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HTA Programme: Health Technology Assessment Report 11

The clinical and cost effectiveness of thromboelastography/thromboelastometry

NHS Quality Improvement Scotland

HTA Programme: Health Technology Assessment Report 11 ~ *June 2008*

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

EXECUTIVE SUMMARY

This Health Technology Assessment (HTA) reports on the clinical and cost effectiveness of using thromboelastography and thromboelastometry analysers (both abbreviated to TE hereafter) compared with standard laboratory tests/assays (SLTs) and clinical discretion (CD) used alone, to improve the diagnosis and subsequent management of patients experiencing unexplained blood loss during or after surgery.

TE analysers are used to measure multiple aspects of blood coagulation in a sample of whole blood. The information can be used by clinicians to assess the cause of bleeding and to plan the appropriate transfusion management for coagulation problems resulting from for example, surgery or trauma. The technology may provide more complete diagnostic information more rapidly and at a similar cost to the routinely used SLTs. If the technology is able to change clinical management to reduce bleeding and the transfusion of blood and blood products, this will reduce subsequent transfusion-related risks and be of benefit to patients in terms of improved health outcomes, as well as to the health service by reducing the consumption of healthcare resources and, consequently decreasing the costs.

It is assumed that the TE results will not be used in isolation but rather as part of a broader diagnostic strategy, together with clinical judgement and the results from other laboratory tests (if required) to inform transfusion decisions in accordance with validated transfusion algorithms.

Objective

The objective of the HTA was to evaluate from the perspective of NHSScotland, the clinical and cost effectiveness of using TE compared with SLTs and CD alone, to diagnose the cause of unexplained bleeding during or after surgery. The topic was selected because it has the potential to reduce the transfusion of red blood cells and other blood products. Given the scarcity of such blood products in Scotland, this is an important outcome.

The scope of the HTA excluded tests to detect the impairment of platelet function produced by the drugs aspirin and clopidogrel. As yet there are few published studies on the use of these tests in patients undergoing surgery.

Methods

A systematic review of TE considered the clinical benefits of the technology. No economic evaluation was identified by the systematic review. Thus economic modelling was conducted to compare the cost effectiveness of using TE compared with SLTs and CD alone. The model considered the use of TE in cardiac surgery and liver transplantation. The model structure was adapted from a previous HTA, and explored the probabilities of transfusion and transfusion-related risks (eg complications and infections). The time horizon was limited to 1 month for the base-case analysis due to lack of data on some of the relevant clinical and cost parameters. A time horizon of 1 year was considered in further analyses.

Whenever possible, clinical parameters were obtained from a systematic review on the use of TE. Where this was not possible, data were synthesised from multiple data sources and when required, assumptions were formulated based on the medical literature and on expert opinion. Health benefits were estimated in terms of life years lived and quality adjusted life years (QALYs) gained. Additionally, the number of transfusions avoided, the number of deaths avoided and the number of patients experiencing transfusion-related complications and/or infections were estimated.

The types of costs included in the analyses were: transfusion-related services, the tests themselves, the management of complications due to surgery or transfusion-related complications and transfusion-transmitted infections.

Discounting was not necessary since the time horizon was less than or equal to 1 year. Costs were reported in pounds at 2005/2006 price levels.

Cost-effectiveness and cost-utility analyses were conducted as these are appropriate for the type of health benefits considered in the study. After excluding the dominated strategies, an incremental cost-effectiveness analysis was conducted. Sensitivity analyses were performed to test the robustness of the results when the values of uncertain parameters were modified. A budget impact analysis was also conducted to assess the applicability of the research findings to NHSScotland.

A survey was undertaken to ascertain the current use of TE in Scotland. Patient perspectives were explored using qualitative data.

Results

The literature search found that TE was not useful in identifying patients who will subsequently experience excessive bleeding. The economic modelling thus considered its intra-operative and post-operative use only.

TE was the dominant strategy for the management of transfusion in cardiac surgery patients, independent of the time horizon or the measure of health benefit considered in the analysis (although health benefits were more evident at 1 year). The results were sensitive to variations in the number of tests conducted annually at each centre and to whether TE tests were conducted intra-operatively and post-operatively, jointly with SLTs.

In liver transplantation, TE was found to be a cost-effective strategy according to the baseline results. Although the cost savings associated with the use of the technology during liver transplantation seemed to be considerable, the improvement in health outcomes did not appear to be as relevant as in the case of cardiac surgery. The benefits of TE were improved when a longer time horizon was

adopted in the analysis. The cost-effectiveness results of using TE in liver transplantation were sensitive to the number of units of blood transfused. There is considerable uncertainty about the number of units transfused in the non-TE arms of the model. In Scotland, all liver transplant operations are conducted with TE available and thus the Scottish National Blood Transfusion Service's data on actual use cannot be applied.

The results of the budget impact analysis are summarised in the table below.

These show that in both medical indications considered (ie cardiac surgery and liver transplantation), savings are expected with the use of TE. Among patients undergoing cardiac surgery, the most significant savings are expected in terms of the costs of hospitalisation not related to complications and the costs of blood products transfused. In liver transplantation, the management of patients with TE instead of SLTs would lead to savings for NHSScotland, mainly in terms of the blood products transfused.

From a patient's perspective, any intervention to reduce blood transfusion is likely to be welcomed.

The survey showed that TE is currently in use in five Scottish hospitals. However, there is variation in operating practices and policies, highlighting the need for a consistent approach to the organisational aspects of TE such as training and quality control. The number of tests undertaken varied from two to over 70 each week. The results of the economic model indicate that in cardiac surgery, TE is the dominant strategy for centres conducting 200 tests annually but at lower volumes (under 50 tests a year) SLT may be the more cost-effective choice.

Conclusion

Assuming a usage of 200 tests annually, TE appeared to be a clinically and cost-effective intervention, since it was shown to reduce the need for inappropriate transfusions and to decrease blood product requirements, therefore improving the management of transfusion. There was a reduction in the number of deaths, complications and infections, and an increase in the number of years lived and the QALYs gained by patients. As a result of the decrease in the number of transfusions, the usage of blood products and healthcare resources needed to deal with complications and infections and their associated costs, were also reduced.

The results of the budget impact analysis showed that, for both cardiac surgery and liver transplantation, savings could be accrued if TE instead of SLTs was used for patient management.

Recommendations

1. The use of TE is recommended in cardiac surgery and liver transplant surgery. TE should be used in intra-operative or post-operative bleeding where the cause of bleeding is uncertain, to ascertain if bleeding is induced by the surgery itself or a haemostasis abnormality and to determine the nature of a haemostasis abnormality and the appropriate treatment.

2. There is no published robust, controlled clinical data to support the use of TE in other major surgery associated with a high blood loss. However, some sites in Scotland have used TE in other surgical settings including vascular surgery, obstetrics and trauma. These sites have demonstrated the technique is safe and efficacious. This is not unexpected; while there are differences in the surgical procedures the main causes of bleeding and subsequent actions are common across all such surgery. This observational evidence supports using TE in such surgical areas.

3. Research data from controlled studies would be beneficial to strengthen the evidence base in surgery other than cardiac and liver but it is recognised that such studies may be difficult to conduct because of the emergency nature of many of the interventions and the small patient numbers.

4. Where TE is used, it will reduce the number of laboratory tests requested during and immediately after surgery. The results from TE, together with clinical judgement and any results from other laboratory tests should inform transfusion decisions in accordance with validated transfusion algorithms.

5. TE should not be routinely used pre-operatively before elective surgery to risk stratify patients likely to bleed excessively.

6. Audit should be undertaken to assess the impact of TE on blood loss, use of blood products and the rate of re-exploratory surgery. Other benefits such as shorter stay in an intensive care unit (ICU) and improved patient outcomes may be more difficult to monitor.

Expected annual total expenditure of using TE compared with standard laboratory tests in cardiac and liver transplant surgery (2005/06 prices)

Intervention	Annual cost TE	Annual cost SLT	Difference
Cardiac surgery	£2,896,912	£3,241,095	£344,183
Liver transplant	£191,506	£287,013	£95,507
Total	£3,088,418	£3,528,108	£439,690

7. All users of TE must adhere to guidance by the Medicines and Healthcare products Regulatory Agency (MHRA) and take account of the Scottish Government's action plan for healthcare science. In particular:
   - formal documented training for staff performing the tests with assessment of competency and review at appropriate intervals should be in place
   - specific training should take place on the use and interpretation of TE for staff requesting such tests to ensure consistency in application
   - rigorously defined and managed clinical protocols should be in place covering all organisational aspects of TE testing, with one person who is clearly responsible for overseeing compliance. These protocols should be linked to blood transfusion protocols so that the information from TE informs patient management decisions
   - all sites that undertake TE testing should join the UK National External Quality Assessment Scheme (NEQAS) for TE testing once established, or a similar external quality control system
   - quality control and quality assurance procedures must be implemented and form an integral part of NHS boards' clinical governance process
   - the hospital haematology laboratory should be involved in discussions on the TE service
   - there must be robust arrangements in place for regular preventative maintenance of analysers and for prompt repair should faults develop
   - there should be clearly documented processes for recording of TE results and any consequences arising from them, with the ultimate aim of interfacing the clinical and laboratory information management systems. This will ensure that other clinicians are aware of the use of TE and also that use of TE can be audited more easily.
8. The Scottish National Blood Transfusion Service should make available to health boards the costs of commonly used blood components to enable users to take decisions on the clinical and cost effectiveness of TE in their own settings.
9. National Procurement should consider offering a central procurement contract for analysers and consumables.

1 INTRODUCTION

1.1 The technology

This Health Technology Assessment (HTA) reports on the clinical and cost effectiveness of using thromboelastography and thromboelastometry analysers (both abbreviated to TE hereafter) compared with standard laboratory tests/assays (SLTs) and clinical discretion (CD) alone, to improve the diagnosis and subsequent management of patients experiencing unexplained blood loss during or after surgery.

TE is a diagnostic point of care test that measures multiple risk factors for coagulation, including initial clotting, platelet interaction and fibrinolysis in a sample of whole blood. It is used to assist with the diagnosis and management of haemostasis disorders, primarily during and after surgery that is associated with high blood loss. The complete results take up to 20 minutes to produce and inform on the presence and type of coagulation disorders. Treatment for such disorders may involve the transfusion of red blood cells and blood products. Timely and accurate diagnostic information should allow clinicians to take effective steps to manage the blood loss.

The technology has the potential to:
- reduce the delays in getting test results in a rapidly changing clinical situation
- reduce the number of laboratory test requests
- improve clinical decision making thereby
- reducing inappropriate use of blood and blood products.

TE would be used in conjunction with clinical judgement and other laboratory test results, if required.

1.2 Objective and methodology

The objective of the HTA was to evaluate the clinical and cost effectiveness of the use of TE. The topic was selected because TE has the potential to reduce the transfusion of red blood cells and other blood products. Given the scarcity of such blood products in Scotland, this is an important outcome.

A systematic review of TE considered the clinical benefits of the technology (Aguiar-Ibáñez *et al*., 2006). No economic evaluation was identified. Thus an economic model was developed to compare the cost effectiveness of using TE compared with SLTs and CD alone, to diagnose the cause of bleeding. The outcomes of the economic model consider the effectiveness of the alternative approaches in relation to transfusions with the intention of informing appropriate transfusion management policies for NHSScotland.

While TE can be used in a variety of surgical indications, the model was initially developed to address the role of the test in cardiac surgery. The rationale for this is that the majority of evidence on the clinical benefits of the test relates to cardiac surgery and this also appears to be the indication where it is most widely used in Scottish practice. Therefore, the study considered patients undergoing cardiac surgery (typically around 65 years of age).

A further analysis was conducted to assess the cost effectiveness of TE in the management of transfusions in patients undergoing liver transplantation. This analysis was constrained by the limited evidence regarding the effectiveness of the technique for this indication.

The systematic review identified that TE has been used in other interventions including vascular surgery, major trauma, orthopaedic surgery, obstetric interventions and paediatric cardiac surgery to diagnose the cause of bleeding and to manage subsequent treatment. However, there was insufficient evidence to conduct cost-effectiveness analyses for these other indications.

Standard TE tests do not detect the impairment of platelet function produced by the drugs aspirin and clopidogrel. New tests for the effects of aspirin and clopidogrel have recently become available for use with the TEG® thromboelastography analyser and there are several other platelet-function analysers which can be used to perform point-of-care tests for the effect of aspirin and/or clopidogrel. However, as yet there are few published studies on the use of these tests in patients undergoing surgery. This report does not therefore consider the use of such tests.

In order to determine the applicability of the research findings to NHSScotland, a budget impact analysis was conducted which was expected to help identify any issues around the implementation of TE.

2 BACKGROUND ON NHS QUALITY IMPROVEMENT SCOTLAND

NHS QIS was set up by the Scottish Parliament in 2003[1] to take the lead in improving the quality of care and treatment delivered by NHSScotland. NHS QIS sets standards, monitors performance and provides NHSScotland with advice, guidance and support on effective clinical practice and service improvements.

Health Technology Assessment

HTA is an internationally recognised process used by NHS QIS to advise NHSScotland about a specific health intervention, eg medicine, equipment or diagnostic test. HTA evaluates the clinical and cost effectiveness of the various ways in which a particular intervention can be used, comparing alternatives where appropriate. Patient and organisational issues are also considered.

Evidence is identified by literature searching and assimilating expert evidence, the views of patient interest groups and manufacturers. The evidence is then critically appraised and robust analyses are undertaken by expert staff. Surveys may also be undertaken to ascertain current clinical practice and patient preferences.

In November 2005, NHS QIS invited tenders for a systematic review of the clinical and cost effectiveness of TE and the development of an economic model to inform on its cost effectiveness. The contract was awarded to the Centre for Reviews and Dissemination (CRD) and York Health Economics Consortium who undertook the work and produced a final report which forms the majority of this document, particularly Sections 5 and 6.

This HTA report also includes the findings of NHS QIS work considering the patient and organisational issues associated with TE. The HTA was conducted with considerable input from health professionals who are expert in the particular area of interest (see Appendix 11.1). Peer review and wide public consultation ensures that all views are considered.

[1] On 3 September 2007, Scottish Ministers formally adopted the title Scottish Government to replace the term Scottish Executive as an expression of corporate identity. The Health Department has been replaced by Health Directorates.

3 SETTING THE SCENE

3.1 Haemostasis disorders

Haemostasis is a normal physiological response. It is the process by which the body arrests blood loss when blood vessels are damaged and results in clot formation to block any vascular breach, ensuring blood fluidity and blood vessel integrity. There are three main components of haemostasis: platelet adhesion and activation; fibrin formation; vascular contraction. Abnormalities in any of these processes can lead to haemostasis disorders and result in bleeding or blood clots (thrombosis).

Such defects (eg haemophilia) can be genetically determined or acquired. Congenital deficiencies in coagulation (clotting) factors are uncommon, and are often identified during childhood or by pre-operative laboratory tests. Acquired clotting defects are more common and are due to ingestion of certain drugs (in particular with the use of anticoagulants such as heparin and anti-platelet drugs), vitamin K deficiency, hypothermia, sepsis and disease such as tumours or liver disease.

Haemostasis disorders can lead to severe complications during and after surgery and in trauma, where there is the potential for high blood loss. However, it is not uncommon for sudden bleeding or thrombosis to occur during or after surgery, and TE can differentiate whether the excessive bleeding is induced by surgery or by abnormalities in haemostasis. Identifying the cause can help to guide appropriate management.

3.2 Surgery associated with high blood loss

Clinical applications of TE include all surgery associated with high potential blood loss, for example cardiac surgery, liver transplant, major vascular surgery, hip replacement (in particular revision surgery), obstetric interventions and trauma. This HTA focuses only on cardiac surgery and liver transplant as there was insufficient evidence regarding the clinical and cost effectiveness of TE in other surgical indications.

These procedures are frequently associated with substantial blood loss, requiring transfusion of red blood cells (RBCs). Table 3-1 shows the number of bleeding episodes, percentage transfused and number of RBC units transfused per episode for four types of cardiac surgery and for liver transplantation. These data were provided by the Scottish National Blood Transfusion Service (SNBTS) (Amanda Stewart, ISD. Personal communication, October 2007). Note the data for liver transplant procedures reflect the benefit of TE which is currently available for all such procedures in Scotland.

3.3 Thromboelastography and thromboelastometry

TE is a diagnostic technology that measures multiple aspects of blood coagulation in a sample of whole blood. It is usually a "point-of-care" test and results are obtained more quickly than is the case when samples are sent to the laboratory. The addition of a number of activators or inhibitors of coagulation to the whole blood sample being tested enables the detection of disorders including low coagulation factor levels, the anticoagulant effect of the drug heparin, a low platelet count or platelet dysfunction, a low fibrinogen level or impaired fibrin polymerisation, and excessive breakdown of clot once it is formed (fibrinolysis). TE may therefore provide more complete information on the presence and type of a coagulation disorder than SLTs.

The potential benefits of TE result from the fact that it can allow healthcare professionals to obtain a more rapid and accurate diagnosis of the presence and cause of an impairment of the blood clotting mechanism. It helps differentiate between blood loss that is the result of bleeding from a damaged blood vessel ('surgical bleeding'), and blood loss due to coagulation disorders or which may result in excessive bleeding during surgery or unexpected bleeding after surgery. Effective treatment of a coagulation disorder depends upon an accurate diagnosis of its cause. Treatment may involve the transfusion of blood products such as platelets, fresh frozen plasma (FFP) or cryoprecipitate or the administration of a drug such as protamine or aprotinin (Seres, 2002).

Table 3-1 Surgical blood use in 2005–06

Procedure	Number of episodes	% Episodes transfused	RBCs units/episode transfused
Coronary replacement operations (minus revisions)	2,359	47.9	1.6
Heart and lung transplant	8	75.0	11.3
Revision coronary replacement operations	29	44.8	2.1
Valves and adjacent structures	758	54.5	2.5
Transplantation of liver	37	83.8	8.1

Source: Surgical blood use, all procedures by OPCS chapter Scotland; prepared by Information Services Division

More effective treatment of coagulopathy may reduce bleeding and thus reduce the units of red blood cells that are transfused. More timely and accurate diagnosis may avoid the inappropriate transfusion of blood products such as platelets and FFP. However, the perceived costs of TE testing may be higher than those incurred when conducting SLTs. The introduction of TE requires both capital and supplies expenditure.

TE may be considered to be best positioned as a complement to existing laboratory testing rather than as a replacement. However, it has been argued that SLTs are less informative in predicting excessive bleeding and, moreover, their usefulness is limited because their results often only become available after an unacceptable time delay, due to the need to take samples to a laboratory and await results (Innerhofer *et al*., 2004). The delay in obtaining laboratory results means that often blood products are ordered in a 'prophylactic' fashion in case the patient experiences excessive bleeding for an unreasonable time. The near-patient testing model provided by TE, with a complete set of results typically taking about 20 minutes to produce and data on some of the factors available within 5 minutes, has the potential to overcome some of these problems and to reduce blood and blood product use.

The unit and software can be positioned in the theatre, in hospital laboratories close to theatres or in ICUs or post-operative recovery units. Moreover, if networked appropriately, the test result can be viewed in real time anywhere in the hospital.

There are two manufacturers of analysers using this type of coagulation test. In each case, a graphic representation of the clot and subsequent lysis is displayed. The trace is used to assess factors such as:

- time to clot formation to guide the use of fresh frozen plasma;
- clot strength to judge platelet infusion;
- degree of lysis to indicate the need for antifibrinolytic therapy; and
- the effect of heparinase to assess the need for protamine (Luddington, 2005).

The term thromboelastography was used as a generic term to describe the technique until 1996 when the term TEG® became a registered trademark of the Haemoscope Corporation and now describes the instrumentation produced by that manufacturer. The alternative assay marketed by Pentapharm Gmbh uses the terminology thromboelastometry for the measurement process and ROTEM® for the instrumentation. Earlier versions of this analyser were called ROTEG®.

The two tests work in slightly different ways. In conventional thromboelastography®, or the TEG® system, a blood sample of 0.36 ml is placed into a heated cup, which rotates to imitate the venous flow with the aim of providing a haemostatic profile (Haemoscope, no date). In rotational thromboelastometry, or the ROTEM® analyser, the sensor shaft rotates, rather than the cup.

The range of tests available and the reagents used also differ between the TEG® and ROTEM® analysers. Different protocols or algorithms to guide the transfusion of blood products have been developed for use with the two analysers and continue to be refined. A comparison of different transfusion protocols in liver transplant surgery based on results from the TEG® analyser, the ROTEM® analyser and conventional coagulation tests (Coakley *et al*., 2006) reported that there was moderate agreement on when to transfuse platelets and fibrinogen but poorer agreement on when to transfuse fresh frozen plasma. The study concluded that transfusion practice could differ according to the analyser and transfusion algorithm used and recommended a case-matched study.

TE does have some shortcomings. Neither the usual TE tests nor SLTs measure the effect of the drugs aspirin and clopidogrel on platelet function. However, several point-of-care analysers for the effects of aspirin and clopidogrel on platelets have recently become available and it is also now possible to undertake additional 'PlateletMapping™' tests on the TEG® analyser for this purpose.

4 CLINICAL AND COST EFFECTIVENESS: METHODOLOGY

4.1 Interventions

The health technology assessed was the use of TE for the identification of patients at risk of excessive bleeding and/or for the management of excessive bleeding by primarily the transfusion of blood products.

In order to define the interventions to be included in the economic evaluation, the studies identified in the systematic review assessing the use of TE in cardiac surgery compared with alternative management strategies (Aguiar-Ibáñez *et al.*, 2006) were listed. A complete list of sources searched and a copy of the search strategies are included in Appendix 11.2. Table 4-1 identifies the relevant tests that had been used to predict significant bleeding and manage transfusions.

Table 4-1 Type of TE tests and comparators identified in the cardiac surgery studies included in the systematic review

Study	Study design	Type of test conducted	Comparator
Anderson *et al.* (2003)	Comparative study with a historical control	Thromboelastometry test (ROTEG®), post-operatively	SLTs
Anderson *et al.* (2006)	Comparative study with a historical control	Thromboelastometry (ROTEM®), post-operatively	CD + SLTs
Avidan *et al.* (2004)	RCT	Thromboelastography-based algorithm; thromboelastography test (TEG®) conducted intra- and post-operatively	SLT-based algorithm CD
Avidan *et al.* (2001)	RCT	Thromboelastography-based algorithm; thromboelastography test (TEG®) conducted intra- and post-operatively	SLT-based algorithm CD
Cammerer *et al.* (2003)	Diagnostic	Thromboelastometry (ROTEG®), pre and intra-operatively	CD
Cherng *et al.* (1998)	Diagnostic	Thromboelastography (TEG®), pre and post-operatively	SLTs
Dua *et al.* (2005)	Comparative study with a historical control	The manufacturer was not clearly reported; the type of test used may have been Thromboelastography TEG®, post-operatively	SLTs
Ereth *et al.* (1997)	Diagnostic	Thromboelastography (TEG®)	PACT SLTs
Mashburn *et al.* (1996)	Diagnostic	Thromboelastography (TEG®), intra-and post-operatively	Comparisons between thromboelastography intra- versus post-operatively
Nuttall *et al.* (1997)	Diagnostic	Thromboelastography (TEG®), post-operatively	SLTs
Nuttall *et al.* (2001)	RCT	Thromboelastography-based algorithm, using SLTs; thromboelastography test (TEG®) conducted intra-operatively	CD +/- SLTs

Study	Study design	Type of test conducted	Comparator
Porite *et al.* (2004)	Cohort (?)*	Thromboelastography-based algorithm; thromboelastography test (TEG®) performed pre-, intra- and post-operatively	SLTs
Poston *et al.* (2005)	Diagnostic	Thromboelastography (TEG®), pre- and post-operatively	SLTs
Royston & von Kier (2001)	Cohort	Thromboelastography (TEG®), pre-, intra- and post-operatively	CD + SLTs
Royston & von Kier (2001)	RCT	Thromboelastography-based algorithm; thromboelastography test (TEG®) performed pre-, intra- and post-operatively	CD +/- SLTs
Shih *et al.* (1997)	Diagnostic	Thromboelastography (TEG®), pre- and post-operatively	SLTs
Shore-Lesserson *et al.* (1998)	RCT	Algorithm based; test conducted intra-operatively (the manufacturer was not clearly reported; the type of test used may have been TEG®)	SLTs
Shore-Lesserson *et al.* (1999)	RCT	Algorithm based; test conducted pre-, intra- and post-operatively (the manufacturer was not clearly reported; the type of test used may have been TEG®)	SLTs
Sorensen *et al.* (2005)	Comparative study with a historical control**	Intra-operatively (the manufacturer was not clearly reported; the type of test used may have been TEG®)	CD
Ti *et al.* (2002)	Diagnostic	Thromboelastography (TEG®), post-operatively	Comparisons between post-operative thromboelastography at 10 minutes versus post-operative thromboelastography at 60 minutes
von Kier & Royston (1998)	RCT	Thromboelastography-based algorithm; thromboelastography test (TEG®) conducted pre, intra- and post-operatively	CD + SLTs

* The study design was not reported and could not be clearly identified from the information reported in the abstract.

** Although this study was published as a full paper, the information reported was very limited since the study was used as a practical example within a teaching guide.

RCT=randomised controlled trial

As shown in Table 4-1, most of the studies included in the systematic review used the TEG® analyser, whilst only three studies used ROTEG®/ ROTEM® (Anderson *et al.*, 2006; Anderson *et al.*, 2003; Cammerer *et al.*, 2003). The reason for the limited use of the ROTEG®/ ROTEM® systems may be related to the more recent development of these systems: the ROTEG® system was developed in the late 1990s and more recently renamed ROTEM®.

BIODIS, the exclusive distributors of the ROTEM® device in the United Kingdom (UK), recommended that the TE tests should be considered as part of a broader diagnostic strategy alongside SLTs, rather than as a substitute for them. However, anecdotal feedback from clinical practice in some Scottish centres shows that the test is used as a unique test in many cases.

According to previous studies (Salooja & Perry, 2001) the pre-operative use of TE has not been successful in identifying those patients who will experience excessive bleeding. Therefore, it was considered that the test would be performed intra- and post-operatively, but not pre-operatively.

The comparators considered in the analyses were:

- the use of SLTs, which represent the current clinical practice in Scotland in those centres in which TE is not used yet
- the use of CD alone, which was included as an additional comparator since this was historically the clinical practice in some centres and it would represent the alternative of 'doing nothing' when compared with the use of SLTs.

Although CD alone has been presented as another course of action in this economic evaluation, based on assessments presented by previous studies (Avidan *et al.*, 2004; Nuttall *et al.*, 2001), it does not seem to be a widespread option nowadays, and it is not current clinical practice in Scotland.

4.2 Structure of the model

4.2.1 Cardiac surgery

The use of TE in cardiac surgery focused on three issues:

1. the identification of patients at risk of bleeding during or after surgery

2. the differentiation of patients requiring treatment with blood products/drugs from those requiring surgical re-exploration to stop bleeding

3. the management of the administration of blood products during and after surgery.

The model structure was adapted from a previous HTA (Davies *et al.*, 2006) which aimed to assess the cost effectiveness of cell salvage transfusion when compared with allogeneic transfusion and other interventions to either reduce surgical blood loss or to minimise the use of peri-operative allogeneic blood. This model structure was adopted as the previous study considered a similar transfusion-related topic and the research was also undertaken to inform Scottish practice. Only the sections related to allogeneic blood transfusion were considered in the current study.

The model starts with the choice of the diagnostic test/ transfusion management strategy to follow, which can use TE, SLTs or CD. During the cardiac procedure, the patient may need transfusion or not, with probabilities of requiring transfusions varying across strategies. Patients requiring transfusion may experience complications and/or transfusion-transmitted infections. Only events for which data were available and that were considered to be serious events associated with blood transfusion were included in the model (Davies *et al.*, 2006). The type of complications considered in the model were categorised as:

- complications related to surgery and related blood loss including renal dysfunction, myocardial infarction (MI), stroke, thrombosis, excessive bleeding requiring re-operation, wound complications and septicaemia
- transfusion-related complications, which included: transfusion-associated graft versus host disease, complications related to the administration of an incorrect blood component (IBC), haemolytic transfusion reactions (either acute or delayed), post-transfusion purpura (PTP), transfusion-related acute lung injury (TRALI) and febrile reaction.

Post-operative bacterial infections were not included in the analysis given that leucodepletion is standard practice in Scotland since 1999 (NHS QIS, 2006) and evidence suggests that these rates are similar for both patients transfused with leucocyte blood depleted and for patients not transfused (Blumberg *et al.*, 2000).

According to the structure adopted for the decision tree, transfusion-related complications occurred independently of complications related either to surgery or transfusions. However, transfusion-transmitted infections could occur across all the patients transfused, independently of whether they experienced or not any type of complication. The transfusion-transmitted infections included were: bacterial contamination, variant Creutzfeldt-Jakob Disease (vCJD), hepatitis A virus (HAV), malaria, human T-cell lymphotropic virus (HTLV), Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).

Appendices 11.3 to 11.8 present the decision trees used in the TE, SLT and CD arms of the model.

A hypothetical cohort of 1,000 patients was considered for the model. The study population of the base-case analysis comprised 65-year-old patients undergoing cardiac surgery. This was in line with the typical patient identified in the studies included in the systematic review who was on average older than 60 years (Anderson *et al.*, 2006; Avidan *et al.*, 2004; Cammerer *et al.*, 2003). The youngest patients were those in the study by Cherng *et al.* (1998),

who were, on average, 51.8 years for those patients undergoing cardiac surgery for the first time, and 53.7 for those undergoing revision surgery. The oldest patients were found in the study by (Nuttall *et al.*, 2001) with a median age between 68 and 69 years. The average age considered for the model was also similar to the average age of patients undergoing cardiac surgery in England, according to the data reported in the Health Survey of England (ie 66 years of age for those undergoing coronary artery bypass graft [CABG] and 63 for those undergoing percutaneous transluminal coronary angioplasty [PTCA]).

Mortality directly related to the surgical procedure was not considered in the analysis since it would be independent of the type of diagnostic test performed. However, mortality associated with transfusion-related complications and infections was included since it may vary across the alternative diagnostic strategies considered.

Since only the differences in outcomes and costs related to the use of TE compared with the other transfusion-management alternatives were of interest, the costs and health outcomes to be included in the analysis were those related to:

- decreased quality of life of patients receiving transfusions
- decreased life expectancy and quality of life of patients with transfusion-related complications and infections.

In order to include the total impact of transfusions and transfusion-related complications and infections on costs and health benefits, it would have been desirable to consider a life time horizon. However, evidence related to the long-term costs and health benefits of some of the complications considered in the analysis was limited. Consequently, the time horizon was limited to 1 month for the base-case analysis to capture the impact of complications and mortality occurring during the period of hospitalisation, and infection caused by bacterial contamination. Bacterial infection was assumed to occur after the surgery but during the hospitalisation period (Davies *et al.*, 2006). A time horizon of 1 year was considered in further analyses so that at least some of the long-term effects of transfusion-related infections could be included in the analysis.

4.2.2 Liver transplantation

The use of coagulation monitoring is less well defined in liver transplantation compared with cardiac surgery, even if it is widely accepted among clinicians that monitoring of coagulation should be undertaken in order to identify the presence of coagulopathy (Kang, 1997).

Uncontrollable bleeding and the consequent requirement of blood transfusions are common issues among patients undergoing liver transplantation. The use of TE in liver transplantation has focused on the monitoring of coagulation and the management of blood products transfused, rather than the identification of patients at risk of excessive blood loss (Ozier *et al.*, 2001). Studies in this area assess the use of coagulation tests, including TE, according to the amount and type of blood products required, on average, by patients, while the initial identification of the number of patients requiring transfusion is not usually reported (Harding *et al.*, 1997; Kang *et al.*, 1985). Two of the three studies on liver transplantation included in the systematic review (Gordon *et al.*, 2002; von Kier & Royston, 1998) reported the average number of units of blood transfused but not the transfusion rates observed during the study. Transfusion of blood products appears to be common practice for most of the patients and therefore the monitoring of coagulation by means of coagulation tests appears to be used to limit the amount of blood transfused to patients rather than to avoid transfusion altogether.

The consequence of this for the modelling exercise was a slight change in the model structure. For liver transplantation, the first section of the model (ie that related to the percentage of patients transfused or not) was considered irrelevant. It was assumed, therefore, that all patients would receive transfusion. The model considers the type of test conducted and the average number of units of blood transfused in patients undergoing liver transplantation. Consequently, the differences across transfusion-management strategies were related mainly to the blood usage and the subsequent transfusion-related complications and infections derived from it.

4.3 Clinical evidence

Economic modelling almost inevitably relies to some extent on a synthesis of multiple data sources as there is rarely a single study available that captures all the relevant costs and benefits of an intervention. Whilst every effort is made to ensure that the data sources are transparent and consistent, this can sometimes mean that models use data from non-randomised sources or expert assumption. Where this does occur, sensitivity analysis allows the uncertainty around these estimates to be tested to determine the impact on the outcomes.

The evaluation of TE is further complicated by the relatively limited evidence base, particularly on long-term outcomes. The section below summarises the main sources of clinical data used to populate the models.

4.3.1 Cardiac surgery

Transfusion rates

Although some of the studies included in the systematic review were randomised controlled trials (RCTs), the probabilities of transfusion related to TE and SLTs were selected from the study by Anderson *et al.* which was a comparative six month study with a historical control (Anderson *et al.*, 2006). During the 12 month period there was no change in senior surgical staff or to the transfusion protocol.

This study was chosen as the primary data source as it had been conducted in a Scottish setting and examined the

interventions under consideration in the economic model (ie TE versus SLTs). As such, the results are expected to be more applicable to Scottish practice than many of the other studies identified in the systematic review. The probability of a patient receiving transfusion was identified from the percentage of patients receiving RBCs in this study. For CD, the probability of transfusion was obtained from the historical controls managed with CD in the study by Avidan *et al.*, (2004).

Re-operation rates

The probability of re-operation for the three interventions was obtained from the study by Avidan *et al.* (2004), which showed similar probabilities for TE and SLTs (ie 1.96%) and a higher rate for CD (2.78%) (see Table 4-2). These estimates are assumed to err on the conservative side (ie they may bias the results against TE). Of the four studies included in the systematic review which reported re-operation rates (Anderson *et al.*, 2006; Avidan *et al.*, 2004; Nuttall *et al.*, 2001; Shore-Lesserson *et al.*, 1999), three were RCTs (Avidan *et al.*, 2004; Nuttall *et al.*, 2001; Shore-Lesserson *et al.*, 1999) and the findings of two of these RCTs showed the probability of re-operation to be zero for TE (Nuttall *et al.*, 2001; Shore-Lesserson *et al.*, 1999).

Transfusion or surgical complications

Most of the probabilities related to transfusion or surgical complications were obtained from studies not included in the systematic review (Blumberg *et al.*, 2000; Davies *et al.*, 2006; Karkouti *et al.*, 2006; Spiess *et al.*, 2004), except for the probability of re-operation (Avidan *et al.*, 2004) (see 'Re-operation rates' section, above). These probabilities had been reported in the literature as probabilities per patient (see Table 4-2) and were adjusted to reflect the conditional probabilities required to populate the model.

The probabilities of having acute renal failure, stroke and septicaemia were obtained from the study by Karkouti *et al.* (2006) which was a comparative study with historical controls that assessed the impact on clinical outcomes of implementing a protocol for the management of cardiac surgery patients with excessive blood loss. The data used from this study were derived from a group managed after the implementation of the protocol, and probabilities of complications selected from this study were assumed to be the same across the alternative transfusion management strategies assessed here (ie TE, SLTs and CD).

Table 4-2 Clinical parameters used in the model of cardiac surgery by type of transfusion management strategy

Parameter	TE	SLTs	CD	Sources
Probability of transfusion	0.5378	0.6025	0.8519	Anderson *et al.* (2006); Avidan *et al.* (2004)
Probability of re-operation	0.136111	0.136111	0.193056	Avidan *et al.* (2004)
Probabilities of experiencing transfusion or surgical complications among patients transfered				
Renal dysfunction/acute renal failure	0.047	0.047	0.047	Karkouti *et al.* (2006), (data for protocol, ie best case scenario)
MI	0.081	0.081	0.081	Spiess *et al.* (2004)
Stroke	0.035	0.035	0.035	Karkouti *et al.* (2006) (data for protocol, ie best case scenario)
Thrombosis	0.0214	0.0214	0.0214	Davies *et al.* (2006)
Re-operation	0.0196	0.0196	0.0278	Avidan *et al.* (2004)
Wound complications	0.02	0.02	0.02	Blumberg *et al.* (2000)
Septicaemia	0.041	0.041	0.041	Karkouti *et al.* (2006), (data for protocol, ie best case scenario)
Total transfusion or surgical complication	0.265	0.265	0.2732	
Probabilities of experiencing transfusion-related complications among patients transfused				
Transfusion-associated graft versus host disease (probability per patient)	0.000002	0.000002	0.000002	Davies *et al.* (2006)

Parameter	TE	SLTs	CD	Sources
IBC (probability per patient)	0.000244	0.000244	0.000244	Davies *et al.* (2006)
Acute haemolytic transfusion reaction (probability per unit of blood transfused)	0.00004	0.00004	0.00004	Taylor & Contreras (2000)
Delayed haemolytic transfusion reaction (probability per unit of blood transfused)	0.0004	0.0004	0.0004	Taylor & Contreras (2000)
PTP (probability per unit of blood transfused)	0.00000008	0.00000008	0.00000008	Davies *et al.* (2006)
TRALI (probability per patient)	0.0002	0.0002	0.0002	Popovski *et al.* (1983), in Looney *et al.* (2004); Taylor & Contreras (2000)
Febrile reactions	0.01	0.01	0.01	MacLaren *et al.* (2005), in Redmond *et al.* (2005)
Total transfusion-related complication (per patient)	0.013789	0.019685	0.019685	
Probabilities of transfusion-transmitted infection per unit of blood transfused				
Bacterial contamination RBCs	0.00000200	0.00000200	0.00000200	Regan & Taylor (2002), based on information from Serious Hazards of Transfusion (SHOT) 2001 and other guidelines
vCJD	0	0	0	Assumed based on Redmond *et al.* (2005)
HAV	0.00000120	0.00000120	0.00000120	Davies *et al.* (2006)
Malaria	0.00000120	0.00000120	0.00000120	Davies *et al.* (2006)
HTLV	0.00000225	0.00000225	0.00000225	MacLaren *et al.* (2005), in Redmond *et al.* (2005)
HIV	0.00000025	0.00000025	0.00000025	Regan & Taylor (2002), based on information from Serious Hazards of Transfusion (SHOT) 2001 and other guidelines
HBV	0.00000625	0.00000625	0.00000625	Regan & Taylor (2002), based on information from Serious Hazards of Transfusion (SHOT) 2001 and other guidelines
HCV	0.00000033	0.00000033	0.00000033	Regan & Taylor (2002), based on information from Serious Hazards of Transfusion (SHOT) 2001 and other guidelines
Total transfusion-transmitted infection (per patient)	0.000016	0.000021	0.000310	

Transfusion-related complications

Some of the probabilities related to transfusion-related complications (ie haemolytic transfusion reaction, TRALI and febrile reactions) had been reported in the literature as the estimated risk per unit of blood transfused, while the others (ie transfusion-associated graft versus host disease, administration of an IBC and PTP) had been reported as risks per patient transfused.

In order to estimate the probability of transfusion-related haemolytic transfusion reaction, acute lung injury and febrile reactions, the type and average quantity of blood products transfused following each transfusion management strategy (see Section 5.5) were taken into account:

- the probability of haemolytic transfusion reaction was estimated according to the number of units of RBCs transfused (Taylor & Contreras, 2000). From the total

haemolytic transfusion reactions occurring, 9.01% were acute haemolytic reactions (ie those occurring within the first 24 hours after transfusion) while 90.91% were delayed haemolytic transfusion reactions (ie those occurring within 5 and 8 days after transfusion)
- the probability of TRALI was estimated according to the number of units of FFP transfused (Looney *et al.*, 2004; Taylor & Contreras, 2000)
- the probability of febrile reaction was estimated according to the number of units of both RBCs and FFP transfused (Redmond *et al.*, 2005).

According to the blood usage data used to populate the model (see Table 4-8), the number of units of blood transfused with TE was lower compared with SLTs and CD. Given that the probability of experiencing transfusion-related complications is proportional to the number of units transfused, the total probability of transfusion-related complications was thus lower with TE, when compared with the other two transfusion management strategies (see Table 4-2).

Transfusion-transmitted infections

The probabilities of transfusion-transmitted infections were obtained from the study by Davies *et al.* (2006) which reported the probability of infection per unit of blood transfused. The probability of a transfused patient being infected with bacterial contamination was estimated as the average number of units of RBCs received multiplied

by the probability of bacterial contamination per unit of blood transfused. The probability of a patient experiencing one of the other transfusion-transmitted infections (ie vCJD, HAV, malaria, HTLV, HIV, HBV and HCV) was estimated as the maximum number of units of RBCs, FFP or platelets administered to patients multiplied by the probability of infection per unit of blood transfused.

Due to the lower number of units of blood transfused in patients who undergo TE, the total probability of transfusion-transmitted infections was lower with TE when compared with the other two transfusion management strategies (see Table 4-2).

Mortality rates

The probability of a patient dying due to the specific transfusion-related complications and infections considered in the model were mainly derived from the study by Davies *et al.* (2006) and have been reported in Table 4-3. No specific Scottish data for these parameters are available from the Scottish clinical management information system that records data for Scottish cardiothoracic departments.

Since the aim of the model was to capture transfusion-related complications and mortality, the mortality rate for patients not transfused was assumed to be the same for all scenarios.

4.3.2 Liver transplantation

Clinical evidence on the use of TE compared with alternative transfusion management strategies in liver surgery was limited. Consequently, the development of the model for this particular indication was justified on the grounds that it would provide some indicative information on the relative costs and benefits of the strategies considered which would be of value to healthcare decision makers. However, there is considerable uncertainty around the data used to populate this model, particularly with respect to the number of units of blood transfused in the non-TE arm. Thus caution should be applied to the interpretation of the findings due to the limited data available.

As previously mentioned, transfusion seems to be a common practice in most of the patients undergoing liver transplantation due to the excessive blood loss experienced during this type of surgery. Therefore, rather than starting with the percentage of patients transfused, the model starts with the average blood usage per patient, as reported in the studies on liver transplantation, by assuming all patients receive transfusion.

Section 4.5.2 presents information on the usage of blood products during liver transplantation according to the type of coagulation assessment performed.

A re-operation rate of 8.13% was assumed for the three alternative transfusion management strategies, and the data used to estimate this parameter were obtained from information reported by Kang (1997). For patients not experiencing complications or infections, a zero mortality rate during the hospitalisation period was assumed.

Lack of evidence regarding transfusion-related complications and infections in liver transplantation led to an assumption that complications and infections due to transfusion would be the same as the rates used in the model of cardiac surgery. There was no need to adjust the probabilities of transfusion-related complications, since these had been reported as probabilities per patient. However, adjustments were made in order to take account of the differences in the amount of blood products transfused during liver transplantation when compared with cardiac surgery (see Table 4-8). For this, the approach followed was similar to the one adopted in the cardiac surgery model (see 'Transfusion-related complications' and 'Transfusion-transmitted infections', in Section 4.3.1).

4.4 Health benefits

The health benefits of using TE compared with the other transfusion management strategies were estimated in terms of the number of life years lived and the number of quality-adjusted life years (QALYs) gained at 1 month (as the reference case) and at 1 year (in further analyses) for the cohort of 1,000 patients considered in the analysis. Additionally, the following health consequences were identified for each alternative:

- the number of patients transfused
- the number of patients that experienced complications related to surgery or transfusion (including renal failure, MI, stroke, thrombosis, re-operation, wound complications and septicaemia)
- the number of patients that experienced transfusion-related complications (ie transfusion-related graft versus host disease, administration of an IBC, haemolytic transfusion reactions, PTP, TRALI and febrile reactions)
- the number of patients that experienced transfusion-transmitted infections (ie bacterial contamination, vCJD, HAV, malaria, HTLV, HIV, HBV and HCV)
- the number of patients that experience any type of complication or infection (including all the complications and infections previously mentioned)
- the number of patients transfused that died after 1 month
- the number of patients transfused that died after 1 year.

Life years lived

Life years lived at 1 month and at 1 year after transfusion for the cohorts of patients managed by the different transfusion management strategies depended on the probability of surviving after surgery and on whether patients experienced a complication or a transfusion-transmitted infection.

Complications related to surgery or transfusion, transfusion-related complications and infection due to bacterial contamination were assumed to occur during the hospitalisation period (Davies *et al.*, 2006) and therefore influenced life expectancy at 1 month. Life expectancy at 1 year after transfusion was additionally influenced by the possibility of being infected with vCJD, HAV, malaria, HTLV, HIV, HBV and HCV, with a mortality rate of 3% within that first year related to each type of transfusion-transmitted infection (Davies *et al.*, 2006) (see Table 4-2).

Table 4-3 Probability of mortality in cardiac surgery according to occurring event

Probability of mortality	Estimated risk per patient	Sources
After no transfusion	0	Assumption
After transfusion or surgical complications		
Renal dysfunction	0.03	Davies *et al*. (2006)
MI	0.03	Davies *et al*. (2006)
Stroke	0.03	Davies *et al*. (2006)
Thrombosis	0.03	Davies *et al*. (2006)
Bleed requiring operation	0.03	Davies *et al*. (2006)
Wound complications	0.03	Davies *et al*. (2006)
Septicaemia	0.03	Davies *et al*. (2006)
After transfusion-related complications		
Transfusion-related graft versus host disease	0.9000	Taylor & Contreras (2000)
IBC	0.0210	Davies *et al*. (2006)
Haemolytic transfusion reaction - acute	0.0430	Davies *et al*. (2006)
Haemolytic transfusion reaction - delayed	0.0380	Davies *et al*. (2006)
PTP	0.0460	Davies *et al*. (2006)
TRALI	0.2370	Davies *et al*. (2006)
Febrile reactions	0.0000	Taylor & Contreras (2000)
Transfusion-transmitted infection		
Bacterial contamination	0.03	Davies *et al*. (2006)
vCJD	0.03	Davies *et al*. (2006)
HAV	0.03	Davies *et al*. (2006)
Malaria	0.03	Davies *et al*. (2006)
HTLV	0.03	Davies *et al*. (2006)
HIV	0.03	Davies *et al*. (2006)
HBV	0.03	Davies *et al*. (2006)
HCV	0.03	Davies *et al*. (2006)
After transfusion and no complications	0.03	Davies *et al*. (2006)
After transfusion and no infections	0	Assumption

A half-cycle correction was applied to the life expectancies of those patients dying either during the period of hospitalisation or between months 1 and 12, in an attempt to adjust for different timings of death across patients. For those patients dying during the hospital stay, life expectancy was assumed to be half of the period the complication lasted. If the patient died because of undergoing a re-operation, it was assumed that the patient would die in the middle of the hospitalisation period.

The impact of bacterial contamination on the life expectancy at 1 month was estimated as follows:

- for those patients dying from complications (either complications related to surgery or transfusion, or transfusion-related complications) during the period of hospitalisation, the life expectancy was assumed to be unaffected in cases where bacterial contamination occurred (therefore, a life cycle correction was applied to the life expectancy/length of hospital stay related to the complication without further adjustments to account for bacterial contamination)
- for patients transfused that either survived other complications or did not experience any complication, their life expectancy was adjusted according to the probability of having bacterial contamination and the subsequent probability of dying during the period of hospitalisation due to bacterial contamination (see Figure 4-1).

Figure 4-1 Estimation of life expectancy at 1 month

Life expectancy at 1 month =

(Probability of bacterial contamination*Probability of dying due to bacterial contamination*Days in 1 month)
+
(Probability of bacterial contamination*Probability of dying due to bacterial contamination*Half cycle correction*Length of hospital stay)

When health benefits at 1 year were estimated, the adjustments of bacterial contamination were considered to estimate the life expectancy until month 1 (see Figure 4-1). Additionally, the estimation of the life expectancy from months 1 to 12 took into account the probabilities of dying during this period due to any other transfusion-related infection. Again, a half-cycle correction was applied to account for differences in time of death during that period, assuming that patients dying between months 1 and 12 after transfusion due to a transfusion-related infection would die at the middle of the period (see Figure 4-2).

Figure 4-2 Estimation of life expectancy at 1 year

Life expectancy at 1 year =

(Probability of transfusion-transmitted infection*Probability of dying due to transfusion-transmitted infection*Days in 1 year)
+
(Probability of transfusion-transmitted infection*Probability of dying during first year after transfusion due to transfusion-transmitted infection*Half cycle correction*Days in 1 year)

QALYs gained

When life expectancy at 1 month and at 1 year were estimated, utility adjustments were conducted in order to estimate the number of QALYs gained. For this, utility values were obtained from the study by Davies *et al.* (2006) which selected utility values for several health states (ie long-standing illness, limiting illness, non-limiting illness and no long-standing illness) from the 1996 Health Survey from England due to the fact that the data on utility values associated with transfusion-related complications were limited. These utility values are shown in Table 4-4.

Table 4-4 Utility values assigned to different health states

Health states	Utility	Source
From surgery to hospital discharge		
No transfusion	0.63	Assumed to be the same as for transfusion without adverse events, Davies *et al.* (2006)
Transfusion or surgical complications	0.63	Davies *et al.* (2006)
Transfusion-related complications	0.63	Davies *et al.* (2006)
Transfusion and no complications	0.63	Davies *et al.* (2006)
Death	0	Assumption
From hospital discharge to 1 month		
No transfusion	0.88	Assumed to be the same as for transfusion without adverse events, Davies *et al.* (2006)
Transfusion or surgical complications		
Renal dysfunction	0.88	Davies *et al.* (2006)
MI	0.88	Davies *et al.* (2006)
Stroke	0.64	Davies *et al.* (2006)
Thrombosis	0.88	Davies *et al.* (2006)
Bleed requiring operation	0.88	Davies *et al.* (2006)
Wound complications	0.88	Davies *et al.* (2006)
Septicaemia	0.88	Davies *et al.* (2006)
Transfusion-related complications		
Transfusion-related graft versus host disease	0.88	Davies *et al.* (2006)
IBC	0.88	Davies *et al.* (2006)
Haemolytic transfusion reaction - acute	0.88	Davies *et al.* (2006)
Haemolytic transfusion reaction - delayed	0.88	Davies *et al.* (2006)
PTP	0.88	Davies *et al.* (2006)
TRALI	0.88	Davies *et al.* (2006)
Febrile reactions	0.88	Davies *et al.* (2006)
Transfusion and no complications	0.88	Davies *et al.* (2006)
1–12 months following surgery		
No transfusion	0.93	Assumed to be the same as for transfusion without adverse events, Davies *et al.* (2006)
Transfusion or surgical complications		
Renal dysfunction	0.88	Davies *et al.* (2006)
MI	0.88	Davies *et al.* (2006)
Stroke	0.64	Davies *et al.* (2006)
Thrombosis	0.88	Davies *et al.* (2006)
Bleed requiring operation	0.88	Davies *et al.* (2006)
Wound complications	0.88	Davies *et al.* (2006)
Septicaemia	0.88	Davies *et al.* (2006)
Transfusion-related complications		
Transfusion-related graft versus host disease	0.88	Davies *et al.* (2006)
IBC	0.88	Davies *et al.* (2006)
Haemolytic transfusion reaction - acute	0.88	Davies *et al.* (2006)
Haemolytic transfusion reaction - delayed	0.88	Davies *et al.* (2006)

Health states	Utility	Source
PTP	0.88	Davies *et al.* (2006)
TRALI	0.88	Davies *et al.* (2006)
Febrile reactions	0.88	Davies *et al.* (2006)
Transfusion-transmitted infection		
Bacterial contamination	0.88	Davies *et al.* (2006)
vCJD	0.88	Davies *et al.* (2006)
HAV	0.88	Davies *et al.* (2006)
Malaria	0.88	Davies *et al.* (2006)
HTLV	0.88	Davies *et al.* (2006)
HIV	0.88	Davies *et al.* (2006)
HBV	0.88	Davies *et al.* (2006)
HCV	0.88	Davies *et al.* (2006)
Transfusion and no complications	0.93	Davies *et al.* (2006)

Discounting of future health benefits was not necessary because the time horizon considered in the analysis was less than or equal to 1 year (ie 1 month for the base-case analysis and 1 year for further analysis).

4.5 Cost estimation

4.5.1 Cardiac surgery

The estimation of costs in the baseline analysis was conducted from the perspective of NHSScotland considering a period of 1 month after the cardiac intervention (a 1-year time horizon was considered in further analyses). According to this perspective, the following categories of costs were included when a time horizon of 1 month was considered:

- the pre-operative and peri-operative costs of transfusion-related services
- the costs of the tests conducted for the identification of patients at risk of bleeding and for the subsequent management of transfusion
- the costs related to complications due to surgery or transfusion, transfusion-related complications and transfusion-transmitted infection due to bacterial contamination.

When a time horizon of 1 year was considered, the costs related to those transfusion-transmitted infections other than bacterial contamination were also captured (ie those incurred during the first year after the cardiac surgery that were incurred due to transfusion-transmitted vCJD, HAV, malaria, HTLV, HIV, HBV and HCV). However, it is accepted that the costs associated with many of these conditions could only be fully captured in a model with a lifetime perspective.

Mean values instead of median values were sought for the identification of relevant healthcare resource utilisation (eg for units of blood transfused, length of hospital stay, etc.).

Pre-operative and peri-operative costs of transfusion-related services

Patients receiving transfusions would incur pre-operative and peri-operative costs related to transfusion (Davies *et al.*, 2006). Among the costs included were those of blood group tests, screening, cross-matching, additional allogeneic blood matching and those related to the use of transfusion sets (see Table 4-5). In many settings all patients will be cross matched in advance to reduce time and risks should a transfusion be required.

Table 4-5 Costs of pre-operative and peri-operative transfusion-related services per patient

Transfusion-related service	Cost (2006 price)
Pre-operative costs of allogeneic blood per transfusion (including group and screen, and cross-match)	£21.47
Peri-operative use of transfusion-related services:	
Additional allogeneic blood match Giving sets used Other peri-operative transfusion-related costs	£0.50 £2.47 £3.22

Source: Davies *et al.* (2006)

Cost of blood products

The cost of blood products is shown in Table 4-6.

Table 4-6 Cost of blood products

Prices for blood components	(2005/06 price)	Source	Country
Red cell	£122.03	Blood & Components price list 2004/5	UK
FFP	£31.36	Blood & Components price list 2004/5	UK
Adult platelet pack	£201.77	Blood & Components price list 2004/5	UK

Costs related to TE

The clinical practice related to the use of TE is rather variable, not only across centres but also for the same centre across different patients. There are different types of tests that can be performed for each device according to the type of activator used and the intended goal of the test. For example, for the case of the ROTEM® system the different types of tests include: EXTEM, INTEM, FIBTEM, APTEM and HEPTEM (see Table 4-7).

For the identification of the type and number of tests used, the clinical practice followed in one Scottish hospital was considered. According to this, patients managed with TE will undergo at least one test, which would give an overview of coagulation. In most cases only one test is used, which can usually be either EXTEM or INTEM. In cardiac surgery, HEPTEM is commonly used as well as a unique test. Depending on local practice and the different protocols adopted, additional tests (such as FIBTEM) may be performed, either routinely or if the results of the initial test were abnormal. Further tests may be repeated several times if the patient has a massive continuing haemorrhage. The unit costs related to each ROTEM® test do not differ substantially from each other and are under £10 per patient (Mr L Loi, Scientific specialist, BIODIS. Personal communication, 25 May 2007).

For the reference case, it was considered that only one test would be performed per patient that did not require transfusion, while for those patients requiring transfusion an intra-operative and a post-operative test would be conducted. A representative unit cost of £8.25 was used for each TE test, which included the costs of reagents, disposable products and pipette tips (although it excluded the costs of the reagents stability after opening and the quality control costs).

In order to include the fixed costs related to the acquisition of the device (which amounts to £17,510 per ROTEM® Gamma device for 2006 in UK, according to information provided by Pentapharm Gmbh) it was considered that the hospital would arrange a 3-year contract leasing programme with the manufacturer (to include the costs of a service contract for potential repairs and replacement). It was assumed that, on average, the centre would perform 200 tests per year. These assumptions were considered to be conservative since both a longer period for the leasing programme and/or a higher number of tests conducted annually in the centre would decrease the unit cost per test performed.

The TEG® system offers more tests and has different price structures to the ROTEM®. However the model has adopted the unit costs and tests above assuming the results will generalise to the other system.

10Standard laboratory tests

The SLT arm of the model assumed that the relevant tests that would be performed, following Scottish clinical practice, are: fibrinogen concentration, prothrombin time (PT) [sometimes reported as international normalised ratio (INR)], platelet count (PC) and activated partial thromboplastin time (APTT). Some settings may use additional tests for both types of surgery.

The unit costs for SLTs were obtained from the Western Infirmary, Glasgow (Mr R Soutar, Consultant in haematology and transfusion medicine, Western Infirmary. Personal communication, February 2007). The total cost per set of SLTs was £20 (2006 price) and included fibrinogen concentration, PT, PC and APTT. These costs assume that the costs on the ward to take the blood and record the results are the same.

Table 4-7 Tests performed by the ROTEM® system

Test	Activator/Inhibitor	Intended goal
EXTEM	Tissue factor	Global assay insensitive to heparin
INTEM	Ellagic acid	Global assay sensitive to heparin
FIBTEM	Platelets inhibitor	Differentiation between platelets/fibrin disorder
APTEM	Fibrinolysis inhibitor	Confirm fibrinolysis
HEPTEM	Heparinase	Patient haemostasis excluding heparin effects

Source: /http://www.pentapharm.de/html/product/reagents.html

The costs exclude the cost of theatre staff who may be required to remain on site when a patient is bleeding until the results of the coagulation screen are known. SLTs will require such staff to be on duty for a longer period.

No training costs have been included for TE or SLTs.

Clinical discretion

The costs incurred in conducting coagulation tests were assumed to be zero if patients were managed by means of CD. No laboratory tests or supplies are assumed to be used in this scenario and any opportunity costs of labour time are assumed to be negligible.

Blood products used

Most of the studies included in the systematic review reported the median blood products used instead of the mean use per patient. Since the mean usage per patient was of interest (to have a representative figure of blood usage to populate the model), the numbers of units of RBCs, FFP and platelets transfused with TE and with SLTs were identified from the study by Shore-Lesserson *et al.* (1999). In this study, the mean blood usage per patient was reported in millilitres transfused, which were divided by 300 to transform the figure to units of blood transfused (Davies *et al.*, 2006). Since there was not an assessment for CD in the same study (Shore-Lesserson *et al.*, 1999), its blood product usage was assumed to be the same as that of SLTs (see Table 4-8).

Table 4-8 Units of blood transfused in cardiac surgery according to the type of transfusion management strategy

Type of blood product	TE	SLTs	CD	Sources
Units of RBCs transfused*	1.18	1.58	1.58	Shore-Lesserson *et al.* (1999); for CD it was assumed to be equal to that of SLTs
Units of FFP transfused*	0.12	0.72	0.72	Shore-Lesserson *et al.* (1999); for CD it was assumed to be equal to that of SLTs
Units of platelets transfused*	0.11	0.28	0.28	Shore-Lesserson *et al.* (1999); for CD it was assumed to be equal to that of SLTs

* The mean number of units of blood transfused was obtained by dividing the number of millilitres transfused by 300 (Davies *et al.* 2006).

Hospitalisation costs

Only one of the studies included in the systematic review reported data on the hospital stay of patients according to whether they had been managed with TE or with SLTs (Anderson *et al.*, 2006). However, the data were reported in terms of the median number of days in hospital, instead of the mean. Therefore, the final data on the length of hospital stay used to populate the model were derived from the HTA by Davies *et al.* (2006) which reported an average length of hospital stay equal to 9.56 days per patient undergoing cardiac surgery. This value was assumed to be similar across all the transfusion management strategies considered. The only study included in the systematic review which reported median length of hospital stay showed non-significant differences between TE and SLTs (Anderson *et al.*, 2006), therefore the assumption about equal length of hospital stay across different transfusion management strategies appears to be appropriate.

The estimation of the costs related to complications and infections during the period of hospitalisation was conducted by assuming that all patients would have the same average length of stay (ie 9.56 days in the base-case analysis) and the differences in costs due to complications and infections would be given by different unit costs per day of hospitalisation (according to the type of complication or infection) and by different durations of the complications or infections. That is, the days of hospitalisation were valued at a different unit cost, depending on whether patients experienced complications and infections in that day, and depending as well on the type of complication or infection experienced. Additionally, the valuation of the length of stay would depend on the average number of days a patient would experience complications related to surgery or transfusions, transfusion-related complications and bacterial contamination (see Table 4-9) (Davies *et al.*, 2006). The mean costs are calculated for a range of patients with different conditions: cardiac surgery patients are likely to require more intensive care than most. The costs may thus understate the costs to manage this patient group.

For those transfused patients that are predicted to die during the period of hospitalisation, the cost of the hospital stay until dying was valued at the cost per day of hospitalisation corresponding to the complication experienced.

Using a half-cycle correction, it was assumed that these patients would die in the middle of the period for which the complication lasted (see Table 4-9), and therefore only costs incurred until that moment were included for those patients. For patients dying after requiring a re-operation, the full cost of the re-operation was included, and it was assumed that they would live for half of the period of hospitalisation, therefore only the costs related to the hospital stay while they survived were included in the cost analysis.

In order to estimate the costs at 1 month, the costs incurred due to bacterial infection were added to the costs of transfusion and complications, given that bacterial contamination was assumed to occur during the hospitalisation period. Again, for those patients dying due to bacterial contamination, it was assumed that the costs related to the infection would be half of those of the period the infection lasted (see Table 4-9) due to the half-cycle approach used to account for different timings of death during that period.

Costs incurred between discharge and month 12 after surgery

In case a transfusion-transmitted infection occurs, the patient will experience a number of infection-related events during the first 12 months after cardiac surgery. Data about the hospitalisations and outpatient visits required by patients according to the type of transfusion-transmitted infection and the unit costs associated with them were obtained from the study by Davies *et al.* (2006) (see Table 4-10).

When the cost estimation was conducted considering a time horizon of 1 year, half-cycle adjustments for patients dying during the first year due to transfusion-transmitted infections were also applied.

The probability of disabling stroke for patients experiencing stroke during the hospitalisation period was 0.58. Patients with disabling stroke would incur an additional annual cost of £11,807, while no further costs would be incurred during the first 12 months after surgery for patients with no disabling stroke (Davies *et al.*, 2006) (see Table 4-11).

Table 4-9 Costs related to complications/infections at 1 month (2006 price)

Type of complication or infection	Length of hospital stay related to complications (days)	Cost per day of hospitalisation due to complications/ infections	Source
Transfusion or surgical complications			
Renal dysfunction	5.68	£257	Davies *et al.* (2006)
MI (non-fatal)	8.91	£118	Davies *et al.* (2006)
Stroke	8.76	£207	Davies *et al.* (2006)
Thrombosis	3.32	£245	Davies *et al.* (2006)
Bleed requiring operation	0	£0	Davies *et al.* (2006)
Wound complications	12	£188	Davies *et al.* (2006)
Septicaemia	7	£208	Department of Health (2006)
Transfusion-related complications			
Transfusion-related versus host disease	6.8	£969	Davies *et al.* (2006)
IBC	11.9	£163	Davies *et al.* (2006)
Haemolytic transfusion reaction - acute	11.9	£628	Davies *et al.* (2006)
Haemolytic transfusion reaction - delayed	11.9	£628	Davies *et al.* (2006)
PTP	2.5	£628	Davies *et al.* (2006)
TRALI	1.98	£1,539	Davies *et al.* (2006)
Febrile reactions	1	£766	Sharma *et al.* (2000)
Transfusion-transmitted infection			
Bacterial contamination	8.4	£163	Davies *et al.* (2006)
Costs related to re-operation (2006 price)	**Additional minutes of surgery**	**Cost per minute of surgery**	**Source**
Bleed requiring operation	190	£11.81	Davies *et al.* (2006)

Table 4-10 Number of infection-related events (ie hospitalisations and outpatient visits) during first year by type of transfusion-transmitted infection

	Number of infection-related events
HAV	
Acute hospitalisations	2
Outpatient visits	3
HBV	
Acute hospitalisations	2
Outpatient visits	3
HCV	
Acute hospitalisations	2
Outpatient visits	3
Malaria	
Acute hospitalisations	2
Outpatient visits	0
HTLV	
Acute hospitalisations	2
Outpatient visits	0
HIV	
Acute hospitalisations	2
Outpatient visits	3

Source: Davies *et al.* (2006)

Table 4-11 Length of hospital stay and unit costs related to transfusion-transmitted infections and transfusion-related complications at 1 year

Type of complication or infection	Length of hospital stay related to complications	Costs/cost per day (2006 price)*
HIV	6.97	£459
HTLV	1	£459
Malaria	3.4	£365
HAV acute	5.1	£365
HBV acute	4.7	£365
HBV chronic	7.4	£365
HCV acute	4.6	£365
HCV chronic	3.5	£262
HIV (outpatient visit)	1	£742
HTLV (outpatient visit)	1	£204
Malaria (outpatient visit)	1	£204
HAV (outpatient visit)	1	£204
HBV (outpatient visit)	1	£204
HCV (outpatient visit)	1	£204
vCJD**	0	£0
Additional annual cost for disabling stroke	–	£11,807
Additional annual cost for non-disabling stroke	–	£0

*Source: Davies *et al.* (2006) **Source: Llewelyn *et al.* (2004)

Indirect costs

The perspective adopted in the analysis is that of NHSScotland and as such no indirect costs (ie productivity losses associated with the alternative transfusion management strategies) were included. Furthermore, given that cardiac patients undergoing surgery are in general over 60 years of age, the exclusion from the analysis of the indirect costs related to productivity losses appears not to be relevant and is unlikely to affect the findings.

Cost adjustments

All costs were adjusted for inflation to reflect costs related to the year 2005/2006. The 2006 PSSRU inflation indices for Hospital and Community Health Services (Curtis & Netten, 2006) were used to adjust for costs reported in price years different to 2005/2006.

Discounting

Discounting of the future costs was not necessary given that the time horizon considered in the analysis is less than or equal to 1 year.

4.5.2 Liver transplantation

The estimation of costs in the model examining liver transplantation followed the same approach as the cardiac surgery model.

Given that during liver transplantation patients are likely to experience greater blood loss, the average number of units of blood transfused was considerably higher than for cardiac surgery. Data on the usage of blood products for patients undergoing liver transplantation that were managed with TE and SLTs were identified from one of the studies included in the systematic review (Gordon *et al.*, 2002):

- for the patient cohort managed with TE in the model, data were obtained from groups 2 and 3 assessed in this study, for which TE was selectively used. The numbers of units of blood transfused (RBCs, FFP and platelets) was estimated as the weighted average of groups 2 and 3 included in the study, for which TE had been used selectively
- for the group managed with SLTs, data selected were derived from group 1, which referred to patients managed with SLTs only.

Due to the lack of evidence, an assumption was formulated regarding the number of units of blood transfused, on average, to the group of patients undergoing liver transplantation for which only CD was used to assess coagulation and guide transfusion. Data about the blood usage for patients managed with CD were collected from the study by Kang (1997). In this study, the volume of blood transfused to patients undergoing liver transplantation was assessed for those patients monitored by TE compared with those patients not monitored by TE. Although this second group appeared to have been monitored with SLTs, the fact that the study had been conducted in 1985 means that the findings may not be applicable to current SLT practice and as such, are used as a proxy for CD in the absence of data.

The reported units of red cells transfused using TE were 9.35, about 15% higher than the 8.1 units reported by SNBTS for this procedure in Scotland in 2005/6 (see Table 4-12). The Scottish data reflect the benefit of using TE for such procedures. Thus the trend has been to reduce the use of blood products. However, the study data are retained for use in the model because the factors behind this reduction are unlikely to be TE specific and should apply across all arms. The alternative of scaling all down by 15% was considered and rejected as not being supportable by evidence.

The estimation of the other cost categories followed that of the model for cardiac surgery (see Section 4.5.1).

4.6 Type of economic evaluation and economic analysis conducted

Economic evaluations are classified as cost-effectiveness analyses, cost-utility analyses or cost-benefit analyses depending on whether the summary measure of health outcomes used is presented in terms of natural units, utility values or monetary units, respectively (Drummond *et al.*, 2005).

Given the type of health outcomes used in this study to summarise the health impact of using TE versus SLTs or CD in patients undergoing cardiac surgery or liver transplantation, cost-effectiveness and cost-utility analyses were conducted. In the cost-effectiveness analysis, the health benefits and costs were combined to provide estimates of the cost per transfusion avoided, the cost per averted death and the cost per life year gained. The synthesis of health benefits and costs was conducted in terms of the cost per QALY gained for the cost-utility analysis.

Table 4-12 Units of blood transfused and length of hospital stay for liver transplantation by type of transfusion management strategy

Parameter	TE	SLTs	CD	Sources
Units of RBCs transfused	9.35	17.9	26.7	Gordon *et al.* (2002), Kang *et al.* (1985)
Units of FFP transfused	6.25	10.7	26.7	Gordon *et al.* (2002), Kang *et al.* (1985)
Units of platelets transfused	2.1	7.5	14.1	Gordon *et al.* (2002), Kang *et al.* (1985)
Length of hospital stay	13.0	13.0	13.0	Davies *et al.* (2006)

The methodology included conducting an incremental cost-effectiveness analysis after ranking the transfusion management strategies from the most to the least cost-effective and excluding, if necessary, the dominated strategies (ie those strategies presenting lower effectiveness and incurring higher costs when compared with any other). The results of the incremental analysis are reported as the incremental cost per additional unit of benefit obtained with the most effective and most expensive strategy when compared with the next most effective and most expensive one.

4.7 Sensitivity analysis

One-way and multi-way sensitivity analyses were conducted in order to test the robustness of the results when the values of parameters were modified. The types of parameters considered in the sensitivity analysis were mainly those that had been estimated through the formulation of assumptions or those parameters for which the evidence was not definitive. Based on these criteria, the parameters assessed in the sensitivity analyses were:

- transfusion rates: to undertake sensitivity analyses around the transfusion rates in cardiac surgery, different scenarios were considered according to the data reported by some of the RCTs included in the systematic review (transfusion rates were identified in some cases as the percentages of patients transfused with RBCs)
- re-operation rates: although some of the studies in cardiac surgery included in the systematic review showed a lower re-operation rate for patients managed with TE (Nuttall *et al.*, 2001; Shore-Lesserson *et al.*, 1999), the re-operation rates considered in the base-case analysis were assumed to be similar for both TE and SLTs, which may be biasing the results against TE
- variability in clinical practice regarding the use of TE: a scenario was considered in which it was assumed that intra- and post-operative TE tests would be performed for all the patients. It was additionally assumed that TE would be performed jointly with SLTs, therefore the costs of performing the coagulation tests were also included in the estimation of the TE costs
- to test for variations in the levels of blood usage, a multi-way sensitivity analysis considered that the number of units of RBCs, FFP and platelets transfused would be the same for patients managed with TE and with SLTs

- duration of leasing programme: the base-case analysis considered that the leasing programme would be agreed for a period of 3 years. It was initially intended to conduct sensitivity analyses assessing the impact on the cost effectiveness of TE when a 4-year leasing programme and a 5-year leasing programme were considered.

These sensitivity analyses focused on the impact of the previous parameter modifications on the number of transfusions avoided, the number of QALYs gained and the cost effectiveness across the three transfusion management strategies considered in the study.

4.8 Budget impact analysis

A budget impact analysis was conducted to estimate the impact on costs of using TE in the management of patients undergoing cardiac surgery and liver transplantation within NHSScotland (Trueman *et al.*, 2001). It was expected that conducting the budget impact analysis would additionally provide a better insight of the main costs driving the results obtained.

For this, the incremental cost of TE in comparison with SLTs was estimated on an individual patient basis. This estimate was weighted by the number of patients that are expected to have access to either cardiac surgery or liver transplantation in NHSScotland.

Data about the number of cardiac interventions undertaken in the NHS Scottish setting were obtained from the Surgical Procedures and Operations reported in the Inpatient, Day Case & Outpatient Activity website by the Information Services Division (ISD) Scotland (Harding *et al.*, 1997). In 2006, 2,447 patients were discharged after a coronary artery bypass intervention within NHSScotland (this figure included discharges after anastomosis). This number was used to assess the expected total annual expenditure of using TE on cardiac surgery interventions.

The number of patients undergoing liver transplantation in Scotland was identified from the data on liver transplantation reported by the NHS Blood and Transplant (Statistics and Audit Directorate, 2006). A total of 42 liver transplants were conducted at the Royal Infirmary of Edinburgh between 1 April 2005 and 31 March 2006. This is the only hospital in Scotland that performs such surgery. The total expenditure of using TE in liver transplantation was estimated by considering that this figure reflected the total number of liver transplants performed in Scotland annually.

5 CLINICAL AND COST EFFECTIVENESS: RESULTS

5.1 Base-case results

5.1.1 Cardiac surgery

The base-case results for the estimated health benefits, costs and incremental cost-effectiveness analysis in the cohort of 1,000 patients undergoing cardiac surgery have been reported in Table 5-1, Figure 5-1 and Table 5-2 respectively.

In terms of the estimated health benefits, TE is the transfusion management strategy that presents higher effectiveness independent of the type of health benefit considered (see Table 5-1):

- the number of patients that would require transfusion was lower (538 compared with 603 for SLTs and 852 for CD)
- the number of complications and transfusion-transmitted infections would be lower for the cohort of patients managed with TE (in total, 150 patients would experience transfusion-related complications and/or infections with TE, compared with 172 with SLTs and 250 with CD)
- fewer patients would die at 1 month after transfusion if managed with TE (ie 16 patients would die with TE compared with 18 with SLTs and 25 with CD). These figures did not vary when a time horizon of 1 year was considered due to the fact that the probabilities of experiencing transfusion-transmitted infections were very low (see Table 4-2)
- there was a very small increase in the number of life years lived after 1 month for the cohort of 1,000 patients managed with TE (82.80 years) when compared with those managed with SLTs (82.07) or with CD (81.55 years). The difference was more evident when a time horizon of 1 year was considered, with 984.27 years lived at 1 year for the cohort of patients managed with TE when compared with 982.46 for those managed with SLTs and 975.20 years if managed with CD
- similarly, although at 1 month the number of QALYs gained among patients managed with TE (ie 65.60 QALYs) was marginally higher in comparison with those managed with SLTs or with CD (65.46 and 64.91 QALYs, respectively), when a 1-year time horizon was considered, the increase in the QALYs gained with TE was more evident.

The results of the base-case analysis showed that TE would be the least expensive coagulation management strategy among cardiac surgery patients, followed by SLTs, while CD would be the most costly (see Figure 5-1). At 1 month, the total cost per cohort of 1,000 patients undergoing cardiac surgery would be £1,058,767 with TE, £1,184,391 with SLTs and £1,861,006 with CD. When a 1-year time horizon was considered, these costs were £1,183,831, £1,324,511 and £1,861,006, respectively.

Given that TE would avoid transfusions, would reduce the number of deaths at 1 month and at 1 year, and would achieve a higher number of life years and QALYs gained while incurring lower costs in comparison with SLTs and CD (see Table 5-2), it was the dominant strategy for the management of transfusion in cardiac surgery patients. This finding was the same regardless of the time horizon or the measure of health benefit considered in the analysis (although health benefits were more evident at 1 year).

5.1.2 Liver transplantation

Table 5-3, Figure 5-2 and Table 5-4 present the base-case results, in terms of estimated health benefits, costs and incremental cost effectiveness, respectively, for the cohort of 1,000 patients undergoing liver transplantation and managed with either TE, SLTs or CD.

Since the model on liver transplantation considered that all patients would require transfusion, and the probability of experiencing complications related to surgery or

Table 5-1 Expected health benefits at 1 month and at 1 year for a cohort of 1,000 cardiac surgery patients

Measure of health benefit	TE	SLTs	CD
Number of patients transfused	537.80	602.50	851.90
Number of patients with complications related to surgery or transfusion	142.52	159.66	232.74
Number of patients with transfusion-related complications	7.42	11.86	16.77
Number of patients with transfusion-transmitted infections	0.01	0.01	0.26
Number of patients with complications and/or infections (including all types of complications)	149.94	171.54	249.77
Patients transfused that died after 1 month	15.93	17.76	25.11
Patients transfused that died after 1 year	15.93	17.76	25.12
Total years lived at 1 month (in years)	82.20	82.07	81.55
Total years lived at 1 year (in years)	984.27	982.46	975.20
QALYs at 1 month	65.60	65.46	64.91
QALYs at 1 year	893.82	890.68	878.52

transfusion depended solely on whether the patient received blood transfusion or not, there were not differences across the management strategies in terms of the number of patients experiencing complications related to surgery or transfusion (with a total of 327 patients experiencing these types of complications across all management strategies). However, given that patients managed with TE would require a lower amount of blood products transfused, and given that some of the transfusion-related complications and the transfusion-transmitted infections depended on the quantity of blood products transfused, less patients managed with TE experienced transfusion-related complications and infections (see Table 5-3).

Figure 5-1 Total estimated costs (2005/2006 prices) for a cohort of 1,000 cardiac surgery patients across the alternative coagulation management strategies at 1 month and at 1 year

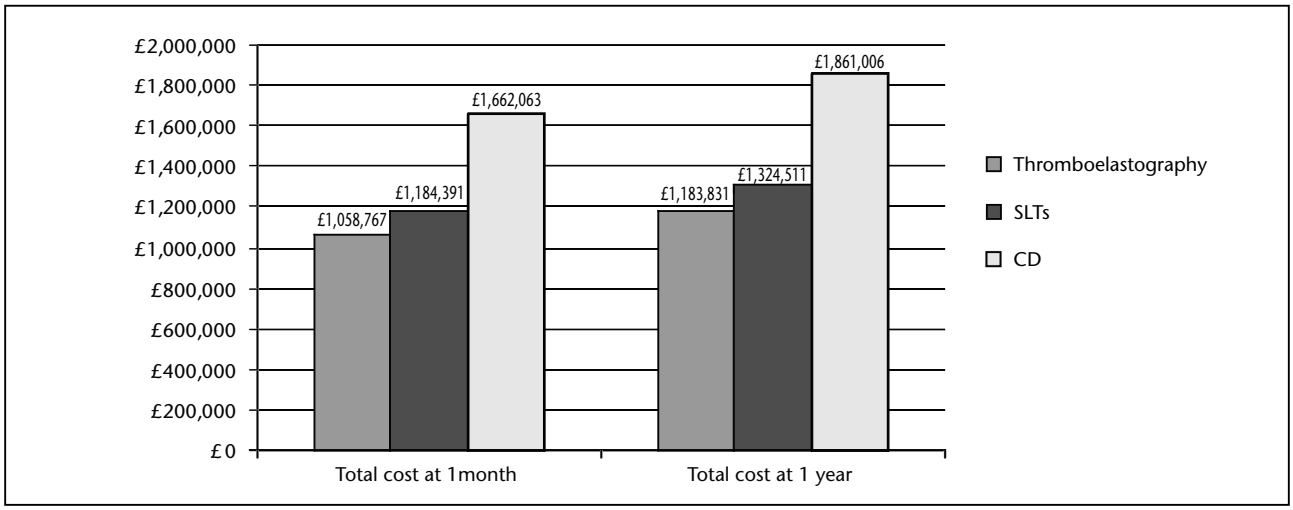

Table 5-2 Incremental cost-effectiveness analysis: base-case results at 1 month and at 1 year for a cohort of 1,000 cardiac surgery patients

	Comparing TE with SLTs	Comparing SLTs with CD	Comparing TE with CD
Results at 1 month			
Incremental cost (comparison)	-£1,256,235	-£477,670	-£603,295
Transfusions averted	64.70	249.40	314.10
Cost per transfusion averted	TE dominant	SLTs dominant	TE dominant
LYs gained at 1 month	0.13	0.52	0.65
Cost per LY gained	TE dominant	SLTs dominant	TE dominant
QALYs gained at 1 month	0.14	0.55	0.69
Cost per QALY at 1 month	TE dominant	SLTs dominant	TE dominant
Deaths averted at 1 month	1.83	7.35	9.18
Cost per averted death	TE dominant	SLTs dominant	TE dominant
Results at 1 year			
Incremental cost comparison	-£140,680	-£536,495	-£677,175
LYs gained at 1 year	1.81	7.26	9.07
Cost per LY gained	TE dominant	SLTs dominant	TE dominant
QALYs gained at 1 year	3.15	12.16	15.30
Cost per QALY at 1 year	TE dominant	SLTs dominant	TE dominant
Deaths averted at 1 year	1.83	7.36	9.190041
Cost per averted death	TE dominant	SLTs dominant	TE dominant

The results obtained after considering a time horizon of 1 month showed that there was a minimal reduction in the number of patients dying at 1 month among those managed with TE when compared with SLTs and CD. These patients experienced an almost negligible increase in the number of life years lived and the number of QALYs gained after 1 month in comparison with the patients managed with either SLTs or CD.

When considering a time horizon of 1 year, the improvement experienced by patients managed with TE in terms of a lower number of deaths or a higher number of life years lived were still negligible, although the number of QALYs gained was shown to be higher among these patients when compared with those managed with either SLTs or CD.

The lowest costs incurred were observed for the cohort of patients managed with TE (£4,326,549 at 1 month and £4,559,433 at 1 year), followed by the SLT group (£6,600,362 at 1 month and £6,833,597 at 1 year), while CD resulted the most expensive management strategy (costing £9,607,594 per cohort of 1,000 patients at 1 month, and £9,841,191 at 1 year; see Figure 5-2).

The results of the incremental cost-effectiveness analysis showed that TE was the dominant strategy for the management of patients undergoing liver transplantation since it achieved better health outcomes at a lower cost when compared with the other two transfusion management strategies (ie SLTs and CD). The improvements in terms of life years and QALYs gained at 1 month were small, and therefore the benefits of TE in liver transplantation would be better observed over a longer period of time (see Table 5-4).

Figure 5-2 Total estimated costs (2005/2006) for a cohort of 1,000 liver transplantation patients across the alternative coagulation management strategies at 1 month and at 1 year

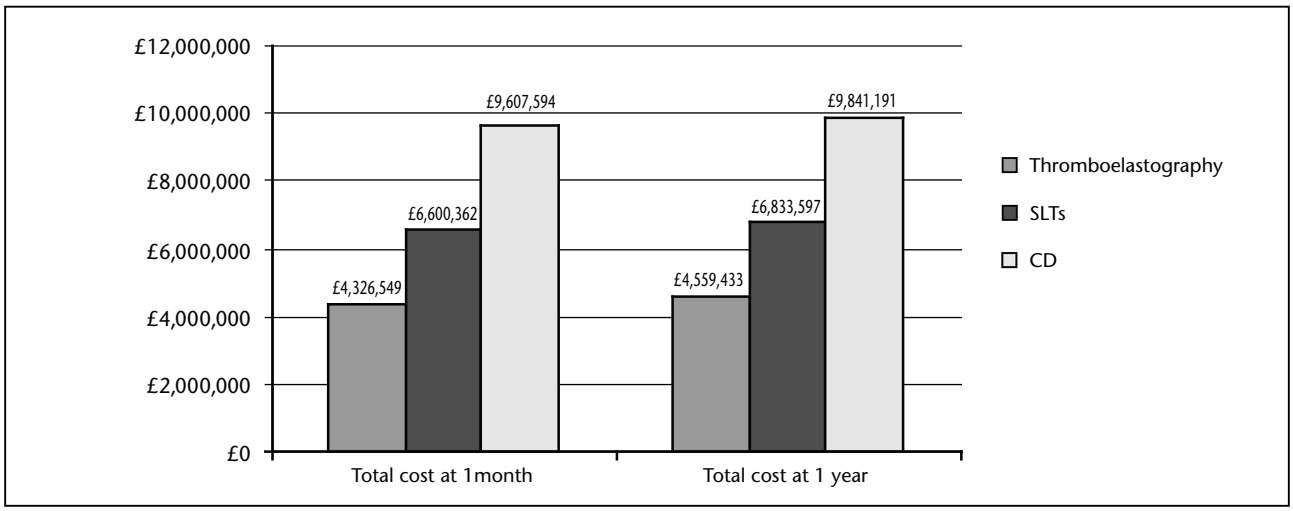

Table 5-3 Expected health benefits at 1 month and at 1 year for a hypothetical cohort of 1,000 liver transplantation patients

Measure of health benefit	TE	SLTs	CD
Number of patients with complications related to surgery or transfusion	326.7	326.7	326.7
Number of patients with transfusion-related complications	161.61	264.26	425.33
Number of patients with transfusion-transmitted infections	0.13	0.24	0.36
Number of patients with complications and/or infections (including all types of complications)	488.44	591.20	752.39
Patients transfused that died after 1 month	10.26	10.62	11.53
Patients transfused that died after 1 year	10.27	10.63	11.54
Total years lived at 1 month (in years)	82.60	82.58	82.50
Total years lived at 1 year (in years)	989.86	989.51	988.60
QALYs at 1 month	63.46	63.44	63.38
QALYs at 1 year	877.83	872.81	864.64

Table 5-4 Incremental cost-effectiveness analysis: base-case results at 1 month and at 1 year for a cohort of 1,000 liver transplantation patients

	Comparing TE with SLTs	Comparing SLTs with CD	Comparing TE with CD
Results at 1 month			
Incremental cost (comparison)	-£2,273,812	-£3,007,232	-£5,281,045
LYs gained at 1 month	0.03	0.07	0.10
Cost per LY gained	TE dominant	SLTs dominant	TE dominant
QALYs gained at 1 month	0.02	0.06	0.08
Cost per QALY at 1 month	TE dominant	SLTs dominant	TE dominant
Deaths averted at 1 month	0.36	0.91	1.26
Cost per averted death	TE dominant	SLTs dominant	TE dominant
Results at 1 year			
Incremental cost (comparison)	-£2,274,164	-£3,007,594	-£5,281,758
LYs gained at 1 year	0.35	0.90	1.26
Cost per LY gained	TE dominant	SLTs dominant	TE dominant
QALYs gained at 1 year	5.01	8.17	13.19
Cost per QALY at 1 year	TE dominant	SLTs dominant	TE dominant
Deaths averted at 1 year	0.36	0.91	1.269824
Cost per averted death	TE dominant	SLTs dominant	TE dominant

5.2 Sensitivity analysis

5.2.1 Cardiac surgery

The results of the sensitivity analyses for the model in cardiac surgery are shown in Appendices 11.9 and 11.10.

When the transfusion rates were modified to reflect those reported in some of the studies included in the systematic review (Avidan *et al.*, 2004; Shore-Lesserson *et al.*, 1998; Shore-Lesserson *et al.*, 1999), TE remained the dominant strategy, achieving more life years and QALYs gained at 1 month and at 1 year when compared with SLTs and CD at a lower cost. However, depending on the source of evidence considered, there were important variations in terms of both health benefits and costs. The highest effectiveness and the greatest savings achieved with TE when compared with SLTs were observed under the scenario based on the transfusion rates reported in the study by Shore-Lesserson *et al.* (1999), given that this study showed a statistically significant reduction in transfusion rates among the group of patients managed with TE. For those scenarios with smaller differences between TE and SLTs in terms of transfusion rates (Avidan *et al.*, 2004; Shore-Lesserson *et al.*, 1998), lower savings and smaller gains in life years and QALYs obtained were observed for the group managed with TE, even if TE was still the dominant strategy (see Appendix 11.10).

A multi-way sensitivity analysis was conducted which assumed the same number of units of blood were transfused for patients managed with TE, SLTs and CD (see Appendix 11.9). Although a reduction in the savings and in the health benefits (ie life years lived and QALYs gained) was observed, TE maintained its status as the dominant strategy.

The number of TE tests conducted per centre during a year had an impact on the ordering of the technologies. If 50 tests per centre were conducted annually, instead of 200 (as considered in the base-case analysis), TE would no longer be the dominant strategy, since it incurred an incremental cost of £78,511 per cohort of 1,000 patients. When TE was compared with SLTs under this scenario, the cost per transfusion averted was £1,213, the cost per QALY gained at 1 month was £568,247 and the cost per QALY gained at 1 year was £20,162. CD was dominated by both TE and SLTs. It can be observed from these results that, for TE to be cost effective in cardiac surgery, the time horizon adopted and the volume of procedures undertaken are both important factors to consider. As the marginal cost per procedure reduces as the number of procedures increases, adopting TE on a larger scale is likely to be a more cost-effective approach than using it on a small scale (eg in a single ward/specialty).

The results were also sensitive to variability in clinical practice regarding the use of TE which was tested by assuming that intra- and post-operative TE tests would be performed for all the patients, and these would be performed jointly with one set of SLTs. In this situation, TE was again no longer dominant. The incremental cost per transfusion averted with TE, compared with SLTs, was £2,828, and the incremental cost per QALY was £1,324,345 for a 1-month time horizon, and £53,354 for a time horizon of 1 year.

As expected, if the re-operation rate was lower among patients managed with TE tests, TE would continue being a dominant strategy since higher savings would be attained, compared with the base-case analysis by using TE; moreover, at 1 year TE would lead to a higher number of QALYs gained compared with the base-case analysis (see Appendix 11.10). Although it was felt that some uncertainty surrounded the reliability of the re-operation rates used to populate the model, no further sensitivity analyses were conducted on this parameter because even when considering similar re-operation rates for TE and SLTs (as for the base-case analysis), TE emerged as the dominant strategy. Therefore, whenever a lower transfusion rate was considered for TE compared with SLTs, it remains the dominant strategy.

Sensitivity analyses considering modifications on the duration of the leasing programme were not conducted since the least favourable leasing programme for TE (ie that lasting 3 years) was considered in the baseline analysis. Therefore, TE will remain the dominant strategy if a more favourable leasing programme (4 or 5 years in duration, which would reduce the cost per TE test conducted) is considered.

5.2.2 Liver transplantation

The results of the sensitivity analyses conducted on the liver transplantation model have been reported in Appendices 11.11 and 11.12.

When evidence on blood product usage among patients managed with TE was derived from the study by Kang *et al.*, (1985) without modifying the base-case values for patients managed with SLTs and CD, SLT became the dominant strategy compared with both TE and CD, since it led to a higher number of QALYs both at 1 month and at 1 year, at a lower cost (see Appendix 11.11).

Given the limited evidence from studies on liver transplantation identified by the systematic review, additional sensitivity analysis was conducted on the usage of blood products by considering the evidence reported by Kang *et al.*, (1985) on the use of blood products for both TE and SLTs, even if this evidence may be out of date and so not applicable to current clinical practice. In this situation, TE would still be the dominant strategy in the analysis, leading to a cost saving per cohort of 1,000 patients undergoing liver transplantation of £35,848 at 1 month and £36,100 at 1 year. The gain in QALYs was equal to 0.03 at 1 month and 3.13 at 1 year (see Appendix 11.11).

Unlike the findings of the cardiac surgery model, changes in the number of tests conducted annually per centre did not affect the cost-effectiveness results in the sense that TE was still the dominant strategy even if the hospital performed 50 TE tests per year only. Additionally, TE remained the dominant management strategy compared with SLTs and CD even in the scenario for which intra-operative and post-operative TE tests were to be performed in conjunction with one set of SLTs (see Appendix 11.11).

No further data on re-operation rates were identified apart from the source used in the base-case analysis (Kang, 1997). Consequently, the assumption that the use of TE led to higher rates of re-operation was tested, even if considered unlikely. For a rate of re-operation of 9%, TE would still be the dominant coagulation management strategy for liver transplantation. However, if this rate increased to 9.5%, TE would still incur lower costs compared with SLTs, although no QALY gains would be observed at 1 month. Conversely, the cohort of patients managed with SLTs would experience a very small gain in QALYs when compared with patients managed with TE (ie 0.0008 QALYs). However, the incremental cost per QALY gained with SLTs would be excessively high (see Appendix 11.12). The results at 1 year showed that TE became the dominant strategy when a longer time horizon was considered under this scenario.

5.3 Budget impact analysis

5.3.1 Cardiac surgery

The results of the budget impact analysis related to the use of TE in cardiac surgery 1 year after the intervention are reported in Table 5-5 and Table 5-6.

When the costs per patient according to the type of cost category were compared between management with TE and with SLTs, the incremental cost of the coagulation tests conducted was £57 for TE. However, relevant savings in most of the other cost categories led to an overall reduction in the management costs per patient for the use of TE of £141 after 1 year. The cost category showing the most significant impact on the overall cost/saving per patient related to the cost of the hospitalisations not related to complications, with a saving per patient managed with TE of £79, followed by the costs incurred in the administration of blood products, which would be £72 lower for a patient managed with TE when compared with SLTs (see Table 5-5).

When these savings per patient were translated to the overall patient population undergoing cardiac surgery within NHSScotland in 1 year (ie 2,447 patients), the total potential savings achieved with the use of TE were over £344,000, with the largest saving observed in the costs of the hospitalisations not related to complications or infections, and the costs of blood products administered (with savings of £193,910 and £177,183 respectively).

5.3.2 Liver transplantation

Table 5-7 and Table 5-8 present the estimated expenditure at 1 year derived from the budget impact analysis for patients undergoing liver transplantation annually within NHSScotland (ie 42 patients in total).

The costs of blood products transfused per patient are considerably higher for patients managed with SLTs (£2,273 higher per patient) because, according to the base-case analysis, the levels of usage of blood products is expected to be much lower for patients managed with TE.

The use of TE in liver transplantation is expected to lead to a saving equal to £2,274 per patient 1 year after the intervention, while the expected total savings for the whole cohort of patients undergoing liver transplantation are expected to be just less than £100,000.

Table 5-5 Total costs per patient (2005/2006 prices) at 1 month and at 1 year by cost category in cardiac surgery

Cost category	Cost for TE	Cost for SLTs	Incremental cost*
Costs of tests performed	£76.83	£20.00	£56.83
Pre-operative costs of transfusion	£11.55	£12.93	-£1.38
Peri-operative costs of transfusion	£3.33	£3.73	-£0.40
Blood products transfused	£91.40	£163.81	-£72.41
Costs of hospitalisation non-related to complications	£664.32	£743.56	-£79.24
Costs of hospitalisation related to complications/infections at 1 month	£211.37	£240.36	-£28.99
Costs of healthcare related to complications/infections between months 1 to 12	£125.06	£140.12	-£15.06
Total			
Costs at 1 month	£1,058.80	£1,184.40	-£125.60
Costs at 1 year	£1,183.86	£1,324.52	-£140.66

* Cost of TE minus cost of SLTs

Table 5-6 Expected total expenditure per year (2005/2006 prices) on using TE compared with SLTs in cardiac surgery

Cost category	Cost for TE	Cost for SLTs	Incremental cost*
Costs of tests performed	£187,998	£48,940	£139,058
Pre-operative costs of transfusion	£28,252	£31,651	-£3,399
Peri-operative costs of transfusion	£8,148	£9,129	-£981
Blood products transfused	£223,662	£400,845	-£177,183
Costs of hospitalisation not related to complications	£1,625,593	£1,819,503	-£193,910
Costs of hospitalisation related to complications/infections at 1 month	£517,227	£588,154	-£70,927
Costs of healthcare related to complications/infections between months 1 to 12	£306,032	£342,873	-£36,841
Total	£2,896,912	£3,241,095	-£344,183

* Cost of TE minus cost of SLTs

Table 5-7 Total costs per patient (2005/2006 prices) at 1 month and at 1 year by cost category in liver transplantation

Cost category	Cost for TE	Cost for SLTs	Incremental cost*
Costs of tests performed	£99.92	£20.00	£80
Pre-operative costs of transfusion	£21.47	£21.47	£0.00
Peri-operative costs of transfusion	£6.19	£6.19	£0.00
Blood products transfused	£1,760.71	£4,033.18	-£2,272.47
Costs of hospitalisation not related to complications	£1,765.72	£1,741.74	£23.98
Costs of hospitalisation related to complications/infections at 1 month	£672.78	£777.83	-£105.05
Costs of healthcare related to complications/infections between months 1 to 12	£232.88	£233.24	-£0.36
Total			
Costs at 1 month	£4,326.79	£6,600.41	-£2,273.62
Costs at 1 year	£4,559.68	£6,833.65	-£2,273.97

* Cost of TE minus cost of SLTs

Table 5-8 Expected total expenditure per year on using TE compared with SLTs in liver transplantation

Cost category	Cost for TE	Cost for SLTs	Incremental cost*
Costs of tests performed	£4,197	£840	£3,357
Pre-operative costs of transfusion	£902	£902	£0.00
Peri-operative costs of transfusion	£260	£260	£0.00
Blood products transfused	£73,950	£169,394	-£95,444
Costs of hospitalisation not related to complications	£74,160	£73,153	£1,00
Costs of hospitalisation related to complications/infections at 1 month	£28,257	£32,669	-£4,412
Costs of healthcare related to complications/infections between months 1 to 12	£9,781	£9,796	-£15
Total	£191,506	£287,013	-£95,507

* Cost of TE minus cost of SLTs

6 PATIENT ISSUES

The use of TE has obvious clinical advantages with regard to preventing inappropriate post-operative blood transfusions and surgical re-explorations compared with SLTs and clinical decision making. The main benefit is the timely provision of results that can change patient management and thereby reduce the inappropriate use of blood products. From the patients' perspective, other issues associated with its use are unlikely to differ greatly from those of any other diagnostic blood test. Consequently, this HTA has used qualitative data collected while investigating other blood tests to explore patient perceptions of the use of TE.

The following issues of potential concern to patients were explored:

- the safety, appropriateness and acceptability of a blood test
- interpretation and communication of results from diagnostic procedures and involvement of patients or carers in the management decisions
- implications of inappropriate blood transfusion.

It was assumed that the issue of informed consent was not key to this HTA given the comparator is SLTs where the same issue applies.

Results from focus groups conducted previously to inform the NICE Guideline on chronic heart failure (NICE, 2003) and the NHS QIS HTA on the organisation of troponin testing services in acute coronary syndromes (NHS QIS, 2004) were considered relevant to this HTA. Information available on the DIPEX website (www.dipex.org) regarding patient experiences of blood testing was also used.

6.1 Knowledge and decision making

With most new diagnostic tests like troponin testing that are administered in emergency settings, patients' knowledge about the test and its consequences is minimal. Moreover, because patients are preoccupied with the severity of the symptoms they would often not absorb information from the healthcare professional about the test that was going to be performed. Almost 100% of the patients who took part in the troponin focus groups denied having any prior knowledge of the diagnostic test, although could recall some explanation about the test being given to them.

"I never heard of it and I've never had any feedback. No, no, not at all……., well I never, I didn't even know we had it, was it a blood test?"

"They did say, I think they said if I remember right, they were testing for an enzyme or something like that, but they didn't tell if the heart muscles had been damaged. They didn't name, they didn't tell me what the name was, they went in too deeply, but they told us why they were taking the blood……blood cells, things like that." (NHS QIS, 2004)

The decision to undergo the blood test was made usually by the patient either because of the urgency of the symptoms which prompted a visit to a healthcare professional, or being prevailed upon by friends or family, although a formal consent was rarely considered necessary. Most patients have no recollection of actually making a decision to seek the test – they remember making the decision to seek healthcare; from that point on their management including appropriate diagnostic tests, are left in the hands of healthcare professionals and their carers.

"I was at my aunt's on Sunday and I came home as I had pains in my chest……I phoned the ambulance and they said what's the problem – well I have been up half the night with pains in my chest and my doctor advised me to phone for an ambulance."

"It was at my work when I started taking chest pain…sitting thinking it will go, it will go, and my boss came in and said, you look terrible, go and phone your doctor up and see if you can go and see him…."

For TE, the situation is somewhat simpler in that the alternative is an SLT that requires the same level of patient intrusion. Moreover, the patient is acutely ill at the time of the test and likely to be subject to several more intrusive interventions.

6.2 The procedure

Patients describe a variety of experiences with blood testing, but rarely object to a simple, relatively non-invasive blood test. Some focus group participants were obviously well informed; others less so, thinking of a blood test as just one of many performed routinely when admitted to hospital. As one patient describes it:

"Well the, they have this little container with a needle in it and, which is sheathed and then they screw in a different coloured like small test tube with a coloured cap and this determines what you're having the blood tested for, I think there's four or five different colours. And so they can actually do different tests with the same needle and they just take that test tube out and put another one in and it's quite, they say a little scratch, it's a little bit more than that but nevertheless I don't find it painful. But I've been having that many over the past four years that my skin where they go in has got quite hard and so we change arms every so often and see if we can give the other one a bit of a rest. "

"You get blood tests done everyday at 8.00 in the morning. A phlebotomist comes around and takes your blood. I know what those tests are for, sometimes I think they do about six little phials and they are looking to see if there is an imbalance of things in your body." (NHS QIS, 2004)

6.3 Receiving results

In the interview transcripts there were several issues that arose regarding the results of the diagnostic test.

Communication of the results – both between patients and healthcare staff as well as between healthcare providers themselves – was often identified as problematic.

There was a general feeling that even if the results of the test foretold a dreaded diagnosis, patients would rather know about it than live in suspense. The sympathetic communication of results was the chief responsibility of the healthcare provider.

"He just said, well you're off home! And that was it. That was me obviously getting my results back. I would have liked to have known what they found…….an explanation of what they saw. But the doctor doesn't tell me."

On several occasions, delay in communications between healthcare professionals, typically between the hospital and GP practice, led to delays in getting the appropriate treatment and much anxiety and stress.

"But I was disappointed when I went to my doctor. I left it for about a fortnight and she had nothing. She had nothing from the hospital and I thought mmm. No she had nothing. So she said you'll need to come back again."

Many patients were thankful that a correct diagnosis had been made, even one with a poor prognosis.

"It's incredibly important to receive a proper diagnosis. If you've got a car, you don't just accept that there is something wrong with it – it's the petrol gauge, it's the big end etc – why would you do it with your body?" (NICE, 2003)

Many patients expressed concern about the accuracy of diagnostic blood tests. However, many felt that an honest appraisal of the situation and a discussion of the pros and cons with healthcare personnel was really helpful.

Again, this is less of an issue for TE because the main benefit of the technology is expediting results to the clinicians to allow them to act immediately.

6.4 Alternative tests

In most focus groups, alternative tests were not discussed. However, in the troponin group, some patients reported a preference for an ECG and treadmill test, rather than troponin testing, in the diagnosis of acute coronary syndromes as these tests were less invasive. However, the alternative for TE is another blood test, so there is unlikely to be any preference for this.

6.5 Avoidance of blood transfusion

A previous HTA on the use of erythropoietin for preventing blood transfusions explored patients' views on the avoidance of inappropriate blood transfusion and elicited a positive response. It is anticipated that this would also apply to the use of TE (Davies *et al.*, 2006).

6.6 Conclusions

As TE is a relatively new diagnostic procedure and not yet widely used, patient knowledge and experience of the test is likely to be limited. Moreover, as it only involves the collection of venous blood, patients are unlikely to recall having had the test as a distinct experience from all the other tests.

As with other blood tests, patients are likely to have little awareness about the safety and appropriateness of TE. In an emergency situation, there was practically no recall about any information received about blood tests. Where less invasive tests were available, there was a slight preference for these.

Irrespective of test or diagnosis, there was almost unanimous agreement among patients regarding the lack of communication from and between healthcare providers. This is of particular relevance to TE as the validity and efficacy of the test rely entirely on the interpretation of the results by health professionals at the point of care.

The importance of keeping patients informed about the purpose and possible results of a test was highlighted. In emergency situations, the cognition and recall of the patient is suboptimal.

The potential for any intervention to reduce blood transfusion is an over-riding issue of importance to patient groups.

7 ORGANISATIONAL ISSUES

7.1 Introduction

This section describes the current use of TE in Scotland, as determined from the questionnaire survey and data from other sources. Organisational issues such as legal considerations, staffing including resources and training, information and management technology and quality assurance/audit are also discussed.

7.2 Current use of TE in NHSScotland

A survey was undertaken in November 2006 to examine the usage of TE for clinical purposes within NHSScotland. Five Scottish hospitals use TE and all five were surveyed: Western Infirmary, Glasgow; Glasgow Royal Infirmary; Golden Jubilee National Hospital, Clydebank; Royal Infirmary of Edinburgh; and Aberdeen Royal Infirmary. These centres may also use TE for research but no information on analysers used solely for research was requested.

Respondents completed one questionnaire for ROTEM® analysers and another for TEG® analysers. A 100% response rate was achieved, which comprised six responses, one each from four of the hospitals, and two from the fifth which uses both types of analyser. The topics covered were: equipment and maintenance; funding of equipment; clinical application; safety and training; and information on tests.

At the time of the survey there were six two-channel TEG® analysers and six four-channel ROTEM® analysers in clinical use in Scotland. The equipment was located in or beside the operating theatres or in ICU. Most of the analysers were static but two hospitals had mobile analysers which can be moved to different areas. One hospital did not have a dedicated area to keep the equipment required to run the machine. The others kept supplies in ICU or the theatre suite. None of the analysers appeared to be laboratory-based.

All six ROTEM® analysers in Scotland are maintained by the company. In one hospital with TEG® analysers, maintenance is carried out by company and the medical physics department. In the others, hospital staff, including operating department personnel, are responsible for maintenance of the TEG® analysers.

The units were purchased between 2001 and 2006. Actual purchase costs were not known by most respondents. Moreover a cost comparison is not straightforward because the different systems may have a different number of channels and different functionality (S Friedman, Medicell Ltd. Personal communication, 4 June 2007).

The six TEG® units were purchased using money allocated to the relevant department by the hospital. Two ROTEM® units were donated to hospitals by the SNBTS, and the other four ROTEM® units were purchased by one hospital with funding from the National Services Division. Ongoing costs include reagents, consumables and servicing. Most respondents did not know the actual sums of money involved, however one respondent noted that the service contract costs £1,500 per year, and reagents approximately £600 per year. Ongoing costs are funded through hospital departmental budgets, apart from in one hospital with four ROTEM® units, which also receives support from the National Services Division.

Five of the six responses indicated that the technology is being used in cardiac surgery, but also in liver surgery, ICU, vascular surgery, trauma, obstetrics and emergency surgery. The number of tests being performed each week varies between 2 to greater than 70. Two respondents with TEG® units indicated that they recorded the results either exclusively on the unit or on the unit as well as in the patient's case notes. The other respondents record the results, either in handwriting or as a print out, in the patient's case notes. The recording of results is not linked to a laboratory reporting system in any of the hospitals surveyed.

Formal responsibility for the safe use of the equipment is not designated in all hospitals. Where it is, this mainly lies with consultant anaesthetists, or in one hospital also with a Specialist Practitioner in Operating Theatre Blood Conservation. Only one hospital has a formal operating policy formulated to comply with health and safety requirements for near-patient testing. Tests were being performed by a variety of staff: consultant anaesthetists; trainee anaesthetists; operating department personnel; trainee surgical staff; specialist practitioners; perfusionists; and ICU nurses. Formal training is provided by the manufacturer in four of the hospitals. Training is provided by hospital staff in five of the hospitals but only in one is this as a formal training programme.

Two responses indicated that there were no quality control procedures in operation. Two have some sort of quality control scheme either monitored by operating department personnel or perfusionists, but are experiencing problems. The final two responses specified that a manufacturer's quality control procedure is followed. One also indicated participation in a pilot National External Quality Assessment Scheme (NEQAS) external quality control study.

For routine laboratory tests, samples are transported to the lab in some hospitals by vacuum tube and in others by porters. Average times from taking a sample from the patient to receipt of results (turnaround time) ranged from 20 to 60 minutes for a full blood count and 30 to 120 minutes for coagulation tests. In contrast, the average turnaround time for TE was either 15 minutes, or immediately after taking the test.

One respondent stated that in clinical practice, the TE results would always influence patient management. For the majority of other respondents, the results would often influence management, or in one case, sometimes influence management.

Respondents were generally in favour of TE usage within their hospitals, or were at least open minded about

continuing to work with it. The stated benefits to clinical practice were:

- reduced blood products usage resulting in reduced costs and avoidance of risks associated with transfusion
- time saved in commencing treatment
- greater intelligence available in making treatment decisions
- rapid diagnosis of coagulation problems in the operating theatre which permits rapid appropriate treatment of patients who are bleeding.

One respondent felt that it should be compulsory for all cardiac surgery patients.

Operational problems had been an issue for some; in one hospital the problem was the lack of any professional group taking ownership of the system, and in another it was the failure to get adequate maintenance and quality control procedures in place initially.

7.3 Medical devices

In 2002, the Medical Devices Agency (MDA) (now Medicines and Healthcare products Regulatory Agency or MHRA) published two documents which are relevant to TE. The first is on the use of *in vitro* diagnostic medical devices to ensure effective use of *in vitro* testing (MDA, 2002b).

The second MDA document is "Management and use of IVD point of care test devices" (MDA, 2002a). This document is to provide advice and guidance on the management and use of point-of-care testing (POCT) *in vitro* diagnostics devices (IVDs). It identifies a number of key issues including:

- the importance of identifying a clinical need before a decision is made to introduce POCT
- clinical governance issues relating to the setting up and management of POCT
- the need for local hospital pathology laboratory involvement in all aspects of a POCT service
- the need for training, updating and monitoring of all staff involved in the POCT service
- quality issues including:
  - accreditation by an external certification body
  - the need for an appropriate quality control procedure
  - membership of an External Quality Assessment (EQA) scheme
- the importance of health and safety
- the need for standard operating procedures (SOPs) and for regular reviews and updates when necessary.

Finally, the MHRA also published guidance for managing medical devices in November 2006 (MHRA, 2006). The aim of this MHRA document is "to outline a systematic approach to the purchasing, deployment, maintenance, repair and disposal of medical devices".

The document highlights legislation which may apply to organisations using medical devices, and has a very helpful list of references and further information. Its contents include systems for medical device management, audit and monitoring, the acquisition and delivery of new equipment, reporting adverse incidents, training, maintenance and repair, and decontamination.

All users of TE devices should follow the recommendations of these MHRA documents.

7.4 Training

The survey highlights the differences in training in NHSScotland among the small number of users of TE. Training requires dedicated resources, including the time of trainers, and these should not be underestimated. If such TE analysers are used, there needs to be agreement on the specific staff who require to be trained to perform and interpret tests for example biomedical scientists, ICU nurses, perfusionists, anaesthetists, surgeons (depending on local circumstances). There also need to be sufficient trained staff to undertake TE when required. These staff must be appropriately trained in accordance with a policy which includes (MHRA, 2006):

- generic device management skills
- specific training for particular devices
- induction of new staff
- inclusion of agency and locum staff and contractors
- periodic review/retraining as required
- continuing professional development (CPD)
- planning training before a new medical device is introduced
- training for those involved in maintenance and repair services.

Issues of relevance covered in the MHRA document relate to storage of reagents, expiry dates and interpretation of results in addition to recording of these data.

7.5 Information management technology

There should be clearly documented processes for recording of TE results and any consequences arising from this, with the ultimate aim of interfacing clinical and laboratory information management systems. This will ensure that other clinicians are aware of the use of TE and also that its use can be audited more easily.

7.6 Quality assurance and clinical governance

Quality assurance (QA) and clinical governance issues for the use of TE analysers should take account of the following. First, the Scottish Government's action plan for healthcare science "Safe, Accurate and Effective" in November 2007 (Scottish Government, 2007) recommends a greater presence for healthcare scientists in POCT and QA. Second, the use of TE analysers should be seen in the broader context of blood transfusion practice. Third, there is a need for specific guidelines and protocols governing the use of TE analysers.

Getting agreement in using Scotland-wide level protocols may not be straightforward but is necessary. There has

been work at a European level to develop specific guidelines for ROTEM® use in cardiac surgery (Görlinger *et al.*, 2007a) and use in non-cardiac surgery and trauma (Görlinger *et al.*, 2007b). These guidelines are published at http://www.essener-runde.de/publikationen.html and could be adapted for Scotland.

It is also essential that users comply with manufacturers' guidance including an adequate maintenance programme for analysers. In addition, QA and clinical governance actions should use the three MHRA documents which highlight specific issues relevant to TE analysers including:

- the UK NEQAS started a second pilot study of near testing for ROTEM® and TEG® users in October 2006. Following this, an EQA scheme will be developed. ROTEM® and TEG® users should participate in the UK NEQAS scheme
- internal quality control processes must be in place
- issues of space for computers, printers, fridges and other equipment need to be addressed
- policies and protocols should be in place regarding whether laboratory tests will continue to be used, and if so how will the use of different ranges and interpretation of results be dealt with
- tests should only be performed by trained staff who are able to analyse and interpret the results
- auditing the use of TE is good practice and an important aspect of clinical governance within organisations since it may inform the development and its use in clinical practice.

Coordination and implementation of this in the hospital should be through a multidisciplinary POCT committee, with input from the laboratory service, which has oversight of all organisational aspects of TE.

7.7 Central purchasing and cost of blood components

The consultation identified that users might find a central procurement contract for analysers and consumables helpful. This would avoid sites having to maintain their own lists of distributors and each undertaking assessments of the advantages and disadvantages of different analysers.

Currently, SNBTS do not charge hospitals for blood components.

Publishing the costs of the more commonly used components such as RBCs, plasma and platelets would enable users to take decisions on the clinical and cost effectiveness of TE in their own settings. In the absence of such information rational purchasing decisions become very difficult. An alternative would be central funding of initiates to reduce the use of blood products.

7.8 Discussion and conclusions

The questionnaire has identified considerable variation in operational practice and in the number of tests undertaken each year. This highlights the need for consistent policy and practices in NHSScotland. The benefits from such tests identified above could be optimised by the actions below. The following should be undertaken by organisations and health staff who use TE in NHSScotland:

- relevant guidance from the MHRA and manufacturers' advice must be followed including an adequate maintenance programme
- there should be rigorously defined and managed clinical protocols covering all organisational aspects of TE testing, with one person who is clearly responsible for overseeing compliance
- all sites that undertake TE testing should join the UK NEQAS scheme for TE testing, once established, or a similar external quality control system
- quality control and quality assurance procedures must be implemented and form an integral part of the board's clinical governance process.

In addition users would welcome:

- consideration by National Procurement of a central procurement contract for analysers, training and consumables and
- SNBTS publishing the costs of commonly used blood components to enable users to take decisions on the clinical and cost effectiveness of TE in their own settings.

Section 6.2 identifies that TE is not the dominant strategy for managing patients undergoing cardiac surgery if the number of TE tests are 50 or fewer. Some centres in Scotland reported relatively low numbers of total TE tests per week. Evidence suggests that it may not be cost effective to use TE on a small scale, eg in a single ward or speciality.

8 PRINCIPAL FINDINGS, LIMITATIONS AND RECOMMENDATIONS

Cost-effectiveness and cost-utility analyses were conducted, using economic modelling, to assess the cost effectiveness of TE compared with SLTs and CD used alone, to diagnose the cause of bleeding or identify patients at risk of excessive blood loss and manage consequent transfusion. The results are of relevance for NHSScotland, for which blood products and availability of critical care beds are scarce.

8.1 Cardiac surgery

The base-case results of the cardiac surgery model showed that TE was the dominant strategy when compared with both SLTs and CD in the management of transfusion since it resulted in higher health benefits (in terms of transfusions avoided, deaths averted, life years lived and QALYs gained at 1 month and at 1 year) at a lower cost. Therefore, savings may be achieved if centres currently using SLTs for the management of their cardiac patients switched to using TE instead. This, besides the improvement in health outcomes observed, would mean that using TE could contribute to a cost-effective use of resources.

The most sensitive parameters in the assessment of cardiac surgery were the number of tests conducted annually per centre and the number of TE tests required during the cardiac intervention. The lower the number of TE tests conducted by a centre in a year, the higher the cost per TE test would be, which would have a relevant impact on the cost effectiveness of TE. If only 50 tests are conducted annually per centre, a long time horizon has to be considered in the analysis for TE to be cost effective in cardiac surgery, since the benefits of this transfusion management strategy are achieved over time.

However, if intra-operative and post-operative TE tests are to be performed jointly with SLTs (as recommended by the manufacturer), the cost effectiveness of managing transfusions by means of TE is questionable. The incremental cost per QALY of £53,354, for a time horizon of 1 year, is outside of the conventional range of acceptable cost-effectiveness values (for example, £20,000–£30,000 per QALY as used by NICE in England and Wales) (NICE, 2004).

8.2 Liver transplantation

In liver transplantation, TE was found to be a cost-effective strategy according to the baseline results. It is worth highlighting that the use of TE in liver transplantation is oriented to the management of coagulation and control of excessive bleeding, rather than to the identification of patients at risk of bleeding and reduction of inappropriate transfusions (as was the case for its use in cardiac surgery). This meant that no health benefits in terms of transfusions avoided were considered in the analysis, and the benefit of using TE for the management of patients was related to the reduction of complications and infections due to lower requirements of blood products per patient and in the increase in the number of QALYs gained at 1 year. However, no relevant improvements were observed in terms of number of deaths and life years lived at 1 month or at 1 year. Although the cost savings associated with the use of TE during liver transplantation seem to be considerable, the improvement in health outcomes did not appear to be as relevant as in the case of cardiac surgery. The benefits of TE may be better observed over a longer time horizon (eg 1 year), similar to the findings of the cardiac surgery model.

The cost-effectiveness results of using TE in liver transplantation were not sensitive to the number of annual tests performed by the centre, although they were sensitive to the number of units of blood transfused. This may be due to the fact that during liver transplantation the need for blood transfusion is high, and therefore the unit cost per TE test performed becomes a less relevant issue for the cost effectiveness of this intervention.

However, there is considerable uncertainty surrounding the number of units of blood transfused in the non-TE arms of the model. In Scotland, all liver transplant operations are conducted with TE available and thus the SNBTS's data on actual use cannot be applied.

8.3 Budget impact analysis

The results of the budget impact analysis showed that both for patients undergoing cardiac surgery and those undergoing liver transplantation, savings were expected if TE was adopted in place of SLTs. Among patients undergoing cardiac surgery, the highest savings are expected to be in terms of the costs of hospitalisation not related to complications and the costs of blood products transfused. In liver transplantation the management of patients by means of TE, instead of SLTs, would lead to savings per patient mainly in terms of the blood products transfused.

Given that the number of patients that undergo cardiac surgery in a year in Scotland is estimated to be higher than 2,000 while around only 42 patients are expected to undergo liver transplantation in a year, the total potential savings resulting from the adoption of TE are much higher when applied to cardiac surgery (even if the savings per patient of using TE instead of SLTs are much higher in liver transplantation, ie £2,274 in liver transplantation versus £141 in cardiac surgery).

8.4 Limitations

The economic modelling exercises attempted to synthesise the available clinical and cost evidence on the use of TE in two interventions: cardiac surgery and liver transplantation. Given the lack of RCTs providing information on all the clinical outcomes considered in the model, for some of the parameters evidence was derived from non-randomised sources, from the formulation of assumptions or from expert opinion. In some cases, assumptions had to be formulated which were not based on the medical literature. Although every effort was made to ensure the transparency and consistency of the model,

there is always uncertainty regarding the appropriateness of some of these estimates to reflect the real clinical benefits and costs related to the interventions analysed. In order to overcome this, sensitivity analyses were conducted around the most uncertain estimates to test the robustness of the results obtained in the baseline analyses.

The comparators in the model assumed that TE tests were independent of clinical judgement. In a clinical setting decision makers will use all available information to take judgements on the most likely cause of bleeding and appropriate clinical management. Thus the model has over-simplified clinical practice. The recommendations assume that the results from the clinical studies of TE generalise to the more complex clinical setting.

The model also assumes that the results from individual clinical trials of TE compared to standard practice can be generalised to the Scottish setting. Coakley *et al.* (2006) suggests that transfusion practice could differ according to the analyser used and the transfusion algorithm. This study implies that it may have been more appropriate to model the results of studies for each analyser separately. Given the quantity and quality of the evidence this was not judged to be desirable.

Some relevant transfusion-related complications were not included in the models (ie air embolism (Statistics and Audit Directorate, 2006) and increase of cancer recurrence (Blumberg *et al.*, 2000)) which may have biased the results, although given that the approach adopted was conservative, the results would have been biased against TE.

Transfusion-related risks were modelled as if they were independent from each other. However, in reality a combination of the risks may be found (Redmond *et al.*, 2005) which was not considered in the HTA. Evidence that could accurately inform the consideration of assumptions regarding the combination of different transfusion-related risks was lacking.

There is no general agreement in the medical literature regarding the usefulness of TE and other coagulation monitoring tests to reduce bleeding among patients undergoing liver transplantation. Some authors argue that coagulation monitoring appears to be beneficial, even though there is no evidence derived from RCTs (Kang, 1997; Kang *et al.*, 1985), whilst others argue that coagulation monitoring is not relevant for transfusion management (Reyle-Hahn & Rossaint, 1997).

The model developed for liver transplantation considered the same structure and clinical outcomes as that developed for cardiac surgery. Data related to the use of TE in liver transplantation were scarce and, moreover, one of the most relevant available studies (Kang *et al.*, 1985) had been published before the period considered for the systematic review (ie 1996–2006). Studies published before 1996 had been excluded from the systematic review given that medical practice could be assumed to have changed during the last decade. Therefore, the data collected from this study (Kang *et al.*, 1985) to estimate some of the parameters may not have been representative of the current practice regarding the use of TE compared with other alternative SLTs or clinical judgement now.

Additionally, some of the parameters used to populate the liver transplantation model were based on data used for the cardiac model. For example, it was assumed that the same type of complications and infections associated with transfusion would be observed in the case of liver transplantation, and that the probabilities of some of these transfusion-related complications and infections would be the same as for cardiac surgery (although some of these probabilities were estimated according to the number of units of blood transfused, which were specific to each medical intervention). These assumptions introduce uncertainty into the results obtained for liver transplantation and therefore caution should be taken when interpreting the results of this model.

The perspective adopted was that of NHSScotland. Therefore, indirect costs related to the lost productivity due to morbidity and mortality were excluded from the analysis, which was a conservative approach. Since evidence on TE shows in general lower transfusion rates and lower requirement of blood products transfused (as considered in the baseline analysis) the base-case results may have been biased against the management strategy using TE. However, in the case of cardiac surgery patients are in general over 60 years old, therefore the exclusion of indirect costs related to productivity losses seems not to be relevant and is unlikely to have affected the findings. Any attempts to identify indirect costs would also have been complicated by the fact that the transfusions considered were a direct result of surgery for an underlying pathology (eg coronary heart disease or liver failure). As such, disentangling the indirect costs attributable to the transfusion and to the underlying pathology would be complex. Given the severity of the surgical indications considered, it is also unlikely that the transfusions *per se* had much of an incremental impact on indirect costs.

The cost of the printer required for the printing of the TE results before these are interpreted was not included in the analysis due to a lack of information on this aspect. These costs may be negligible in comparison with the total costs of performing the TE test and therefore, it is believed that their exclusion has not affected the final cost-effectiveness results.

The consideration of a life time horizon would have been appropriate for this analysis, especially taking into account that, under specific circumstances, TE was found to be cost effective only when a long-term time horizon (ie 1 year) was considered. However, evidence related to the long-term costs and prognosis for some of the complications considered in the analysis (such as the long-term effects of transfusions on the life expectancy) were scarce and, furthermore, seemed to be limited to a follow up of 5 years (Engoren *et al.*, 2002). The adoption of the 1-month and 1-year time horizons are also likely to be directly applicable to healthcare decision making as budgets are usually allocated on this basis.

No economic evaluations on the use of TE were identified through a previously conducted systematic review (Aguiar-Ibáñez *et al*., 2006). Therefore, it was not possible to compare the results of this study with those of other studies conducted in the same topic.

8.5 Conclusion

TE, currently used in five Scottish hospitals, appears to be a cost-effective intervention. It has the potential to reduce the need for inappropriate transfusions and can decrease blood product requirements; this is likely to be welcomed by patients.

Overall, TE appears to have a positive impact on patients' health by reducing the number of deaths, complications and infections, and increasing the number of life years and QALYs.

A further consequence observed was the reduction in the associated costs, related to the decrease in the number of transfusions, in the average usage of blood products and in the healthcare resources needed to deal with complications and infections. The results of the budget impact analysis showed that both for patients undergoing cardiac surgery and liver transplantation, savings are expected if TE, instead of SLTs, is used for their management.

8.6 Recommendations

1. The use of TE is recommended in cardiac surgery and liver transplant surgery. TE should be used in intra-operative or post-operative bleeding where the cause of bleeding is uncertain, to ascertain if bleeding is induced by the surgery itself or a haemostasis abnormality and to determine the nature of a haemostasis abnormality and the appropriate treatment.

2. There is no published robust, controlled clinical data to support the use of TE in other major surgery associated with a high blood loss. However, some sites in Scotland have used TE in other surgical settings including vascular surgery, obstetrics and trauma. These sites have demonstrated the technique is safe and efficacious. This is not unexpected; while there are differences in the surgical procedures the main causes of bleeding and subsequent actions are common across all such surgery. This observational evidence supports using TE in such surgical areas.

3. Research data from controlled studies would be beneficial to strengthen the evidence base in surgery other than cardiac and liver but it is recognised that such studies may be difficult to conduct because of the emergency nature of many of the interventions and the small patient numbers.

4. Where TE is used, it will reduce the number of laboratory tests requested during and immediately after surgery. The results from TE, together with clinical judgement and any results from other laboratory tests should inform transfusion decisions in accordance with validated transfusion algorithms.

5. TE should not be routinely used pre-operatively before elective surgery to risk stratify patients likely to bleed excessively.

6. Audit should be undertaken to assess the impact of TE on blood loss, use of blood products and the rate of re-exploratory surgery. Other benefits such as shorter stay in an intensive care unit (ICU) and improved patient outcomes may be more difficult to monitor.

7. All users of TE must adhere to guidance by the Medicines and Healthcare products Regulatory Agency (MHRA) and take account of the Scottish Government's action plan for healthcare science. In particular:

   - formal documented training for staff performing the tests with assessment of competency and review at appropriate intervals should be in place
   - specific training should take place on the use and interpretation of TE for staff requesting such tests to ensure consistency in application
   - rigorously defined and managed clinical protocols should be in place covering all organisational aspects of TE testing, with one person who is clearly responsible for overseeing compliance. These protocols should be linked to blood transfusion protocols so that the information from TE informs patient management decisions
   - all sites that undertake TE testing should join the UK National External Quality Assessment Scheme (NEQAS) for TE testing once established, or a similar external quality control system
   - quality control and quality assurance procedures must be implemented and form an integral part of NHS boards' clinical governance process
   - the hospital haematology laboratory should be involved in discussions on the TE service
   - there must be robust arrangements in place for regular preventative maintenance of analysers and for prompt repair should faults develop
   - there should be clearly documented processes for recording of TE results and any consequences arising from them, with the ultimate aim of interfacing the clinical and laboratory information management systems. This will ensure that other clinicians are aware of the use of TE and also that use of TE can be audited more easily.

8. The Scottish National Blood Transfusion Service should make available to health boards the costs of commonly used blood components to enable users to take decisions on the clinical and cost effectiveness of TE in their own settings.

9. National Procurement should consider offering a central procurement contract for analysers and consumables.

8.7 Further research

Robust evidence on new potential uses of TE would be beneficial. Such indications include pre-operative use to identify patients at risk of bleeding and intra- and post-operative use for other interventions associated with high blood loss such as obstetrics, orthopaedic, trauma and off-pump coronary artery bypass. Other potential uses include monitoring haemostatic disorders eg haemophiliac patients. The challenges in conducting RCTs in some of these indications are acknowledged and researchers may want to consider alternative study designs, such as the use of registries of long-term observational studies.

Many of the existing studies were conducted before the widespread use of newer anti-platelet and anticoagulant drugs. Research on the use of TE should consider its use in patients receiving such drugs. Furthermore, future research should report clearly how TE was incorporated into the management of blood loss and what other blood management strategies were used alongside TE to ensure that any benefits can be attributed to TE.

It is also important that future research studies have a clearly defined primary outcome measure determined *a priori*. The use of well-defined outcome measures that are likely to have both clinical and economic implications would be beneficial, such as a reduction in the number of transfusion units required (as opposed to blood loss) or the number of transfusion-related adverse events. The impact on the volume of laboratory tests would also be useful to help determine the economic value of TE.

Research into optimising algorithms such that surgical units with more liberal use of blood components converge to the usage rates observed in units with more conservative blood component usage would also be informative.

9 ACKNOWLEDGEMENTS

NHS Quality Improvement Scotland is grateful to all experts and peer reviewers (Appendix 11.1) who have given generously of their time to contribute constructively to the appraisal of the evidence and the writing of this report. We hope this has also achieved an important goal of sharing knowledge and best practice across Scotland.

Particular thanks is given to CRD and York Health Economics Consortium for undertaking the systematic review of the clinical and cost effectiveness of TE, developing the economic model and drafting the report.

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APPENDICES

11 APPENDICES

11.1 Experts and peer reviewers

EXPERTS

Dr Lynne Anderson	Consultant Anaesthetist	Western Infirmary, Glasgow
Mrs Pat Bryson	Public Partner	Glasgow
Mr Tony Collins	Public Partner	Bannffshire
Mr John Duncan	Consultant Surgeon	Raigmore Hospital, Inverness
Dr Charlotte Gilhooly	Consultant Anaesthetist	Glasgow Royal Infirmary
Dr Annielle Hung	Haematologist	Wishaw General Hospital
Mr Robert Jeffery	Cardiothoracic Surgeon	Aberdeen Royal Infirmary
Mr Alan Kirk	Cardiothoracic Surgeon	Western Infirmary, Glasgow
Dr Marian MacKinnon	Specialist Registrar	Western General Hospital, Edinburgh
Dr Alastair Nimmo	Consultant Anaesthetist	Royal Infirmary of Edinburgh
Dr Keith Oldroyd	Consultant Cardiologist	Western Infirmary, Glasgow
Ms Marina Shannon	Practice Development Specialist for Critical Care & Theatres	Wishaw General Hospital
Dr Richard Souter	Consultant in Haematology & Transfusion Medicine	Western Infirmary, Glasgow

PEER REVIEWERS

Dr Ravi Gill	Consultant Cardiac Anaesthetist	Southampton General Hospital
Dr Robert Kong	Consultant Cardiac Anaesthetist	Royal Sussex County Hospital
Dr David Royston	Consultant Anaesthetist	Harefield Hospital, London
Dr Paul Trueman	Director	York Health Economics Consortium

11.2 Strategy for literature searches

MEDLINE and In-Process MEDLINE (Ovid Gateway). 1996–2006/May week 5. 14th June 2006.

The MEDLINE and In-Process MEDLINE databases were searched on the 14th June 2006. 488 records were retrieved in MEDLINE and 28 were retrieved in In-Process MEDLINE.

1. Thrombelastography/
2. (thromboelastogra$ or thrombelastogra$ or thrombo elastogra$ or thromboelastom$ or thrombo elastom$).ti,ab.
3. (ROTEM or ROTEG).ti,ab.
4. TEG.ti,ab.
5. or/1-4
6. Animals/
7. Humans/
8. 6 not (6 and 7)
9. 5 not 8

EMBASE (Ovid Gateway). 1996–2006/week 23. 14th June 2006.

The EMBASE database was searched on the 14th June 2006 and retrieved 582 records.

1. Thromboelastography/
2. (thromboelastogra$ or thrombelastogra$ or thrombo elastogra$ or thromboelastom$ or thrombo elastom$).ti,ab.
3. (ROTEM or ROTEG).ti,ab.
4. TEG.ti,ab.
5. or/1-4
6. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
7. exp animal/
8. Nonhuman/
9. or/6-8
10. exp human/
11. exp human experiment/
12. 10 or 11
13. 9 not (9 and 12)
14. 5 not 13

CINAHL (Ovid Gateway). 1996–2006/Jun week 1. 14th June 2006.

The CINAHL database was searched on the 14th June 2006 and retrieved 53 records.

1. THROMBELASTOGRAPHY/
2. (thromboelastogra$ or thrombelastogra$ or thrombo elastogra$ or thromboelastom$ or thrombo elastom$).ti,ab.
3. (ROTEM or ROTEG).ti,ab.
4. TEG.ti,ab.
5. or/1-4
6. limit 5 to yr="1996 - 2006"

Cochrane Central Register of Controlled Trials (CENTRAL). Cochrane Library Issue 2. 1996–2006. 14th June 2006.

The CENTRAL database was searched on the 14th June 2006. 81 records were retrieved.

Thrombelastography/MeSH
thromboelastogra* or thrombelastogra* or thromboelastom*
ROTEG or ROTEM
TEG
#1 or #2 or #3 or #4

BIOSIS (EDINA). 1996–2006/6th Jun. 14th June 2006.

The BIOSIS database was searched on the 14th June 2006 and retrieved 556 records.

al:(thromboelastogra* or thrombelastogra* or thrombo w1 elastogra* or thromboelastom*)
al:(ROTEG or ROTEM)
al:TEG
#1 or #2 or #3
al:(rat or rats or mouse or mice or murine or hamster or hamsters or animal or animals or dogs or dog or pig or pigs or cats or bovine or cow or sheep or ovine or porcine or monkey)
tn: animals
#5 or #6
al:human
tn: humans
#8 or #9
#7 not (#7 and #10)
#4 not #11

Science Citation Index (SCI) (Web of Science). 1996–2006/10th Jun. 14th June 2006.

The SCI database was searched on the 14th June 2006 and retrieved 682 records.

TS=(thromboelastogra* or thrombelastogra* or thrombo elastogra* or thromboelastom* or thrombo elastom*)
TS=(ROTEM or ROTEG)
TS=(TEG)
#1 or #2 or #3
TS=(rat or rats or mouse or mice or murine or hamster or hamsters or animal or animals or dogs or dog or pig or pigs or cats or bovine or cow or sheep or ovine or porcine or monkey)
#4 not #5

NHS EED (CRD online database). 1996– 2006/May. 14th June 2006.

The NHS EED database was searched on the 14th June 2006 for economic evaluations and retrieved 1 record.

s thromboelastogra$ or thrombelastogra$ or thrombo(w)elastogra$ or thromboelastom$
s ROTEM or ROTEG
s TEG
s s1 or s2 or s3
s 1996:2006
s s4 and s5

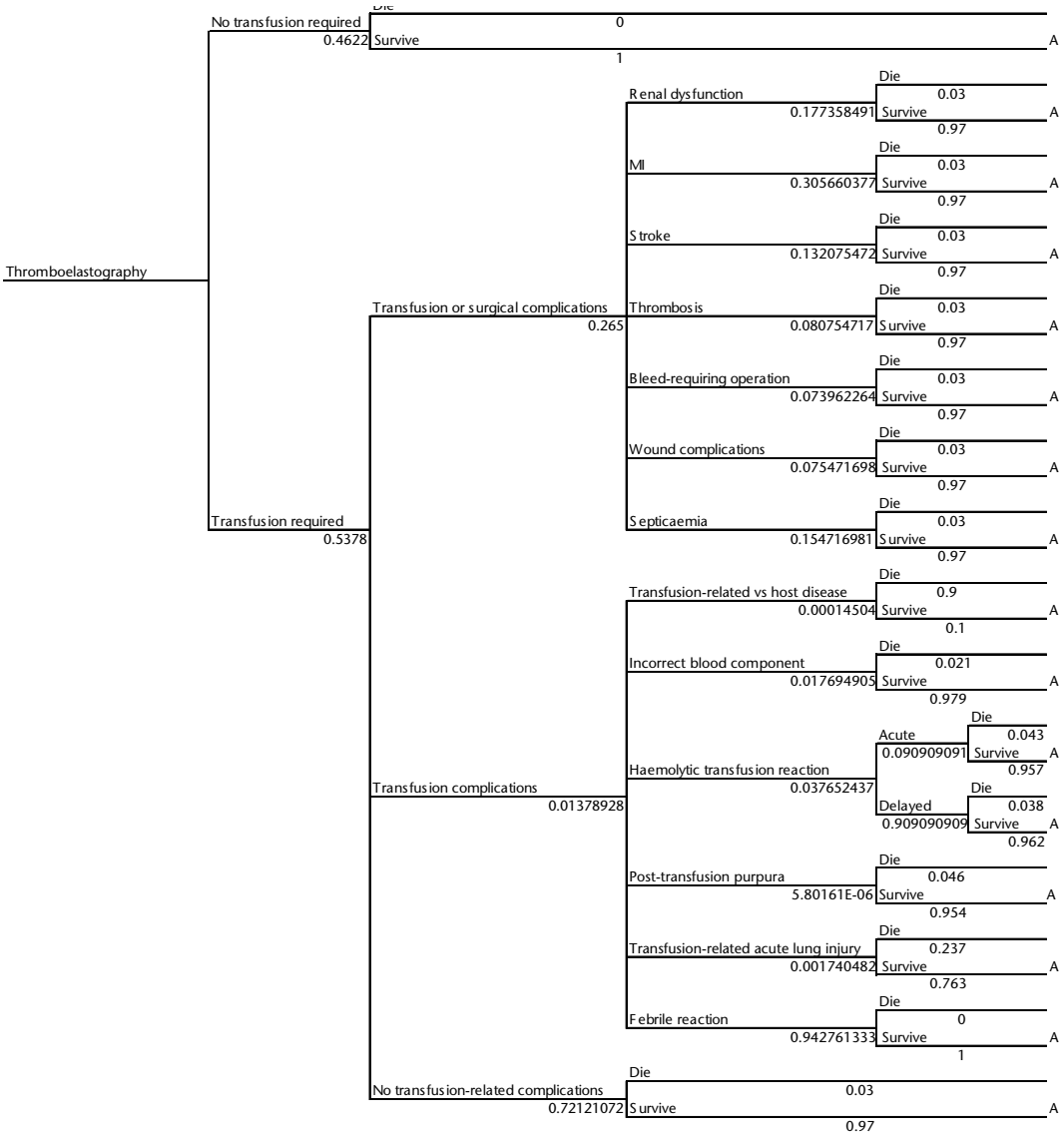
Health Economic Evaluation Database (HEED). CD-ROM, June 2006. 14th June 2006.

The HEED database was searched on the 14th June 2006 for economic evaluations and retrieved 1 record.

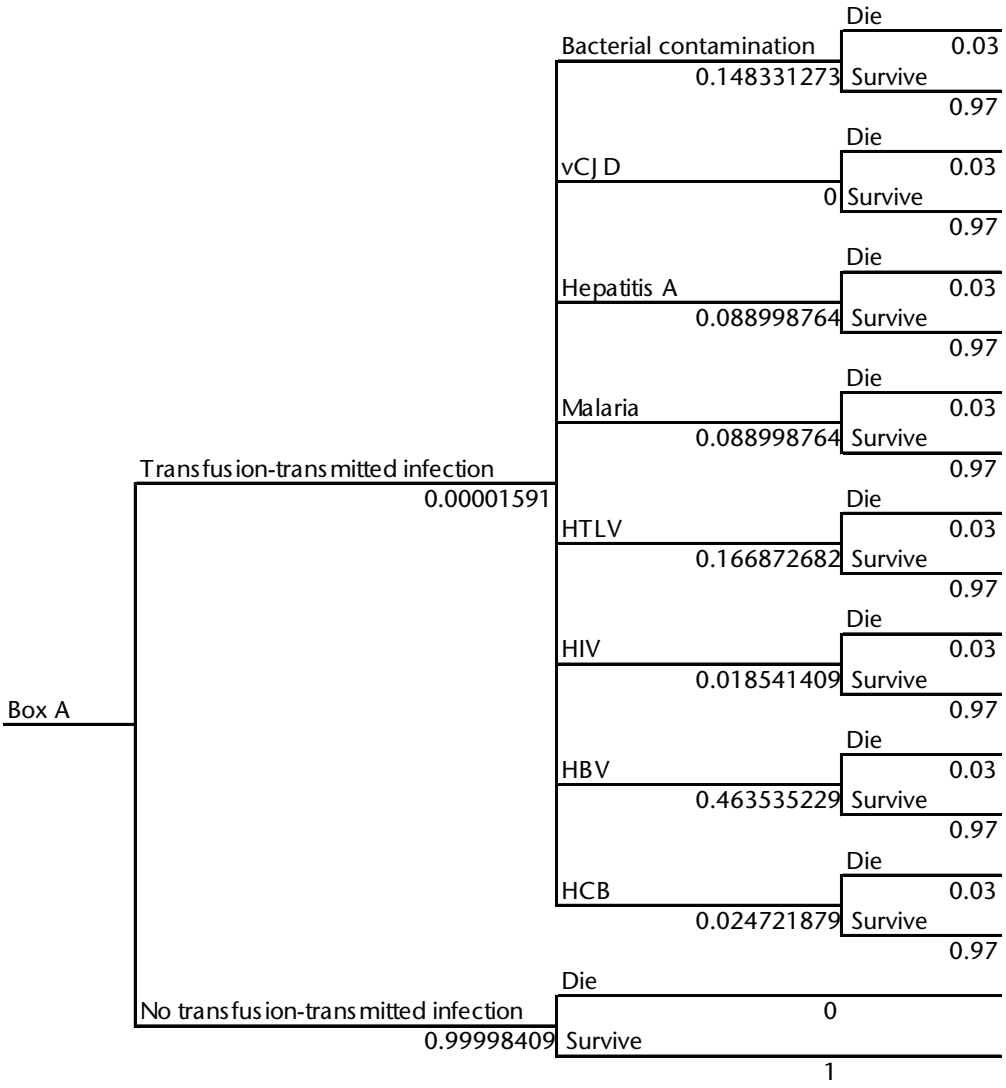
AX=(thromboelastography or thrombelastography or thrombo elastography or thromboelastogram or thromboelastograms or thrombelastogram or thrombelastograms or thromboelastometer or thromboelastometry)

AX=(ROTEM or ROTEG)
AX=(TEG)
CS=1 or 2 or 3
JD>=1996
CS=4 and 5

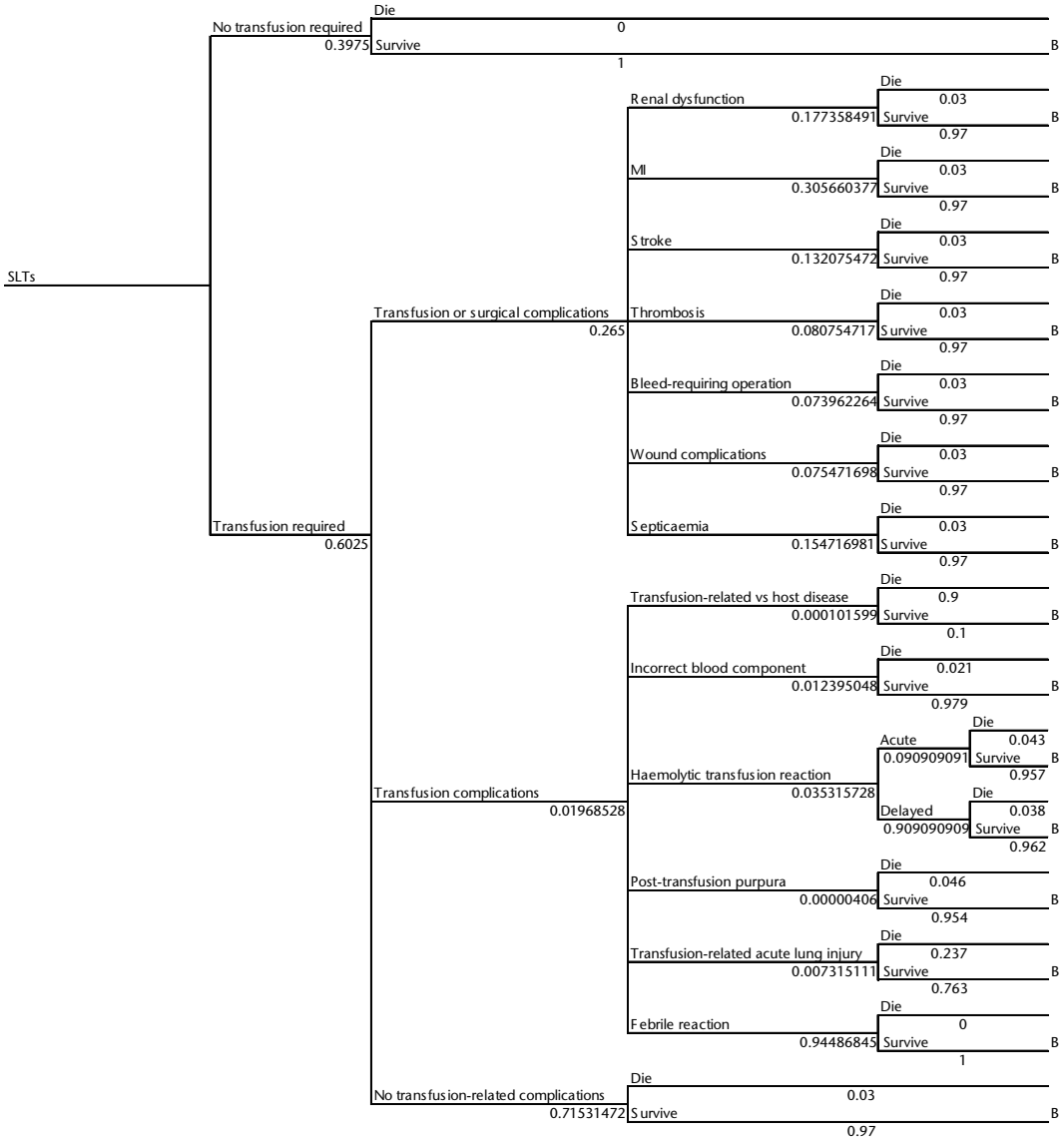
11.3 TE model (I): Transfusion rates, complications related to transfusion or surgery, and transfusion-related complications



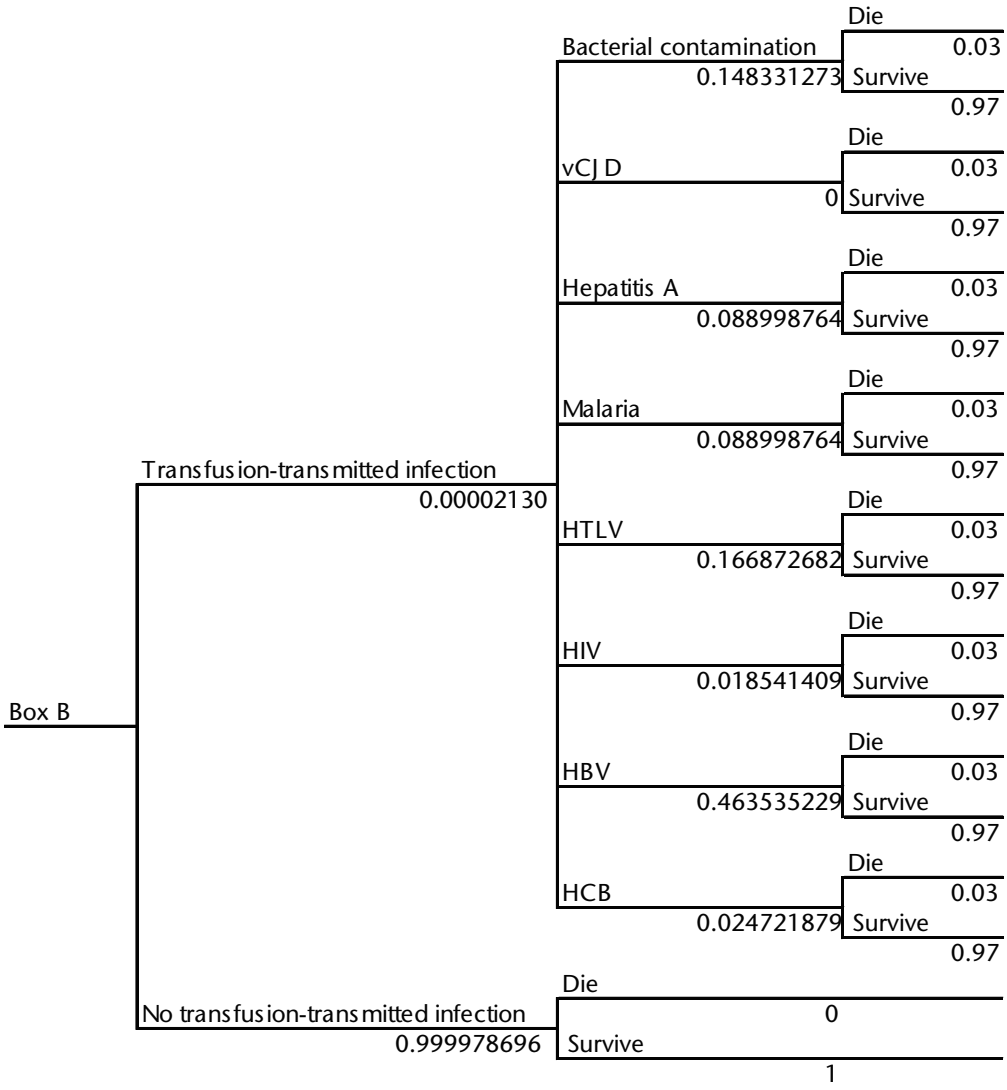
11.4 Transfusion-transmitted infections in the TE model (II): Box A



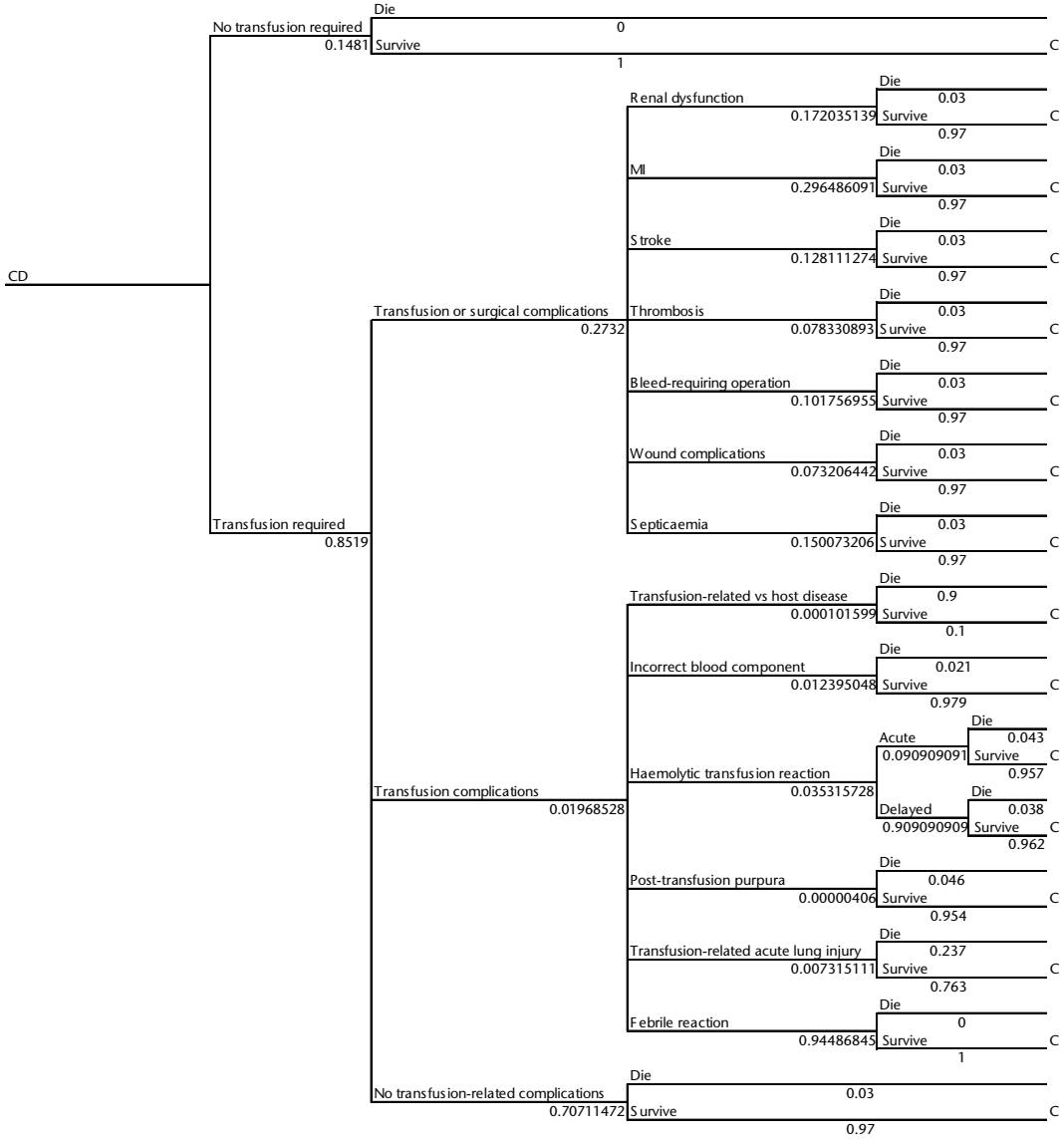
11.5 SLTs model (I): Transfusion rates, complications related to transfusion or surgery, and transfusion-related complications



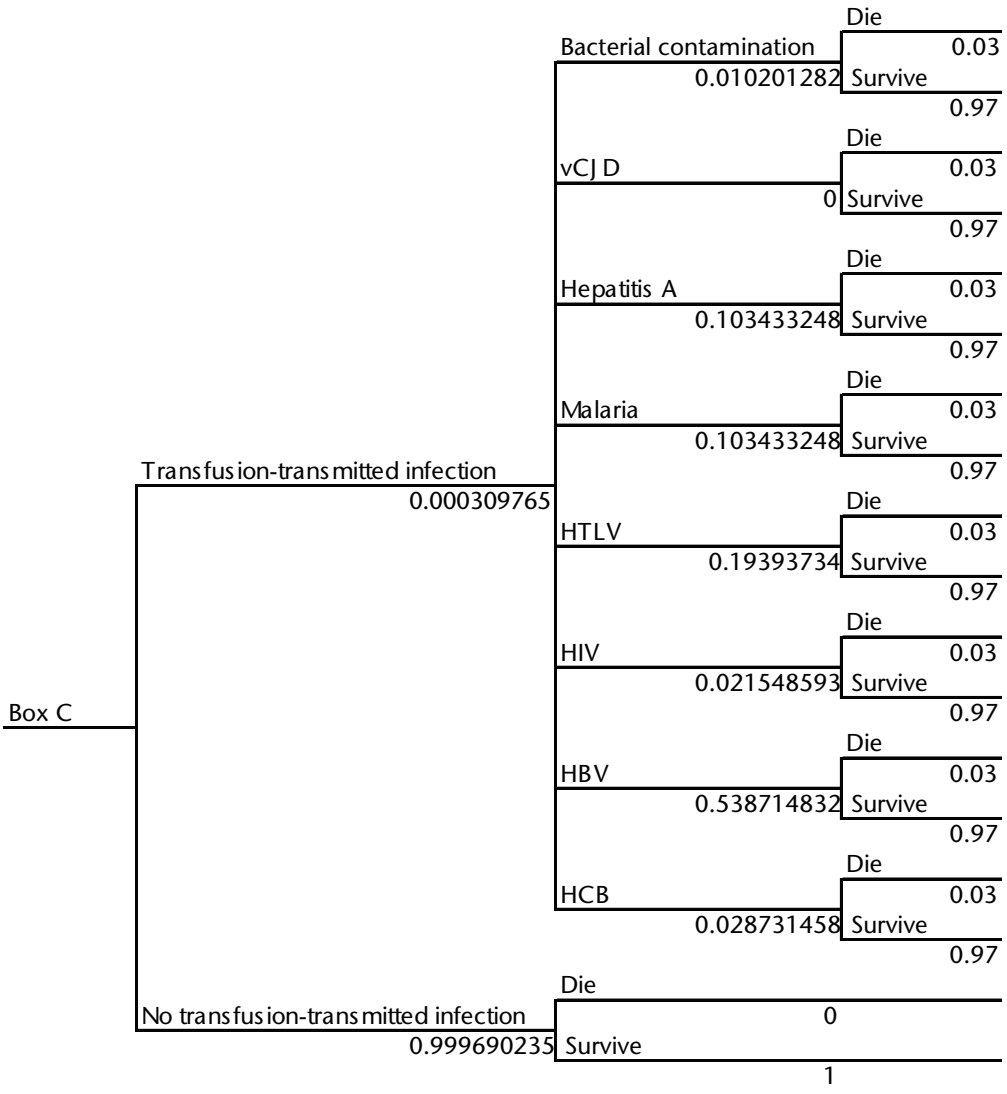
11.6 Transfusion-transmitted infections in the SLTs model (II): Box B



11.7 CD model (I): Transfusion rates, complications related to transfusion or surgery, and transfusion-related complications



11.8 Transfusion-transmitted infections in the CD model (II): Box C



11.9 Results of the sensitivity analyses after modification of the probabilities of transfusion and the number of units of blood products transfused during cardiac surgery

Variable	Base	Parameter	Comparison	Incremental cost at 1 month	Transfusions averted	Cost per transfusion averted	Incremental QALY at 1 month	Cost per QALY gained at 1 month	Incremental cost at 1 year	Incremental QALY at 1 year	Cost per QALY gained
Probability of transfusion											
Evidence from study by Avidan *et al.* (2004)											
TE	0.54	0.67	Comparing TE to SLTs	-£45,785	19.60	TE dominant	0.04	TE dominant	-£50,354	1.02	TE dominant
SLTs	0.60	0.69	Comparing SLTs to CD	-£315,720	165.60	SLTs dominant	0.36	SLTs dominant	-£355,054	8.18	SLTs dominant
CD	0.85	0.85	Comparing TE to CD	-£361,504	185.20	TE dominant	0.40	TE dominant	-£405,408	9.20	TE dominant
Evidence from study by Shore-Lesserson *et al.* (1999). (Probability for CD was assumed).											
TE	0.54	0.42	Comparing TE to SLTs	-£343,610	181.10	TE dominant	0.40	TE dominant	-£385,734	8.66	TE dominant
SLTs	0.60	0.60	Comparing SLTs to CD	-£193,489	103.80	SLTs dominant	0.23	SLTs dominant	-£218,305	5.19	SLTs dominant
CD	0.85	0.70	Comparing TE to CD	-£537,099	284.90	TE dominant	0.62	TE dominant	-£604,039	13.84	TE dominant
Evidence from study by Shore-Lesserson *et al.* (1998). (Probability for CD was assumed).											
TE	0.54	0.20	Comparing TE to SLTs	-£24,303	22.20	TE dominant	0.05	TE dominant	-£29,469	1.08	TE dominant
SLTs	0.60	0.22	Comparing SLTs to CD	-£135,879	77.80	SLTs dominant	0.17	SLTs dominant	-£154,261	3.80	SLTs dominant
CD	0.85	0.30	Comparing TE to CD	-£160,182	100.00	TE dominant	0.22	TE dominant	-£183,731	4.89	TE dominant
Blood products usage (assuming same number of units of blood transfused for TE and SLTs)											
RBCs											
TE	1.18	1.58									
SLTs	1.58	1.58									
CD	1.58	1.58									
FFP											
TE	0.12	0.72	Comparing TE to SLTs	-£66,755	64.70	TE dominant	0.15	TE dominant	-£81,802	3.03	TE dominant
SLTs	0.72	0.72	Comparing SLTs to CD	-£477,672	249.40	SLTs dominant	0.55	SLTs dominant	-£536,495	12.16	SLTs dominant
CD	0.72	0.72	Comparing TE to CD	-£544,426	314.10	TE dominant	0.70	TE dominant	-£618,297	15.18	TE dominant
Platelets											
TE	0.11	0.28									
SLTs	0.28	0.28									
CD	0.28	0.28									

11.10 Results of the sensitivity analyses after modification of the number of TE tests; the annual number of TE tests performed per centre and the re-operation rates during cardiac surgery

Variable	Base	Parameter	Comparison	Incremental cost at 1 month	Transfusions averted	Cost per transfusion averted	Incremental QALY at 1 month	Cost per QALY gained at 1 month	Incremental cost at 1 year	Incremental QALY at 1 year	Cost per QALY gained
Annual number of TE tests performed per centre											
Number of tests performed per year	200	50	Comparing TE to SLTs	£78,511	64.70	£1,213	0.14	£568,247	£63,455	3.15	£20,162
			Comparing SLTs to CD	-£477,672	249.40	SLTs dominant	0.55	SLTs dominant	-£536,495	12.16	SLTs dominant
			Comparing TE to CD	-£399,161	314.10	TE dominant	0.69	TE dominant	-£473,040	15.30	TE dominant
Number of TE tests performed during the intervention, assuming 50 tests would be annually conducted per centre											
Patients not requiring transfusion	1	2	Comparing TE to SLTs	£182,976	64.70	£2,828	0.14	£1,324,345	£167,920	3.15	£53,354
Patients requiring transfusion	2	2	Comparing SLTs to CD	-£477,672	249.40	SLTs dominant	0.55	SLTs dominant	-£536,495	12.16	SLTs dominant
SLTs conducted in non-transfused TE group	0	1	Comparing TE to CD	-£294,696	314.10	TE dominant	0.69	TE dominant	-£368,575	15.30	TE dominant
SLTs conducted in transfused TE group	0	1									
Re-operation rates (evidence for TE and SLTs from Spiess *et al.* (2004). (Re-operation rates for CD were assumed to be the same as for SLTs)											
TE	0.0196	0.0150	Comparing TE to SLTs	-£181,705	64.70	TE dominant	0.14	TE dominant	-£196,760	4.26	TE dominant
SLTs	0.0196	0.0570	Comparing SLTs to CD	-£482,939	249.40	SLTs dominant	0.55	SLTs dominant	-£541,763	12.26	SLTs dominant
CD	0.0278	0.0570	Comparing TE to CD	-£664,644	314.10	TE dominant	0.69	TE dominant	-£738,523	16.52	TE dominant

11.11 Results of the sensitivity analyses after modification of the number of units of blood products transfused, the number of TE tests performed and the annual number of TE tests performed per centre during liver transplantation

Variable	Base	Parameter	Comparison	Incremental cost at 1 month	Incremental QALY at 1 month	Cost per QALY gained at 1 month	Incremental cost at 1 year	Incremental QALY at 1 year	Cost per QALY gained
Blood products usage									
TE (evidence from Kang *et al.* (1985)									
RBCs	9.35	17.00	Comparing TE to SLTs	£2,952,206	-0.02	SLT dominant	£2,952,315	-4.89	SLT dominant
FFP	6.25	18.30	Comparing SLTs to CD	-£3,007,232	0.06	SLT dominant	-£3,007,594	8.17	SLT dominant
Platelets	2.10	20.80	Comparing TE to CD	-£55,027	0.03	TE dominant	-£55,280	3.28	TE dominant
TE and SLTs as reported in evidence from Kang *et al.* (1985)									
TE			Comparing TE to SLTs	-£35,848	0.03	TE dominant	-£36,100	3.13	TE dominant
RBCs	9.35	17.00							
FFP	6.25	18.30							
Platelets	2.10	20.80							
SLTs									
TE	17.90	26.70							
SLTs	10.70	26.70							
CD	7.50	14.10							
Annual number of TE tests performed per centre									
Number of tests performed per year	200	50	Comparing TE to SLTs	-£2,008,862	0.02	TE dominant	-£2,009,213	5.01	TE dominant
			Comparing SLTs to CD	-£3,007,232	0.06	SLT dominant	-£3,007,594	8.17	SLT dominant
			Comparing TE to CD	-£5,016,094	0.08	TE dominant	-£5,016,807	13.19	TE dominant
Number of TE tests performed during the intervention, assuming 50 tests would be annually conducted per centre									
Patients not requiring transfusion	1	2	Comparing TE to SLTs	-£1,988,910	0.02	TE dominant	-£1,989,262	5.01	TE dominant
Patients requiring transfusion	2	2	Comparing SLTs to CD	-£3,007,232	0.06	SLT dominant	-£3,007,594	8.17	SLT dominant
SLTs conducted in non-transfused TE group	0	1	Comparing TE to CD	-£4,996,143	0.08	TE dominant	-£496,856	13.19	TE dominant
SLTs conducted in transfused TE group	0	1							

11.12 Results of the sensitivity analyses after modification of the re-operation rates during liver transplantation

Variable	Base	Parameter	Comparison	Incremental cost at 1 month	Incremental QALY at 1 month	Cost per QALY gained at 1 month	Incremental cost at 1 year	Incremental QALY at 1 year	Cost per QALY gained
Re-operation rates (evidence for TE and SLTs from Spiess *et al.* (2004) (re-operation rates for CD were assumed to be the same as for SLTs)									
TE	0.0813	0.0900	Comparing TE to SLTs	-£2,254,599	0.01	TE dominant	-£2,254,951	4.39	TE dominant
SLTs	0.0813	0.0813	Comparing SLTs to CD	-£3,007,232	0.06	SLT dominant	-£3,007,594	8.17	SLT dominant
CD	0.0813	0.0813	Comparing TE to CD	-£5,261,832	0.06	TE dominant	-£5,262,545	12.56	TE dominant
TE	0.0813	0.0950	Comparing TE to SLTs	-£2,243,556	-0.0008	£2,889,029,504	-£2,243,908	4.03	TE dominant
SLTs	0.0813	0.0813	Comparing SLTs to CD	-£3,007,232	0.06	SLT dominant	-£3,007,594	8.17	SLT dominant
CD	0.0813	0.0813	Comparing TE to CD	-£5,250,789	0.05	TE dominant	-£5,251,502	12.20	TE dominant

GLOSSARY

12 GLOSSARY

allogenic
Blood from the same species but not the same individual so that when the blood is introduced into a body it stimulates the production of an antibody.

appraised
Evaluation of evidence from scientific studies against objective criteria.

APTT
Activated partial thromboplastin time

audit
Systematic review of the procedures used for diagnosis, care, treatment, rehabilitation, examining how associated resources are used and investigating the effect care has on the outcome and quality of life for the patient.

bias
A systematic error or deviation in results or inferences. Bias can arise from systematic differences in the groups that are compared (selected bias), the care that is provided, or exposure to other factors apart from the intervention of interest (performance bias), withdrawals or exclusions of people entered into the study (attrition bias) or how outcomes are assessed (detection bias).
Bias does not necessarily carry an imputation of prejudice, such as the investigator's desire for particular results.

CABG
Coronary artery bypass graft

CD
Clinical discretion

clinical effectiveness
The extent to which specific clinical interventions, when deployed, do what they are intended to do, ie maintain and improve health, securing the greatest possible health gain from the available resources.

clinical governance
Ensures that patients receive the highest quality of care possible, putting each patient at the centre of his or her care. This is achieved by making certain that those providing services work in an environment that supports them and places the safety and quality of care at the top of the organisation's agenda.

Management of clinical risk at an organisational level is an important aspect of clinical governance.
Clinical risk management recognises that risk can arise at many points in a patient's journey, and that aspects of how organisations are managed can systematically influence the degree of risk.

coagulation
The process of blood clot formation.

control
Standard against which comparison is made in a clinical trial or an experiment.

cost
Cost of activities, both direct and indirect, involving any negative impact, including money, time, labour, disruption, goodwill, political and intangible loss.

cost effectiveness
A form of economic analysis which compares two interventions in terms of both their costs and their effect on patients, to ascertain whether the additional cost of the more expensive intervention gives rise to sufficient additional benefits to warrant the additional cost.

CPD
Continuing professional development

CRD
Centre for Reviews and Dissemination

diagnosis
Identification of an illness or health problem by means of its signs and symptoms. This involves ruling out other illnesses and possible causes for the symptoms.

discharge
A discharge marks the end of an episode of care.
Types of discharge include inpatient discharge, day-case discharge, day-patient discharge, outpatient discharge and discharge from the care of allied health professionals.

economic evaluation
The comparative analysis of alternative courses of action, estimating the likely health effects (ie clinical effectiveness) and corresponding resource implications.

economic model
This simplifies the patient pathway to a level that describes the essential choices and consequences within treatment options. Linking patient outcomes to resource usage enable different courses of action to be compared from an economic viewpoint. Modelling may also be used to extrapolate from existing data into the longer term.

EQA
External quality assessment

false positive
A test result which indicates an abnormality, when one does not exist.

FFP
Fresh frozen plasma

FIB
Fibrinogen level

guidelines
Systematically developed statements which help in deciding how to treat particular conditions.

HAV
Hepatitis A virus

HBV
Hepatitis B virus

HCV
Hepatitis C virus

health technology assessment
A multi-disciplinary field of policy analysis which studies the medical, social, ethical and economic implications of development, diffusion and use of health technology.

HIV
Human immunodeficiency virus

HTA
Health technology assessment

HTLV
Human T-cell lymphotropic virus

IBC
Incorrect blood component

ICU
Intensive care unit

Information Services Division
The Information Services Division is part of NHS National Services Scotland. Health service activity, manpower and finance data are collected, validated, interpreted and disseminated by ISD. These data are received from NHS boards and general practices.
Website: www.isdscotland.org

intra-operative
During surgery

INR
International normalised ratio

ISD
Information Services Division

LMWH
Low molecular weight heparin

MDA
Medical Devices Agency

mean
The average value, calculated by adding all the observations and dividing by the number of observations.

median
The value halfway through an ordered data set of times, below and above which there lies an equal number of values.

MHRA
Medicines and Healthcare products Regulatory Agency

MI
Myocardial infarction

National Procurement
This division of NHS National Services Scotland (NHS NSS) was launched in 2005 to fully enable the various health boards of NHSScotland to 'buy together'.

NEQAS
National External Quality Assessment Scheme

NHS
National Health Service

NHS board
There are 22 NHS boards of two types: 14 territorial boards responsible for healthcare in their areas and eight special health boards which offer supporting services nationally.

NHS QIS
NHS Quality Improvement Scotland

NHS Quality Improvement Scotland
NHS QIS has been established (January 2003) to lead in improving the quality of care and treatment delivered by NHSScotland. To do this it sets standards and monitors performance, and provides NHSScotland with advice, guidance and support on effective clinical practice and service improvements. Website: nhshealthquality.org

NHSScotland
The National Health Service in Scotland

opportunity cost
The opportunity cost of selecting a particular health technology is the amount of alternative health technologies that could have been obtained had that selection not been made.

outcome
The end result of care and treatment and/or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care and treatment, and/or rehabilitation.

PACT
Platelet activated clotting test

PC
Platelet count

peri-operative
Around the time of surgery

policy
The highest level statement of intent and objectives within an organisation. A policy can also be a required process or procedure within an organisation.

probability
The chance or likelihood of a specific event or outcome measured by the ratio of specific events or outcomes to the total number of possible events or outcomes. Probability may vary in value from 0 (no chance) to 1 (certain). It is sometimes expressed as a percentage.

protocol
Set of operational instructions to regulate activity. Protocols may be national, or agreed locally to take into account local requirements.

PT
Prothrombin time

PTCA
Percutaneous transluminal coronary angioplasty

PTP
Post-transfusion purpura

QA
Quality assurance

QALY
Quality-adjusted life year

quality assurance
Improving performance and preventing problems through planned and systematic activities including documentation, training and review.

randomised controlled trial
Where there is already a treatment for a condition, a new treatment may be compared to the existing treatment and this is called a controlled trial. The treatments are randomly allocated and this prevents further bias.

RBC
Red blood cell

RCT
Randomised controlled trial

Scottish Government
The devolved government for Scotland, with responsibilities including health policy and the administration of NHSScotland. Until September 2007, the devolved government was named the Scottish Executive.

SLTs
Standard laboratory tests

SOP
Standard operating procedure

systematic review
Synthesis of original studies such as controlled trials and RCTs.

TE
Thromboelastography/thromboelastometry

thromboelastography
A method of testing the efficiency of coagulation in the blood.

thromboelastometry
See thromboelastography.

TRALI
Transfusion-related acute lung injury

transfusion
The introduction of whole blood or blood component directly into the blood stream.

UK
United Kingdom

vCJD
Variant Creutzfeldt-Jakob disease