National Institute for Health and Care Excellence

Final

Head injury: assessment and early management (update)

The cost effectiveness of tranexamic acid

NICE guideline NG232

Economic analysis report

May 2023

Final

Developed by National Institute for Health and Care Excellence

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Contents

1. Introduction

There was a published economic evaluation of tranexamic acid (TXA), Williams 2020[25] based on the CRASH-3 randomised controlled trial. There were some limitations with the economic evaluation itself. The guideline technical team adjusted the results, to reduce the bias – see Evidence Report A. However, the following issues with the CRASH-3 trial itself remain:

- Mild and moderate traumatic brain injury (TBI) were analysed together, even though there are far fewer TBI deaths in a mild TBI group.
- The setting was in-hospital but since the trial there has been a move towards pre-hospital use because, as shown in the CRASH-3 trial, the benefits for people with mild and moderate TBI are greater the earlier TXA is administered.

The other main trial in the guideline's systematic review of clinical effectiveness was the Prehospital TXA for TBI trial (Rowell 2020[19]). This randomised controlled trial showed a trend towards reduced all-cause mortality and improved Glasgow Outcome Scale score at 6 months for the prehospital use of a 2g bolus of TXA compared to placebo. These outcomes were statistically significant for those patients (52%) with an intracranial haematoma.

Requests were sent to both trial teams for the data to be re-analysed by TBI severity group, but this was achieved only for the Prehospital TXA for TBI trial.

The committee decided to estimate the cost effectiveness of TXA based on the findings of the Prehospital TXA for TBI trial because it had a pre-hospital setting and because outcomes could be estimated separately for people with moderate TBI.

2. Methods

2.1 Model overview

A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting and including discounting at 3.5% for costs and health effects.[12] An incremental analysis was undertaken.

The analysis was based upon a randomised study: The Prehospital TXA for TBI trial (Rowell 2020[19]).

2.1.1 Comparators

The following comparators were included in the analysis:

1. Tranexamic acid – 2g intravenous bolus in the out of hospital setting (Rowell 2020[19] n=345)
2. No tranexamic acid (based on the placebo group of Rowell 2020[19] n=309)

Rowell 2020[19] also reported effectiveness data for 1g bolus (tranexamic acid). However, 1g bolus was not found to be effective compared to placebo, therefore modelling was not conducted for 1g bolus tranexamic acid.

2.1.2 Population

The population of the analysis was adults with a moderate or severe traumatic brain injury and the model population is that of the trial by Rowell 2020[19].

The population in the trial was people aged ≥15 with blunt and penetrating traumatic mechanism with a Glasgow Coma Scale (GCS) score of 3 to 12, at least 1 reactive pupil, and systolic blood pressure of at least 90 mm Hg prior to randomisation. In Rowell 2020[19], people were eligible to receive tranexamic acid only if an intravenous (IV) catheter was in place, the study drug could be administered within 2 hours of injury, and the predefined emergency medical services transport destination was a participating trauma centre.

Rowell 2020[19] included mainly people with moderate and severe TBI (GCS score of 12 or less). In Rowell 2020[19] 4% of people experienced a mild TBI, 39% of people experienced a moderated TBI and 57% of people experienced a severe TBI.

Of note, a sensitivity analysis was conducted to assess the cost effectiveness of tranexamic acid for people with a mild TBI at relatively high risk of an intracranial haemorrhage (ICH).

2.2 Approach to modelling

Two separate Markov models were developed for people who experienced a moderate traumatic brain injury and a severe traumatic brain injury, respectively.

Health states were determined by the Glasgow Outcome Scale (GOS) score at 6 months reported in Rowell 2020[19]:

- 1 Dead,
- 2 Vegetative state,

- 3 Severe disability,
- 4 Moderate disability, and
- 5 Good recovery.

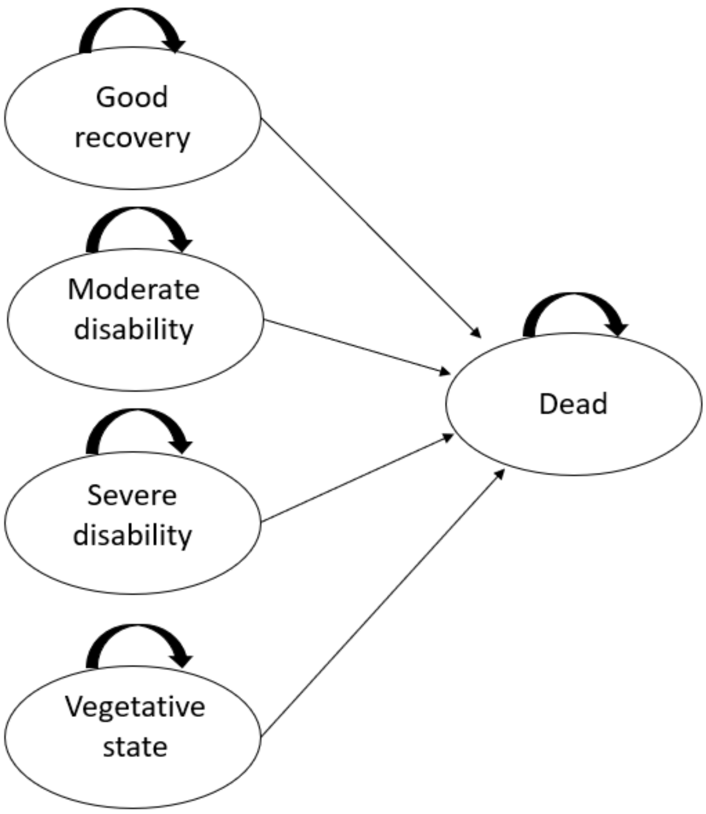
The Markov models comprised two six-month cycles at the beginning of the model and subsequent yearly cycles for the remainder of the life-time horizon.

Transitions were modelled up to the age of 100. The number of cycles was determined by the start age of the cohort (see 2.3.2). People in the moderate TBI model passed through 2 six-month cycles and then 57 annual cycles; people in the severe TBI model passed through 2 six-month cycles and then 65 cycles of 1 year each.

People remained in the same GOS state or transitioned to the dead state. There was no movement between the live GOS states. By definition, people who have transitioned to the dead state, stay in that state.

The model structure is a simplification because in reality some people would transition to a better GOS state and others would worsen, although the majority would remain the same. There were data from a cohort of people presenting with TBI in Glasgow (see 2.3.4) for the number of people transitioning between health states, however these transitions were only reported for the entire cohort of people (mainly mild TBI) and were not disaggregated by TBI severity. The Markov model structure can be found in Figure 1.

Figure 1: Model structure



Time spent in each health state was calculated to determine costs and QALYs associated with each intervention. The comparison between the mean results of each intervention allowed us to identify the most cost-effective strategy. To account for uncertainty, a probabilistic analysis was undertaken.

2.2.1 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. 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 – 5,000 times for the base case for both a moderate and severe TBI population respectively.

When running the probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis we checked for convergence in the incremental costs, QALYs and incremental net health benefit at a threshold of £20,000 per QALY gained for tranexamic acid versus no tranexamic acid. This was done for both model populations (moderate and severe) by plotting the number of runs against the mean outcome at that point – see examples in Figure 2 and Figure 3. Both models appeared to have reached convergence by the 3000th run.

Figure 2: Incremental net health benefit (£20,000 per QALY) for Tranexamic acid vs No Tranexamic acid for the moderate TBI population

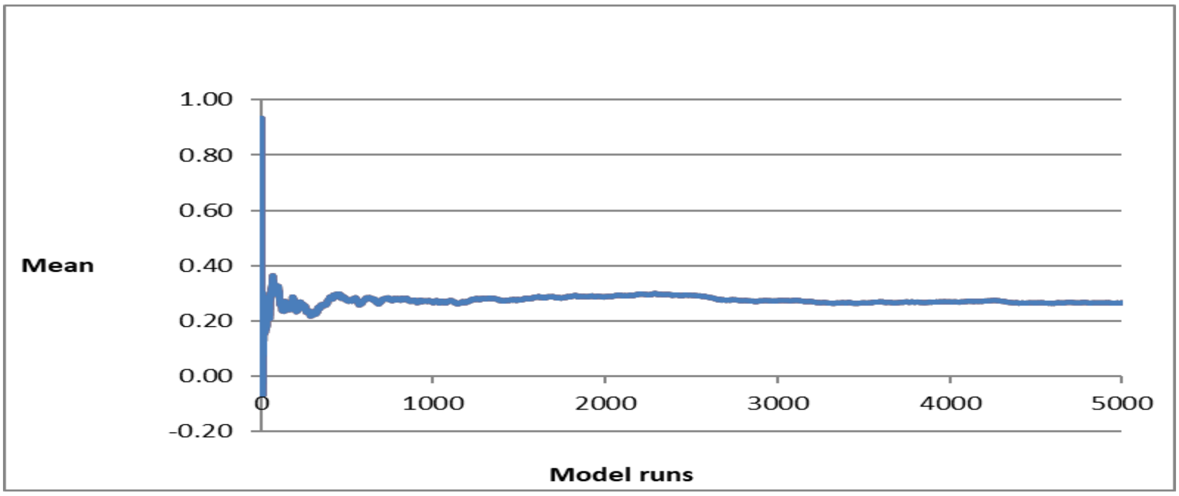
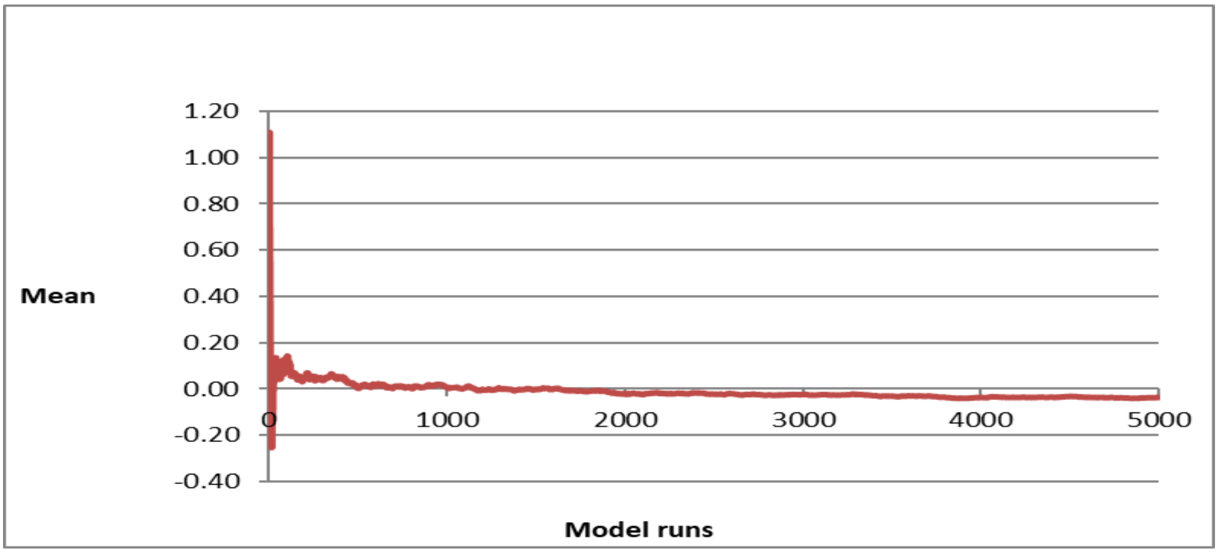


Figure 3: Incremental net health benefit (£20,000 per QALY) for Tranexamic acid vs No Tranexamic acid for the severe TBI population



The way in which distributions are defined reflects the nature of the data, so for example event probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that the probability of an event occurring cannot be less than 0 or greater than 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1 and in the relevant input summary tables in section 2.3. 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 analysis

Parameter	Type of distribution	Properties of distribution
Probability of being in a particular GOS sub-group (Good recovery, Mild, Moderate, Severe, Vegetative state, and Dead)	Dirichlet	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0–1 interval. Derived by the number of patients in the sample and the number of patients in a particular subgroup.
Probability of death Probability of needing surgery	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: • Alpha = (number of patients hospitalised) • Beta = (number of patients) − (number of patients hospitalised)
Utility decrements Days in hospital Unit costs: • Hospital costs • Surgery costs • Post-discharge costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and beta values were calculated as follows: • Alpha = $(\text{mean/SE})^2$ • Beta = SE^2/Mean Where the standard error was not known, it was assumed to be 20% of the mean.

Abbreviations: GOS; Glasgow Outcome Scale; SE = standard error.

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

- the cost-effectiveness threshold,
- the national population mortality
- the cost of the paramedic (assumed to be fixed according to national pay scales and programme content)
- tranexamic acid costs and the cost of consumables to administer tranexamic acid

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. Details of the sensitivity analyses undertaken can be found in methods section 2.5 Sensitivity analyses.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. 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 base case model

Input	Data	Source	Probability distribution
Comparators	• Prehospital TXA (2g bolus)[(a)] • No TXA	Rowell 2020[19]	n/a
Population	Adults with Moderate or Severe TBI	Rowell 2020[19]	n/a
Perspective	UK NHS & personal social services	NICE reference case[12]	n/a
Time horizon	Lifetime		n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case[12]	n/a
Cohort settings			
Cohort starting age Moderate Severe	 43 years 35 years	Rowell 2020[19]– bespoke analysis for the guideline	n/a
Percentage male	75%	Rowell 2020[19]	n/a
Glasgow outcome scale at 6 months			
Moderate Good recovery Moderate disability Severe disability Vegetative state Dead	 62% 14% 17% 0.1% 7%	Rowell 2020[19] – bespoke analysis for the guideline	Dirichlet Alpha = Number of people in Table 3, Beta=1
Severe Good recovery Moderate disability Severe disability Vegetative state Dead	 38% 18% 23% 0.6% 21%		
Mortality from 1 year to 13 years			
Moderate From 1 year to 5 – 7 years From 5-7 years to 12 – 14 years	 4.9% 3.0%	Whitnall 2006[23] and McMillan 2012[9]	Beta Alpha=26, Beta=91 Alpha=18, Beta=73
Severe From 1 year to 5 – 7 years From 5-7 years to 12 – 14 years	 3.5% 3.9%		 Alpha=12, Beta=61 Alpha=15, Beta=46
Mortality beyond 13 years			
Mortality beyond 13 years	National Life Tables 2017 - 2019	Office for National Statistics [16]	n/a

Input	Data	Source	Probability distribution
Health-related quality of life (utilities)			
Full health	1.000	By definition	n/a
Good recovery	0.894	Fuller 2017[22]	Gamma for decrement vs full health Alpha=575, Beta=0.00
Moderate disability	0.675	Fuller 2017[22]	Gamma for decrement vs GR Alpha=605, Beta=0.00
Severe disability	0.382	Fuller 2017[22]	Gamma for decrement vs MD Alpha=439, Beta=0.00
Vegetative state	-0.178	Fuller 2017[22]	Gamma for decrement vs SD Alpha=51, Beta=0.01
Dead	0.000	By definition	n/a
Costs			
Intervention costs			
TXA (2g)	£6.00	BNF[3]	n/a
Consumables	£5.00	Assumption	n/a
Paramedic time administering TXA	£6.10	PSSRU 2021[7] assuming 23 minutes to administer TXA	n/a
Hospital costs			
First day cost	£521	Estimated based on data from NHS reference costs 2017/18[4] and NHS reference costs 2019/20[15]	Gamma Alpha=25, Beta=21
Subsequent bed day cost	£359	NHS reference costs 2019/20[15]	Gamma Alpha=25, Beta=14
ICU bed-day cost	£1,616	NHS reference costs 2019/20[15]	Gamma Alpha=25, Beta=65
Resource use			
Number of days on a non-ICU ward TXA No TXA	 5.00 4.90	Calculated from data reported in Rowell 2020[19]	Gamma Alpha=25, Beta=0.2 Alpha=25, Beta=0.2
Number of days on ICU TXA No TXA	 6.2 5.4	Calculated from data reported in Rowell 2020[19]	Gamma Alpha=25, Beta=0.25 Alpha=25, Beta=0.21
Surgery costs			
Surgery costs (excluding bed days)	£7,137	Estimated based on data from NHS reference costs 2017/18[4] and NHS reference costs 2019/20[15] (See 2.3.8.2)	Gamma Alpha=25, Beta=285
Resource use			

Input	Data	Source	Probability distribution
Percentage of neurosurgical procedures TXA No TXA	 22% 17%	Rowell 2020[19]	Beta Alpha=76, Beta=269 Alpha=53, Beta=256
Post-discharge costs			
First year – Good recovery	£313	Reported in Williams 2020[25], derived from Beecham 2009[1]	Gamma Alpha=25, Beta=13
First year – Moderate disability	£22,361	Williams 2020[25], derived from Beecham 2009[1]	Gamma Alpha=25, Beta=894
First year – Severe disability	£44,176	Williams 2020[25], derived from Beecham 2009[1]	Gamma Alpha=25, Beta=1767
Subsequent years – Good recovery	£28	Williams 2020[25]	Gamma Alpha=25, Beta=1
Subsequent years – Moderate disability	£1,843	Williams 2020[25]	Gamma Alpha=25, Beta=74
Subsequent years – Severe disability	£14,404	Williams 2020[25]	Gamma Alpha=25, Beta=576
Vegetative state (first and subsequent years)	£109,475	Formby 2015[5]	Gamma Alpha=25, Beta=4379

Abbreviations: BNF: British National Formulary; ICU: Intensive care unit; TBI: Traumatic brain injury; TXA: Tranexamic acid

2.3.2 Initial cohort settings

The starting age of people entering the Markov models was based on data from Rowell 2020[19]:

- moderate traumatic brain injury (TBI) was 43 years and
- severe TBI was 35 years.

The proportion of males in the model was 75%, which was also obtained from the 2g bolus and placebo arms of Rowell 2020[19].

2.3.3 Glasgow outcome scale at 6 months

The trial analysis did not publish results stratified by TBI severity. A bespoke analysis was conducted by the trial team for the guideline. The 6-month GOS outcomes are reported in Table 3. Missing values were imputed based on the following baseline characteristics: age, sex, site, prehospital GCS score, penetrating injury, injury severity score and head abbreviated injury score.

Table 3: Glasgow Outcome Scale at 6 months

	TXA		No TXA	
Health state	**Number of people**	**Proportion**	**Number of people**	**Proportion**
Moderate TBI				
Good recovery	99	62%	65	57%
Moderate disability	22	14%	20	18%
Severe disability	27	17%	17	15%
Vegetative state	0	0%	0	0%
Dead	11	7%	13	11%
Severe TBI				
Good recovery	66	38%	76	41%
Moderate disability	32	18%	23	12%
Severe disability	41	23%	38	20%
Vegetative state	1	1%	3	2%
Dead	37	21%	46	25%

A Dirichlet distribution was applied to these outcomes in the probabilistic analysis.

To estimate costs and QALYs over the first 6 months, it was assumed that people alive at 6 months were in the same state over the previous 6 months. For those that had died by 6 months, it was assumed that they had severe disability up to the time of their death.

2.3.4 Mortality from 6 months to 13 years

2.3.4.1 Glasgow cohort data

Mortality beyond 6 months up to 13 years (Table 4) was estimated from a cohort of people who had a head injury treated in a hospital in Glasgow in the late 1990s. Follow-up data were reported at different time points in three studies Thornhill 2000[21], Whitnall 2006[23] and McMillan 2012[9]. Patients were followed-up by phone and post. They were also followed up at the General Register Office for Scotland to see if they had died. This was done for those who responded to the last follow-up.

Table 4: Follow-up data from Glasgow cohort

TBI severity at injury	n	Thornhill 2000 – 1 year			Whitnall 2006 – 5-7 years			McMillan 2012 – 13-14 years		
		Dead or VS	**Lost**	**Alive**	**New deaths**	**New Lost**	**Alive**	**New deaths**	**New Lost**	**Alive**
Mild	507	29	145	333	84	99	150	17	73	60
Moderate	133	16	36	81	19	21	41	9	17	15
Severe	101	28	28	45	8	12	25	7	7	11
Not recorded	28	4	11	13	3	6	4	1	2	1

Most of the Glasgow cohort had mild TBI and so the populations are not similar to the Rowell 2020 trial population. So only data from the Moderate TBI and Severe TBI subgroups were used in the model to improve consistency. Unfortunately, the papers did not report baseline demographics separately for these sub-populations, so it is not possible to assess how similar the age/sex profile of these populations were to the equivalent populations in the trial.

2.3.4.2 Calculation of transition probabilities

Table 5: Mortality probabilities derived from Glasgow cohort

TBI severity at injury	Probabilities		Probabilities adjusted for loss to follow-up		Transition probabilities		
	1 year to 5-7 years	5-7 years to 12-14 years	1 year to 5-7 years	5-7 years to 12-14 years	Annual 1 year to 6 years	Annual 6 years to 13 years	6 months to 1 year
Moderate	24%	22%	22.1%	19.4%	4.9%	3.0%	2.5%
Severe	18%	28%	16.1%	24.5%	3.5%	3.9%	1.7%

There was a concern that crude mortality rates from the followed-up patients would over-estimate mortality, as it is known that head injury patients that do not respond to follow-up often have better outcomes. To estimate the transition probabilities, the following steps were undertaken:

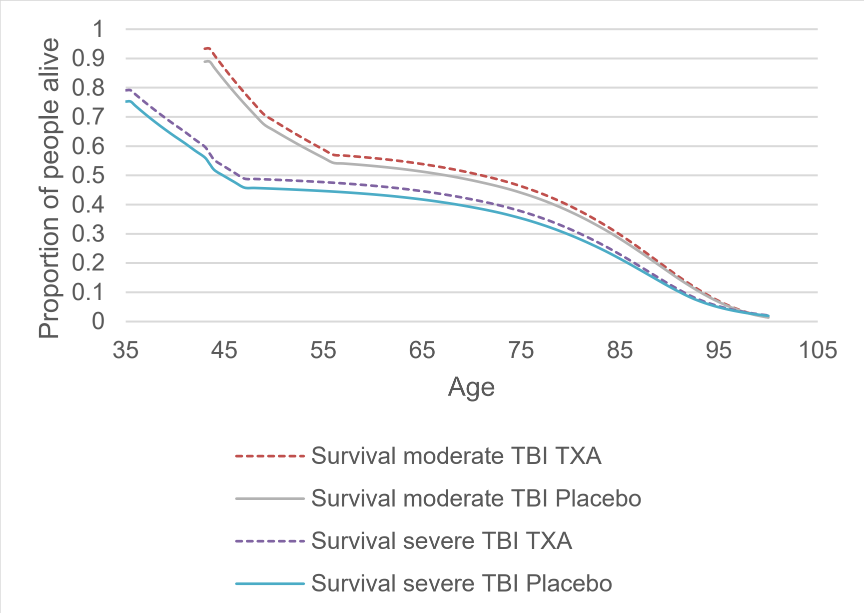
- The crude probability of death by TBI severity (Table 5) was calculated from the data in Table 4
- The number of people who died that were lost to follow-up was estimated. There was another paper (McMillan 2011[10]) that reported total deaths in the cohort over the entire period was 305. This meant that there were 80 deaths among those that were lost to follow up at 1 year or at 5-7 years.
- By iteration a mortality hazard ratio of 0.762 was estimated for the lost patients compared to the followed-up patients (across all TBI groups) that would bring the total deaths to 305.
- The total number of deaths were re-calculated for each severity group, applying this hazard ratio.
- Adjusted probabilities were calculated from the adjusted numbers of deaths (Table 5).
- The adjusted probabilities were converted to hazard rates.
- The rates were converted into annual transition probabilities which were subsequently used in the model (Table 5).

There was no data for the period 6 months to 1 year, so it was assumed that the mortality hazard rate would be the same as for 1 year to 6 years. A 6-month transition probability was calculated from this hazard rate (Table 5).

The calculated transition probabilities for mortality from 6 months up to 13 years were applied to the model for health states, good recovery, moderate disability, and severe disability. Vegetative state mortality was calculated separately and details can be found in section 2.3.6.

Table 5 shows that the mortality in the moderate TBI group was higher than in the severe TBI group but this seemingly paradoxical finding is in part due to the higher average age in the moderate severity group and the higher mortality in the severe group before one-year. Figure 4 shows the survival curves from the model from 6 months onwards. Survival in the severe TBI group was lower in the severe TBI group at all ages.

Figure 4: Survival curves from 6 months outputted from base case model



2.3.5 Mortality beyond 13 years

Mortality beyond 13 years for good recovery, moderate disability and severe disability was assumed to be the same as the general population in the base case analysis.

General population mortality was obtained from The National Life Tables for England 2017 – 2019[16]. Age/sex specific mortality was calculated for each cycle taking into account the starting age and gender split of the cohort.

2.3.6 Mortality for vegetative state

The Multi-Society Task Force on Persistent Vegetative State reported the mean length of survival for adults in a vegetative state as 3.6 years (stated in Pandor 2011[18]). From this an annual hazard rate was estimated to be 0.278 (= 1/3.6). This was then translated in to 6-month and 1-year probabilities of 24.3% and 13.0% respectively.

2.3.7 Utilities

Utilities are measures of health-related quality of life on a scale from 0 (no better than being dead) to 1 (full health). A systematic search was conducted in Medline and Embase to find utilities relating to head injury (see Appendix A:). Several small studies had estimated utilities for people with head injury by Glasgow Outcome Scale score but the study by Fuller 2017[22] was by far the most relevant. This study mapped GOS to the UK tariff of the EQ-5D-3L, which is preferred by NICE, for 3,457 people with TBI and complete information at 12 months on the Victoria State Trauma Registry.

These utility values are presented in Table 6.

Of note, the utility value for vegetative state is less than 0, which is worse than being dead. However, a sensitivity analysis was conducted where it was assumed the utility of vegetative state was 0.

To make the utility values probabilistic, utility decrements between states were calculated. For example, Good recovery minus Moderate disability is 0.894-0.675=0.219. A gamma distribution was applied to each decrement to ensure that the ranking of the utilities was maintained in every simulation of the probabilistic analysis.

Table 6: Utility values (EQ-5D) from Fuller 2017

Health state	Mean	SD	n
Full health	1.000		
Good recovery	0.894	0.16	1309
Moderate disability	0.675	0.27	122
Severe disability	0.382	0.35	900
Vegetative state	-0.178	0.19	6

Abbreviations: n: number of people; SD: standard deviation

Sensitivity analyses using an alternate data source for utility were also conducted. Details of these sensitivity analyses can be found in section 2.5.1.

For the good recovery state, in the short to medium term (up to 13 years, where the model uses head-injury specific mortality and utility data) the utility value from Fuller 2017 was used but for the longer-term national age-specific utilities were used. Not adjusting utilities for increasing age would have led to QALYs being overestimated over the lifetime for this state. For the other states, the utility scores were kept constant over time, since these utilities were already lower than the general population averages for older people.

Age/sex-specific general population EQ-5D-3L utilities were derived from the Health Survey for England.[6]

2.3.8 Resource use and costs

2.3.8.1 Intervention costs

The costs of the intervention itself are presented in Table 7.

Table 7: Intervention costs

Intervention costs	Cost	Source
Tranexamic acid	£6.00	British National Formulary[3] (accessed April 2022)
Consumables	£5.00	Committee estimate
Paramedic time administering tranexamic acid	£6.10	PSSRU 2021[7] assuming 23 minutes (committee opinion) to administer TXA by slow injection

The cost of consumables was estimated by the committee as opposed to being micro costed due to the low expected cost of the consumables and the potential challenge in identifying all consumables in the NHS supply chain catalogue. The committee noted the £5 estimate was likely to be an overestimate. However, given that this cost is negligible compared to the cost of admission and long-term care there was no need to conduct a sensitivity analysis.

Consumables for accessing the vein include:

- Pair of gloves
- Sharps box
- Antiseptic swab
- Cannula
- Vecafix (to secure the cannula)
- 10ml syringe
- 10ml sodium chloride ampul to push through the cannula
- Drawing up needle

Consumables for administering tranexamic acid include:

- 20ml syringe
- Drawing up needle

Consumables to flush tranexamic acid through after administration include:

- 10ml syringe
- 10ml sodium chloride ampule
- Drawing up needle

2.3.8.2 Hospital costs

Hospital costs comprised of an initial first day cost, subsequent bed day costs and ICU-bed days costs.

All hospital related bed day costs were made probabilistic using a gamma distribution where the standard error was assumed to be 20% of the mean.

Non-ICU bed day costs

The costs used in the calculation of the non-ICU stay are presented in Table 8.

Table 8: Non-elective Short stay cost (used as a proxy for the cost of the first day of admission and excess bed day cost used as a proxy for subsequent days

		Short stays		Excess bed days	
Currency code	Currency description	Stays	National average unit cost 2019/20	Days	National average unit cost 2017/18
AA26C	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 15+	5,489	£1,256	11,566	£289
AA26D	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 12-14	8,639	£654	17,938	£289
AA26E	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 9-11	14,996	£580	26,060	£302
AA26F	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 6-8	23,237	£520	26,635	£311
AA26G	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 3-5	33,460	£465	20,949	£331
AA26H	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-2	31,230	£386	11,256	£365
All		117,031	**£521**	**113,684**	**£314**

Abbreviations: CC score: Complication and Comorbidity score; FCE: Finished Consultant Episode

Cost for bed days were unavailable in the 2019/20 NHS reference costs[15], but excess bed costs for brain injury (HRG code AA26) were available in the 2017/18 NHS reference costs[4]. Therefore, to calculate the cost of a bed day cost reflective of 2019/20 prices, the cost reported in the 2017/18 NHS reference costs was inflated by a multiplier reflective of the price increase observed for short stay cost.

The multiplier was calculated as the cost of a short stay 2019/20 prices divided by the cost a short stay at 2017/18 prices (£521/£455), resulting in a multiplier of 1.14. The 2019/2020 average cost of a bed day was £359 (£314*1.14).

Since excess bed days occur after the main treatment has been given, the excess bed day cost is likely to under-estimate the cost of the hospital stay. Therefore, the cost of a short stay was used for the first day of the stay, where one would expect the treatment to be most intense. The cost of a short stay was taken from NHS reference costs 2019/2020 (Table 8).

ICU bed-day cost

The cost of an ICU bed-day (£1616) was the weighted average cost per day for critical care units where neurosciences adult patients predominate in the NHS Reference costs (Table 9).

Table 9: ICU bed-day costs "Neurosciences adult patients predominate"

Currency code	Currency description	Activity	National average unit cost 2019/20
XC01Z	Adult Critical Care, 6 or more Organs Supported	98	£2,032
XC02Z	Adult Critical Care, 5 Organs Supported	1,454	£1,945
XC03Z	Adult Critical Care, 4 Organs Supported	9,011	£1,833
XC04Z	Adult Critical Care, 3 Organs Supported	21,309	£2,022
XC05Z	Adult Critical Care, 2 Organs Supported	16,660	£1,375
XC06Z	Adult Critical Care, 1 Organ Supported	18,969	£1,330
XC07Z	Adult Critical Care, 0 Organs Supported	2,278	£886
All		69,779	**£1,616**

Mean number of days in hospital

The mean number of days in hospital (ICU and non-ICU) were derived from the trial - Table 10. This was not stratified by TBI severity in the trial and therefore it was subjected to sensitivity analysis.

Table 10: Mean number of days in hospital

	2g bolus	placebo	Source
a. Mean hospital-free days at day 28	14.1	13.6	Rowell 2020 Table 2
b. Mean ICU free days at day 28	19.1	18.5	Rowell 2020 Table 2
c. Mean days alive at day 28	25.3	23.9	Rowell 2020 Figure 2*
d. Mean days in hospital	11.2	10.3	=c minus a
e. Mean number of days on ICU ward	6.2	5.4	=c minus b
f. Mean number of days on a non-ICU ward	5.0	4.9	=d minus e

**Extracted using Digitize.*

For a proportion of people who experience a TBI, surgery is required. The total cost of surgery was estimated as the cost of surgery multiplied by the proportion of people requiring surgery for each treatment (TXA versus No TXA).

Neurosurgical procedure costs

Surgery costs were estimated using cost data from NHS reference costs 2017/18[4] and NHS Reference costs 2019/20[15]. The total cost of surgery was estimated excluding bed day costs to avoid double counting because the mean number of days on a non-ICU and ICU ward were included separately as outlined in section 2.3.8.2.

The total cost of surgery was estimated as the cost of a surgery admission (£11,800) minus the first day cost (£521) then minus the cost of a bed day (£408) multiplied by the mean length of stay minus one (11.1 – 1). This calculation provided a cost estimate of the cost of surgery excluding the bed day costs included in NHS reference costs. Since excess bed day costs are not reported in the latest NHS reference costs, those reported in 2017/18 were inflated to 2019/20. Further details of the calculation of surgery costs can be found in Table 11.

Table 11: Nurosurgical procedure costs (weighted averages)

	Healthcare Resource Group codes	NHS Reference costs 2017/18	NHS Reference costs 2019/20
Surgery mean length of stay	Non-elective long stay AA50A-AA57A Intracranial procedures age 19+	11.1	11.1[(a)]
First day cost	Non-elective short stay AA26C-H Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury	£455	£521
Bed day cost	Excess bed day AA50A-AA57A Intracranial procedures age 19+	£376	£408[(b)]
Surgery admission	Non-elective long stay AA50A-AA57A Intracranial procedures age 19+	£10,850	£11,800
Total cost of surgery (excluding bed days)			**£7,137**[(c)]

(a) *Assumed to be the same value reported in 2017/18 NHS reference costs*
(b) *Calculated bed day cost from NHS reference costs 2017/18 multiplied by a multiplier calculated as surgery admission cost from NHS reference costs 2019/20 divided by surgery admission cost from NHS reference cost 2017/18 (£376*[£11,800/£10,850])*
(c) *£11,800 – £408*(11.1 – 1) - £521.*

Neurosurgical procedure costs were made probabilistic using gamma distribution. The standard error was assumed to be 20% of the mean.

Proportion of people undergoing neurosurgery

The proportion of people undergoing surgery was reported in Rowell 2020[19]: 22% in the 2g bolus arm and 17% in the placebo arm.

Therefore, the total cost of surgery for people receiving TXA was calculated as £7,137 multiplied by 22% and the total cost of surgery for people receiving No TXA was calculated as £7,137 multiplied by 17%.

This outcome was not stratified by TBI severity in the trial and therefore we subjected it to sensitivity analysis.

The proportion of people receiving neurosurgical procedures was made probabilistic using a beta distribution.

2.3.8.3 Post-discharge costs

Post-discharge costs were obtained primarily from the economic evaluation of the CRAH-3 trial, Williams 2020[25] and Formby 2015[5]. Post-discharge costs were split into to two categories – first year post-discharge costs and subsequent years post-discharge costs.

Post-discharge costs for Good recovery, Moderate disability and Severe disability were obtained from Williams 2020[25], and post-discharge costs for vegetative state were obtained from Formby 2015[5]. Vegetative state costs were obtained from Formby 2015 because

Williams 2020 assumed vegetative state costs were the same as Severe disability costs and the committee concluded it was highly unlikely the costs for severe disability and vegetative would be same due to the increased levels of care provision required for people in a vegetative health state.

First-year post-discharge costs reported in Williams 2020 were derived from Beecham 2009[1].Subsequent years post-discharge costs reported in Williams 2020 were obtained from a previous UK health technology assessment, Lecky 2016, with costs estimated by expert opinion.[8]

The study by Beecham 2009[1] is a costing analysis form a UK perspective assessing the treatment paths and costs for young adults (18–25-year-olds) with an acquired brain injury. The study by Formby 2015[5] is an incremental costing analysis assessing the costs of legal declaratory relief requirement for withdrawing Clinically Assisted Nutrition and Hydration (CANH) for people in a permeant vegetive state (PVS) in England and Wales. Costs in Formby 2015[5] were obtained and micro costed from predominantly NHS costing resources. The cost used in the model was the total cost of being in a PVS, which comprised of a weighted average cost for care at home care (with 95% of people requiring specialist nursing care at home and 5% of people requiring home care) and the cost of hospital events.

Costs reported in Williams 2020 were inflated to 2022[17] prices and are presented in Table 12.

Table 12: Post-discharge costs

	Post-discharge costs
First year post-discharge costs – Good recovery	£313
First year post-discharge costs – Moderate disability	£22,361
First year post-discharge costs – Severe disability	£44,176
Subsequent years post-discharge costs – Good recovery	£28
Subsequent years post-discharge costs – Moderate disability	£1,843
Subsequent years post-discharge costs – Severe disability	£14,404
Vegetative state costs (first year and subsequent years)	£109,475

Vegetative state costs were assumed to be the same for first-year post-discharge and subsequent years. The committee noted that vegetative state costs were unlikely to decrease in subsequent years due to the high level of provision of care required for people residing in this health state.

A sensitivity analysis was conducted where post-discharge costs were excluded.

Post-discharge costs were made probabilistic using a gamma distribution where the standard error was assumed be 20% of the mean.

2.4 Computations

The model was constructed in Microsoft Excel version 2206 and was evaluated by cohort simulation. Time dependency was built in by cross referencing tables containing data on mortality.

Patients start at time 0 and their health state was determined by data from the randomised controlled trial by Rowell 2020[19]. Some patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities.

Life years for the cohort were computed each cycle by adding up the number of people still alive. To calculate QALYs for each cycle, the proportion of the cohort in each state was multiplied by a utility score for that state. A half-cycle correction was applied.

QALYs were then discounted to reflect time preference (discount rate 3.5%). The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. In the base case, rehabilitation costs were applied in cycle 1 only. If a difference in post-rehabilitation costs was being included, this was applied in cycle 2 and beyond. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$	Where: *r*=discount rate per annum *n*=time (years)

In the deterministic and probabilistic analyses, the total number of QALYs and resource costs accrued for each arm was recorded. The total costs and QALYs accrued was summed over the life-time horizon to calculate a cost per patient and QALYs per patient.

2.4.1.1 Calculating transition probabilities used in the model

To calculate the transition probabilities, the reported probabilities were converted into rates using the following formula:
$-LN(1 - probability\ of\ dying)/time$

These rates were subsequently converted back to probabilities to obtain a yearly probability of dying for each cycle using the following formula:
$1 - EXP(-rate)$

2.5 Sensitivity analyses

The sensitivity analyses outlined in sections 2.5.1- 2.5.6 were conducted for both a moderate and severe TBI population. A sensitivity analysis modelling a mild TBI population was also conducted, and this analysis is outlined in section 2.5.7.

A sensitivity analysis altering GOS scores was conducted for all model populations (mild, moderate, and severe) and this analysis is outlined in section 2.5.6.

2.5.1 Alternative utility scores

In the base case, the utility for vegetative state was less than zero (-0.178), which indicates the utility is worse than dead. A sensitivity analysis was conducted assuming the utility of vegetative state was equal to zero (no worse than being dead). All other utilities used in this sensitivity analysis were the same as the base case.

Sensitivity analyses were also conducted using the utility values reported in Smits 2010[20]. This study was inferior to Fuller 2017[22], since it:

- was based on a much smaller sample size (87 vs 3,437)
- did not use the UK tariff of the EQ-5D.
- did not include the vegetative state
- its value for severe disability seemed much lower than other studies – see Fuller 2017[22] for a comparison of existing estimates.

However, it was chosen for use in a sensitivity analysis since it had already been used in previous economic evaluations.

Because Smits 2010[20] did not report a utility value for Vegetative state, a utility value of -0.178 or zero was used in two separate analyses.

The utility values used in this sensitivity are presented in Table 13.

Table 13: Alternative utility values (Smits 2010) for good reovery, moderate disability and severe disability

Health state	Fuller 2017	Smits 2010
Good recovery	0.89	0.88
Moderate disability	0.68	0.51
Severe disability	0.38	0.15
Vegetative state	-0.178	[-0.178 or 0]

2.5.2 Standardised mortality ratio applied to mortality

In the base case analysis mortality after 13 years was assumed to equal general population mortality. A sensitivity analysis was therefore conducted where a standardised mortality ratio (SMR) of 2.26 was applied to the general population mortality from year 14 onwards. This SMR was obtained from the Glasgow cohort[10].

2.5.3 Halving the time to administer TXA

A sensitivity analysis was conducted assuming it took half the time to administer TXA resulting in a cost of £3.05 to administer TXA. This sensitivity analysis was conducted as the committee acknowledged that in practice the 2g might be pushed in over a few minutes or delivered in a saline bag enabling staff may be able to carry out additional tasks whilst TXA is being administered. In the trial itself, there is anecdotal evidence that TXA was delivered in this manner.

2.5.4 Altering the number of ICU days

The number of days in ICU was obtained from Rowell 2020[19], however the data reported in Rowell 2020[19] was the mean number of days in ICU for all people, not stratified by TBI severity. A sensitivity analysis was therefore conducted assuming that the increase in ICU days was entirely in the severe TBI cohort. In the severe TBI cohort the mean days in ICU in the TXA arm was increased from 6.2 to 7.2.

2.5.5 Five-year time horizon

A sensitivity analysis assuming the model had a five-year time horizon was conducted because outcomes are more uncertain in the future.

An additional sensitivity analysis was conducted where all downstream costs (post-discharge costs) were excluded.

2.5.6 Adjusting Glasgow Outcome Scale outcomes for differences in baseline characteristics

In the base case analysis, a bespoke analysis of data from the Rowell 2020[19] trial was used to obtain 6-month Glasgow Outcome Scale outcomes for moderate TBI and severe TBI. However, within the trial there were some imbalances between baseline covariates within these strata. Table 14 shows that although there were more people with severe TBI in the placebo arm of the trial, within the severe TBI arm stratum, the level of severity was worse in the Tranexamic acid 2g bolus arm. The same was true for the moderate TBI stratum.

Table 14: Pre-hospital TBI severity by trial arm (Derived from Rowell 2020 Table 1)

TBI severity	Glasgow Coma Scale score	2g bolus	Placebo
Severe	3-8	51%	60%
	of which:		
	3-4	45%	37%
	5-6	29%	33%
	7-8	25%	30%
Moderate	9-12	46%	37%
	of which:		
	9-10	48%	38%
	11-12	52%	62%
Mild	13-15	3%	3%

Rowell 2020[19] also reported adjusted odds ratios (in the supplementary material) for 6-month outcomes for people with and extended Glasgow Outcome Scale (GOSE) score greater than 4 (GOS>3) adjusting for differences in baseline patient characteristics.

Two adjusted odds ratios for 2g bolus TXA vs placebo were taken from Rowell 2020[19]. The first odds ratio of 1.24 was calculated based on imputed values for all patients and only adjusted for regional sites. Whereas an odds ratio of 1.32 was calculated based on unimputed outcomes, adjusting for regional site, age, sex, penetrating head injury versus blunt head injury, GCS group, injury severity score and the abbreviated injury scale.

In total, four sensitivity analyses were conducted as the split within GOS>4 category was calculated in two ways for both odds ratios. Firstly, GOS>4 was split by keeping the ratio of those in Good recovery and Moderate disability the same as the base case analysis. Alternatively, Good recovery the same as the base case and only Moderate disability was increased, which is a more conservative approach.

A description of the four different scenarios are outlined below:

- Odds ratio of 1.24 with the ratio of Good recovery and Moderate disability the same as the base case
- Odds ratio of 1.24 with no adjustment to Good recovery
- Odds ratio of 1.32 with the ratio of Good recovery and Moderate disability the same as the base case
- Odds ratio of 1.32 with no adjustment to Good recovery

These sensitivity analyses were applied to both the moderate TBI and severe TBI strata. For each stratum, the outcomes for the No TXA arm were the same as in the base case analysis and only the outcomes for the TXA arm were changed.

The adjusted odds ratios were not applied in the base case analysis, since they were not specific to the moderate TBI and severe TBI strata but were calculated for the trial as a whole.

2.5.7 Modelling for a mild TBI population

The two populations in the base case analysis were people who experienced a moderate or severe TBI. However, some people with mild TBI could also benefit from TXA in a pre-hospital setting, although their baseline risks are lower and so absolute benefits might be lower. A sensitivity analysis was conducted to assess the cost effectiveness of TXA for people with a mild TBI who are at high risk of an intracranial haemorrhage (ICH). This was conducted to inform a research recommendation.

The population of interest was deemed to be adults with mild TBI who would meet the guideline's criteria to be CT scanned urgently:

- [GCS score less than 15 at 2 hours after the injury on assessment in the emergency department. – not applicable here as TXA has to be administered early]
- Suspected open or depressed skull fracture.
- Any sign of basal skull fracture
- Post-traumatic seizure.
- Focal neurological deficit.
- More than 1 episode of vomiting.

2.5.7.1 Estimating cost-effectiveness of tranexamic acid for people with an ICH

There were few people in the Rowell 2020[19] trial that had mild TBI but in a supplementary table GOS>3 was reported for patients experiencing an ICH, which was considered useful as indirect evidence, if the prevalence of ICH could be estimated for the population of interest.

To assess the cost effectiveness of TXA for people with mild TBI but at high risk of an ICH, outcomes (GOS) were calculated separately for those patients that have an ICH and those that do not. Outcomes of the models were subsequently weighted by the proportion of people with and without an ICH to obtain the overall cost per QALY gained. Two analyses were conducted, one for the overall population where it was assumed that 10% of people have an ICH and a subgroup with GCS score of 13-14 where 20% of people had an ICH (based on committee opinion).

TXA benefit was assumed to occur only in those people with an intracranial haematoma. Those without an ICH had a slight increase in non-TBI mortality with TXA.

2.5.7.2 Data and assumptions

All data inputs were the same as the base case analysis, except for:

- the 6-month GOS outcomes
- mortality from year 1 to year 15.

6-month outcomes

In the trial 197 people had an ICH in the 2g bolus TXA arm and 171 people had an ICH in the placebo arm. Treatment effects (Odds ratios) from Rowell 2020 – people with ICH on CT only:

- 6-month GOSE>4 1.20 (1.34 adjusted)
- 28-day mortality 0.57* (0.50* adjusted). In the absence of 6-month mortality, the 28-day mortality odds ratios were applied to 6-month mortality.

To capture the main adverse effects of TXA non-TBI mortality was estimated. This was not explicitly reported in the trial. Therefore, an estimate using data from the CRASH-3 trial was used (mild and moderate TBI, TXA administered within 3 hours). There was a risk difference of 0.19% (=29/2844 – 23/2766). The non-TBI deaths were inferred by subtracting TBI deaths from all-cause deaths.[2]

Baseline outcomes in the no TXA arm were based on committee expert opinion:

- ICH - 6-month mortality: 5%

- ICH - 6-month GOS>3: 65%
- No ICH - 6-month mortality: 3%
- No ICH - 6-month GOS>3: 85%.

The proportion of people in each health state based on the above data and assumptions is reported in Table 14.

Table 15: 6-month Glasgow Outcome Scale - mild TBI population

	Tranexamic acid	No tranexamic acid
No ICH		
Good recovery	64.8%	64.9%
Moderate disability	20.1%(	20.1%
Severe disability	12.0%	12.0
Vegetative state	0.0%	0.0
Dead	3.2%	3.0%
ICH		
Good recovery	52.7%	49.6%
Moderate disability	16.3%	15.4%
Severe disability	28.1%	30.0%
Vegetative state	0.0%	0.0%
Dead	2.9%	5.0%

Abbreviations: ICH: Intracranial haemorrhage; TXA: Tranexamic acid

<u>Mortality from 6 months to 15 years</u>

The probability of dying for people with Good recovery, Moderate disability and Severe disability was based on the survival curve from a cohort of 2428 adults with mild TBI - McMillan 2014.[11] This data was available up to year 15.

From year 16 onwards age-specific mortality rates were those of the general population. The starting age of the cohort was 39 years, the median age from McMillan 2014.[11]

Additional analyses were conducted using an adjusted odds ratio from Rowell 2020 of 1.34 for GOS>3.

2.6 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee 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 experienced health economist from the guideline development team; this included systematic checking of the model calculations.

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 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold, then 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.

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

2.8 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[12-14] 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.

3. Results

3.1 Base case analyses

3.1.1 Moderate TBI

The total cost of tranexamic acid for a moderate TBI population was higher compared to no tranexamic acid £4,720 (95% CI: -£17,687, £27,110). A breakdown of costs for a moderate TBI population are presented in Table 15.

The difference in cost is mostly attributed to the long-term care costs followed by hospital stay costs.

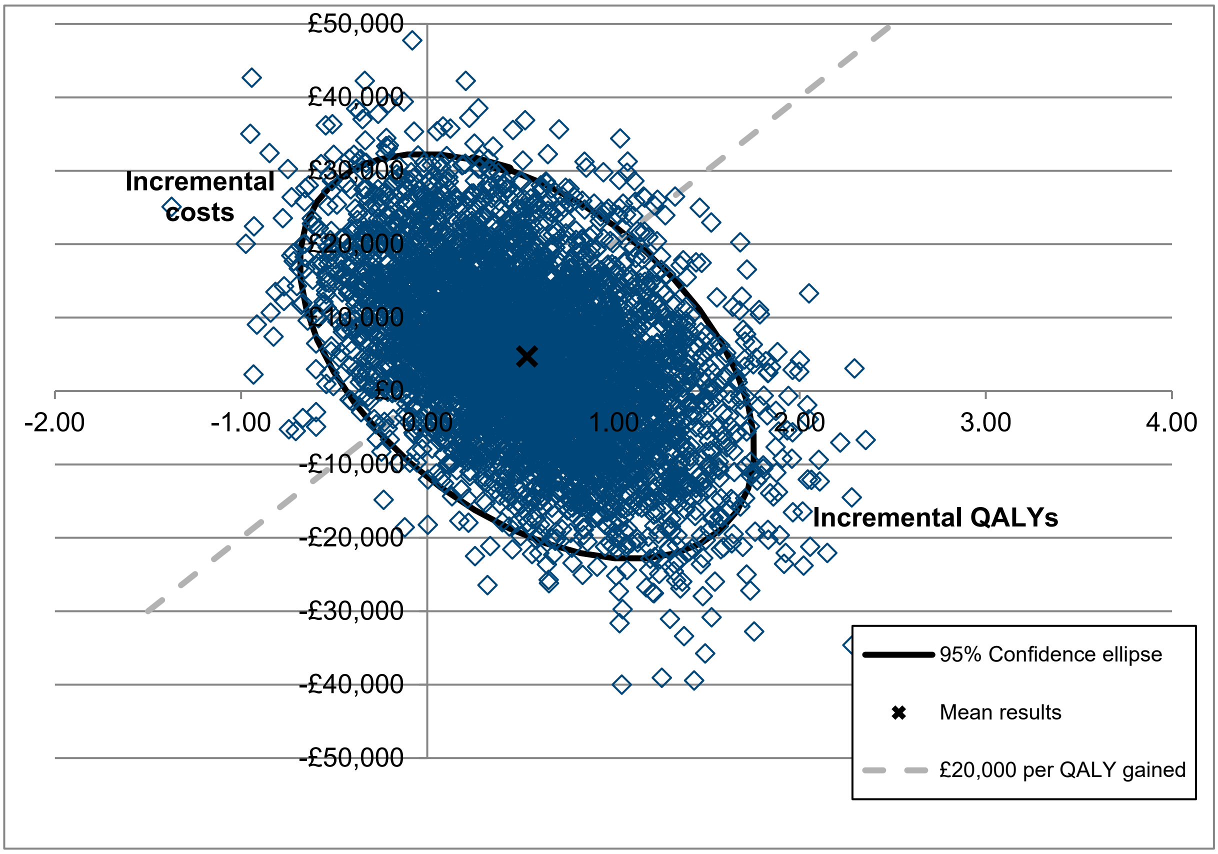
Table 16: Breakdown of costs for a moderate TBI population (probabilistic) – Mean per patient

	TXA	No TXA	TXA minus No TXA
Intervention costs	£17	£0	£17
Hospital stay costs	£11,932	£10,566	£1,366
Surgery costs	£1,572	£1,215	£357
Post-discharge costs	£49,892	£46,912	£2,980
Good recovery	£442	£400	£42
Moderate disability	£6,712	£8,414	-£1,702
Severe disability	£42,476	£37,547	£4,929
Vegetative state	£263	£551	-£289
Total cost	£63,413	£58,693	£4,720
Life years (undiscounted)	25.37	24.14	1.23
QALYs (undiscounted)	18.49	17.57	0.92
QALYs	10.61	10.08	0.54
Incremental cost per QALY gained			£8,805
Probability cost effective at £20,000 per QALY threshold	62%	38%	
Probability cost effective at £30,000 per QALY threshold	69%	31%	

The mean QALYs where higher for tranexamic acid, 0.54 (95% CI: -0.39, 1.55). The base case results indicated tranexamic acid was cost effective at NICE's £20,000 threshold with a cost per QALY of £8,805.

The scatterplot in Figure 4 shows the base case results of the probabilistic analysis.

Figure 5: Base case cost effectiveness of TXA compared to No TXA: scatterplot of 5,000 probabilistic iterations on the cost effectiveness plane – moderate TBI



3.1.2 Severe TBI

Table 17: Breakdown of costs for a severe TBI population (probabilistic) – mean per patient

	TXA	No TXA	TXA minus No TXA
Intervention costs	£17	£0	£17
Hospital stay costs	£11,932	£10,566	£1,366
Surgery costs	£1,572	£1,215	£357
Post-discharge costs	£76,593	£71,222	£5,369
Good recovery	£281	£307	-£25
Moderate disability	£9,063	£6,245	£2,818
Severe disability	£64,764	£57,564	£7,197
Vegetative state	£2,485	£7,106	-£4,621
Total cost	£90,115	£83,002	£7,109
Life years (undiscounted)	25.61	24.06	1.55
QALYs (undiscounted)	17.06	16.42	0.64
QALYs	8.96	8.64	0.32
Incremental cost per QALY gained			£22,310
Probability cost effective at £20,000 per QALY threshold	48%	52%	
Probability cost effective at £30,000 per QALY threshold	53%	47%	

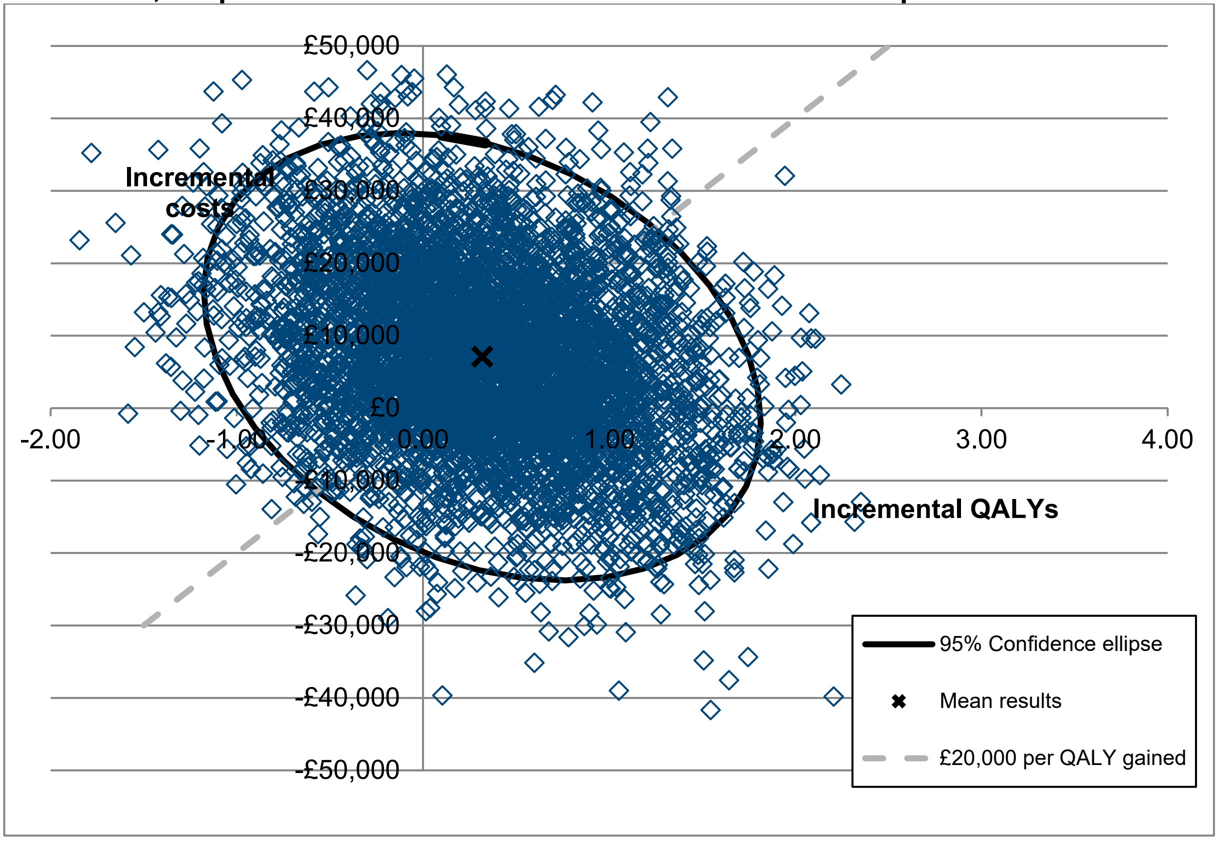
The total cost of tranexamic acid for a severe TBI population was higher than tranexamic acid, £7,109 (95% CI: -£17,759, £32,093). A breakdown of costs for a moderate TBI population are presented in Table 16.

Once again, the difference in cost is mostly attributed to the long-term care costs followed by the hospital stay costs.

The mean QALYs were higher for tranexamic acid, 0.32 (95% CI: -0.87, 1.52). The base case results indicated tranexamic acid was not quite cost effective at NICE's £20,000 threshold with a cost per QALY of £22,310.

The scatterplot in Figure 5 shows the base case results of the probabilistic analysis.

Figure 6: Base case cost effectiveness of TXA compared to No TXA: scatterplot of 5,000 probabilistic iterations on the cost effectiveness plane – severe TBI



3.2 Sensitivity analyses

Sensitivity analyses outlined in sections 2.5.1 to 2.5.6 were conducted for both moderate TBI and severe TBI.

A separate sensitivity analysis was also conducted for a high-risk mild TBI population.

3.2.1 Moderate TBI

The results of all sensitivity analyses were below NICE's £20,000 threshold for the moderate TBI population (Table 17).

Table 18: Sensitivity analyses for the moderate TBI population (deterministic)

Analysis	Mean cost difference (TXA – No TXA)	Mean QALY difference (TXA – No TXA)	Cost per QALY gained
Base case (probabilistic)	£4,720	0.54	£8,805
Base case (deterministic)	£4,771	0.52	£9,102
Utilities			
Utility for vegetative state (VS) equals zero	£4,771	0.52	£9,110
Alternative values for utility (Smits 2010) and VS utility equals the base case value	£4,771	0.53	£8,990
Alternative values for utility (Smits 2010) and VS utility equals zero	£4,771	0.53	£8,997
Resource use and cost			
Halving the time to administer TXA	£4,768	0.52	£9,096
One less day in ICU in TXA arm	£3,217	0.52	£6,138
Five-year time horizon	£5,128	0.52	£9,783
Double the impact on surgery	£1,705	0.52	£3,253
Treatment effects (GOS≥4)			
Odds ratio of 1.24 (with the ratio of good recovery and moderate disability the same as the base case)	£1,980	0.66	£3,000
Odds ratio of 1.24 (with no adjustment to good recovery)	£2,609	0.62	£4,187
Odds ratio of 1.32 (with the ratio of good recovery and moderate disability the same as the base case)	£158	0.75	£211
Odds ratio of 1.32 (with no adjustment to good recovery)	£1,198	0.69	£1,742
Other			
SMR of 2.2 applied to mortality after year 13	£4,483	0.49	£9,133
Five-year time horizon	£2,026	0.15	£13,361

3.2.2 Severe TBI

For the severe TBI population the results were most sensitive to the alternative utility value set from Smits 2010[20] where the cost per QALY gained was over £100,000. The results were also quite sensitive to the number of days in ICU in the TXA arm. When it was increased by 1 day, the cost per QALY gained increased to £27,500. The cost per QALY gained was well below £20,000 when the long-term care costs were omitted or when the treatment effect was adjusted for differences in baseline patient characteristics.

Table 19: Sensitivity analyses for the severe TBI population (deterministic)

	Mean cost difference (TXA – No TXA)	Mean QALY difference (TXA – No TXA)	Cost per QALY gained
Base case (probabilistic)	£7,109	0.32	£22,310
Base case (deterministic)	£7,161	0.32	£22,256
Utilities			
Utility for vegetative state (VS) equals zero	£7,161	0.31	£22,797
Alternative values for utility (Smits 2010) and VS utility same as the base case value	£7,161	0.06	£112,978
Alternative values for utility (Smits 2010) and VS utility equals zero	£7,161	0.06	£128,444
Resource use and cost			
Halving the time to administer TXA	£7,158	0.32	£22,247
Extra day in ICU in TXA arm	£8,840	0.32	£27,473
Double the impact on surgery rate	£7,518	0.32	£23,365
Excluding post-discharge costs	£1,705	0.32	£5,300
Treatment effects (GOS≥4)			
Odds ratio of 1.24 (with the ratio of good recovery and moderate disability the same as the base case)	£2,930	0.64	£4,569
Odds ratio of 1.24 (with no adjustment to good recovery)	£4,009	0.57	£6,996
Odds ratio of 1.32 (with the ratio of good recovery and moderate disability the same as the base case)	£908	0.79	£1,143
Odds ratio of 1.32 (with no adjustment to good recovery)	£2,503	0.69	£3,610
Other			
SMR of 2.2 applied to mortality after year 13	£6,630	0.30	£22,165
Five-year time horizon	£1,781	0.08	£22,084

3.2.3 Mild TBI

The QALYs and breakdown of costs for people who experience an ICH and don't experience an ICH are presented in Table 19.

Table 20 shows the cost effectiveness of TXA vs no TXA, which is a weighted average of the results in Table 19. Table 22 shows estimates of cost effectiveness using treatment effects adjusted for trial-arm differences in baseline patient characteristics.

Table 20: Brekadown of costs for a mild TBI population (deterministc)

	People with an intracranial haematoma		People with no intracranial haematoma	
	TXA	No TXA	TXA	No TXA
Intervention costs	£17	£0	£17	£0
Hospital stay costs	£11,915	£10,583	£11,915	£10,583
Surgery costs	£1,570	£1,213	£1,570	£1,213
Post-discharge costs	£85,489	£90,456	£43,728	£43,791
Good recovery	£397	£374	£488	£489
Moderate disability	£8,374	£7,887	£10,294	£10,314
Severe disability	£76,717	£82,195	£32,946	£32,988
Vegetative state	£0	£0	£0	£0
Total cost	£98,990	£102,252	£57,229	£55,588
Life years (undiscounted)	30.47	29.82	30.38	30.44
QALYs (undiscounted)	20.67	19.89	22.71	22.75
QALYs	11.31	10.89	12.46	12.48

Table 21: Incremental costs and QALYs for TXA vs no TXA – High-risk mild TBI

	High-risk mild TBI	High-risk mild TBI - GCS score 13-14
Intervention costs	£17	£17
Hospital stay costs	£1,331	£1,331
Surgery costs	£357	£357
Post-discharge costs	-£554	-£1,044
Good recovery	£1	£4
Moderate disability	£31	£81
Severe disability	-£586	-£1,130
Vegetative state	£0	£0
Total cost	£1,151	£661
Life years (undiscounted)	0.01	0.08
QALYs (undiscounted)	0.04	0.12
QALYs	0.02	0.07
Cost per QALY gained	£54,640	£9,994

Table 22: Altering the odds ratio (GOS≥4) for a high-risk mild TBI population (deterministic)

	Mean cost difference (TXA – No TXA)	Mean QALY difference (TXA – No TXA)	Cost per QALY gained
All high-risk mild TBI			
Unadjusted odds ratio of 1.20	£1,151	0.02	£54,640
Odds ratio of 1.34 (with the ratio of good recovery and moderate disability the same as the base case)	£641	0.04	£15,903
Odds ratio of 1.34 (with no adjustment to good recovery)	£730	0.03	£21,020
GCS score 13-14			

	Mean cost difference (TXA – No TXA)	Mean QALY difference (TXA – No TXA)	Cost per QALY gained
Unadjusted odds ratio of 1.20	£661	0.07	£9,994
Odds ratio of 1.34 (with the ratio of good recovery and moderate disability the same as the base case)	-£360	0.10	TXA dominant
Odds ratio of 1.34 (with no adjustment to good recovery)	-£181	0.09	TXA dominant

4. Discussion

4.1 Summary and interpretation of results

4.1.1 Moderate TBI

An original cost-utility analysis found that tranexamic acid for people with a moderate TBI is cost effective compared to no tranexamic acid (£8,800 per QALY gained). This was assessed as directly applicable with minor limitations.

This was robust to all sensitivity analyses. However, the confidence ellipse was wide, which reflected that the evidence was from a single trial, which showed no statistically significant difference in its primary outcome.

4.1.2 Severe TBI

An additional original cost-utility analysis modelling for a severe TBI population found that tranexamic acid for people with a severe TBI is not cost effective compared to no tranexamic acid (£22,300 per QALY gained) at NICE's £20,000 threshold but is cost effective at NICE's £30,000 threshold. This analysis was assessed as directly applicable but with potentially serious limitations due to the sensitivity of the results.

Being over £20,000 per QALY, the cost effectiveness would seem borderline. There were sensitivity analyses where the cost per QALY gained was even higher:

- When alternative (lower) utility values for disability were used, TXA cost £113,000 per QALY. The moderate and severe TBI groups saw similar absolute reductions in mortality at 6 months but only in the severe TBI group this was offset by an increase in severe disability. However, there were reasons to conclude that the base case utility values were much more robust, being based on the UK tariff of the EQ-5D-3L and in a much larger population.
- Length of stay was available for the trial population as a whole and not separately severe TBI. The committee pondered what if increased time in ICU was all attributable to the severe TBI patients and none of it to the moderate TBI patients. When the increase in ICU stay was doubled from 1 day to 2 days, TXA cost £27,500 per QALY. However, this was considered unlikely, as the absolute improvement in survival in the trial was the same for the moderate and severe TBI strata.

However, there were reasons to believe that the cost per QALY was over-estimated:

- Due to lack of data, the model assumed that people stay in the same GOS state over their lifetime, whereas it is likely that some people will continue to improve beyond 6-months. This means that the QALYs would have been under-estimated.
- Baseline characteristics were substantially poorer in the 2g bolus arm than in the placebo arm of the trial. When a sensitivity analysis was conducted using the adjusted odds ratio for GOSE>4 from the trial the cost per QALY gained reduced to as low as £1,100. The adjusted odds ratio was not applied in the base case analysis since it was not specific to the severe TBI strata but was calculated for the whole trial population. Hence this sensitivity analysis is not necessarily better than the base case analysis, but it does hint that the effectiveness in the model might have been under-estimated.

As with the moderate TBI analysis, the confidence ellipse was wide, which reflected that the evidence was from a single trial, which showed no statistically significant difference in its primary outcome.

4.2 Generalisability to other populations or settings

4.2.1 In-hospital setting

The model was based on a trial in a pre-hospital setting. The CRASH-3 trial was set in-hospital. That trial found that for people with moderate and mild TBI, the earlier that TXA is administered the better the patient outcomes. Therefore, it is not likely to be as cost effective administered in-hospital, even though TXA would be no more expensive to administer in-hospital.

For patients that present at the hospital and are not treated at the scene, TXA is still likely to be cost effective if administered in-hospital if:

- it is administered early enough (and within 2 hours)
- it does not delay the patient receiving a CT scan.

4.2.2 Mild TBI population

A sensitivity analysis found that TXA might be cost effective for people with mild TBI, especially in the subgroup of people who have a GCS score of 13-14. However, trial evidence is required, as this analysis was dependent on expert opinion to a great extent. The committee decided to recommend the development of a clinical trial for the pre-hospital use of TXA in this population, since the model showed that potentially TXA could be cost effective in this context.

Another economic model using different assumptions, also suggested that TXA could be cost effective for older people with mild TBI.[24] This study was used to support the rationale for the CRASH-4 trial, which is under way.

4.2.3 Children

There was no evidence for children. However, for children of equivalent risk as the adults in the model it seems likely that the cost effectiveness will be similar or even better, as the life years will be greater for each life saved.

4.2.4 Other countries

The trial data were collected in various centres in North America. However, costs used in the model were from the NHS in England. Utilities were using the UK tariff of the EQ-5D and the longer-term mortality data were based on a UK cohort. The cost effectiveness estimates, therefore, might not necessarily be applicable to other country settings.

4.3 Comparisons with published studies

There was one published economic evaluation of tranexamic acid (TXA), Williams 2020[25], which was based on the CRASH-3 randomised controlled trial. The guideline model has the following advantages over the published evaluation:

- It is based on a trial in a pre-hospital setting. Generally, the use of TXA has moved to a pre-hospital setting, for example in major trauma, because of the better outcomes with earlier use.
- The trial that the model was based on had 6-month GOS outcomes (compared to 28-day disability rating scale outcomes with CRASH-3, which had to be converted to GOS in order to estimate QALYs).
- The model did not make the simplifying assumption that utility (quality of life) would be the same in each model arm.

- The model used all-cause mortality, not just TBI mortality and did not assume that non-TBI mortality was the same in both arms.
- The model captured the cost of increased length of stay and surgery.
- The model had outcomes specifically for a moderate risk population.

Despite of these differences, the results of the two models were similar. Both showed that the cost effectiveness of TXA was borderline cost effective for severe TBI. Both showed that the TXA was highly cost effective for moderate TBI (although Williams 2020 combined people with moderate TBI with people with mild TBI and an intracranial abnormality on CT).

4.4 Conclusions

4.4.1 Implications for practice

Overall, it seems that pre-hospital TXA is likely to be cost effective from an NHS perspective for people with moderate and severe TBI.

4.4.2 Implications for future research

A sensitivity analysis showed that pre-hospital TXA could be cost-effective for people with mild TBI, but trial research is needed, since this is a population at lower risk of bleeding and so for them it is less clear if the benefits will outweigh the risk of thromboembolic events.

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Appendices

Appendix A: Search strategy

A.1 Health Economics literature search strategy

Quality of life evidence was identified by conducting searches using terms for a broad Head Injury population. Searches were run in Medline and Embase covering all years.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Quality of Life 1946 – 22 June 2022	Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Quality of Life 1974 – 22 June 2022	Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language

Medline (Ovid) search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/

13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	quality-adjusted life years/
27.	sickness impact profile/
28.	(quality adj2 (wellbeing or well being)).ti,ab.
29.	sickness impact profile.ti,ab.
30.	disability adjusted life.ti,ab.
31.	(qal* or qtime* or qwb* or daly*).ti,ab.
32.	(euroqol* or eq5d* or eq 5*).ti,ab.
33.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
34.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
35.	(hui or hui1 or hui2 or hui3).ti,ab.
36.	(health* year* equivalent* or hye or hyes).ti,ab.
37.	discrete choice*.ti,ab.
38.	rosser.ti,ab.
39.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
40.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
41.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
42.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
43.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
44.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
45.	or/26-44
46.	25 and 45

Embase (Ovid) search terms

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.

6.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	quality-adjusted life years/
28.	"quality of life index"/
29.	short form 12/ or short form 20/ or short form 36/ or short form 8/
30.	sickness impact profile/
31.	(quality adj2 (wellbeing or well being)).ti,ab.
32.	sickness impact profile.ti,ab.
33.	disability adjusted life.ti,ab.
34.	(qal* or qtime* or qwb* or daly*).ti,ab.
35.	(euroqol* or eq5d* or eq 5*).ti,ab.
36.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
37.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
38.	(hui or hui1 or hui2 or hui3).ti,ab.
39.	(health* year* equivalent* or hye or hyes).ti,ab.
40.	discrete choice*.ti,ab.
41.	rosser.ti,ab.
42.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
43.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
44.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
45.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
46.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
47.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.

48.	or/27-47
63.	26 and 48