National Institute for Health and Care Excellence

Final

Joint replacement (primary): hip, knee and shoulder

Network meta-analysis and cost analysis of methods for tranexamic acid administration

NICE guideline NG157

Network meta-analysis report

June 2020

Final

This evidence review was developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1 Network meta-analysis: administration methods of tranexamic acid

1.1 Introduction

A hierarchical Bayesian network meta-analysis (NMA) was performed for the tranexamic acid (TXA) review question. This type of analysis allows for the synthesis of data on multiple interventions, including both direct and indirect evidence for each comparison, without breaking randomisation. NMA delivers a coherent set of estimates that may be ranked to inform recommendations.[9, 10]

The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to one another. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the evidence found in the clinical review.

Network meta-analysis assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). This assumption is the same as that made in conventional pairwise meta-analysis, but we also have to be particularly careful that the studies making different comparisons do not differ in effect modifiers (the data are consistent).

TXA is an anti-fibrinolytic agent that is used to reduce perioperative blood loss during primary elective joint replacement surgery. As a synthetic lysine analogue, TXA binds to lysine receptor sites on plasminogen in the blood. Plasminogen is the precursor to the enzyme plasmin; this enzyme breaks down fibrin which helps to clot the blood. As such, TXA stops the breakdown of fibrin in the blood, which is needed to form clots to prevent blood loss. Transfusions are associated with costs and a risk of infection, and therefore should be minimised from both a healthcare and patient perspective.

TXA can be administered via an oral tablet, intravenously, topically or in a combination of these forms. Although use of the drug is established as effective in reducing the need for transfusions, it is not evident which form of administration is the most clinically and cost effective method.

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2 Study selection

To estimate the relative risks, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence.

The committee agreed that blood loss is generally similar for both hip and knee replacements. For shoulder replacements blood loss may be less, however, for this analysis no shoulder replacement studies were includable. Therefore this analysis combines studies that look at hip and knee replacements. Furthermore, in the clinical evidence review hip, knee and shoulder populations were combined, as agreed by the committee.

The full details of the TXA evidence review can be found in evidence review G.

2.1 Outcomes

Transfusion was chosen as the only outcome as:

- it was designated a critical outcome
- it was commonly reported in the trials
- it has cost implications
- pairwise meta-analyses showed some differences between comparators.

Other outcomes that were included in the initial clinical review were not considered for the NMA as they either showed no clinically relevant difference, or were infrequently reported across the studies.

2.2 Population

People indicated for primary elective joint replacement, it was assumed that all of these surgeries have a moderate risk of blood loss (500ml-1000ml), as agreed by the committee.

2.3 Comparators

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in Evidence Review G of the full guideline. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported transfusion events and matched the inclusion criteria of the systematic review) then it was included in the network meta-analysis, otherwise it was excluded.

The comparators included in the NMA were:

- Intraarticular (IA) TXA, (monotherapy)
- Intravenous (IV) TXA, (monotherapy)
- Oral TXA, (monotherapy)
- IA and IV TXA, (combination therapy)
- IA and oral TXA, (combination therapy)

As agreed with the committee, placebo and no treatment were not included as comparators as it is established practice that administration of some form of TXA is clinically and cost-effective in comparison. Combination therapies were treated as distinct interventions and not the sum of the effects of the individual components.

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2.4 Time horizon

The time horizon was initial inpatient stay

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3 Statistical methods

3.1 Synthesis methods

A hierarchical Bayesian NMA was performed using the software WinBUGS 1.4.3.[48] [10]

A generalised linear model with a binomial likelihood and logit link was fitted with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. Non-informative Normal (0,10000) priors were assigned to the trial-specific baseline and treatments effects (log odds ratios), while a Uniform(0,5) prior was assigned to the between-study standard deviation in the random effects models. [10]

This model accounts for the correlation between study level effects induced by multi-arm trials. In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network

Studies with zero or 100% events in all arms were excluded from the analysis because these studies provide no evidence on relative effects.[10] Where a study had an arm with 0 events, a correction factor was applied where 0.5 was added to the event rate for all arms in that study and 1 was added to the sample size for all arms in that study.

We tested the goodness of fit of the model by calculating the residual deviance. If the posterior mean residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

3.1.1 Fixed and random effects

When considering models for network meta-analysis (NMA), there are several aspects of the data that will impact the choice of parameters included in the model. To assess the validity of an NMA it is essential to assess the extent of heterogeneity and consistency. Heterogeneity concerns the differences in treatment effects between trials within each treatment contrast, while consistency concerns the differences between the direct and indirect evidence informing the treatment contrasts.[8] Section 3.2 explains how inconsistency was assessed.

A fixed effects NMA model is the simplest model available to estimate the effects of interventions separately while simultaneously synthesizing all available evidence. This model assumes no heterogeneity between trials within each treatment contrast. In other words, all trials are estimating the same treatment effect, regardless of any differences in the conduct of the trials, populations, or treatments (i.e., administration or dose). If this assumption is unreasonable, then a random effects NMA model may be considered. This model accounts for any differences in treatment effects between trials that are beyond chance through measures such as the between-study standard deviation. When critiquing NMA models, it is good practice to assess and compare the fit of both fixed and random effects models, as differences may provide evidence of potential between-study heterogeneity[10].

3.1.2 Baseline model and data

The baseline risk is defined as the risk of achieving the outcome of interest in the baseline treatment (IA TXA) of the included trials.[14] This allows us to convert the results of the NMA from odds ratios to risk ratios. Twenty eight studies were identified that included IA as a comparator. Out of these, two were European (Aguilera 2015[4], a Spanish study and Digas 2015[16], a Greek study). In the absence of UK based studies, these studies represented the closest population to an NHS population and gave the best external validity. Out of these two studies only Aguilera 2015[4] was chosen to inform the baseline model as in the clinical review it was the only of the two European studies rated as having a low risk of bias. As only one

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study was included in the baseline model, the fixed effects baseline model was used. Aguilera 2015[4] reported 4 transfusion events (n=50) in its IA arm. Table 1 shows the details of the baseline model.

Table 1: Posterior distribution of the baseline probability of transfusion for the random and fixed effects baseline models

Model and node	Mean (95% confidence intervals)	Deviance information criterion (DIC)
Fixed effects		5.223
Probability (predictive distribution)	0.080 (0.023, 0.17)	-
Log odds (predictive distribution)	-2.561 (-3.762, -1.588)	-
Sum of the residual deviance	1.045 (0.001, 5.249)	-

3.1.3 Number of simulations and checking convergence

For all analyses (both baseline and NMA), a series of 60,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and bgr plots. Kernel density plots were examined to ensure there was enough evidence to sufficiently estimate between study standard deviation. Each analysis was run with 3 chains, each with a different set of initial values, to ensure that the model had converged and was not influenced by the initial values.

3.2 Methods of assessing inconsistency

An important assumption made in NMA concerns the consistency, that is, the agreement of the direct and indirect evidence informing the treatment contrasts.[11, 15] There should be no meaningful differences between these two sources of evidence.

To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects, model.[11, 15] The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that the consistency assumption can only be assessed when there are closed loops of direct evidence on 3 or more treatments that are informed by at least 3 independent sources of evidence.[12] The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model.[12] Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point).

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study contributes 1 data point per arm in the case of arm-level data, 1 point per relative effect in the case of contrast-level data)

In addition to assessing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean deviance and the effective number of parameters, and thus penalizes model fit with model complexity.[12] Lower values are preferred and differences of 3 points were considered meaningful.

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Where the base-case model assumes random effects, if the inconsistency model has smaller heterogeneity (measured by the posterior median between-study standard deviation) compared to the consistency model, then this indicates potential inconsistency in the data.

To visually assess if specific data-points are contributing to inconsistency, we plot contributions to the posterior mean residual deviance for each data-point for the inconsistency model vs the consistency model. Points lying below the line of equality indicate data-points contributing to inconsistency.

We performed further checks for evidence of inconsistency through node-splitting through the R2WinBUGS package in R (41). [11, 13, 41, 43] This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared.[13, 43].

3.3 Costs and resource use

Costs were divided into the intervention costs (drug and disposables) and the cost of a transfusion.

3.3.1 Intervention costs

The cost for each arm of the included studies was calculated by extracting the dosage of TXA used, the saline volume used (if applicable) and disposables used (if applicable). Unit costs for TXA solution, TXA tablets, saline and syringes were then obtained from eMIT[7] or NHS Supply Chain Catalogue 2018[33] (see Table 2) and multiplied by the relevant resource use for each treatment in each included study. An unweighted average of the cost of each treatment for each relevant study was then taken from all the relevant studies (see Appendix B).

Table 2: UK unit costs for TXA, saline and a syringe

Resource	Unit cost	Source
Syringe	£0.35	NHS Supply Chain Catalogue 2018[33]
TXA solution (500mg/ml)	£0.55	eMIT[19]
TXA tablets (500mg)	£0.05	eMIT[19]
Saline ampoule (20ml of 0.9%)	£0.11	eMIT[19]

As a range of volumes of saline were available on eMIT [19] with different costs, for consistency the proportional cost of a 20ml 0.9% ampoule was applied. For example, if a study stated it used 100ml of saline, the unit cost of a 20ml 0.9% saline ampoule was multiplied by 5. As suggested by the committee, the only additional disposables required were syringes for the IV and IA arms.

Where a study indicated that a dose of TXA not in a multiple of 500mg was given, the dose was costed to the nearest 500mg or 500mg/ml. This was done as eMIT only provides oral doses in 500mg tablets or 500mg/ml solution for IA or IV. For example, if a study stated people given oral TXA received 550mg in total, this would be rounded down to 500mg. Where an included study gave the dosage used as a certain amount per kilogram of the patient, a weighted average of 76.8kg was used based upon male and female data from the Office for National Statistics[34].

After consulting with the guideline committee, staff costs were not applied as TXA is administered in parallel to other processes by staff that would be present even if TXA was not being administered. Studies which included an oral TXA arm were checked that the dose

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was given on the morning of surgery rather than any other time as this would have represented an additional cost in terms of personnel. Other costs relating to surgery and running the operating room were assumed to be the same between different comparators and excluded on this basis. The average dosage used for each intervention was included upon request by the committee (see Table 3). The median dose was calculated as the mean dosage was skewed towards higher values. This figure checked if the studies represented a similar dosage to those that are used by the NHS. Drug cost was calculated by taking away the costs of a syringe and 100ml of saline (except for oral where this did not apply).

Table 3: Average intervention costs for each administration method and median dose of TXA

Method	Average intervention costs (including syringe and saline)	Drug cost	Median dose (grams) of TXA
IA	£2.82	£1.93	2.00
IV	£2.25	£1.37	1.54
Oral	£0.27	£0.27	3.07
IA + IV	£5.34	£4.10	3.02
IA + oral	£2.31	£1.85	3.50

3.3.2 Cost of transfusion

The unit cost of a transfusion was calculated from Stokes 2018[39] and the NICE Blood Transfusion guideline[31]. Stokes[39] included all laboratory and equipment costs associated with processing a blood transfusion. The standard volume of a unit of red blood cells (RBCs) was assumed as 280ml with a range of 220-340ml.

The mean number of units transfused per transfusion event was calculated for each intervention as there is a significant cost associated with each unit transfused. All studies included in the clinical review were analysed to calculate this. Where available, the total units or volume transfused; the volume of each unit; and total transfusion events were extracted from each study for each arm. This data was then aggregated to find the mean total volume transfused per transfusion event for each intervention.

However in practice, volume transfused per transfusion event was inconsistently reported in the included trials. For certain studies it was possible to calculate the average number of units transfused per transfusion event, but the volume in each unit was not specified. For other studies it was possible to calculate the total volume transfused per transfusion event; this was preferable as it was then possible to calculate this volume in terms of standard UK RBC units. For other studies it was not possible to calculate the total units or total volume transfused per transfusion event. Due to these inconsistencies, it was not deemed possible to conduct an NMA for volume transfused per transfusion event. Where it was possible to extract volume transfused per transfusion event, most studies reported 1.5-2 units. Therefore for the base case it was assumed that 2 units of blood are transfused for all interventions.

Table 4: Average cost of a blood transfusion by first and subsequent units of red blood cells

Resource	Unit cost	Source
Administration of first unit of red blood cells (RBC)s	£57.19	Stokes 2018[39]
Administration of subsequent unit of RBCs	£36.13	Stokes 2018[39]
Unit of RBCs (first and subsequent)	£128.99	NHSBT 2018/19[32]

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Resource	Unit cost	Source
Total cost of first RBC unit	£186.18	
Total cost of a subsequent RBC unit	£165.12	

3.3.3 Total cost calculation

The total cost for each administration method was given by the formula:

P(transfusion.event) x (C(first.unit) + C(subs.unit)) + C(intervention)

Where the probability of a transfusion event occurring [P(transfusion.event)] is the output of the NMA. The cost of a transfusion event [C(first.unit) + C(subs.unit)] is the cost of transfusing an initial unit and 1 subsequent unit. The cost of each intervention [C(intervention)] was calculated as outlined in section 3.3.1.

This formula was applied for all 5 comparators with the least costly representing the best value for money when factoring in the probability of a transfusion occurring.

3.3.4 Methods of sensitivity analyses

A series of one way deterministic sensitivity analyses were conducted to test the robustness of the result given the assumptions made. Firstly, an analysis was conducted where the intervention costs were doubled for all administration methods. Another analysis was done where the intervention costs were doubled only for the combination therapies whilst intervention costs for the monotherapies remained the same.

Lastly, the assumption of 2 units of RBCs being transfused per transfusion event was tested. In order to test this, an analysis was conducted where only 1 unit was transfused per transfusion event.

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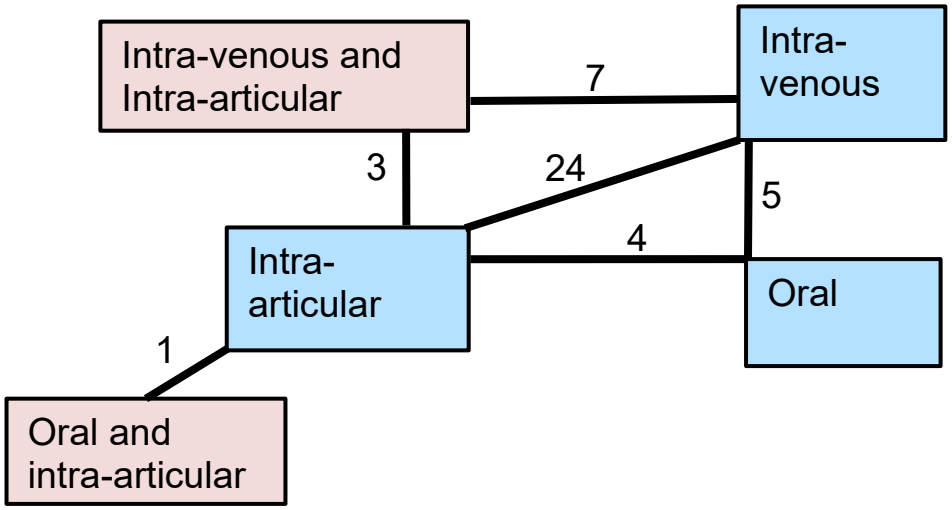
4 Results

4.1 Network

Forty-two studies were identified that reported transfusion events as an outcome. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 36 studies involving 5 treatments were included in the network for transfusion events. Four of these studies were 3- arm trials such that there were 44 direct pairwise comparisons in total. The 3– arm trials were Song 2017[38] (IA vs IV vs IA+IV), Xie 2016[49] (IA vs IV vs IA+IV), Luo 2018[27] (IA vs IV vs oral) and Yuan 2017[51] (IA vs IV vs oral).

The network can be seen in Figure 1 and the trial data for each of the studies included in the NMA are presented in Table 5: Study data for transfusion events NMA

Figure 1 TXA transfusion event NMA structure. Blue shapes indicate a monotherapy and red shapes indicate a combination therapy. Numbers show the amount of studies comparing the relevant interventions



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4.2 Data

Table 5: Study data for transfusion events NMA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				events	N	events	N	events	N
Lin 2015[25]	IV + IA	IA	-	0.5[(a)]	41	1.5	41	NA	NA
Song 2017[38]	IV + IA	IA	IV	0.5[(a)]	51	1.5	51	0.5	51
Xie 2016[49]	IV + IA	IA	IV	0.5[(a)]	71	4.5	71	3.5	71
Cankaya 2017[5]	Oral + IA	IA		0.5[(a)]	51	3.5	51	NA	NA
Adravanti 2018[2]	IV + IA	IV	-	0.5[(a)]	51	2.5	51	NA	NA
Huang 2014[21]	IV + IA	IV	-	3	92	4	92	NA	NA
Jain 2016[22]	IV + IA	IV	-	1	59	4	60	NA	NA
Yi 2016[50]	IV + IA	IV	-	1	50	8	50	NA	NA
Abdel 2018[1]	IA	IV	-	5	320	2	320	NA	NA
Aggarwal 2016[3]	IA	IV	-	0.5[(a)]	36	7.5	36	NA	NA
Aguilera 2015[4]	IA	IV	-	4.5[(a)]	51	0.5	51	NA	NA
Chen 2016[6]	IA	IV	-	1	50	2	50	NA	NA
Digas 2015[16]	IA	IV	-	5	30	7	30	NA	NA
George 2018[18]	IA	IV	-	3.5[(a)]	59	0.5	56	NA	NA
Luo 2018[27]	IA	IV	Oral	7	60	5	60	4	60
Maniar 2012[28]	IA	IV	-	3	40	16	160	NA	NA
May 2016[29(b)]	IA	IV	-	0.5[(a)]	63	1.5	70	NA	NA
Patel 2014[35]	IA	IV	-	1.5[(a)]	48	0.5	43	NA	NA
Pinsornsak 2016[36]	IA	IV	-	9	30	7	30	NA	NA

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Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				events	N	events	N	events	N
Prakash 2017[37(c)]	IA	IV	-	8	100	3	50	NA	NA
Stowers 2017[40]	IA	IV	-	1.5[(a)]	61	0.5	61	NA	NA
Ugurlu 2017[42]	IA	IV	-	2	42	2	40	NA	NA
Wang 2017[46]	IA	IV	-	0.5[(a)]	51	1.5	51	NA	NA
Wei 2014[47]	IA	IV	-	6	102	6	101	NA	NA
Yuan 2017[51]	IA	IV	-	17	140	15	140	15	140
Zhang 2016[52]	IA	IV	-	0.5[(a)]	25	1.5	24	NA	NA
Fillingha-m 2016[17]	Oral	IV	-	1	34	1	37	NA	NA
Jaszczyk 2015[23]	Oral	IV	-	3	40	1	43	NA	NA
Zhao 2018[53]	Oral	IV	-	1	40	2	40	NA	NA
Luo 2018a[26]	IA	Oral	-	2	58	1	59	NA	NA
Wang 2018a[45]	IA	Oral	-	4	75	3	75	NA	NA
Lauruen-gthana 2019[24]	IA	IV	-	15	76	14	76	NA	NA
Mehta 2019[30]	IA	IV	-	44	100	37	100	NA	NA
Wang 2018b [44]	IA	IV	-	2	60	4	60	NA	NA
Zhou KD 2018[54]	IA	IV	-	20	57	24	57	NA	NA
Gulabi 2019[20]	IV	IA + IV	-	3	26	2	22	NA	NA

(a) Continuity correction applied for a 0 event arm. 1 has been added to the sample size and 0.5 to the events for all arms in these studies
(b) Four IV arms were included in this study that were added into a single arm for this analysis
(c) Two IA arms were included in this study that were added into a single arm for this analysis

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4.3 NMA Results

4.3.1 Results of estimation

No meaningful difference was found between the fixed and random effect posterior models for the NMA. Therefore the fixed effect model results were used. Table 6 summarises

- the (fixed effects) results of the conventional meta-analyses in terms of risk ratios from studies directly comparing different interventions, and
- the (fixed effects) results of the NMA in terms of risk ratios for every possible treatment comparison.

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Table 7 presents the base case summary statistics for the network, including the probability of a transfusion occurring, the overall NHS cost, ranking and probability of the intervention being the best. The combination therapy ranking probabilities are skewed towards more favourable ranks, as shown by Figure 2.

Table 6: Risk ratios for transfusion events; direct pairwise meta-analysis results and NMA results

Comparator	Intervention	Direct (95% confidence interval)	Fixed effects NMA - median (95% credible interval)
IA	IV	Presented as risk difference in clinical review	0.925 (0.732, 1.161)
	Oral	0.781 (0.474, 1.282)[(a)]	0.840 (0.518, 1.319)
	IA + IV	Presented as Peto odds ratio in clinical review	0.294 (0.126, 0.611)
	IA + Oral	Presented as Peto odds ratio in clinical review	0.070 (0.000, 1.102)
IV	Oral	1.01 (0.59, 1.73)	0.909 (0.561, 1.432)
	IA + IV	0.27 (0.11, 0.67)	0.318 (0.140, 0.642)
	IA + Oral	n/a	0.076 (0.000, 1.208)
Oral	IA + IV	n/a	0.350 (0.137, 0.816)
	IA + Oral	n/a	0.083 (0.000, 1.377)
IA + IV	IA + Oral	n/a	0.239 (0.000, 4.311)

(a) The inverse risk ratio to the one presented in the evidence review is presented here for comparison

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Table 7: Absolute outcomes and ranking of interventions

Transfusions			
	Probability of a transfusion event - median (95% CrIs)	**Intervention rank - median (95% CrIs)** 1=least transfusions, 5=most	**Probability that intervention is best (least transfusions)**
IA	0.072 (0.025, 0.187)	5 (3, 5)	0.00%
IV	0.066 (0.023, 0.178)	4 (3, 5)	0.00%
Oral	0.060 (0.019, 0.175)	3 (2, 5)	0.06%
IA + IV	0.021 (0.005, 0.074)	2 (1, 2)	20.14%
IA + Oral	0.005 (0.000, 0.098)	1 (1, 5)	79.80%
NHS cost			
	Cost of each intervention including transfusion costs – mean (95% CrIs)	**Intervention rank - median (95% CrIs)** 1=least cost, 5=most cost	**Probability that intervention is best (least cost)**
IA	£31.13 (11.76, 68.36)	5 (3, 5)	0.00%
IV	£28.63 (10.22, 64.65)	4 (3, 5)	0.00%
Oral	£24.70 (6.92, 61.65)	3 (2, 5)	1.15%
IA + IV	£14.34 (7.23, 31.42)	2 (1, 3)	12.23%
IA + Oral	£7.76 (2.31, 36.82)	1 (1, 5)	86.62%

Figure 2: Rank-o-gram showing the probability of each intervention being ranked 1-5 for transfusion events (1 being the best and 5 the least good)

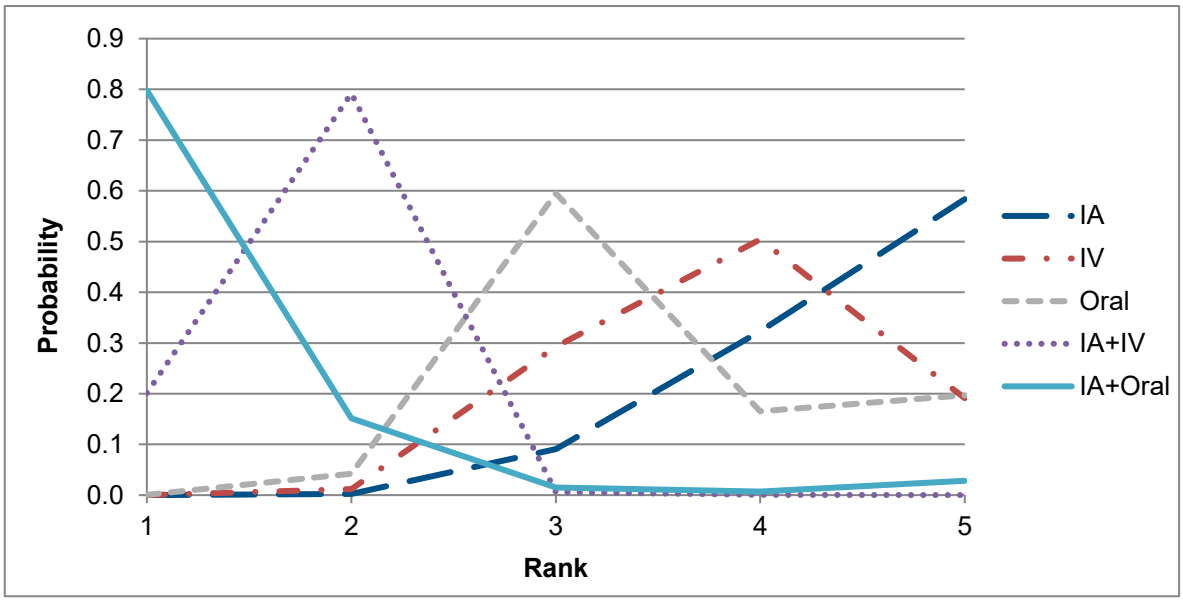

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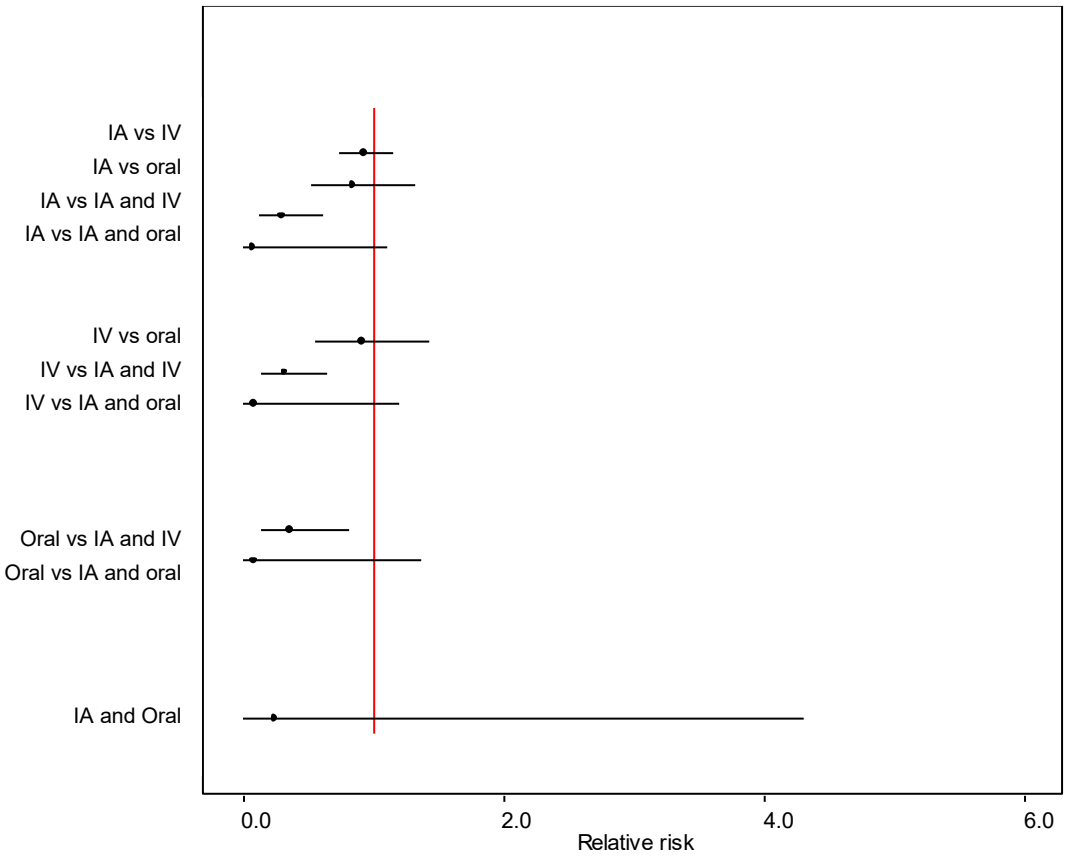
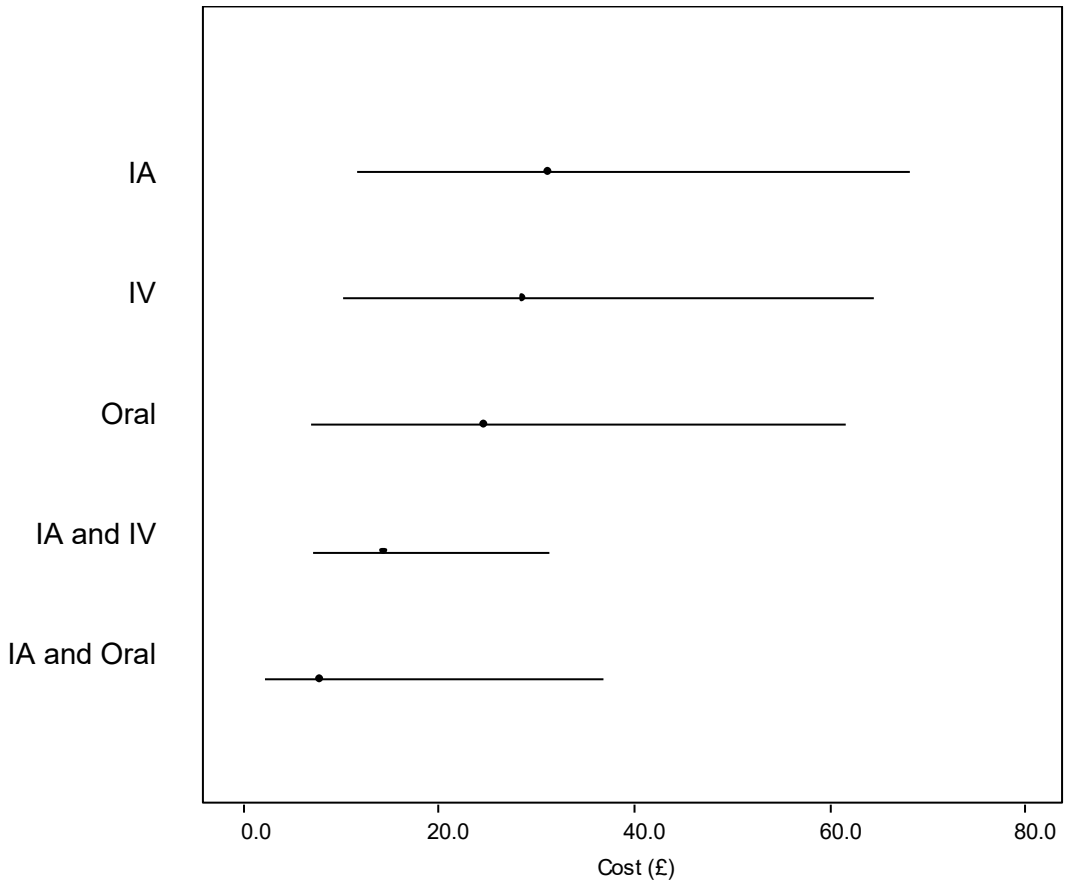
Figure 3: A) Base case median risk ratios (RR) for interventions. RR of 1 shown in red for reference B) Base case mean NHS cost for interventions when factoring in the probability of a transfusion event





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4.3.2 Results of cost sensitivity analyses

Table 8 explores the different cost and transfusion assumptions made in the model. In each sensitivity analysis the probability of a transfusion occurring was kept constant.

Table 8: Sensitivity analyses

	NHS cost of each intervention including transfusion costs – mean (95% CrIs)			
	Base case – 2 units are transfused per transfusion event with average direct costs	2 units are transfused per transfusion event and the intervention costs are doubled	2 units are transfused per transfusion event and the intervention costs for only the combination therapies are doubled	1 unit is transfused per transfusion event and intervention costs remain the same
IA	£31.13 (11.76, 68.36)	£33.94 (14.57, 71.17)	£31.13 (11.76, 68.36)	£17.82 (7.56, 37.55)
IV	£28.63 (10.22, 64.65)	£30.88 (12.47, 66.90)	£28.63 (10.22, 64.65)	£16.23 (6.47, 35.32)
Oral	£24.70 (6.92, 61.65)	£24.97 (7.19, 61.92)	£24.70 (6.92, 61.65)	£13.22 (3.79, 32.8)
IA + IV	£14.34 (7.23, 31.42)	£19.67 (12.56, 36.75)	£19.67 (12.56, 36.75)	£10.11 (6.34, 19.16)
IA + Oral	£7.76 (2.31, 36.82)	£10.07 (4.62, 39.13)	£10.07 (4.62, 39.13)	£5.20 (2.31, 20.60)

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4.3.3 Inconsistency and goodness of fit

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC (Table 9). Convergence was assessed as satisfactory at 120,000 iterations, and the consistency and inconsistency models were compared using results based on samples from 60,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in 39.

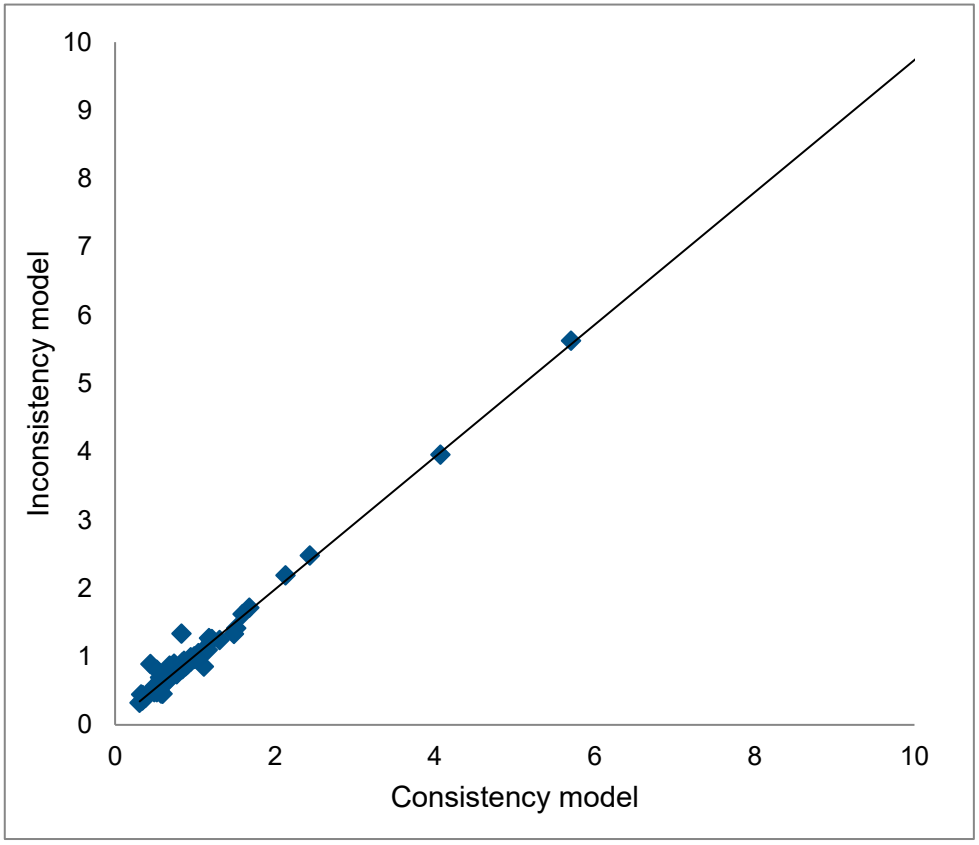
There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 9). The deviance contributions plot (Figure 4) shows no data-points where the inconsistency model better predicted data points (no points below the line of equality).

Table 9 Model fit statistics for transfusion events

Model[a]	Posterior total residual deviance[b]	DIC[c]
Consistency model - FE	71.13	323.724
Consistency model - RE	70.22	325.238
Inconsistency model - FE	72.39	326.793

a) Continuity correction applied to studies containing zero cells
b) Posterior mean residual deviance compared to 76 total data points
c) Deviance information criteria (DIC) – lower values preferred

Figure 4: Deviance contributions for the fixed effect consistency and inconsistency models for transfusion events



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Fixed effect node-split models were run for 150,000 iterations after a burn-in of 50,000 iterations. Convergence was satisfactory across all models. There is no evidence of inconsistency, as there are no meaningful differences between the fit of the fixed effect NMA model (which assumes consistency) and the node-split models (Table 10). In addition, there is no evidence of inconsistency between the direct and indirect estimates (Figure 5).

Table 10 Node split model fit statistics for transfusion events

Node split model[a]	Posterior total residual deviance[b]	DIC	p-value[c]
IV vs. IA	71.55	324.96	0.43
Oral vs. IA	71.72	325.16	0.53
Oral vs. IV	71.99	325.38	0.58
IA and IV vs. IA	71.93	325.40	0.67
IA and IV vs. IV	72.33	325.59	0.86
NMA (no nodes split)	71.13	323.724	**---**

a) Continuity correction applied to studies containing zero
b) Posterior mean residual deviance compared to 76 total data points
c) p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

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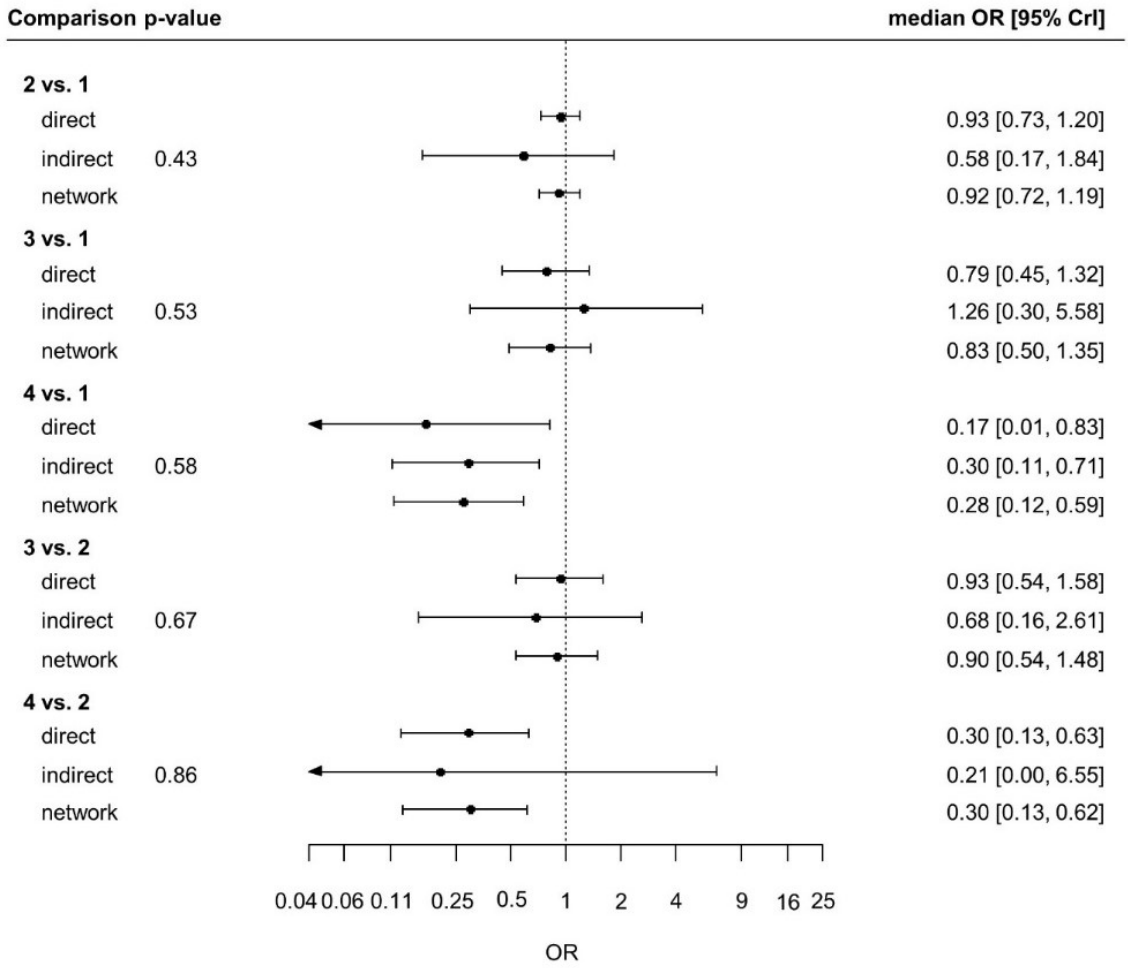
Figure 5: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – IA, 2 – IV, 3 – Oral, 4 – IA and IV, 5 – IA and Oral.



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5 Risk of bias

There are several methods available for assessing the risk of bias in an NMA. For this analysis, the risk of bias conducted for the outcomes included in the pairwise meta-analysis provides an overall assessment.

As seen in **Error! Reference source not found.**, the majority of the relevant evidence for the NMAs had a high risk of bias. For studies where there was high or very high risk of bias, this was due to concerns about selection bias. Full risk of bias details can be found in Evidence Review G of the guideline

Table 11: Included studies risk of bias (RoB) for transfusion events

Study	Transfusion events RoB
Abdel 2018[1]	Low
Adravanti 2018[2]	High
Aggarwal 2016[3]	High
Aguilera 2015[4]	Low
Cankaya 2017[5]	High
Chen 2016b[6]	High
Digas 2015[16]	High
Fillingham 2016[17]	High
George 2018[18]	Low
Huang 2014[21]	High
Jain 2016[22]	High
Jaszczyk 2015[23]	Very high
Lin 2015[25]	High
Luo 2018[27]	High
Luo 2018a[27]	High
Maniar 2012[28]	Very high
May 2016[29]	Low
Patel 2014[35]	Very high
Pinsornsak 2016[36]	High
Prakash 2017[37]	Very high
Song 2017[38]	Low
Stowers 2017[40]	Low
Ugurlu 2017[42]	High

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Study	Transfusion events RoB
Wang 2017[46]	High
Wang 2018[45]	Low
Wei 2014[47]	Low
Xie 2016[49]	High
Yi 2016[50]	High
Yuan 2017[51]	High
Zhang 2016[52]	High
Zhao 2018[53]	High
Lauruengthana 2019[24]	Very high
Mehta 2019[30]	High
Wang 2018[44]	Low
Zhou KD 2018[54]	High
Gulabi 2019[20]	Low

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6 Evidence statements

Transfusion events

- Thirty-six studies were included in the network; IA with oral TXA was ranked as the best intervention in reducing the risk of a transfusion event, although there was considerable uncertainty about its estimated effectiveness (95% credible interval for rank ranged from best to worst). IA with oral ranked second best, and this result was more certain (95% credible interval for rank ranged from 1st to 2nd best). IA was ranked as the least effective intervention in reducing the risk of a transfusion event. No inconsistency was identified in the network.

NHS costs

- Thirty-six studies were included in the network; IA with oral TXA was ranked as the most cost effective intervention when factoring in the probability of a transfusion occurring. Although, there was considerable uncertainty about its estimated cost effectiveness (95% credible interval for rank ranged from most cost effective to least cost effective). IA with oral ranked second best, and this result was more certain (95% credible interval for rank ranged from most cost effective to 3rd most cost effective). IA was ranked as the least cost effective intervention. No inconsistency was identified in the network.

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7 Discussion

An NMA was conducted for transfusion events when using different methods of administrating TXA. Five different ways of administering TXA (monotherapies and combination therapies) were included in the network. These results were used in committee decision-making when making recommendations.

7.1.1 Summary of clinical evidence

Thirty-six studies were included. IA in combination with oral was ranked as the most clinically effective way of administering TXA in reducing blood transfusion events. IA in combination with IV was the second most clinically effective intervention, followed by oral and then IV. IA alone was the least clinically effective intervention. There was a large degree of uncertainty in the ranking of the monotherapies. Although IA is ranked as the least effective, all of the monotherapies had similar rank credible intervals (from rank 3 to rank 5 for IA and IV and rank 2 to rank 5 for oral), so it could not conclusively be said that one is better or worse than the other.

The rank credible intervals were more conclusive for IA in combination with IV, which did not span above the point estimate of rank 2. Although IA in combination with oral was clearly ranked as the best intervention, it comes with the caveat that it was linked to the network by a single study. The uncertainty is reflected by the upper credible interval being rank 5. Furthermore this study was judged to have a high risk of bias in the clinical review (see Cankaya 2017[5]). The IA in combination with oral arm of this trial had 0 events so a correction factor was applied. However it is also noteworthy that the other combination therapy, IA in combination with IV, was better connected to the network and was also ranked better than the monotherapies with a high degree of certainty.

7.1.2 Summary of cost evidence

When factoring in the probability of transfusion events, IA in combination with oral was the most cost effective way of administering TXA. IA in combination with IV was the second most cost effective, followed by oral and then by IV. IA was the least cost effective method of administration when factoring in transfusions. Similarly to the clinical evidence, all of the monotherapies showed wide credible intervals. Given this, it is difficult to draw conclusions if one of the monotherapies is more cost effective than any other. The finding that combination therapies are the most cost effective administration method when factoring in transfusion events remained a robust finding in all sensitivity analyses. The results of the sensitivity analyses found that overall costs were most sensitive to the cost of a blood transfusion.

IA in combination with oral was the most cost effective intervention; however the rank credible intervals spanned from most cost effective to least cost effective. Furthermore, as stated previously this intervention was linked to the network by a single study which was judged as having a high risk of bias. Further studies including IA in combination with oral as an intervention and transfusions as an outcome are needed to explore the validity of this result.

7.1.3 Goodness of fit summary

The network appeared to fit the data well, as demonstrated by the DIC and residual deviance statistics, with no inconsistencies identified.

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8 Conclusion

The results indicated that topical (intra-articular) in combination with oral had the lowest probability of a transfusion event and was also the cheapest. However, the committee were keen to note that the intervention was linked to the network by a single study that had a high risk of bias in the clinical review. Furthermore, use of oral tranexamic acid is off license and generally not part of current practice, use of topical (intra-articular) tranexamic acid is off license but is part of current practice. As both methods of administration are off label, the committee agreed they did not want to make a recommendation for topical (intra-articular) in combination with oral. Although, as previously noted, topical (intra-articular) tranexamic acid is off label; its use in combination with IV tranexamic acid is not uncommon in current practice. Given the clinical and economic evidence in favour of this combination, the committee decided to make an offer for topical (intra-articular) in combination with IV.

There was discussion about the higher median dosage used in the topical (intra-articular) and intravenous method that was recommended. Although there was suggestion that this could have been a contributing factor to the results, the committee still felt the evidence was strong enough to offer topical (intra-articular) in combination with IV. The median dosage was considered over the mean as the mean was skewed towards higher values. The committee discussed the total dosage they use in current practice, which varied between 2-3g when combining IV and topical (intra-articular). The median dosage of topical (intra-articular) in combination with IV study arms included in the network roughly equated to the upper end of dosage discussed by the committee. Therefore the committee agreed dosage should not exceed 3g in total.

The NMA and cost comparison analysis is directly applicable to hip and knee replacements as the clinical data concerned only these populations. Although no evidence was available for tranexamic acid use for shoulder replacements, the committee agreed that the analysis could support a recommendation for the shoulder population. This was done on the basis that although blood loss may be slightly less for shoulder replacements, there is still benefit in reducing bleeding. The recommendation will be cost saving for shoulder replacements although the savings will be relatively less than for hip and knee replacements. This is because avoided transfusions drive cost savings and shoulder replacements generally require less transfusions than knee/hip replacements.

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Appendices

Appendix A: WinBUGS Code

A.1 Main code

A.1.1 Fixed effects

```
# Binomial likelihood, logit link
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)      # vague priors for all trial baselines
    for (k in 1:na[i])  {       # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
        rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
             +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
      }
# summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
     }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)}
# Provide estimates of treatment effects T[k] on the natural (probability)
scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }

rr[1]<- 1
for (k in 2:nt)  {
rr[k]<- T[k]/T[1]  }                                  # calculate relative
risk


# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
               rk[k]<-rank(rr[],k)
best[k]<-equals(rank(rr[],k),1)}
      # calculates probability that treat k is h-th best
                for (h in 1:nt){  prob[k,h] <- equals(rk[k],h) }
                }

                                          # cost comparison code
for (i in 1:5){   Cost[i]<-(T[i]*cost_trans+cost[i]) }


           # incremental cost code
for (c in 1:(nt-1))
         {  for (k in (c+1):nt)
```

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```
                {  incCost[c,k] <- Cost[k] - Cost[c]}}

# Ranking and prob - treatment k is least cost
 for (k in 1:nt) {
               rkcost[k]<-rank(Cost[],k)
bestcost[k]<-equals(rank(Cost[],k),1)}

# pairwise ORs and RRs
for (c in 1:(nt-1))
          {  for (k in (c+1):nt)
                {  lor[c,k] <- d[k] - d[c]
                   log(or[c,k]) <- lor[c,k]
                   lrr[c,k] <- log(rr[k]) - log(rr[c])
                   log(rrisk[c,k]) <- lrr[c,k]

                }
           }
}

}                                                    # *** PROGRAM ENDS


 Data
# ns= number of studies; nt=number of treatments
list(ns=36, nt=5, meanA=-2.561, precA=3.262,
cost=c(2.82,2.25,0.27,5.34,2.31), cost_trans=351.3)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] t[,1] t[,2] t[,3] na[]
0.5   41    1.5   41    NA    NA    4     1     NA    2
0.5   51    1.5   51    0.5   51    4     1     2     3
0.5   71    4.5   71    3.5   71    4     1     2     3
0.5   51    3.5   51    NA    NA    5     1     NA    2
0.5   51    2.5   51    NA    NA    4     2     NA    2
3     92    4     92    NA    NA    4     2     NA    2
1     59    4     60    NA    NA    4     2     NA    2
1     50    8     50    NA    NA    4     2     NA    2
5     320   2     320   NA    NA    1     2     NA    2
0.5   36    7.5   36    NA    NA    1     2     NA    2
4.5   51    0.5   51    NA    NA    1     2     NA    2
1     50    2     50    NA    NA    1     2     NA    2
5     30    7     30    NA    NA    1     2     NA    2
3.5   59    0.5   56    NA    NA    1     2     NA    2
7     60    5     60    4     60    1     2     3     3
3     40    16    160   NA    NA    1     2     NA    2
0.5   63    1.5   70    NA    NA    1     2     NA    2
1.5   48    0.5   43    NA    NA    1     2     NA    2
9     30    7     30    NA    NA    1     2     NA    2
8     100   3     50    NA    NA    1     2     NA    2
1.5   61    0.5   61    NA    NA    1     2     NA    2
2     42    2     40    NA    NA    1     2     NA    2
0.5   51    1.5   51    NA    NA    1     2     NA    2
6     102   6     101   NA    NA    1     2     NA    2
17    140   15    140   15    140   1     2     3     3
0.5   25    1.5   24    NA    NA    1     2     NA    2
1     34    1     37    NA    NA    3     2     NA    2
3     40    1     43    NA    NA    3     2     NA    2
1     40    2     40    NA    NA    3     2     NA    2
2     58    1     59    NA    NA    1     3     NA    2
4     75    3     75    NA    NA    1     3     NA    2
15    76    14    76    NA    NA    1     2     NA    2
44    100   37    100   NA    NA    1     2     NA    2
2     60    4     60    NA    NA    1     2     NA    2
20    57    24    57    NA    NA    1     2     NA    2
```

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```
3     26    2     22    NA    NA    2     4     NA    2

END

 Initial Values

list(d=c( NA, 0,0,0,0), mu=c(0, 0, 0, 0, 0,   0, 0, 0, 0, 0,   0, 0, 0, 0,
0,   0, 0, 0, 0, 0,    0, 0, 0, 0,0,    0, 0, 0, 0, 0,   0, 0, 0, 0, 0,
0))

list(d=c( NA, -1,-1,-1,-1), mu=c(-3, -3, -3, -3, -3,    -3, -3, -3, -3, -3,
-3, -3, -3, -3, -3,    -3, -3, -3, -3, -3,    -3, -3,-3, -3, -3,    -3, -3,
-3, -3, -3,    -3, -3, -3, -3, -3,  -3))

list(d=c( NA, 2,0,3,-2), mu=c(-3, 3, -1, -3, 2,  -3, -4, -3, -3, 0,  -3, -
3, 0, 3, 1,  -3, -3, -1, -3, -2,  -3, -3, 0, -3, 0,   3, 1, -3, -3, -1,   -
3, 3, 1, -3, -3,   -1))
```

A.1.2 Random effects

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         # LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
    for (k in 1:na[i]) {             # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
        logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))         }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])           # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability)
scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
```

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```
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }

rr[1]<- 1
for (k in 2:nt)  {
rr[k]<- T[k]/T[1]  }                                    # calculate relative
risk


# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
               rk[k]<-rank(rr[],k)
best[k]<-equals(rank(rr[],k),1)}


                                # calculate cost comparison
for (i in 1:5){   Cost[i]<-(T[i]*cost_trans+cost[i]) }

for (c in 1:(nt-1))
          {  for (k in (c+1):nt)
                 {  incCost[c,k] <- Cost[k] - Cost[c]}}

# Ranking and prob - treatment k is least cost
 for (k in 1:nt) {
               rkcost[k]<-rank(Cost[],k)
bestcost[k]<-equals(rank(Cost[],k),1)}


# pairwise ORs and RRs
for (c in 1:(nt-1))
          {  for (k in (c+1):nt)
                 {  lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    lrr[c,k] <- log(rr[k]) - log(rr[c])
                    log(rrisk[c,k]) <- lrr[c,k]

                 }
           }
}

}


# *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=36, nt=5, meanA=-2.561, precA=3.262,
cost=c(2.82,2.25,0.27,5.34,2.31), cost_trans=351.3)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] t[,1] t[,2] t[,3] na[]
0.5   41    1.5   41    NA    NA    4     1     NA    2
0.5   51    1.5   51    0.5   51    4     1     2     3
0.5   71    4.5   71    3.5   71    4     1     2     3
0.5   51    3.5   51    NA    NA    5     1     NA    2
0.5   51    2.5   51    NA    NA    4     2     NA    2
3     92    4     92    NA    NA    4     2     NA    2
1     59    4     60    NA    NA    4     2     NA    2
1     50    8     50    NA    NA    4     2     NA    2
5     320   2     320   NA    NA    1     2     NA    2
0.5   36    7.5   36    NA    NA    1     2     NA    2
4.5   51    0.5   51    NA    NA    1     2     NA    2
```

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```
1     50    2     50    NA    NA    1     2     NA    2
5     30    7     30    NA    NA    1     2     NA    2
3.5   59    0.5   56    NA    NA    1     2     NA    2
7     60    5     60    4     60    1     2     3     3
3     40    16    160   NA    NA    1     2     NA    2
0.5   63    1.5   70    NA    NA    1     2     NA    2
1.5   48    0.5   43    NA    NA    1     2     NA    2
9     30    7     30    NA    NA    1     2     NA    2
8     100   3     50    NA    NA    1     2     NA    2
1.5   61    0.5   61    NA    NA    1     2     NA    2
2     42    2     40    NA    NA    1     2     NA    2
0.5   51    1.5   51    NA    NA    1     2     NA    2
6     102   6     101   NA    NA    1     2     NA    2
17    140   15    140   15    140   1     2     3     3
0.5   25    1.5   24    NA    NA    1     2     NA    2
1     34    1     37    NA    NA    3     2     NA    2
3     40    1     43    NA    NA    3     2     NA    2
1     40    2     40    NA    NA    3     2     NA    2
2     58    1     59    NA    NA    1     3     NA    2
4     75    3     75    NA    NA    1     3     NA    2
15    76    14    76    NA    NA    1     2     NA    2
44    100   37    100   NA    NA    1     2     NA    2
2     60    4     60    NA    NA    1     2     NA    2
20    57    24    57    NA    NA    1     2     NA    2
3     26    2     22    NA    NA    2     4     NA    2


END

 Initial Values
#chain 1
list(d=c( NA, 0,0,0,0), sd=1, mu=c(0, 0, 0, 0, 0,   0, 0, 0, 0, 0,   0, 0,
0, 0, 0,   0, 0, 0, 0, 0,    0, 0, 0, 0, 0,    0, 0, 0, 0, 0,    0, 0, 0,
0, 0, 0))
#chain 2
list(d=c( NA, -1,-1,-1,-1), sd=4, mu=c(-3, -3, -3, -3, -3,    -3, -3, -3, -
3, -3,    -3, -3, -3, -3, -3,    -3, -3, -3, -3, -3,    -3, -3,-3, -3, -3,
-3, -3, -3, -3, -3,   -3, -3, -3, -3,-3, -3))
#chain 3
list(d=c( NA, 2,0,3,-2), sd=2, mu=c(-3, 3, -1, -3, 2,  -3, -4, -3, -3, 0,
-3, -3, 0, 3, 1,  -3, -3, -1, -3, -2,  -3, -3, 0, -3, 0,   3, 1, -3, -3, -
1,   -3, -2, -3, -3,0,  0))
```

A.2 Baseline code

A.2.1 Fixed effects

```
# Binomial likelihood, logit link
# Baseline fixed effect model
model{                          # *** PROGRAM STARTS
for (i in 1:ns){                # LOOP THROUGH STUDIES
    r[i] ~ dbin(p[i],n[i])            # Likelihood
    logit(p[i]) <- m                              # Log-odds of response

            # expected value of the numerators
    rhat[i] <- p[i] * n[i]
            #Deviance contribution
    dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))
             +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
  }
totresdev <- sum(dev[])                     # total residual deviance
```

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```
m ~ dnorm(0,.0001)              # vague prior for mean
logit(R) <- m                   # posterior probability of response
}

 Data

list(ns=1)  # ns=number of studies

r[]   n[]
4   50

END

 Inits
list(m=0)

list(m= -1)

list(m = 1)
```

A.3 Inconsistency model

```
# Binomial likelihood, logit link
# Fixed effects INCONSISTENCY model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)      # vague priors for all trial baselines
    for (k in 1:na[i])  {       # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,1],t[i,k]]
# expected value of the numerators
        rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
             +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
      }
# summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
     }
totresdev <- sum(resdev[])      # Total Residual Deviance

# vague priors for treatment effects
for (c in 1:(nt-1)){
            d[c,c]<-0
       for (k in (c+1):nt){
            d[c,k] ~ dnorm(0,.0001)              # priors for all mean trt
effects
            or[c,k] <- exp(d[c,k])                    # all pairwise ORs
                                    d[k,c]<- -d[c,k]
       }
            }
d[nt,nt]<-0
}                                                     # *** PROGRAM ENDS


 Data
# nt=no. treatments, ns=no. studies
list(nt=5,ns=36)
```

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```
r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] t[,1] t[,2] t[,3] na[]
0.5   41    1.5   41    NA    NA    4     1     NA    2
0.5   51    1.5   51    0.5   51    4     1     2     3
0.5   71    4.5   71    3.5   71    4     1     2     3
0.5   51    3.5   51    NA    NA    5     1     NA    2
0.5   51    2.5   51    NA    NA    4     2     NA    2
3     92    4     92    NA    NA    4     2     NA    2
1     59    4     60    NA    NA    4     2     NA    2
1     50    8     50    NA    NA    4     2     NA    2
5     320   2     320   NA    NA    1     2     NA    2
0.5   36    7.5   36    NA    NA    1     2     NA    2
4.5   51    0.5   51    NA    NA    1     2     NA    2
1     50    2     50    NA    NA    1     2     NA    2
5     30    7     30    NA    NA    1     2     NA    2
3.5   59    0.5   56    NA    NA    1     2     NA    2
7     60    5     60    4     60    1     2     3     3
3     40    16    160   NA    NA    1     2     NA    2
0.5   63    1.5   70    NA    NA    1     2     NA    2
1.5   48    0.5   43    NA    NA    1     2     NA    2
9     30    7     30    NA    NA    1     2     NA    2
8     100   3     50    NA    NA    1     2     NA    2
1.5   61    0.5   61    NA    NA    1     2     NA    2
2     42    2     40    NA    NA    1     2     NA    2
0.5   51    1.5   51    NA    NA    1     2     NA    2
6     102   6     101   NA    NA    1     2     NA    2
17    140   15    140   15    140   1     2     3     3
0.5   25    1.5   24    NA    NA    1     2     NA    2
1     34    1     37    NA    NA    3     2     NA    2
3     40    1     43    NA    NA    3     2     NA    2
1     40    2     40    NA    NA    3     2     NA    2
2     58    1     59    NA    NA    1     3     NA    2
4     75    3     75    NA    NA    1     3     NA    2
15    76    14    76    NA    NA    1     2     NA    2
44    100   37    100   NA    NA    1     2     NA    2
2     60    4     60    NA    NA    1     2     NA    2
20    57    24    57    NA    NA    1     2     NA    2
3     26    2     22    NA    NA    2     4     NA    2


END

INITS

list(mu=c(0, 0, 0, 0, 0,   0, 0, 0, 0, 0,   0, 0, 0, 0, 0,   0, 0, 0, 0, 0,
0, 0, 0, 0, 0,    0, 0, 0, 0, 0,    0, 0, 0, 0, 0, 0),
d = structure(.Data = c(NA,0,0,0,0,  NA, NA,0,0,0,  NA,NA,NA,0,0,
NA,NA,NA,NA,0,   NA,NA,NA,NA,NA), .Dim = c(5,5)))


list(mu=c(0,1,-1,2,-2,  0,1,-1,2,-2,  0,1,-1,2,-2,  0,1,-1,2,-2,  0,1,-
1,0,0, 0,1,-1,2,-2,  0, 0, 0, 0, 0, 0),
d = structure(.Data = c(NA,1,0,2,0,  NA, NA,0,-1,0,  NA,NA,NA,-2,1,
NA,NA,NA,NA,0,   NA,NA,NA,NA,NA), .Dim = c(5,5)))

list(mu=c(3,2,-2,4,-1,  3,2,-2,4,-1,  3,2,-2,4,-1,  3,2,-2,4,-1,  3,2,-
2,1,2, 3,2,-2,4,-1,  3, 0, 0, 0, 0, 0),
d = structure(.Data = c(NA,1,1,2,0,  NA, NA,0,-1,1,  NA,NA,NA,-2,1,
NA,NA,NA,NA,2,   NA,NA,NA,NA,NA), .Dim = c(5,5)))
```

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A.4 Node-splitting – to run in R2WinBUGS package in R

```
model{

# MTC Fixed effects model

for(i in 1:ns){

      delta[i,bi[i]] <- 0

      mu[i] ~ dnorm(0,.0001)                                    # vague
priors for trial baselines

      for (k in 1:na[i])  {

            #Likelihood

            r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])         # binomial likelihood

            #model

            logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]

            index[i,k] <- split[i] * (equals(t[i,k], pair[1]) +
equals(t[i,k], pair[2])

            # Deviance for observed events

            rhat[i,k] <- p[i,t[i,k]] * n[i,k] # expected value of the
numerators

            # Deviance contribution

            dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))

                  +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))

      }

      # summed residual deviance contribution for each trial

      resdev[i] <- sum(dev[i,1:na[i]])

      for (k in 2:na[i]) {

            # trial-specific LOR distributions, split into direct and
indirect (through MTC)

            delta[i,si[i,k]] <-  (d[si[i,k]] - d[bi[i]] )*(1-
index[i,m[i,k]]) + direct*index[i,m[i,k]]

      }

  }


d[1]<-0

direct ~ dnorm(0,1.0E-6)                  # vague prior for direct
comparison parameter

for (k in 2:nt){d[k] ~ dnorm(0,.0001) }   # vague priors for basic
parameters
```

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```
# Total Residual Deviance
totresdev <- sum(resdev[])   # observed events
# pairwise ORs
for (c in 1:(nt-1)) {  for (k in (c+1):nt)  { or[c,k] <- exp(d[k] - d[c] )
                                              lor[c,k]<-(d[k]-d[c])}  }
# calculate probability posterior distribution of direct > indirect
prob <- step(direct - lor[pair[1], pair[2]])
}
```

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Appendix B: Intervention cost calculations

B.1 Intervention cost calculations

Table 12. Reported dose and disposable use in each included study and NHS cost

Study	Intervention	Resources	NHS Cost
Adravanti 2018[2]	Intravenous + intraarticular	3 doses of 1g IV + 3g IA	£ 7.30
Gulabi 2019[20]		2g IV in 100ml saline + 3g in 100 ml	£ 7.27
Huang 2014[21]		1.5g in 50ml saline IA + 1.5g IV	£ 4.27
Jain 2016[22]		3 IV doses: 15 mg/kg, then 2 IV doses:10 mg/kg + 2g in 30ml saline IA	£ 8.56
Lin 2015[25]		1g IV + 1g IA	£ 2.90
Song 2017[38]		10mg/kg pre + post-operative IV and 1.5g in 50ml saline IA	£ 4.27
Xie 2016[49]		1g IV + 2g IA in 150 ml saline	£ 4.80
Yi 2016[50]		15mg/kg IV + 800mg and 80ml saline IA	£ 3.33
		Average cost	**£ 5.34**
Cankaya 2017[5]	Oral + Intra-articular	2g (max) oral + 1.5g IA	£ 2.31
		Average cost	**£ 2.31**
Abdel 2018[1]	Intraarticular	3g in 45ml saline	£ 3.89
Aggarwal 2016[3]		15 mg/kg in 100 mL saline	£ 1.98
Aguilera 2015[4]		1g in 10mL saline	£ 1.50
Cankaya 2017[5]		1g in 20ml saline	£ 1.56
Chen 2016[6]		1.5g in 100ml saline	£ 2.53
Digas 2015[16]		2g	£ 2.55
George 2018[18]		1.5g in 100ml saline	£ 2.53
Laoruengthana 2019[24]		15mg/kg	£ 1.45
Lin 2015[25]		1g (100mg/ml) in 20ml saline	£ 1.56
Luo 2018[27]		2g diluted in 150mL saline	£ 3.35
Maniar 2012[28]		3g diluted in 100 mL saline	£ 4.18

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Study	Intervention	Resources	NHS Cost
May 2016[29]		2g in 50ml saline	£ 2.82
Mehta 2019[30]		2.5g in 25ml saline	£ 3.10
Patel 2014[35]		2g in 100 ml of saline	£ 1.52
Pinsornsak 2016[36]		750mg in 15 mL saline	£ 1.53
Prakash 2017[37]		3g in 50ml saline	£ 3.92
Song 2017[38]		1.5g in 50 ml saline	£ 2.27
Stowers 2017[40]		1.5g in 20mL saline	£ 2.11
Ugurlu 2017[42]		3g in 100ml saline	£ 4.18
Wang 2017[46]		1g in 50 mL saline	£ 1.72
Wang 2018[45]		3g in 100 mL of saline	£ 4.18
Wei 2014[47]		3g mixed with 100ml saline.	£ 4.18
Xie 2016[49]		3g in 150ml saline	£ 4.45
Yuan 2017[51]		3g in 60 mL solution	£ 3.97
Zhang 2016[52]		1g in 100ml saline	£ 1.98
Zhou 2018[54]		3g in 60ml saline	£ 3.97
Average			**£ 2.82**
Abdel 2018[1]	Intravenous	1g	£ 1.45
Adravanti 2018[2]		3 doses of 1g	£ 3.65
Aggarwal 2016[3]		15 mg/kg	£ 1.45
Aguilera 2015[4]		2 doses of 1g.	£ 2.55
Chen 2016[6]		1.5g in 100ml saline	£ 2.53
Digas 2015[16]		15ml/kg	£ 1.45
Fillingham 2016[17]		1g in 10 mL saline	£ 1.50
George 2018[18]		2 doses of 10mg/kg	£ 2.00
Gulabi 2019[20]		2 dose 1g in 100 ml saline	£ 3.08
Huang 2014[21]		3g	£ 3.65
Jain 2016[22]		3 IV doses: 15 mg/kg, then 2 IV doses:10 mg/kg	£ 3.10
Jaszczyk 2015[23]		1g in 10mL saline	£ 1.50
Laoruengthana 2019[24]		10mg/kg	£ 1.45
Luo 2018[27]		20 mg/kg in 100ml saline	£ 2.53
Maniar 2012 1[28]		10mg/kg	£ 1.45

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Study	Intervention	Resources	NHS Cost
Maniar 2012 2[28]		2 doses of 10 mg/kg	£ 2.00
Maniar 2012 3[28]		3 doses of 10mg/kg	£ 3.10
May 2016[29]		2 doses of 1g in 100ml saline	£ 3.08
Mehta 2019[30]		1g	£ 1.45
Patel 2014[35]		10mg/kg	£ 1.45
Pinsornsak 2016[36]		750mg in 15ml saline.	£ 1.53
Prakash 2017[37]		3 doses of 10mg/kg	£ 3.10
Song 2017[38]		3 doses of 10 mg/kg	£ 3.10
Stowers 2017[40]		1.5g	£ 2.00
Ugurlu 2017[42]		20mg/kg	£ 2.00
Wang 2017[46]		1g IV in 50 mL	£ 1.72
Wang 2018[45]		20mg/kg in 100ml	£ 2.53
Wei 2014[47]		3g infusion	£ 3.65
Xie 2016[49]		1.5g single dose	£ 2.00
Yi 2016[50]		15mg/kg dose	£ 1.45
Yuan 2017[51]		2 doses 20 mg/kg	£ 3.65
Zhang 2016[52]		1g diluted in 250ml saline	£ 2.78
Zhao 2018[53]		15 mg/kg	£ 1.45
Zhou 2018[54]		2 doses 10mg/kg in 100 ml saline	£ 3.07
Average			**£ 2.25**
Fillingham 2016[17]	Oral	3 tablets of 650 mg	£ 0.20
Jaszczyk 2015[23]		3 tablets of 650 mg	£ 0.20
Luo 2018[27]		2g	£ 0.20
Wang 2018[44]		4g (2 pre, 2 post)	£ 0.40
Yuan 2017[51]		2 doses of 20mg/kg	£ 0.30
Zhao 2018[53]		2 doses 20mg/kg	£ 0.30
Average			**£ 0.27**

Where a study included the same comparator with the same dosage multiple times, it was only included once in cost calculations.

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