Review title
Tranexamic acid (TXA) in surgery to reduce blood transfusion requirements: a systematic review of predictive accuracies of risk assessment tools, and a systematic review and economic evaluation of TXA in varying levels of blood loss

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Stage of review at time of submission
Preliminary searches

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Conflict of interest
The review team members listed above have no relevant conflicts of interest with regard to these materials. As this is a review requested by NICE, we will adhere to the standard NICE guidance on declarations of conflicts of interest, including at any committee meetings attended.

Collaborators
We are collaborating with relevant stakeholders who are providing advice on the design, undertaking, interpretation and dissemination of the review. These include:

- Local topic experts in fields of thrombosis/haemostasis – Dr Catherine Bagot and surgery – Prof Campbell Roxbourgh, (both at University of Glasgow, NHS Greater Glasgow and Clyde)
- Additional topic experts – Professor Michael Murphy, consultant haematologist for NHSBT and Professor Ian Roberts, London School of Hygiene and Tropical Medicine (LSHTM), both of whom are on the Joint Royal Colleges Tranexamic acid in Surgery Implementation Group
- PPI contributors

Review questions
The review is composed of two interdependent questions with differing evidence synthesis methodology. The two reviews share many common aspects, for example population and approach to searching. However, there are distinct approaches to formulating the question and creating a synthesis of the evidence for the two review types, and where necessary the two reviews may be considered separately in this protocol.

The prognostic review is framed according to the PICOTS system with details of each PICOTS component below. The intervention review is framed according to the standard PICOS system with full details of each PICOS component below.

I. Prognostic review question: to what extent are multicomponent prediction tools able to predict need for transfusion during and immediately following surgery.

   Population: surgical patients
   Intervention (model): multi-component prediction tools
   Comparator: (if available) other multi-component prediction tools
   Primary outcome: (risk of) transfusion
   Secondary (subgroup) analyses:
   - Timing – during and immediately post-surgery (first 48 hours)
   - Setting – emergency and elective surgery, including obstetrics

II. Intervention review question: at what levels of expected blood loss from surgery is TXA effective at reducing the need for blood transfusion? In addition (co-primary question), is TXA effective in surgery in patients with anticipated minor blood loss.

   Population: surgical patients
   Intervention: tranexamic acid given in the peri-operative period using any mode of application.
   Comparator: placebo or no additional treatment.
   Primary outcome: proportion of patients requiring transfusion
   Secondary outcomes:
   - All-cause mortality at 30 days
   - Quality of life (all timepoints)
   - Length of stay (hospitalisation)

- Number of units of allogeneic blood transfused/volume of allogeneic blood transfused (in ml)
- Surgical bleeding
- Serious adverse events as defined by the study including thrombotic complications

Study designs to be included: randomised controlled trials (and systematic reviews to identify them)

Context

The review is intended to assist surgical practice in the UK NHS. The findings will also inform planned evidence synthesis looking at effectiveness of TXA at differing levels of predicted blood loss. In particular, the co-primary aims of this review will help assess whether an update of TXA guidelines in NICE Blood transfusion guideline (NG24) is required. From scoping the literature, and searching the PROSPERO database, there has not been a previous systematic review on this topic.

Searches

The following databases will be searched:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- Embase (Ovid SP)
- MEDLINE (Ovid SP)
- ClinicalTrials.gov
- WHO trials portal: ICTRP

Searches will be restricted by:

- Date limit – we will search from January 2015 onwards (to ensure data are relevant, recognising the temporal changes in surgical technique and bleeding risk). For earlier trials of TXA (from 2000 onwards) we will use published systematic reviews to identify trials relevant for this review. This includes two previous reviews conducted as part of NICE guidelines (NG24 (Blood transfusion) published in 2015 and the associated 2020 surveillance document and NG157 (Joint replacement (primary): hip, knee and shoulder), published in 2020). We will also rely on data extraction from these reviews and any other high-quality previous systematic reviews identified where available, but obtain original trial reports to seek further information if necessary.
- We will apply the Cochrane validated RCT sensitivity-maximising methodological filters where appropriate.
- We will exclude animal and pre-clinical studies.
- Search will be limited to English language in the first instance.
- Search will be limited to studies published in peer reviewed scientific journals (i.e. there will be no searching of pre-print servers or other grey literature).

Other searches:

We will check the reference lists of all potentially includable studies and relevant reviews for any additional potential studies. The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.

Results screening

If the number of de-duplicated search results exceeds 5,000 results, we will use Cochrane's crowdsourcing service Screen4Me to remove off-topic material. Once complete the core author team will assess the remaining results.

Condition or domain being studied

This review will consider surgical blood loss. Under the term 'surgical' we will include emergency and elective procedures and obstetric procedures.

Participants/population

All surgical patients will be considered, including both adult (≥16 years) and paediatric (1-16 years inclusive). These populations will be combined in the primary analysis if data allow and based on input from our expert panel (recognising that blood loss in paediatric populations may be assessed as percentage rather than volume – see definitions below). If combined, the two groups will then be explored as separate subgroups. Further, we will stratify population based on expected blood loss. For our co-primary question, where data exist, we will restrict analysis to those with anticipated low volume blood loss.

All surgical procedures will be considered including emergency and elective. Obstetric procedures will be included. Decisions on whether to combine these differing surgeries in the primary analysis will be decided by our clinical collaborators, if a combined analysis is used then the different surgeries will be explored as separate subgroups.

Prognostic tool(s) (prognostic review)

The focus of the prognostic review will be multicomponent prediction tools, (sometimes called multivariable tools, prognostic models or risk scores). A multicomponent prediction tool is a mathematical equation that relates multiple predictors for a particular individual to the probability of or risk for the future occurrence of a particular outcome. For this review the tools must combine at least three items, including clinical, demographic or laboratory data. The tools can be generic or specific to certain surgical interventions. Our experts in surgery and thrombosis will assess whether the included models contain those variables considered most important in clinical practice. This will be an iterative process. We will identify variables in advance and will then present them to our clinical experts for discussion.

As agreed at scoping, the focus will be on tools that have evidence of at least one validation exercise. Tools that have been described in a development study only will not be included. Tools that describe bleeding risk in other situations, for example trauma or following exposure to anticoagulation, will not be included in the main analysis, but their performance and component items will be considered for context in the discussion of the results from this review.

An example of a multicomponent prediction tool is the BIMS (Bleeding Independently associated with Mortality after noncardiac Surgery) tool, which includes the following variables: type of surgery, preoperative haemoglobin, age, sex, functional status, kidney function, history of high-risk coronary artery disease, and active cancer. Other examples of relevant prediction tools include, the Transfusion Risk and Clinical Knowledge score (TRACK), the Transfusion Risk Understanding Scoring Tool (TRUST), and the Papworth Bleeding Risk Score (BRiSc). Online tools exist that have been developed for use in clinical practice. https://qxmd.com/calculate/calculator_436/port-score-for-perioperative-risk-of-blood-transfusion-in-cardiac-surgery-by-acta or http://perioperativerisk.com/bims/.

Initial feedback from surgical experts is that while there is an awareness of these prediction tools in UK practice, they are not used routinely. Part of our evaluation of results will be to ask our expert panel and any other stakeholders they suggest about barriers and facilitators to using those tools that seem to have greatest prognostic utility. The format of this exercise will be determined based on the size and complexity of the review results, the anticipation is that this will be a structured discussion over a video call.

Comparator/control (prognostic review)
Various multicomponent prediction tools for estimating blood loss have been described. Where papers include more than one tool and compare prognostic accuracy, these data will be collected. Summaries of the aggregate prognostic accuracy of each tool will allow for high level comparisons across the available tools.

There is the potential to develop methods to allow indirect comparisons. This will not form part of the main analysis, but could inform a study within a review (SWAR) project.

Types of study to be included (prognostic review)
Eligible studies will describe original research where a prediction tool for estimating transfusion or blood loss is assessed against peri-operative transfusion requirement or actual blood loss. Studies describing a prognostic factor in isolation will not be eligible. Studies that describe the association of multiple variables with blood loss, but do not attempt to create a model for clinical use will also not be eligible. Reviews will not be included, but their reference lists will be hand searched for relevant titles.

Main outcomes (prognostic review)
The primary outcome will be the dichotomous outcome 'transfusion required in the perioperative period'. Where the perioperative period includes the time from first incision up to 48 hours post operation.

The models may describe risk of transfusion (binary outcome) or estimated risk of transfusion (percentage). Where studies describe blood loss using absolute values and offers a transfusion threshold, we will attempt to derive transfusion equivalents (where one unit of packed red blood.

Additional outcomes (prognostic review)
Secondary outcomes will be:

- Absolute volume of peri-operative blood loss (mls)
- Number of peri-operative blood transfusions
- Post-operative haemoglobin (absolute value or proportion below a threshold, for example <70gL-1)
- Clinically significant bleeding (as defined by study authors)

Bleeding causing death or other harm (prolonged length of stay, need for higher level of care in the post-operative period)

Interventions (intervention review)
The focus of the intervention review will be TXA given either pre-operatively or during surgery. In the initial search we will include all doses of TXA and all routes of administration. The primary analysis will focus on intravenous TXA given pre-operatively. We will collect data on dose and route of administration and compare differing approaches if possible. We will also capture where TXA is used along with other interventions to reduce blood loss, for example cell salvage. We do not anticipate use of cell salvage in operations with anticipated low blood loss.

Comparator/control (intervention review)
The main comparator will be placebo or no TXA. If such trials exist, we will include head to head trials of differing doses or routes of administration of TXA. Studies of TXA versus another intervention to prevent blood loss will be included at title searching stage. Decisions to include these in the main analyses will be on a case-by-case basis and guided by clinical expert and PPI collaborators recruited for this review.

Types of study to be included (intervention review)
Eligible studies will be published randomised controlled trials of TXA as an intervention to prevent surgical blood loss. We will note reviews of TXA and hand search references to ensure no eligible studies have been missed in the primary search. We will include full studies published in peer reviewed scientific journals (i.e. there will be no searching of pre-print servers or other grey literature). Abstracts will be noted and will trigger a focussed search to ensure no full paper has been published. Abstracts will not be included in analyses but added to the review section describing unpublished and ongoing studies. Ongoing studies identified through published protocol or searching trial registers will be noted.

Main outcomes (intervention review)
The primary outcome will be the dichotomous outcome 'transfusion required in the perioperative period'. Where the perioperative periods include first incision up to 48 hours post operation.

Where studies describe blood loss using absolute values and offers a transfusion threshold, we will attempt to derive transfusion equivalents (where one unit of packed red blood cells contains approximately 280 ml of blood). Where the outcome is measured but not reported in the main text, we will contact study authors.

Additional outcomes (intervention review)
Secondary outcomes as suggested by our expert panel are:
- Mortality: 30 day (dichotomous)
- Length of stay (days)
- Quality of life within 6 weeks (continuous)
- Blood volume transfused (allogeneic or autologous)
- Surgical bleeding (dichotomous or continuous depending on reporting)
- Post operative bleeding (dichotomous or continuous depending on reporting)
- Adverse events: acute myocardial infarction(dichotomous); postoperative thrombosis (dichotomous) and rate of serious adverse event.

Data extraction
All references identified by the searches and from other sources will be uploaded into reference management software and de-duplicated. Building on the usual NICE process, 20% of the titles and abstracts will be reviewed by two reviewers for eligibility, with any disagreements resolved by discussion or, if necessary, a third independent reviewer will have the final say. Where there is more that 20% disagreement on included studies, all abstracts will be reviewed by a second reviewer.

The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies. Data extraction will be performed by one reviewer and cross checked by a second reviewer.

Data to be extracted will include (based on scoping and PRISMA guidance):
- Study specific: year of paper, study dates, country, number of centres, development or validation (internal / external)
- Surgery details: surgery classification (acute/elective), surgical procedure (open/laproscopic), surgical site (anatomical), operation(s),
- Baseline features: age, sex (% female), ethnicity, pre-operative Hb, comorbidity (eg ASA score)
- Operative: use of autologous blood saving, operation time
- Outcomes: need for transfusion, blood loss (and how measured), other outcomes as per protocol above. Number with/without primary and secondary outcomes, or mean (SD) value of outcome.

- Risk variables (intervention review only): Average blood loss in control group, % control group who receive transfusion
- Interventions (intervention review only): use of TXA, modes of administration of TXA, doses of TXA, use of cell salvage and type (pre, inter, post), control group treatments
- Methods (prognosis review only): original dataset details (prospective, retrospective),
- Model (prognosis review only): variables included in model, variables considered and not included in model,
- Performance (prognosis review only): measures used to assess model performance, unadjusted association between each candidate predictor and outcome, full prediction model, application (eg apps, calculators, websites)

Study investigators may be contacted for missing data where time and resources allow.
Where possible, data already extracted for existing identified systematic reviews will be relied on for data extraction to expediate the process.

Risk of bias assessment (prognosis review)
Risk of bias will be assessed using the PROBAST (Prediction model Risk Of Bias ASsessment Tool) checklist as described in Developing NICE guidelines: the manual. Risk of bias assessment will be performed by two reviewers working independently and comparing results with final decision based on consensus and discussion with the broader team.

PROBAST assesses both risk of bias and concerns regarding applicability of primary studies that developed or validated multivariable prediction models for diagnosis or prognosis. It involves assessment of the following 4 domains to cover key aspects of prediction model studies: participants, predictors, outcome, and analysis. The first 3 domains are also rated for concern regarding applicability (low, high, or unclear) to the review question.

On the basis of the ROB classifications for each domain, assessors will judge the overall ROB of the prediction model as low, high, or unclear. We will present risk of bias at study level and aggregate, using a 'traffic light' style data visualisation. If data allow, we will perform a sensitivity analysis restricted to studies at low risk of bias.

Risk of bias assessment (intervention review)
Risk of bias will be assessed using the Cochrane Risk of Bias tool for randomised controlled trials (RCTS) Risk of bias assessment will be performed by two reviewers working independently and comparing results with final decision based on consensus and discussion with the broader team.

On the basis of the ROB classifications for each domain, assessors will judge the overall ROB of the study as low, high, or unclear. We will present risk of bias at study level and aggregate, using a 'traffic light' style data visualisation. If data allow, we will perform a sensitivity analysis restricted to studies at low risk of bias.

Strategy for data synthesis (prognosis review)
In the first instance data will be presented using a mix of data visualisation, tabulation and narrative description. We will present a data visualisation of the items contained in each prediction tool, and items considered and then not included.

We will tabulate study level summaries of model performance, where possible these data will be presented in terms of discrimination (for example, C statistic or area under the ROC curve) and calibration (based on the O:E ratio i.e. total number of observed (O) and expected (E) events). If necessary, we will use bespoke software methods to calculate performance data if these are not

described in the main text, for example the standard error of C. These methods are implemented in the R package "metamisc" (https://CRAN.R-project.org/package=metamisc).

Meta-analysis, if possible, will be performed at prediction tool level. The meta-analysis will produce a summary result with its corresponding 95% confidence interval and an approximate 95% prediction interval. We will use standard techniques for creating the summary estimates. code is available for summary estimates of C. We will consider meta-analysis when the identified studies are considered sufficiently robust and comparable, and where there are data from more than three independent data-sets to include. A random effects approach will be used to allow for unexplained heterogeneity across studies. If necessary, data will be transformed to facilitate the meta-analyses (e.g. logit transformation for c-statistics, a ln transformation for all ratio's (e.g. O:E ratios)).
We expect heterogeneity in relation to the population age and acuity of the surgery, we plan subgroup analyses to explore both of these factors. Heterogeneity across all the prediction tools may be seen by surgical procedure and we will assess this visually and by calculating tau2, I2.

We will use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to rating the confidence in our summary of each study, taking into account study design, risk of bias, inconsistency, imprecision, indirectness, publication bias, size and trend of effect in the effect. We will present these data using the Cochrane Summary of Findings table format.

Analysis of subgroups or subsets (prognosis review)
If data allow, we plan the following subgroup and sensitivity analyses:
Age (adult versus paediatric populations)
Surgery acuity (emergency versus elective)
Risk of bias (restricted to studies at low risk of bias)

Strategy for data synthesis (intervention review)
In the first instance data will be presented using a mix of data visualisation, tabulation and narrative description. Pairwise meta-analysis will be undertaken for all outcomes where possible. Mean differences will be used for continuous outcomes and odds ratios for binary outcomes. Heterogeneity is anticipated and random effect models will be used throughout and heterogeneity quantified using the between study variance parameter estimate and the presentation of prediction intervals around pooled effects.

Whilst it would be possible to conduct many separate analyses based on factors that differ between studies or for which individual trial subgroup data are available (i.e. mode of application of TXA, dose of TXA, use of cell salvage, comparator group (usual care or placebo), risk of requiring a blood transfusion, type of surgery (elective or emergency) for each outcome. The principle adopted will be to conduct analyses which include all studies, irrespective of the specific factor combinations used, and explore the impact of each factor by including them as variables via meta-regression. Where possible, multiple important covariates will be included to build a final model. Where control group outcome is included as an indicator of risk of transfusion (e,g, proportion of patients requiring transfusion in control group or average blood loss in the control group) appropriate methods will be used that allow for measurement error in this measure which avoids the risk of exaggerated associations in the regression due to regression to the mean (Sharpe et al. 1996). This would permit examination of the effectiveness of TXA at varying levels of blood loss. Where possible, multiple important covariates will be included simultaneously to build "final" models and explain as large a percentage of heterogeneity as possible.

Where possible, publication bias will be assessed through the construction of contour enhanced funnel plots and associated statistical tests following recommendations regarding the minimum

numbers of studies required for such assessments. (Sterne et al. 2011). If data allow, we will perform a sensitivity analysis restricted to studies at low risk of bias. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome.

Analysis of subgroups or subsets
As outlined, subgroups will generally be avoided in favour of modelling trial differences using meta-regression. Data will be restricted to low risk of bias in a sensitivity analysis if possible.

For consideration of the populations of adult and children, we will take the same approach to these subgroups as the previous NICE evidence review. In children, the classification will take into consideration both the type of surgery and the blood volume. In children, moderate blood loss will be defined as blood loss greater than 10% of blood volume. In adults, high degree of blood loss is defined as blood loss greater than 1 litre; a corresponding equivalent blood loss with respect to body weight in children would qualify as a high degree of blood loss.
If papers include both adult and paediatric populations, they will be included in the 'adult' analysis if the majority of the population is aged over 16, and downgraded for indirectness at GRADE assessment if the overlap into those aged less than 16 is greater than 20%.

Type and methods of review
Intervention and prognostic

Language
English

Other registration details
Nil

Reference and or URL for published protocol
Individual protocols for each review have been published on PROSPERO

Economic Evaluation
We will conduct an economic evaluation to determine whether the use of TXA in surgical patients with low risk of bleeding is cost-effective at reducing the need for blood transfusion, through a model-based health economic evaluation informed by evidence from the intervention review (described above) and the wider literature. A model-based health economic evaluation will be undertaken from the perspective of the UK NHS and PSS over a lifetime horizon. All costs and benefits incurred beyond the first year will be discounted at 3.5% in accordance with NICE reference case.

Dissemination plans
The review has been requested by NICE and depending on results may inform NICE resources. NICE may use a range of different methods to raise awareness. These include standard approaches such as:

- notifying registered stakeholders of publication
- publicising the guideline through NICE's newsletter and alerts
- issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

Alongside the NICE dissemination plans, we would plan to publish the review in a peer reviewed scientific journal. Our topic experts in surgery and haematology will advise, once the review is complete, whether there is potential to present the results at a discipline specific meeting. If presenting these data, we will encourage our early career team member to take a lead on this aspect.

Keywords
Bleeding, prediction, prognosis, surgery, RCTS, tranexamic acid, transfusion

Details of any existing review of the same topic by the same authors
Nil

Current review status
Ongoing

Any additional info
Involvement of stakeholders: We will work with our PCPI lead and other team members to develop a strategy around involving stakeholders. We anticipate that we will include potential 'end users' of our review findings i.e. surgical and haematology experts, and potential beneficiaries of any change to policy i.e. those with experience of surgery and/or transfusion.

It has been identified that obtaining individual patient data (IPD) and conducting an IPD analysis for this review topic may be beneficial in more precisely answering the review question. If the team are able to access relevant individual patient level data this may allow for further validation of scores and comparative analyses in a common dataset. This IPD analysis is dependent on availability of data and would not form part of the main review and deliverables.

A separate protocol will be developed for IPD meta-analysis. The use of methods to establish the likely benefits of obtaining IPD will be explored using emerging methods (e.g. Riley et al 2020 & 2022, Simmonds & Higgins 2007).

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