%	51%	33%	59%	42%
	80%	64%	45%	72%	56%
	90%	80%	65%	85%	74%
	99%	98%	95%	98%	97%

Abbreviations: ICS = intra-operative cell salvage; n/a = not applicable; PCS = post-operative cell salvage; TXA = tranexamic acid

The baseline volume transfused and difference in volume transfused for each intervention used in the first two threshold analyses (TA1 and TA2) are summarised in Table 42. In order to conduct this analysis the data for the difference in volume transfused was converted from an absolute to a relative effect. This was done by calculating the relative percentage reduction in volume transfused for each intervention versus baseline using the base case data. Included in the table are the base case volume and differences in volume transfused for the baseline and interventions, the relative treatment effect (percentage reduction) and the volume for the baseline and difference in volume for each intervention used in the threshold analysis.

Table 42: Volume and difference in volume (units) transfused for TA1 and TA2

Data	Baseline	TXA	PCS	ICS	ICS+TXA
Base case	4.16	-0.87	-1.02	-0.84	-2.17
Relative effect	n/a	-20.91%	-24.56%	-20.15%	-52.18%

Data	Baseline	TXA	PCS	ICS	ICS+TXA
Increments for threshold analysis	5.00	-1.05	-1.23	-1.01	-2.61
	6.00	-1.25	-1.47	-1.21	-3.13
	7.00	-1.46	-1.72	-1.41	-3.65
	8.00	-1.67	-1.97	-1.61	-4.17
	9.00	-1.88	-2.21	-1.81	-4.70
	10.00	-2.09	-2.46	-2.01	-5.22
	11.00	-2.30	-2.70	-2.22	-5.74
	12.00	-2.51	-2.95	-2.42	-6.26
	13.00	-2.72	-3.19	-2.62	-6.78

Abbreviations: ICS = intra-operative cell salvage; n/a = not applicable; PCS = post-operative cell salvage; TXA = tranexamic acid

In the two subsequent analyses, the relative difference in volume transfused was increased for interventions containing ICS and kept constant for those without ICS. These analyses are more favourable for interventions containing ICS. For those containing ICS, as the baseline volume transfused increases by one unit at each iteration, so does the difference in volume transfused for each intervention. For the other interventions, the relative difference in volume transfused remains constant. The data used in these threshold analyses for volume transfused are summarised in Table 43. Included in this table is the base case volume and differences in volume transfused for the baseline and interventions, the relative treatment effect (for TXA and PCS) and the volume for the baseline and difference in volume for each intervention used in the threshold analysis TA3 length of stay was excluded and in TA4 length of stay was included in the analysis.

Table 43: Volume and difference in volume (units) transfused for TA3 and TA4

	Baseline	TXA	PCS	ICS	ICS+TXA
Base case	4.16	-0.87	-1.02	-0.84	-2.17
Relative effect	n/a	-20.91%	-24.56%	n/a *	n/a *
Increments for threshold analysis	5	-1.05	-1.23	-1.84	-3.17
	6	-1.25	-1.47	-2.84	-4.17
	7	-1.46	-1.72	-3.84	-5.17
	8	-1.67	-1.97	-4.84	-6.17
	9	-1.88	-2.21	-5.84	-7.17
	10	-2.09	-2.46	-6.84	-8.17
	11	-2.30	-2.70	-7.84	-9.17
	12	-2.51	-2.95	-8.84	-10.17
	13	-2.72	-3.19	-9.84	-11.17

Abbreviations: ICS = intra-operative cell salvage; PCS = post-operative cell salvage; TXA = tranexamic acid
**For interventions containing ICS the difference in volume versus baseline increase by one unit for each additional unit transfused in the baseline.*

In all analyses the costs of cell salvage are the same; that is it is assumed that cell salvage is set up and used for all patients. This implies that the patients or patient group this analysis might apply to is identifiable in advance. For example, certain types of surgery or patients may be associated with higher average blood loss than others even within the high risk group.

Results

The results for TA1, TA2, TA3 and TA4 are summarised in Table 44, Table 45, Table 46 and Table 47.

The results of TA1 and TA2 indicate that as the baseline probability of transfusion increases and the volume transfused increases, keeping the intervention effects constant, the optimal strategy at £20,000 per QALY changes from TXA (base case) to ICS+TXA. In the analyses where the relative difference in volume transfused was increased for interventions containing ICS and kept constant for those without (TA3 and TA4), it can be seen that ICS+TXA becomes the optimal strategy at a lower probability transfused and lower volume transfused than in TA1 and TA2.

The change in optimal strategy occurs sooner when the length of stay is excluded from the analysis (TA2, and TA4) than when it is included (TA1 and TA3). This can be explained due to the increased length of stay of ICS+TXA compared to standard treatment, which means the QALYs for this intervention are lower than TXA and the total costs of the combination increased as a result of longer length of stay.

Table 44: Results of exploratory threshold analysis TA1 (length of stay excluded)

TA1		Baseline volume transfused									
		4.16	5	6	7	8	9	10	11	12	13
Baseline probability transfused	47%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	50%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	60%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	70%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	80%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	90%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	ICS+TXA
	99%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA

Table 45: Results of exploratory threshold analysis TA2 (length of stay included)

TA2		Baseline volume transfused									
		4.16	5	6	7	8	9	10	11	12	13
Baseline probability transfused	47%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	50%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	60%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA
	70%	TXA	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	80%	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	90%	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	99%	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA

Table 46: Results of exploratory threshold analysis TA3 (length of stay excluded)

TA3		Baseline volume transfused									
		4.16	5	6	7	8	9	10	11	12	13
probability transfused	47%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	50%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	60%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA
	70%	TXA	TXA	TXA	TXA	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA
	80%	TXA	TXA	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	90%	TXA	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA

	99%	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA

Table 47: Results of exploratory threshold analysis TA4 (length of stay included)

TA4		Baseline volume transfused									
		4.16	5	6	7	8	9	10	11	12	13
Baseline probability transfused	47%	TXA	TXA	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	50%	TXA	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	60%	TXA	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	70%	TXA	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	80%	TXA	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	90%	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA
	99%	TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA	ICS+TXA

M.4 Discussion

M.4.1 Summary of results

This analysis found that TXA was the most cost-effective option for reducing allogeneic blood transfusion in adults undergoing surgery in both moderate and high risk subgroups.

In the high risk group (treatment options: standard treatment, ICS, PCS, TXA and ICS+TXA), TXA was found to have the greatest benefit for patients (highest QALYs) largely due to a reduction in mortality at 30 days that was not seen with other treatment options. TXA had the second lowest cost after PCS; this was driven by a combination of the lowest intervention cost, moderate blood savings and a small saving due to a reduced length of stay. Of note, TXA was not the most blood saving intervention; it was the combination of ICS and TXA that resulted in the greatest blood savings.

In the moderate risk group (treatment options: standard treatment, ICS+PCS, PCS and TXA), there was no difference in the incremental QALYs versus standard treatment between interventions to the 3rd decimal place. TXA had the lowest costs compared to all other interventions due to a combination of the lowest intervention cost, greatest savings associated with blood costs and length of stay.

This conclusion was robust to all sensitivity analyses with the exception of three in the high risk group. The first was where the baseline mortality rate at 30 days was reduced to 0%. In this analysis, PCS became most cost-effective strategy. However, while this mortality rate was the lower end of the range observed in the RCTs included in the review, the GDG considered this scenario implausible for a high risk subgroup and likely due chance as a result of low event rates and so it did not impact decision making. A further two sensitivity analyses in the high risk group resulted in PCS becoming the most cost-effective option. These were analyses where the mortality after 30 days and the quality of life were adjusted to reflect MI and stroke populations. The results indicated that the QALY difference between TXA and PCS was reduced compared to difference observed in the base case. This impact on QALYs occurs because patients are less well (higher mortality rate and worse quality of life) and therefore they have less to gain from TXA's

mortality benefit. When combined with the very low total costs of PCS (which are driven by the length of stay savings), PCS is the most cost-effective option. The GDG highlighted concerns with the length of stay data for PCS in the high risk group, that is that the length of stay estimate was informed by one study only and that this study had an unusually high baseline length of stay which likely accounted for the large difference in length of stay reported. To explore this further, these two sensitivity analyses were combined with a sensitivity analysis to account for the unusually large difference in length of stay for PCS. When these analyses were combined, TXA returned to being the most cost-effective option, thus indicating that the length of stay data for PCS is a key driver. The GDG considered that these sensitivity analyses highlighted some uncertainty in the base case, however the further exploration mitigated the need for this to impact their decision making.

Exploratory threshold analyses indicated that the combination of ICS and TXA could potentially become the cost-effective strategy. This is seen particularly in patients or patient groups where the probability of being transfused and the volume transfused is expected to be very high; if it was assumed that ICS+TXA had the same mortality benefit as TXA and that relative treatment benefits for ICS were maintained or increased. These analyses assumed that cell salvage is set up and used for all patients (as in the primary analyses).

M.4.2 Limitations and interpretation

This analysis suggests that TXA is the most cost-effective strategy for reducing allogeneic blood transfusion in adults undergoing surgery. Uncertainties in the analysis were explored through probabilistic sensitivity analyses of the base case for each subgroup and extensive sensitivity analyses which did not change conclusions with the exception of three sensitivity analyses in the high risk group. In the first sensitivity analysis, the baseline 30-day mortality was reduced to 0%. The GDG discussed this input and agreed that a 0% mortality rate in this risk group was not plausible and likely due to chance as a result of low event rates observed in the trials. The group therefore felt the results of this sensitivity analysis were not significant and did not change the overall conclusion.

A further two sensitivity analyses, where the mortality after 30 days and the quality of life were adjusted to reflect MI and stroke populations, resulted in PCS becoming the most cost-effective option. This outcome was due to the smaller difference in QALYs between PCS and TXA and the very low total costs of PCS (as a result of length of stay savings). To explore this further, these two sensitivity analyses were combined with a sensitivity analysis to account for the unusually large difference in length of stay for PCS. This resulted in TXA returning to being the most cost effective option. The GDG considered that these sensitivity analyses highlighted some uncertainty in the base case, however the further exploration mitigated the need to change the overall conclusion.

PCS was the most cost saving intervention in the high risk group; this was due primarily to the large reduction in hospital length of stay. As described above, when the mortality effect of TXA was removed, PCS had the highest QALYs which were attributable to the reduced length of stay. Furthermore, when the QALY difference between PCS and TXA was reduced, as seen with the MI and stroke sensitivity analyses, the length of stay savings were a key driver in establishing the most cost-effective option. The length of stay data for this comparator was based on one RCT with a high baseline length of stay. The GDG had concerns about the applicability of this evidence and therefore sensitivity analyses adjusting for this length of stay and excluding length of stay were undertaken. These resulted in TXA remaining the most cost-effective option.

The GDG highlighted that PCS may have use when blood is lost in chest drains in cardiac surgical patients, which is in a minority of cases. However, they acknowledged that in current practice it may not be considered an appropriate intervention for all high risk surgeries on its own, particularly in patients who have extensive bleeding post-operatively and therefore may require reoperation to stem the bleeding (rather than PCS). The GDG noted that this was unlike ICS which could be used across all high risk surgeries.

Intra-operative cell salvage is used reasonably widely across the NHS in current practice, particularly in surgeries with high risk of bleeding. The GDG accepted that TXA alone was the most cost-effective option overall based on the available evidence, but they felt that for certain patients with particularly high blood loss the addition of ICS to TXA may still be a cost-effective option. This was on the basis that the mechanisms of action are different for TXA and cell salvage and so it was considered that the relative benefit of cell salvage over TXA in terms of avoiding allogeneic transfusions is likely to increase with greater blood loss. The evidence identified in the clinical review was not able to support or refute this because no data was available in such a population and it was not possible to explore this very high risk population within the context of RCT level clinical data. In addition, they felt that in reality the mortality benefit seen with TXA alone was likely to also be achieved with TXA+ICS and the reason that this has not been observed in the evidence could be attributed to a lack of data. A series of exploratory threshold analyses were therefore undertaken within the cost-effectiveness analysis to help the GDG explore whether conclusions might change under these assumptions. These exploratory threshold analyses indicated that under certain circumstances, like those described above, it is plausible that the combination of ICS and TXA may become a cost-effective option. However, it is highlighted that these scenarios are theoretical and not based on evidence.

As in the base case analysis, these exploratory threshold analyses assumed that patients bleeding risk is assessed in advance and if they are considered to be very high risk then ICS is set up and used for all patients, that is the cost is incurred for all patients. This implies that the patients or patient group this analysis applies to is identifiable in advance. However, the GDG acknowledged the difficulty of predicting a patient's bleeding risk. They noted that for some cases, it may be possible to predict risk prior to surgery based on type of surgery and patients' characteristics thus allowing ICS to be set-up in advance. In other cases, troublesome bleeding may occur during surgery, for example when there is trauma to a vessel, and the equipment would need to be set up during surgery. The costs may be cheaper than those reported in this analysis if ICS is only set up for those who need it during surgery, however some of the benefit of ICS may be lost due to delays in setting up equipment. Furthermore, in hospitals where the number of surgical patients eligible for ICS is expected to be low, hiring cell salvage equipment may not be feasible due to the requirement from manufacturers of having a minimum disposable order. For these hospitals, purchasing the equipment may be the only solution and this may make the intervention no longer a cost-effective option.

The objective of this analysis was to identify the intervention that provided the greatest health benefit (quantified in terms of QALYs) at an acceptable cost to the NHS (that is with an acceptable incremental cost-effectiveness ratio as per NICE methodological guidance). The GDG highlighted that another objective for these interventions is to conserve allogeneic blood, as it is a scarce resource. Although this was not the objective set out in our analysis, if this objective were to be considered, the combination of ICS and TXA would be the favoured intervention for the high risk group in terms of effectiveness, but cost-effectiveness would be unclear as there is no threshold for this. The group did highlight that there is currently no shortage of allogeneic blood in the UK

and so were satisfied that using the cost per QALYs analysis was appropriate for decision making for the guideline. As well as conserving allogeneic blood, another objective may be to limit exposure to allogeneic blood to account for unquantifiable unknown risks.

Another benefit of avoiding allogeneic transfusion, which was not incorporated into the model, is that it eases cross-matching if these individuals need transfusions in the future as they will not have antibodies.

This new economic analysis was assessed as directly applicable with minor limitations.

Mortality differences

The results of the high risk subgroup analysis are dependent on the mortality benefit obtained with TXA and not with other treatments. The GDG discussed why the mortality benefits might be seen with TXA and no other treatment options, especially those with similar or greater blood savings. While they felt it was not possible to establish this, they noted the different mechanisms of actions of TXA versus cell salvage options and they were satisfied that the clinical evidence for TXA was robust. They did also consider it plausible that this benefit would be seen with combination treatments of cell salvage with TXA and that it may be a lack of data that accounts for the lack of effect seen in the evidence review. This was explored in a series of sensitivity analyses and even when ICS+TXA was attributed the same mortality benefit as TXA alone, TXA remained the most cost-effective option due to the high cost of ICS relative to the additional blood savings.

The data from the clinical review for the other comparators demonstrated a great deal of uncertainty around the estimates. As a result, the GDG decided not to use the clinical review data in the base case for these comparators, and instead assumed there was no mortality difference compared to standard treatment. A sensitivity analysis was conducted where the clinical review data was used and it found that TXA remained the most cost-effective option.

Cost of cell salvage

The GDG noted that the cost of ICS disposables in the analysis was likely to be higher than prices available to hospitals through negotiations with suppliers. These lower costs could not be included as they are not publicly available. The cost of the disposables was explored in a sensitivity analysis, this demonstrated that the conclusion was not sensitive to changes in this input. The GDG considered the results of this sensitivity analysis to be important as it indicates that even if the cost of the ICS disposables was lower, TXA would remain the dominant strategy. The GDG noted that this sensitivity analysis along with the exploratory threshold analyses imply that ICS (alone or in combination with TXA) should not be used for all high risk surgeries but rather it should be reserved for those cases with high baseline risk of transfusion and high expected volume of blood loss.

Length of stay data as a proxy for the impact of acute adverse events

A limitation of this analysis is the use of length of stay as a proxy for the impact of acute transfusion- and treatment-related adverse events. Alternatives were considered during development such as explicitly modelling these events; however it was felt that this would be overly complicated and there was a lack of data to inform this approach. The GDG concluded that in principle length of stay was a reasonable proxy for the impact of these acute events. The GDG

noted the general issue of length of stay data being impacted by setting (e.g. country) and in particular that there was an unusually large difference in length of stay for PCS in the high risk group that might be accounted for due to the unusually high baseline length of stay in that study. The GDG considered omitting length of stay from the base case analysis but felt that attempting to capture the impact on patients outweighed this concern. Furthermore they felt it was preferable to maintain the link with the clinical data review in the base case analysis. It was agreed that this issue required exploration in sensitivity analyses and taking into consideration when interpreting results.

A further limitation of this approach was that it used utility values from a different patient population which was not surgical patients receiving or not receiving transfusions. However, more relevant data was not identified.

To address these limitations, as part of the sensitivity analyses, length of stay was excluded, and therefore differences in quality of life and related costs. Removing length of stay did not change the conclusions.

ICS in moderate risk group

The GDG noted that ICS is still being used for orthopaedic surgeries (first time knee or hip replacements) which are considered to be at moderate risk of bleeding. There was limited evidence for the use of ICS in these types of surgery, half of which was from prior to 2003 and therefore was not incorporated in the analysis. As highlighted in the Full Guideline (section 6.4.3), the GDG agreed that substantial changes in transfusion practice over time with respect to the use of cell salvage meant that studies published prior to 2003 were not relevant to current clinical practice. Studies published before 2003, therefore should not inform the decision making process or the economic model. Although the use of ICS in moderate risk surgery was not assessed in our economic analysis, the GDG highlighted that as blood loss has decreased now in these surgery types ICS may not be a cost-effective strategy.

Adverse events

A further limitation is the exclusion of long term transfusion-related adverse events. Between 2010 and 2013, SHOT reported two incidents of hepatitis B, two incidents of hepatitis E and one incident Paro-virus B19 in the UK.[82] The GDG acknowledged the severity of these infections, however considered that they were extremely rare and were unlikely to impact on the results of the economic model. Had these infections been incorporated into the analysis, they would have favoured the interventions that reduced the exposure to allogeneic blood. For the moderate risk group, this would have further supported the use of TXA which was the most blood saving intervention. In the high risk group, this would have increased the benefit of ICS+TXA. However it is considered unlikely to change the conclusions.

The main adverse event for TXA was considered to be thrombotic complications. The clinical evidence review suggested there was a non-significant reduction of risk of thrombotic complications for TXA compared to placebo; therefore the GDG decided that it was unnecessary to include this outcome in the model. If it had been modelled explicitly, the results would have been even more favourable towards TXA as the thrombotic events were lower in those receiving TXA compared to placebo.

M.4.3 Generalisability to other populations or settings

The population of this analysis was all surgical patients at moderate or high risk of bleeding, however it is acknowledged that the trials used to inform the analysis do not reflect all possible surgery types within each risk group. The trials in the high risk group were conducted primarily in cardiac surgery populations and in the moderate risk group in orthopaedic surgery patients.

As highlighted in the introduction, due to limited or no clinical data, we were unable to model any of these interventions in paediatric surgical patients. The clinical evidence for TXA compared to standard treatment in children suggested that TXA may result in a reduction of post-operative blood loss. Based on this limited evidence, the low intervention cost of TXA and the cost-effectiveness evidence in adults, it was judged highly likely that it would be a cost-effective option in paediatric surgical patients.

No clinical evidence was identified for ICS or PCS alone in children. The GDG extrapolated the findings regarding the lack of cost-effectiveness of ICS alone in high risk adults and of PCS alone in both high and moderate risk adults to children. The GDG did note however, that special consideration should be given for paediatric cardiac patients as cell salvage is widely used in paediatric cardiac surgery to reduce exposure to allogeneic blood. TXA however, may not always be used in the same clinical situation due to uncertainty about the optimal dose and possible side effects.

Finally, there was limited and low quality evidence in children suggesting ICS+TXA may result in fewer patients transfused and a lesser volume of total blood transfused compared to ICS alone. Based on this limited evidence and the economic analysis conducted in adults, the GDG agreed to extrapolate the findings in adults to children.

M.4.4 Comparisons with published studies

No analyses were identified that compared the same treatment strategies as our analyses.

Two economic evaluations comparing ICS + PCS (alone or in combination) with no cell savage in cardiac and or orthopaedic surgical adult patients were identified.[193,392] The first was a cost-utility analysis by Davies 2006[193] which found that cell salvage (ICS or PCS) was dominant compared to no cell salvage (less costly and more effective). This analysis was assessed as partially applicable with minor limitations. The second by Klein 2008[392] was a cost-consequence analysis based on a single RCT which found that cell salvage was more costly and more effective at reducing the number of units transfused than no cell salvage. This analysis was assessed as partially applicable with potentially serious limitations. A cost-utility analysis by Samnaliev 2013[619] comparing ICS with no cell salvage in orthopaedic and cardiac surgical paediatric patient found that ICS was dominant compared to no cell salvage (less costly and more effective). This analysis was assessed as partially applicable with potentially serious limitations. Note, the effectiveness data used in the analysis was from a non-randomised trial and therefore not reported in the clinical evidence. No economic evaluations were identified for the use of PCS alone in paediatric surgical patients. Two of these studies were inconsistent with the analysis conducted by the centre which found that ICS increased costs compared to usual care[193,619]. In both studies the cost of cell salvage used was less than the cost used the analysis conducted by the centre. In the study by Davies 2006[193] the cost of cell salvage used in their base case analysis for both types of ICS and PCS was based on the unit cost of ICS and was £93 to £217 per patient dependent on the case load of the hospital and the brand of equipment used. Although the cost is from the UK, it does date from 2003 and therefore

is unlikely to reflect current NHS context. The second study (Samnaliev 2013[619]) is a US analysis and uses a unit cost of £59 per patient for ICS. As this analysis is from a US healthcare payer perspective, the unit cost is unlikely to reflect current NHS context.

Finally, none of the published studies included all the interventions in their analyses. The GDG felt that the new economic analysis conducted for this guideline superseded these studies which were based on older clinical evidence and in the case of two of these analyses, based on single trials.

Two economic evaluations were identified comparing TXA with placebo or no TXA in total hip replacement surgery patients and found that TXA was dominant (less costly and more effective).[25,588] These studies were assessed as partially applicable with potential serious limitations. This is consistent with the results of analyses conducted by the centre, which took into account other treatment options.

No applicable studies were identified that compared combinations of cell salvage and TXA to single interventions or no interventions.

M.4.5 Conclusions

An original cost-utility analysis found that in surgical patients at high risk of bleeding, tranexamic acid was the most cost-effective option when compared with standard treatment, intra-operative cell salvage, post-operative cell salvage and the combination of tranexamic acid and intra-operative cell salvage. It was dominant (less costly and more effective) compared to all options except post-operative cell salvage. It was cost-effective compared to post-operative cell salvage (ICER: £14,058 per QALY gained). This analysis was assessed as directly applicable with minor limitations.

An original cost-utility analysis found that in surgical patients at moderate risk of bleeding, tranexamic acid was the most cost effective option when compared to standard treatment, post-operative cell salvage and the combination of intra-operative cell salvage and post-operative cell salvage. It was dominant (less costly and more effective) compared to all options except post-operative cell salvage. It was cost-effective compared to post-operative cell salvage (ICER: £797,101 per QALY gained). This analysis was assessed as directly applicable with minor limitations.

M.4.6 Implications for future research

Further research that would improve the model would include additional studies reporting 30-day mortality as an outcome, in particular for the combination of TXA with ICS. In addition, studies targeted at surgical patients at very high risk of bleeding would be helpful. In this model, we lacked utility estimates for hospitalisation; while this was not a great driver of QALYs in this analysis, published utility values would improve the accuracy of this and future analyses. We were unable to include some interventions in this analysis due to a lack of clinical evidence (for example PCS + TXA in both risk groups, ICS and ICS+TXA in moderate risk group) further research into these would allow them to be incorporated in future analyses. Similarly, there was limited clinical evidence for any of the interventions in a paediatric surgical population, further research in this area would allow for economic modelling in this population.

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Appendix N: Unit costs

N.1 Erythropoietin and iron

Relevant unit costs for intravenous and oral iron are provided below to aid consideration of cost effectiveness. These costs were taken from the NICE clinical guideline entitled 'anaemia management in chronic kidney disease' (AMCKD, NG8).

Oral iron

The cost of oral iron therapy was taken from the Prescription Cost analysis, England 2013[309], and was a weighted average of the two most commonly prescribed tablets.

Table 48: Cost of oral iron therapy

Drug	Tablets (thousands)	Cost per tablet, £	Tablets per day	Cost per month, £
Ferrous Fumarate 210 mg	185,729	0.02738	3	2.50
Ferrous Sulfate 200 mg	152,787	0.03699	3	3.38
Totals	338,516			2.90

Intravenous iron

The cost of intravenous iron therapy for pre-operative anaemia management was assumed to be equivalent to that of a non-haemodialysis, high-dose low frequency dose (1000 mg).

In the AMCKD guideline, the cost was estimated based on: drug cost, staff time, clinic space, administrator time and transport. Detail regarding the sources and assumptions used for costing are outlined below.

Iron unit cost was taken from the British National Formulary.[360,360] Staff time was estimated by GDG members and included time for preparation, infusion and observation. Preparation included drug preparation and cannulation. Infusion time varied according to the drug's Summary Product Characteristics. Observation (30 minutes) is required for all regimens. It was assumed that a nurse would observe 2 patients concurrently. The cost of a band 6 nurse at a rate of £42 per hour was applied.[183]

Cost of nurse time, administrator time, transport, and clinic space all vary according to the number of infusions. The cost of clinic space also varied according to the duration of infusion and hence the throughput achievable. The following costs were taken from a published cost analysis for pre-dialysis patients conducted at Kings College Hospital, London[798]:

- Clinic space - £5 per patient-hour
- Administrator time (clerical staff) - £3.28 per visit
- Transporting a patient to hospital (if required) - £45 for return visit

They assumed 10% of non-haemodialysis patients would require NHS transport to hospital.

Disposables were assumed to cost £5 per visit (including cannula, needles, syringes, dressing, IV giving set and sodium chloride solution).

Table 49: Intravenous Iron therapy costs – non-haemodialysis high-dose low-frequency

Regimen				Drug cost, £		Nurse time per infusion, minutes			Nurse cost, £	Other, £			Total, £
	Iron mg/ vial	Vials/ visit	Visits	Cost/ vial	Total drug cost	Preparation	Infusion	Observation	Nurse time	Consumables	Transport	Admin time and Clinic space	
Ferric Carboxymaltose	500	2	1	95.50	191.00	15	15	30	26.25	5.00	4.50	8.28	235.03
Iron dextran	500	2	1	39.85	79.70	15	300	30	126.00	5.00	4.50	32.03	247.23
Iron isomaltoside 1000	500	2	1	84.75	169.50	15	30	30	31.50	5.00	4.50	9.53	220.03
Ferumoxytol	510	1	2	65.00	130.00	15	15	30	52.50	10.00	9.00	16.56	218.06
Un-weighted average					**142.55**				**59.06**	**6.25**	**5.63**	**16.60**	**230.09**

N.2 Red blood cells

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Allogeneic red blood cells cost £122.09 per unit according to the NHS Blood and Transplant 2013/2014 price list.[530] This cost doesn't include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. This was estimated using the resource estimates from a UK costing study by Agrawal 2006[17], GDG expert opinion and PSSRU unit costs 2013. Note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications.

N.3 Platelets

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Platelets (1.0 ATD) cost £208.09 per unit according to the NHS Blood and Transplant 2013/2014 price list.[530] This cost doesn't include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests.

A US study by Riley 2012[601] estimated that the additional costs per unit for transfusion. The cost year is unclear and assumed to be 2011 US dollars. The costs are presented below as 2011 UK pounds by converting using 2013 purchasing power parities[551]:

- patient care unit = £40 per transfusion
- blood bank cost = £15 per transfusion
- cost of reaction (assuming 1% likelihood of reaction) = £1

Therefore the additional costs associated with platelet transfusion are £56 and based on the estimates outlined above the total cost of platelet transfusion is estimated to be £264 per transfusion.

This may be an underestimate of the total cost of transfusion. This cost doesn't include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. This was estimated using the resource estimates from a UK costing study by Agrawal 2006[17], GDG expert opinion and PSSRU unit costs 2013. Note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications.

N.4 Fresh frozen plasma

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Clinical FFP (UK sourced) costs £27.98 per unit according to the NHS Blood and Transplant 2013/2014 price list.[530] Octaplas® costs £53 per 200 ml bag. For patients born on or after 1st January 1996 FFP is sourced from countries with a low risk of vCJD. Either Octaplas® or methylene blue FFP (MBFFP) both pathogen inactivated, are used for these recipients. The cost of MBFFP (non-UK sourced) is £177.01 per unit according to the NHS Blood and Transplant 2013/2014 price

list.[530]. These costs do not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests.

As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. This was estimated using the resource estimates from a UK costing study by Agrawal 2006[17], GDG expert opinion and PSSRU unit costs 2013. Note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications.

N.5 Cryoprecipitate

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Pooled cryoprecipitate costs £180.54 per pool according to the NHS Blood and Transplant 2014/2015 price list.[530] One pool of cryoprecipitate is derived from five units of donated blood. For patients born after to 1st January 1996 methylene blue cryoprecipitate is required. Methylene blue cryoprecipitate-pooled (non-UK sourced) costs £1,080.48 per pool according to the NHS Blood and Transplant 2014/2015 price list.[530] One pool of methylene blue cryoprecipitate is derived from six units of donated blood. These costs do not include all costs associated with a transfusion such as staff time, disposables, and storage, wastage and laboratory tests.

As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. This was estimated using the resource estimates from a UK costing study by Agrawal 2006[17], GDG expert opinion and PSSRU unit costs 2013. Note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications.

N.6 Prothrombin complex concentrate

Relevant unit costs are provided to aid consideration of cost effectiveness. Two brands of dried PCC are listed in the BNF: Beriplex and Octaplex. The unit costs are summarised below:

Table 50: Unit cost of PCC

Drug	Preparation	iu/vial	Cost/vial [(a)(b)]
Octaplex	Powder in vial	500	£245[(b)]
Beriplex	Powder in vial	250	£127.50[(b)]
		500	£255[(b)]
		1000	£510[(b)]

(a) Cost includes water for injection and admin set
(b) Source: Octaplex Product update[543]
(c) Source: MIMS August 2014[308]

N.7 Monitoring for acute reactions

Relevant unit costs are provided below to aid consideration of cost effectiveness.

The BCSH guidelines recommend that the monitoring of adult conscious transfusion patients is undertaken prior to transfusion, 15 minutes after starting the transfusion and at the end of transfusion.[95] Based on GDG expert opinion, these observations are estimated to take ten minutes each and would be done by a nurse.

A hospital-based ward nurse costs £85 per hour of patient contact according to PSSRU 2012.[182] Therefore the total cost of monitoring a transfusion patient by a ward nurse is estimated to be £42.50.

For unconscious or paediatric transfusion patients, additional hourly observations are undertaken during the transfusion period (approximately four hours). Therefore a total of six ten-minute observations would be undertaken. The total cost of monitoring these patients would be £85.

N.8 Patient information

In the absence of economic evidence, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 51: Unit costs of healthcare professionals

	Costs per hour
Nurse, 24-hour ward (band 5)	£41[(a)]
Registrar	£59[(b)]
Consultant: medical	£139[(c)]

Source: PSSRU 2013[183]

(a) Per hour, including qualifications

(b) Per contact hour, based on a 48 hour week, including qualifications

(c) Per contact hour, including qualifications

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