NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems) to assist with detecting, managing and monitoring of haemostasis

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. It includes a brief description of the topic, a description of the analytical structure and model, a discussion of the analytical difficulties, and a brief summary of the results. It is not a complete summary of the diagnostics assessment report, and it is assumed that the reader is familiar with that document. This overview contains sections from the original scope and the diagnostics assessment report, as well as referring to specific sections of these documents.

1. Background

1.1 Introduction

The ROTEM system (TEM International) was selected by the Medical Technologies Advisory Committee (MTAC) for the Diagnostics Assessment Programme to develop recommendations on its use in the NHS. Two other point-of-care analysers, Thromoboelastography (TEG) system (Haemonetics) and the Sonoclot Coagulation and Platelet Function Analyser (Sienco, Inc.) were identified during the scoping phase and included in the assessment as alternative technologies.

The purpose of this assessment is to evaluate the clinical and cost effectiveness of using the ROTEM, TEG and Sonoclot systems to assist with

detecting, managing and monitoring of haemostasis. Provisional recommendations on the use of these technologies in the NHS will be formulated by the Diagnostics Advisory Committee at the Committee meeting on 11 March 2014.

1.2 The condition

Viscoelastometric point-of-care testing is intended for use during surgery to identify the probable cause of intraoperative bleeding by discriminating between poor platelet function and poor clotting. The results allow the clinician to select the correct therapy. It is also used in the immediate post-operative period to help control haemostasis and help guide the clinician to determine whether bleeding is a result of a coagulopathy or a surgical bleed.

Viscoelastometric (VE) tests are mainly used in adult patients undergoing major surgeries who are at risk of bleeding. Bleeding is a potential complication of any surgical procedure, and the risk is proportional to the size and complexity of the surgery. High blood loss is associated with certain types of surgery such as cardiac and liver surgeries, as well as major trauma (including burns), certain orthopaedic procedures (such as hip replacement) and obstetric surgery. Major blood loss occurs frequently and is associated with a marked rise in in-hospital mortality.

Haemostasis

Haemostasis is a term used to describe the process of blood clotting and the subsequent dissolution of the clot, following repair of the injured tissue. During haemostasis four steps occur in a rapid sequence:

- Vascular constriction is the first response as the blood vessels constrict to allow less blood to be lost.

- In the second step, platelets become activated by thrombin and aggregate at the site of injury, forming a temporary, loose platelet plug. The protein fibrinogen is primarily responsible for stimulating platelet clumping. Platelets clump by binding to collagen, which becomes exposed following

rupture of the endothelial lining of vessels, and cover the break in the vessel wall.

- The third step is called coagulation or blood clotting. Coagulation reinforces the platelet plug with fibrin threads that act as a “molecular glue”.

- Finally, the clot must be dissolved in order for normal blood flow to resume following tissue repair. The dissolution of the clot occurs through the action of plasmin.

Platelets are a large factor in the haemostatic process. They allow for the creation of the “platelet plug” that forms almost directly after a blood vessel has been ruptured. Within seconds of a blood vessel’s epithelial wall being disrupted platelets begin to adhere to the sub-endothelium surface. It takes approximately sixty seconds until the first fibrin strands begin to intersperse among the wound. After several minutes the platelet plug is completely formed by fibrin.

During surgical procedures the normal clot management process by the body can become severely disrupted leading to a condition known as acquired hyperfibrinolysis. The fibrinolysis system is responsible for removing blood clots. Hyperfibrinolysis occurs when fibrinolytic activity becomes greater than fibrin formation leading to breakdown of the clot. This results in pronounced coagulopathy and sometimes fatal bleeding.

Hyperfibrinolysis, characterised by severe bleeding in the patient, cannot currently be easily detected by laboratory testing because the classical coagulation tests such as PT (prothrombin time) and aPTT (activated partial thromboplastin time) are not very sensitive for hyperfibrinolysis. Failure to recognise and to treat can lead to uncontrollable bleeding. Acquired HF is much more common and has been observed in a variety of clinical scenarios including liver transplantation, postpartum haemorrhage, cardiac surgery, vascular surgery and severe trauma.

Abnormalities, either acquired or of a genetic origin, in any of the haemostasis steps can lead to bleeding (during and after surgery) or thrombosis.

1.3 Patient issues and preferences

Some of the benefits of viscoelastometric testing mentioned during scoping are:

- Decreased time in critical care unit which may be particularly important for women who have had a post-partum haemorrhage as they may be able to be reunited with their baby more quickly.

- Shortening of hospitalisation time, meaning that patients can return home sooner and start to return to normal daily activities. This may also be a benefit to carers and families as they won't have to visit hospital for as long.

- Reduction in complications from blood transfusion such as infection, immune system response and problems matching blood types.

1.4 Diagnostic and care pathways

Diagnosis

Pre-surgery

Most patients who undergo elective surgery have normal coagulation but if the patient's history includes any haemostatic disorders then blood coagulation and fibrinogen tests are completed. In the absence of a history of abnormal bleeding, UK guidelines[i] do not recommend pre-operative coagulation testing. However, some clinicians choose to order coagulation testing (which includes Prothrombin Time (PT), Partial Thromboplastin Time (PTT), Platelet Count and International Normalised Ratio (INR) tests). These tests look at specific areas of the clotting cascade and help determine how quickly the blood clots when carrying out some surgical procedures, such as cardiac surgery. During these procedures it is important that the blood does not clot as quickly as normal and medications may be given to slow the clotting time. Conversely, if the patient's blood does not clot quickly enough, medications may be given to speed up the clotting process. Coagulation testing involves a blood sample

being taken from the patient and sent to the nearest laboratory. The quickest estimated time for the results to be returned is 45 minutes. According to expert opinion, this method is currently used in most NHS hospitals.

During and after surgery

In the absence of VE testing, clinical judgement, in addition to the standard coagulation testing (which includes routine laboratory-based coagulation tests PT, PTT, Platelet Count, INR and Fibrinogen) is most commonly used during surgery to assess coagulation status of patients who are experiencing high blood loss. The same tests are used after surgery to monitor coagulation status.

Using laboratory-based tests during and immediately after surgery has been questioned as this can cause delays of about 45 to 60 minutes from blood sampling to obtaining results[ii]. Moreover, laboratory rests are carried out on plasma rather than whole blood and at a standard temperature of 37^{o} rather than patient temperature.

Management

Targeted therapy includes surgical intervention, blood and blood products, factor concentrates, protamine and anti fibrinolytics. The following management of bleeding has been recommended:

- Early and sufficient blood product support should be given to patients with major blood loss and to those with dilutional coagulopathy.
- Supportive care with Fresh Frozen Plasma (FFP) and platelets should be given to patients with severe coagulopathy whilst the underlying condition is being treated.
- Patients with haematological disorders such as myelodysplasia, or factor VIII inhibitors will require specialist care. Pharmacological agents can be used to increase haemostatic capacity but should be used by clinicians with appropriate experience. Such drugs include DDAVP,

tranexamic acid, and off-licence use of drugs such as recombinant factor VIIa. Aprotonin is used with caution because of the risk of thrombotic complications, including death, and renal impairment.

- Surgical re-intervention is undertaken to ascertain the cause of postoperative bleeding. It involves re-opening the surgical site and, according to clinical experts, is associated with a substantial (30%) increase in morbidity and mortality. As such, it is employed as a last resort after all other interventions have failed to arrest bleeding.

Complications associated with transfusion include transfusion-associated graft versus host disease, complications that arise from the administration of an incorrect blood component, haemolytic transfusion, transfusion-related acute lung injury, febrile reaction and infections (HIV, Hepatitis A, B and C, Malaria etc.).

There is no NICE clinical guideline on the management of blood coagulation during and after surgery.

1.5 The population

The population groups included in this assessment are:

- Adults undergoing cardiac surgery
- Emergency management of major bleeding in adults (for example, trauma and post-partum haemorrhage)

Cardiac surgery

For most surgical procedures, mortality ranges from less than 0.1% for most routine surgery to 1% to 2% for cardiac surgery and 5% to 8% for elective vascular cases. Mortality may be greatly increased when severe bleeding occurs during the operative procedure[iii].

Cardiac surgery is often associated with profuse bleeding. Excessive bleeding (greater than 2 litres) is encountered in 5% to 7% of people undergoing cardiac surgery. If conventional methods fail, reoperation to arrest the bleeding (in 3.6% to 4.2% cases) may be required[1]. Major blood loss is linked to adverse outcomes and is associated with an eightfold increase in the odds of death.

More than 30,000 people have heart surgery in the United Kingdom each year and adult cardiac surgery accounts for approximately 15% of all allogeneic red cell and allogeneic blood coagulation transfusions[iii].

In cardiac patients (who are frequently on antiplatelet medication such as aspirin or clopidogrel), platelet function analysers are routinely used in conjunction with VE testing. Platelet function analysers are designed for testing platelet function in whole blood samples in near-patient or laboratory settings.

Trauma surgery

Major trauma describes serious and often multiple injuries where there is a strong possibility of death or disability. In England, the most common cause is a road accident. There is an estimated minimum of 20,000 cases of major trauma each year in England resulting in 5,400 deaths. A further 28,000 cases that may not meet the precise definition of major trauma, are cared for in the same way. Major trauma patients often require complex reconstructive surgery.

Post-partum haemorrhage

Major obstetric haemorrhage occurs in approximately 6.7 per 1000 births in the UK[iv] and is a common cause of maternal morbidity and mortality. The recognition of major obstetric haemorrhage can be challenging. Blood loss may be concealed and can be difficult to quantify due to dilution with amniotic fluid. In addition the physiological changes of pregnancy may mask the normal clinical signs of hypovolaemia (decrease in volume of blood plasma).

2. The technologies

2.1. The ROTEM System (TEM International)

The ROTEM system is a point-of-care (POC) analyser used to assist with the detection, management and monitoring of haemostasis during and after surgery associated with high blood loss. The device uses thromboelastometry, a viscoelastic method, to test for haemostasis in whole blood including the initiation of clotting, platelet count (although not function), fibrinogen and fibrinolysis.

ROTEM is intended for use during surgery to help identify the probable cause of intraoperative bleeding. The results help to guide the clinician in selecting the correct therapy. It is also intended for use in the immediate post-operative period to help guide the clinician in determining whether bleeding is a result of a coagulopathy (when the blood's ability to clot is impaired) or a surgical bleed.

ROTEM uses a combination of five assays (INTEM, EXTEM, FIBTEM, APTEM and HEPTEM) to characterise the coagulation profile of a whole blood sample (Table 1). Initial testing is performed using the INTEM and EXTEM assays which can indicate whether a clotting factor deficiency is present. If the initial test results appear normal, it is an indication that surgical bleeding rather than coagulopathy is present. Additional assays include FIBTEM which can indicate a fibrinogen deficiency, APTEM which can indicate hyperfibrinolysis or HEPTEM which can indicate whether coagulopathy is due to the presence of residual heparin.

Table 1: ROTEM assays

Assay	Activator/Inhibitor	Role
INTEM	Ellagenic acid (contact activator)	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway.
EXTEM	Tissue factor	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the extrinsic pathway. Not influenced by heparin. EXTEM is also the base activator for FIBTEM and ABTEM.
HEPTEM	Ellagenic acid + heparinase	Assessment of clot formation in heparinised patients. INTEM assay performed in the presence of heparinise; the difference between HEPTEM and INTEM confirms the presence of heparin.
FIBTEM	Tissue factor + platelet antagonist	Assessment of fibrinogen status allows detection of fibrinogen deficiency or fibrin polymerisation disorders
APTEM	Tissue factor + fibrinolysis inhibitor (aprotonin)	In-vitro fibrinolysis inhibition: Fast detection of lysis when compared to EXTEM.
Na-TEM	None	Non-activated assay. Can be used to run custom haemostasis tests.

The ROTEM analysis is generally performed with citrated whole blood near the patient during the surgery although the instrument may be positioned in the laboratory. A blood sample is taken from the patient and is placed into a cuvette. A cylindrical pin is then immersed and is oscillated by a spring to the right and the left. The movement of the pin is unrestricted as long as the blood is liquid but encounters resistance as the blood begins to clot. The clot increasingly restricts the rotation of the pin with rising clot firmness.

It is claimed that the complete results of ROTEM will:

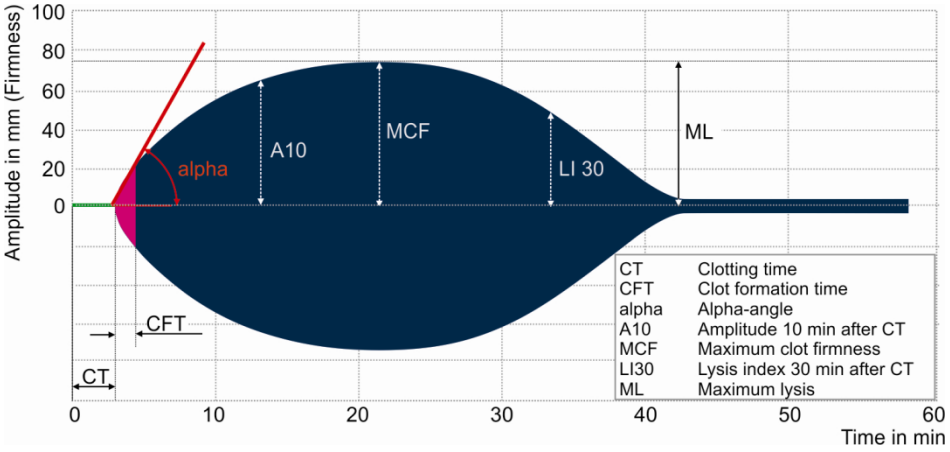
- Determine the presence and type of coagulopathy.

- Indicate a requirement for fibrinogen or platelet administration, and facilitate heparin and protamine monitoring.

- Provide information on the qualitative aspect of clot formation by looking at the elasticity of a clot to identify how well certain parameters of the sample are forming.

The graphical output of results produced by the ROTEM system is shown in figure 1 below.

Figure 1: ROTEM graphical format[v]



Numerical values for each of the following are also calculated and presented below the graph:

- CT: Clotting time – time from adding the start reagent until the blood starts to clot. A prolonged clotting time indicates abnormal clot formation.

- CFT: Clot formation time – time from CT until a clot firmness of 20 mm point has been reached and a: Alpha angle ¬– angle of tangent between 2 and the curve. These measures indicate the speed at which the clot is forming and are mainly influenced by platelet function but are also affected by fibrinogen and coagulation factors.

- A10: Amplitude 10 minutes after CT – used to predict maximum clot firmness at an earlier stage and so allows earlier therapeutic decisions.

- MCF: maximum clot firmness – the greatest vertical amplitude of the trace. A low MCF value suggests decreased platelet numbers or function, decreased fibrinogen levels of fibrin polymerisation disorders, or low factor XIII activity.

- ML: maximum lysis. Fibrinolysis is detected by ML >15% or by better clot formation in APTEM compared to EXTEM.

Initial results are available within 5-10 minutes and full qualitative results are available in 20 minutes

2.2. Thromoboelastography (TEG) system (Haemonetics)

This is a non-invasive device that is designed to detect, monitor and analyse clot formation in a blood sample. Like ROTEM, the TEG system is based on the viscoelastometric method but its mechanical system is slightly different.

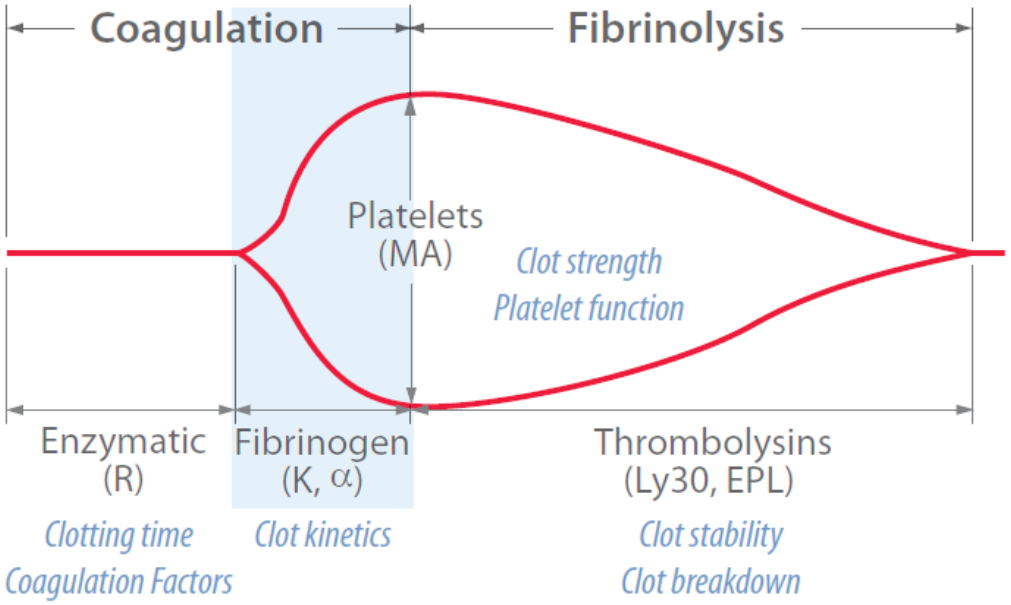
Whole blood is pipetted into a warmed disposable cup. A disposable pin is then lowered into the fluid blood. TEG works using kinetic torsion detection, which is a pendulum principle. The cup is rotated every 10 seconds and the pin is initially stationary. As the first fibrin strands are formed the pin becomes tethered to the cup and starts to follow its motion. When maximum clot firmness is achieved the cup and pin move in unison. The motion of the pin is detected by a torsion wire linked to a transducer; hence a mechanical-electrical signal is relayed through a computer interface where real-time analysis is displayed.

Like ROTEM, TEG measures and graphically displays the changes in viscoelasticity at all stages of the developing and resolving clot (figure 2). These include the time until initial fibrin formation (reaction time), the kinetics of fibrin formation and clot development (kinetics, α angle [α]), the ultimate strength and stability of the fibrin clot (maximum amplitude [MA]), and clot lysis (fibrinolysis). The assays used in TEG are summarised in table 2 below.

Table 2: Summary of TEG assays

Assay	Activator/Inhibitor	Role
Kaolin	Kaolin	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway.
Heparinase	Kaolin + heparinise	Assessment of clot formation in heparinised patients (both unfractionated and low molecular weight)
Platelet Mapping	ADP Arachidonic acid	To assess platelet function and monitor antiplatelet therapy (e.g. aspirin)
RapidTEG	Kaolin + tissue factor	Provides more rapid results than standard kaolin assay (mean 20 minutes versus 30 minutes for standard TEG® with initial results in less than one minute)
Functional fibrinogen assay	Lyophilized tissue factor + platelet inhibitor	Partitions clot strength (MA) into contributions from platelets and contribution from fibrin
Native	None	Non-activated assay. Can be used to run custom haemostasis tests.

Figure 2: TEG analysis and interpretation of results[vi]



2.3. Sonoclot Coagulation and Platelet Function Analyser (Sienco, Inc.)

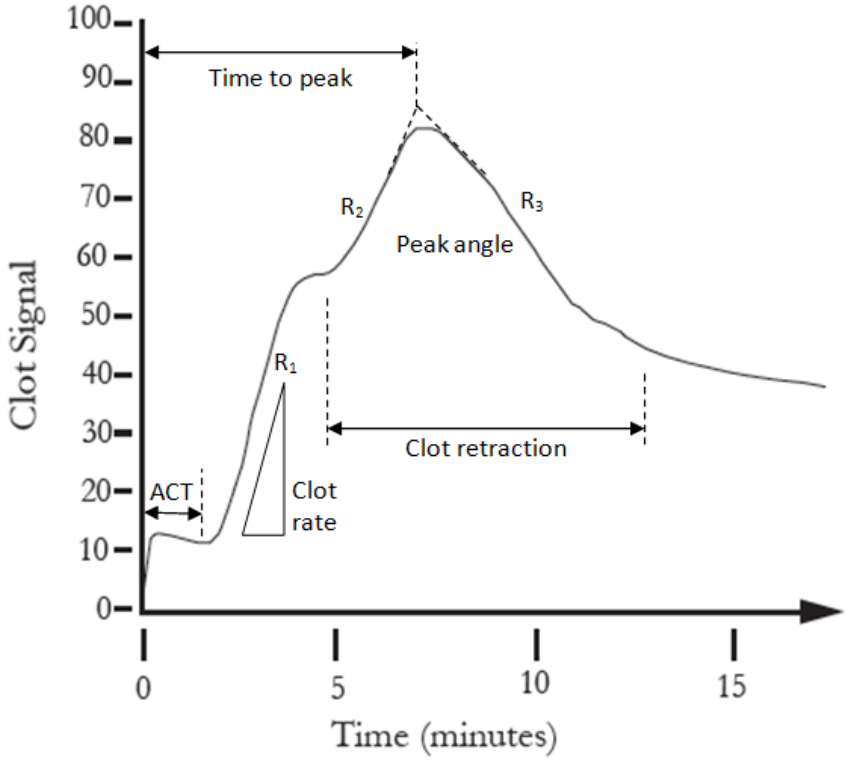
This is also a viscoelastic monitor used for measuring coagulation and platelet function. It provides information on the haemostasis process including coagulation, fibrin gel formation, clot retraction (platelet function) and fibrinolysis. Table 3 below, summarises the Sonoclot assays.

Table 3: Summary of Sonoclot assays

Assay	Activator/Inhibitor	Role
SonACT	Celite	Large-dose heparin management without aprotonin
kACT	Kaolin	Large-dose heparin management with/without aprotonin
aiACT	Celite + Clay	Large-dose heparin management with aprotonin
gbACT+	Glass beads	Overall coagulation and platelet function assessment for use on non-heparinised patients.
H-gbACT+	Glass beads + Heparinase	Overall coagulation and platelet function assessment in presence of heparin
Native	None	Non-activated assay. Can be used to run custom haemostasis tests.

The Sonoclot test is performed by placing whole blood into a pre-warmed cuvette into which a vertically vibrating probe is suspended. As the blood clots, increased viscosity causes changes in the mechanical impedance which are exerted on the probe and measured on a recorder. The Sonoclot Analyser generates both a qualitative graph (known as the Sonoclot signature, figure 3) and quantitative results on the clot formation time (activated clotting time, ACT), and the rate of fibrin polymerization (clot rate) for identifying numerous coagulopathies including platelet dysfunction, factor deficiencies, anticoagulant effect, hypercoagulable tendencies and hyperfibrinolysis.

Figure 3: Sonoclot Analysis and interpretation of results



2.4. The Comparator

The comparator for this assessment is a combination of clinical judgement and standard laboratory tests. Standard laboratory coagulation analyses include the following:

- Prothrombin time – also used to derive measures prothrombin ratio (PR) and international normalised ratio (INR).
- Activated partial thromboplastin time (aPTT)
- Activated clotting/coagulation time (ACT)
- Platelet count
- Plasma fibrinogen concentration

These tests were not developed to predict bleeding or guide coagulation management in a surgical setting. They are only able to identify when blood is

not clotting properly but are not able to identify what part of the clotting process is disrupted. They are performed at a standardised temperature of 37^{o} C which limits the detection of coagulopathies induced by hypothermia. These tests are also not able to provide information regarding clot formation over time or on fibrinolysis and so they cannot detect hyperfibrinolysis. They generally take between 40 and 90 minutes from taking the blood sample to give a result; this turnaround time may be too long for the current state of the coagulation system to be reflected by the test results

3. The evidence

This section summarises data from the diagnostics assessment report compiled by the External Assessment Group.

3.1 Clinical effectiveness

The External Assessment Group conducted a systematic review to summarise the evidence on the clinical effectiveness of VE point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis asthma. Details of the systematic review can be found starting on page 38 of the diagnostics assessment report

The purpose of the review was to address the following 3 questions:

1. How do clinical outcomes differ among patients who are tested with VE devices during or after cardiac surgery compared to those who are not tested?

    - Where there were no data on one of more of the VE devices the EAG evaluated the accuracy of those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) during or after cardiac surgery.

2. How do clinical outcomes differ among patients with coagulopathy induced by trauma who are tested with VE devices compared to those who are not tested?

- Where there were no data on one of more of the VE devices the EAG evaluated the accuracy of those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) in patients with trauma induced coagulopathy.

3. How do clinical outcomes differ among patients with PPH who are tested with VE devices compared to those who are not tested?

    - Where there were no data on one of more of the VE devices the EAG evaluated the accuracy of those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) in patients with PPH.

Inclusion criteria for each of the three clinical review questions are summarised in table 4 below.

Table 4: Inclusion criteria (available page 41 of the DAR)

Question	1. Clinical outcomes in cardiac surgery	Prediction in cardiac surgery	2. Clinical outcomes in trauma-induced coagulopathy	2a. Prediction in trauma-induced coagulopathy	3. Clinical outcomes in PPH	3a. Prediction in PPH
Participants	Adult (age ≥18 years) patients undergoing cardiac surgery		Adult (age ≥18 years) with clinically suspected coagulopathy induced by trauma		Women with post-partum haemorrhage	
Index test	VE devices (ROTEM, TEG or Sonoclot) alone or combined with platelet testing (e.g. multiplate test) or SLTs	VE devices (ROTEM, TEG or Sonoclot)	VE devices (ROTEM, TEG or Sonoclot) or SLTs	VE devices (ROTEM, TEG or Sonoclot)	VE devices (ROTEM, TEG or Sonoclot) or SLTs	VE devices (ROTEM, TEG or Sonoclot)
Comparators	No testing, SLTs, or other VE device	Any other VE device or None	No testing, SLTs, or other VE device	Any other VE device or None	No testing, SLTs, or other VE device	Any other VE device or None
Reference standard	NA	Patient relevant outcomes e.g. transfusion, bleeding	NA	Patient relevant outcomes e.g. transfusion, bleeding	NA	Patient relevant outcomes e.g. transfusion, bleeding
Outcomes	Any reported outcomes. We anticipate that outcomes will include postoperative mortality, bleeding and transfusion outcomes, complications and re-intervention outcomes.	Sufficient data to construct a 2x2 table of test performance	Any reported outcomes. We anticipate that outcomes will include postoperative mortality, bleeding and transfusion outcomes, complications and re-intervention outcomes.	Sufficient data to construct a 2x2 table of test performance **or prediction model data**	Any reported outcomes. We anticipate that outcomes will include postoperative mortality, bleeding and transfusion outcomes, complications and re-intervention outcomes.	Sufficient data to construct a 2x2 table of test performance **or prediction model data**
Study design	RCTs*	Diagnostic cohort studies/prediction studies	RCTs*	Diagnostic cohort/**prediction studies**	RCTs*	Diagnostic cohort/**prediction studies**

The methodological quality of included RCTs was assessed using the Cochrane Risk of Bias Tool. Prediction studies were assessed for methodological quality using QUADAS-2. The results of the risk of bias assessments are summarised and presented in full, by study, in Appendix 3, page 247 of the DAR.

In total, 39 publications of 33 studies were included in the systematic review: 11 RCTs (14 publications) evaluating ROTEM and TEG and three prediction studies that evaluated Sonoclot (as no RCTs evaluating Sonoclot were identified) in cardiac surgery patients; one ongoing RCT, one CCT and 15 prediction studies (18 publications) in trauma patients and two prediction studies in women with PPH.

How do clinical outcomes differ among patients who are tested with VE devices during or after cardiac surgery compared to those who are not tested?

The EAG included 11 RCTs (n=1089, range 22 to 228) (14 publications) for the assessment of VE devices in patients undergoing cardiac surgery; six assessed TEG, four assessed ROTEM and one assessed ROTEG (an early version of ROTEM). Two RCTs were only available as abstracts. The RCTs were conducted in Australia, Austria, Germany, Spain, Turkey, UK and USA. Most included patients undergoing surgery irrespective of whether or not they had a bleeding event, however, two RCTs assessing ROTEM were restricted to patients who had experienced bleeding above a certain level. A further RCT of TEG was restricted to patients at moderate to high risk for transfusion procedures. One RCT was restricted to patients undergoing aortic surgery, two included patients undergoing coronary artery bypass graft (CABG) and the remainder included patients undergoing mixed cardiac surgery. Mean or median age, where reported, ranged from 53 to 72 years and the proportion of men ranged from 56% to 90%. The majority of studies did not place any restriction on entry based on anti-coagulation use, but one study excluded patients who had used low molecular weight heparin up to the day of operation. The ROTEM/TEG algorithms varied across studies. Six studies

used an algorithm based on TEG or ROTEM alone. Two studies combined TEG with SLTs, two combined ROTEM with platelet function testing (point of care in one), and one combined ROTEM with clinical evaluation. The timing of the VE test varied across studies.

All except one study which performed TEG on arrival at the intensive care unit (ICU) administered multiple VE tests. Timing included baseline/before bypass/before anaesthesia, after cardio-pulmonary bypass (CPB), after protamine administration, on admission to ICU and up to 24 hours post CPB in one study. Four studies only performed VE testing post-surgery in patients who were continuing to bleed. Four studies used an algorithm based on SLTs in the control group; all other studies stated that control groups included combinations of clinical judgements and SLTs. The baseline details of the RCTs can be found in table 7 on page 49 of the DAR. A more detailed overview of the included studies is provided in Appendix 2, page 205 of the DAR.

There were a number of methodological issues with the RCTs included in this assessment. Only three of the 11 RCTs were rated as 'low' risk of bias with respect to their randomisation procedures. The trials were generally poorly reported; all were rated as 'unclear' or 'high' risk of bias on at least 50% of the assessed criteria. The results of the risk of bias assessment are summarised in Table 8 and Figure 5 on page 52 of the DAR and full risk of bias assessments for each study are provided in Appendix 3 of the DAR.

RBC transfusion

Eight RCTs evaluated red blood cell (RBC) transfusion within 24 to 48 hours as a continuous outcome (table 9, page 58 of the DAR). All eight RCTs reported less volume of RBC transfusion in the VE algorithm group compared to the control group but this was only statistically significant in three RCTs (two of ROTEM and one of TEG); one RCT, which used ROTEM as the index test, did not report on the statistical significance of the difference. Six RCTs provided dichotomous data on the number of patients who received an RBC

transfusion in each intervention group. The summary relative risk was 0.88 (95% CI 0.80-0.96) suggesting a significant beneficial effect of the VE testing algorithm in reducing the number of patients who received an RBC transfusion (Figure 6, page 53 of the DAR). There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to VE device: relative risk 0.86 (95% CI 0.72-1.02) for the three RCTs that evaluated TEG and 0.88 (95% CI 0.78-1.00) for the three RCTs that evaluated ROTEM and ROTEG.

Any blood transfusion

Three RCTs evaluated any blood product transfusion as a continuous outcome (Table 9, page 58 of the DAR). All three reported less volume of any blood product transfusion in the VE algorithm group compared to the control group. This was statistically significant in two (one ROTEM and one TEG) while the third did not report on the statistical significance of the difference.

Two RCTs provided dichotomous data on the number of patients who received any blood product transfusion in each intervention group. One assessed ROTEM (relative risk 0.89, 95% CI 0.78-1.02) and the other assessed TEG (relative risk 0.63, 95% CI 0.44-0.92). The summary relative risk was 0.79 (95% CI 0.57-1.08) suggesting a beneficial effect of the VE testing algorithm in reducing the number of patients who received any blood product transfusion. However, this effect did not reach statistical significance (Figure 7, page 54 of the DAR) and there was some evidence of heterogeneity across studies (I^2=64%).

Factor VIIa Transfusion

Two RCTs that assessed ROTEM provided dichotomous data on the number of patients who received a factor VIIa transfusion in each intervention group. The summary relative risk was 0.19 (95% CI 0.03-1.17) suggesting a beneficial effect of the ROTEM testing algorithm. However, this difference did not reach statistical significance (p>0.05) (Figure 8, page 55 of the DAR). There was no evidence of heterogeneity across studies (I^2=0%).

Fresh frozen plasmas (FFP) transfusion

All of the included RCTs evaluated FFP transfusion as either a continuous or dichotomous outcome. Ten RCTs evaluated FFP transfusion within 24 to 48 hours as a continuous outcome (Table 9, page 58 of the DAR). All but two RCTs reported less volume of FFP transfusion in the VE algorithm group compared to the control group. This was statistically significant in six (two of ROTEM and four of TEG) while three RCTs did not report on the statistical significance of the difference. Five RCTs provided dichotomous data on the number of patients who received FFP transfusion in each intervention group. The summary relative risk was 0.47 (95% CI 0.35-0.65) suggesting a significant beneficial effect of the VE testing algorithm in reducing the number of patients who received an FFP transfusion (Figure 9, page 56 of the DAR). There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to VE device: relative risk 0.52 (95% CI 0.20-1.35) for the three RCTs that evaluated TEG and 0.46 (95% CI 0.34-0.63) for the two RCTs that evaluated ROTEM.

Fibrinogen transfusion

Three RCTs evaluated any fibrinogen transfusion as a continuous outcome (Table 9, page 58 of the DAR). All three reported no difference between the VE algorithm group compared to the control group in the volume of fibrinogen transfused. Two of these RCTs also provided dichotomous data on the number of patients who received a fibrinogen transfusion in each intervention group. The summary relative risk was 0.94 (95% CI 0.77-1.14) suggesting no difference between the treatment groups (Figure 10, page 56 of the DAR).

Platelet transfusion

All of the included RCTs evaluated platelet transfusion as either a continuous or dichotomous outcome. Eight RCTs evaluated platelet transfusion within 24 to 48 hours as a continuous outcome (Table 9, page 58 of the DAR). All RCTs reported less volume of platelet transfusion in the VE algorithm group compared to the control group but this was only statistically significant in five

(two of ROTEM and three of TEG). Two RCTs did not report on the statistical significance of the difference. Six RCTs provided dichotomous data on the number of patients who received a platelet transfusion in each intervention group. The summary relative risk was 0.72 (95% CI 0.58-0.89) suggesting a significant beneficial effect of the VE testing algorithm in reducing the number of patients who received a platelet transfusion (Figure 11, page 57 of the DAR). There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to VE device: relative risk 0.56 (95% CI 0.36-0.86) for the three RCTs that evaluated TEG and 0.78 (95% CI 0.60-1.00) for the three RCTs that evaluated ROTEM and ROTEG.

Prothrombin transfusion

Three RCTs evaluated any prothrombin transfusion as a continuous outcome (Table 9, page 58 of the DAR). All three reported less volume of prothrombin transfusion in the VE algorithm group compared to the control group but this was only statistically significant in one ($p<0.001$). One RCT did not report on the statistical significance of the difference. Two of these RCTs also provided dichotomous data on the number of patients who received a prothrombin transfusion in each intervention group. The summary relative risk was 0.39 (95% CI 0.08-1.95) suggesting no difference between the treatment groups (Figure 12, page 58 of the DAR).

Bleeding

Nine RCTs evaluated bleeding as a continuous outcome (Table 10, page 63 of the DAR). The majority reported less bleeding in the VE intervention group, however, only two studies reported a statistically significant difference in bleeding between the two groups.

Re-operation

Seven RCTs provided dichotomous data on the number of patients who required re-operation to investigate bleeding in each intervention group. The

summary relative risk was 0.72 (95% CI 0.41-1.26) suggesting a beneficial effect of the VE testing algorithm in reducing the number of patients requiring re-operation. However, this difference was not statistically significant (Figure 13, page 63 of the DAR). There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to VE device: relative risk 0.75 (95% CI 0.31-1.83) for the five RCTs that evaluated TEG and 0.69 (95% CI 0.33, 1.44) for the two RCTs that evaluated ROTEM.

Surgical source of bleeding identified on re-operation

Four RCTs provided dichotomous data on the number of patients in whom a surgical source of bleeding was identified on re-operation in each intervention group. The summary relative risk was 1.04 (95% CI 0.42-2.57) suggesting no difference between the intervention groups (Figure 14, page 61 of the DAR). There was very little evidence of heterogeneity across studies (I^2=3%). One RCT assessed ROTEM and reported a relative risk of 0.86 (95% CI 0.26-2.87), the summary estimate for the three RCTs assessing TEG was similar at 0.99 (95% CI 0.18-5.36).

Length of ICU stay

Four RCTs evaluated the length of ICU stay as a continuous outcome (Table 10, page 63 of the DAR). All reported shorter stays in the VE group compared to control but this difference was only statistically significant in one study.

Length of hospital stay

Four RCTs evaluated the length of hospital stay as a continuous outcome (Table 10, page 63 of the DAR). All studies reported similar durations of stay in the two treatment groups; none reported a statistically significant difference between groups.

Mortality

Four RCTs provided dichotomous data on the number of deaths (within 24 hours, 48 hours, in hospital or "early mortality") in each intervention group. The summary relative risk was 0.87 (95% CI 0.35-2.18) suggesting no difference between the intervention groups (Figure 15, page 62 of the DAR). There was no evidence of heterogeneity across studies (I^2=0%). One RCT assessed ROTEM and reported a relative risk of 0.86 (95% CI 0.26-2.87) and the summary estimate for the three RCTs assessing TEG was similar at 0.88 (95% CI 0.21-3.66).

Summary

Pooled estimates, derived from meta-analyses of dichotomous data, indicated that VE testing (TEG or ROTEM) was associated with significant reductions in the numbers of patients receiving red blood cell transfusion, platelet transfusion and FFP transfusion, compared with a strategy based on standard laboratory tests. There were no significant differences between the VE testing and standard laboratory tests in terms of factor VIIa transfusion, any blood product transfusion, or prothrombin transfusion, although data suggested a beneficial effect of the VE testing algorithm but these outcomes were only evaluated in two studies. There was no difference between groups in terms of fibrinogen transfusion. Continuous data on blood product use, although inconsistently reported across studies, supported these findings; the only blood product which was not associated with a reduced volume of use in the VE testing group was fibrinogen. There was a suggestion that bleeding was reduced in the VE testing groups but this was only statistically significant in two of the nine RCTs that evaluated this outcome. Clinical outcomes (re-operation, surgical cause of bleed on re-operation and mortality) did not differ between groups. There was some evidence of reduced bleeding and ICU stay in the VE testing groups compared to control but this was not consistently reported across studies. There was no difference in length of hospital stay between groups. There was no apparent difference between ROTEM or TEG for any of the outcomes evaluated.

How well do VE devices predict relevant clinical outcomes during or after cardiac surgery?

As none of the RCTs evaluated the Sonoclot VE test, the EAG included three prediction studies which evaluated Sonoclot. Two of these also evaluated TEG and so provided a direct comparison between the two devices. The studies were conducted in Switzerland and USA. All of the studies included patients undergoing mixed cardiac surgery irrespective of whether or not they had a bleeding event. One study excluded patients with a known coagulopathy and another excluded patients with abnormal pre-operative coagulation studies; both of these studies excluded patients receiving anti-coagulant medication and one also excluded patients on anti-platelet medications. Mean or median age, where reported, ranged from 63 to 65 years and the proportion of men ranged from 61% to 69%. Baseline data from these studies are summarised in table 12 on page 66 of the DAR and the full details of the studies are provided in Appendix 2, page 205 of the DAR.

The EAG assessed the risk of bias and the applicability of the 3 studies. The main areas of concern were the participant selection process, which was unclear in all cases, and the applicability to the objectives of the assessment of the way in which VE testing was applied. Two of the studies were rated as having 'high' applicability concerns for the index test because they assessed the predictive ability of selected individual parameters of VE testing, rather than the device as a whole, or reporting data for all assays and parameters measured by the device. The results of QUADAS-2 assessments are summarised in Table 13, page 67 of the DAR and full results are provided in appendix 3, page 247 of the DAR.

All three studies provided data that allowed calculation of odd ratios for the prediction of bleeding in patients who tested positive on a particular test or test parameter (Sonoclot, TEG or standard laboratory tests) compared to those who tested negative (Figure 16, page 69 of the DAR). Positive results on conventional tests, TEG and Sonoclot were all associated with an increased risk of bleeding with no clear differences according to test. One

study evaluated individual components of each of the tests separately and found that all of the parameters investigated with the exception of one TEG and one Sonoclot parameter, were associated with a significant ($p<0.05$) increased risk of bleeding. Two of the standard laboratory tests (PT and aPTT) showed higher odd ratios than other parameters, but confidence intervals overlapped with other standard laboratory tests and TEG and Sonoclot parameters.

One study[vii] evaluated individual test parameters of the Sonoclot test. All three Sonoclot parameters assessed in the study, showed a strong positive relationship with bleeding. Another study[viii] evaluated each test class as a whole i.e. it evaluated a positive "TEG" result rather than the results for individual parameters of TEG. This study reported that a positive TEG or Sonoclot result were both highly predictive of bleeding. However, this study was very small and confidence intervals were wide. The limited data suggested that TEG results were more predictive than Sonoclot, but confidence intervals overlapped. The standard laboratory tests performed less well and were not predictive of bleeding; this study was performed in 1989 and so may not be reflective of current practice.

How do clinical outcomes differ among patients with coagulopathy induced by trauma who are tested with VE devices compared to those who are not tested?

The EAG identified one ongoing RCT[ix] that is comparing the TEG (rapid assay) with standard laboratory testing (INR, PTT, fibrinogen, D-dimer) in adults with blunt or penetrating trauma who are likely to require a transfusion of RBCs within six hours from admission as indicated by clinical assessment. The study authors provided the EAG with additional information (in the form of a study protocol) on this trial. The outcomes being evaluated in this study include quality and quantity of blood products transfused (packed RBCs, FFP, cryoprecipitate and apheresis platelets), patterns of transfusion ratios of RBC: FFP, haemorrhage-related deaths specified as very early mortality (<2 hours post-injury) and early mortality; late mortality; cessation of coagulopathic

bleeding; multiple organ failure (MOF). Results from this study are not yet available.

As no other RCTs were identified, the EAG considered lower levels of evidence for this objective. One Controlled Clinical Trial[x] reported as an abstract was included. This study compared a rapid-TEG guided protocol with a standard transfusion protocol in adult trauma patients requiring massive transfusion (defined as more than 12 RBC units in 24 hours or more than 4 RBC units in four hours). Although the study did not report numerical or statistical outcome data, it stated that there were no statistically significant differences between groups for death, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), multi-system organ failure, sepsis, DVT, stroke, acute coronary syndrome, or days to discharge. There was non-significant trend towards reduced pneumonia, days on the ventilator, and ICU days and a significant trend toward increasing platelet use in the TEG treated group. Baseline data from these studies are summarised in Table 14 (page 71 of the DAR). Full details of the studies are provided in Appendix 2 of the DAR. No other studies with a concurrent control group were identified for the trauma population.

- How well do VE devices predict relevant clinical outcomes in patients with coagulopathy induced by trauma?

Due to insufficient data from studies that evaluated differences in clinical outcomes between VE tested and untested populations, the EAG included lower levels of evidence to answer this question. Fifteen prediction studies (18 publications; n=4217) were included. Nine studies evaluated TEG and four of these also evaluated standard laboratory tests; the other six studies evaluated ROTEM and four of these also evaluated standard laboratory tests. No studies of Sonoclot were identified. None of the studies evaluated both TEG and ROTEM in the same patients. Baseline data from these studies are summarised in Table 15 on page 74 of the DAR and full details of the studies are provided in Appendix 2 of the DAR (page 219).

The prediction studies in trauma patients were conducted in UK, USA, Switzerland, Netherlands, Denmark and Austria. The majority included mixed trauma patients but three were restricted to patients with blunt trauma and two were restricted to patient with traumatic brain injury. One study excluded patients with traumatic brain injury, and one excluded patients with isolated head injury. None of the studies restricted inclusion based on bleeding. One study excluded patients who had previously taken anti-coagulant medication and another excluded patients who had recently taken clopidogrel or warfarin. The mean or median age, where reported, ranged from 33 to 49 years. The proportion of men ranged from 59% to 82%. Mean injury severity score (ISS), reported in 11 studies, ranged from 12 to 34. Mean Glasgow Coma Scale scores ranged from 11 to 14 but were only reported in six studies.

Outcomes assessed in the studies included any blood product transfusion, FFP transfusion, massive transfusion, massive transfusion of cryoprecipitate, massive transfusion of plasma, massive transfusion of platelets, plasma transfusion, platelet transfusion, RBC transfusion, bleeding, neurosurgical intervention, and death. Six studies used multiple logistic regression models to estimate odd ratios for the association of individual TEG or ROTEM parameters or standard laboratory tests with the outcomes of interest controlled for various factors such as red blood cells transfusion, age, sex, mechanism of injury, trauma/injury severity, haemoglobin levels and race.

The main areas of concern with regard to these studies were the process of participant selection and the applicability to the objectives of the assessment of the way in which both VE testing and the reference standard were applied. With two exceptions, all studies were rated as ‘high’ or ‘unclear’ risk of bias in the participant selection process. 10 of the 15 studies were rated as having ‘high’ applicability concerns for the index test because they assessed the predictive ability of selected individual components of VE testing, rather than assessing the device as a whole, or reporting data for all assays and parameters measured by the device. Two further studies were rated as having ‘unclear’ applicability because no details of the assay(s) used or parameters

measured were reported. Ten studies were rated as having 'high' applicability concerns with respect to the reference standard, where the reference standard was one or more measure(s) of transfusion requirements, because it was unclear whether or not the decision to transfuse was informed by VE testing results. This also resulted in an 'unclear' risk of bias rating with respect to the reference standard. The remaining five studies were rated as 'low' applicability concerns because they reported objective reference standards (e.g. mortality). The results of QUADAS-2 assessments are summarised in Table 16 and Figure 17 on page 78 of the DAR and a full QUADAS-2 assessments for each study are provided in Appendix 3, page 247 of the DAR.

The differences in clinical outcomes between VE and SLT tested groups are as follows:

RBC transfusion

Three studies (two of TEG, one of ROTEM and standard laboratory tests) evaluated the ability of VE devices to predict RBC transfusion (Figure 18, page 79 of the DAR). One used an endpoint of any RBC transfusion within 12 hours, one within six hours and one did not specify the time point. A positive result on each of the parameters assessed, with the exception of CT on ROTEM, was associated with an increased risk of RBC transfusion. There were no clear differences between ROTEM parameters or ROTEM and standard laboratory tests in the one study that reported multiple evaluations.

Any blood transfusion

Three studies evaluated the ability of VE devices to predict any blood product transfusion (Figure 19, page 81 of the DAR). Two evaluated TEG and one evaluated ROTEM; one of the studies of TEG also evaluated standard laboratory tests. A positive result on each of the parameters assessed was associated with an increased risk of any blood product transfusion; an overall TEG results suggesting the patient was hypercoaguable was associated with a decreased risk of transfusion (OR 0.14, 95% CI 0.03- 0.76). One of the

studies did not provide sufficient data to calculate confidence intervals and so the significance of the odd ratios from this study could not be assessed. The other two studies both reported statistically significant ($p<0.05$) associations for all parameters assessed. An overall TEG result indicating that the patient was hypocaoguable was found to be associated with the greatest increased risk of transfusion, but confidence intervals were very wide (OR 180.00 , 95% CI 14.15-2289.13). Odd ratios for individual TEG, ROTEM or standard laboratory tests were much smaller ranging from 2.50 to 15.26.

Massive transfusion

Six studies evaluated the ability of VE devices to predict massive RBC transfusion. Three evaluated and three evaluated ROTEM; all but one also evaluated standard laboratory tests. All used a threshold of ≥10 units of RBC transfused to define massive transfusion but the time frame within which this had to occur ranged from 6 to 24 hours. Three studies provided data as adjusted odd ratios for at least one of the VE test components; a further study provided data that permitted calculation of odd ratios (Figure 20, page 82 of the DAR). The other two studies only provided data on area under the curve (AUC) for the ROC curve together with 95% CIs (Figure 21, page 83 of the DAR). A positive result on each of the parameters assessed was associated with an increased risk of massive transfusion; however, this difference was not statistically significant for some of the ROTEM parameters and standard laboratory tests. There were no clear differences between ROTEM, TEG or standard laboratory tests, or individual test parameters, in terms of ability to predict massive transfusion. AUCs, where reported, were between 0.70 and 0.92 with no clear differences between ROTEM, TEG or standard laboratory tests.

Mortality

Seven studies evaluated the association of VE devices with mortality. Five evaluated TEG and two evaluated ROTEM, three also evaluated standard laboratory tests. Two studies provided data as adjusted odd ratios; three

further studies provided data that permitted calculation of odd ratios and associated CIs (Figure 22, page 86 of the DAR). The other two studies only provided data on AUC for the ROC curve together with 95% CIs; these data were also reported in one of the studies that reported adjusted odd ratios (Figure 23, page 86 of the DAR). A positive result was associated with a statistically significant increased risk of death for most parameters assessed. The only exceptions were two parameters that were associated with a decreased risk of death, although this difference was not statistically significant: the presence of moderate hyperfibrinolysis (0.76, 95% CI 0.09-6.20) and an overall TEG result suggesting that a patient was hypocaguable (OR 0.23, 95% CI 0.03-1.91). Three studies that evaluated a ROTEM or TEG result indicating the presence of hyperfibrinolysis showed the strongest association with death with odd ratios ranging from 25 to 147, although CIs were wide. AUCs were between 0.63 and 0.93 with no clear differences between ROTEM, TEG or standard laboratory tests.

Other outcomes

Data were also reported on other outcomes (FFP transfusion, massive transfusion of cryoprecipitate, massive transfusion of plasma, massive transfusion of platelets, plasma transfusion, platelet transfusion, substantial bleeding, and neurosurgical intervention). These outcomes were reported in single studies and were not discussed in detail in the DAR. Full results, however, can be found in Appendix 2, page 205 of the DAR.

How do clinical outcomes differ among patients with PPH who are tested with VE devices compared to those who are not tested?

No studies were identified that compared clinical outcomes among patients with PPH who were tested with VE devices compared to those who were not tested.

- **How well do VE devices predict relevant clinical outcomes in patients with PPH?**

As no studies evaluated differences in clinical outcomes between VE tested and untested populations, the EAG included lower levels of evidence for this objective. Two prediction studies, available only as abstracts, were included in the review (n=245). Baseline data from these studies are summarised in Table 17 (page 89 of the DAR) and full details of the studies are provided in Appendix 2 of the DAR. Both studies were conducted in the UK. The outcomes evaluated in the studies varied – one assessed the prediction of coagulopathy requiring treatment, FFP transfusion and platelet transfusion the other assessed the prediction of RBC transfusion and invasive procedures. One included women with PPH defined as ≥1000mL blood loss, the other included women with major obstetric haemorrhage defined as ≥1500mL blood loss.

As with the trauma studies, the main areas of concern with regard to the two prediction studies conducted in patients with PPH were the applicability to the objectives of the assessment of the way in which both VE testing and the reference standard were applied. The results of QUADAS-2 assessments are summarised in Table 18 (page 90 of the DAR). Full QUADAS-2 assessments for each study are provided in Appendix 3, page 247 of the DAR.

Both studies provided data that allowed calculation of odd ratios for the prediction of outcomes in patients who tested positive on ROTEM compared to those who tested negative (Figure 24, page 90 of the DAR). The study which evaluated ROTEM and standard laboratory tests only reported data in a format that allowed calculation of odd ratios for the ROTEM parameter (MCF based on FIBTEM analysis) for the prediction of RBC transfusion of at least four units. There was a strong positive relationship between this parameter and RBC transfusion (OR 41.54, 95% CI 9.01-191.59).

The other study reported that a positive ROTEM result was associated with coagulopathy requiring treatment (OR 168.0, 95% CI 15.6-1814.7). This

study also evaluated FFP transfusion and platelet transfusion; data were available to calculate odd ratios for these outcomes but not associated CIs. The ROTEM results were also predictive of both these outcomes but the significance of the association was unclear. The size of the odd ratio was smaller than for the association with coagulopathy requiring treatment (OR 76 for FFP transfusion and 19 for platelet transfusion).

3.2 Costs and cost effectiveness

Economic analysis

Review of existing economic analyses

Searches were undertaken to identify cost-effectiveness studies of VE point-of-care testing. The searches identified 331 records of which five studies fulfilled the inclusion criteria. Two were only available as conference abstracts, three were conducted in cardiac patients, one in patients undergoing liver transplant and one in both cardiac and liver transplant patients.

One study[xi] was a formal cost-effectiveness analysis of VE devices in cardiac and liver transplant patients. This study was conducted for the Scottish NHS. The other four studies were cost-minimisation studies performed alongside a retrospective before/after study. All four studies compared the volume and costs of blood transfused before and after the introduction of a VE device. Three studies evaluated ROTEM and one evaluated TEG. All four found that costs were reduced as a result of the introduction of a VE device. Only one[xii] of the four studies reported a detailed breakdown of cost savings. It showed that after the introduction of ROTEM, the cumulative average monthly costs of all blood products decreased from €66.000 to €45.000 (-32%) and the average monthly costs for ROTEM were €1.580.

De novo cost-effectiveness model

a) Model aim

The aim of the economic analysis undertaken by the External Assessment Group was to address the question: what is the cost-effectiveness of ROTEM,

TEG, and Sonoclot (VE devices) compared to standard laboratory tests (no VE devices) to assist with the diagnosis, management and monitoring of haemostasis in the patient populations of interest: cardiac surgery patients and trauma patients with suspected coagulopathy.

b) Model structure

The EAG adopted the model structure used by the HTA undertaken for NHS Scotland in 2008. This was largely based on a cost-effectiveness study of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion by Davies et al (2006)[xiii]. These studies were undertaken in 2008 and 2006 respectively, so the EAG used more recent data sources wherever possible to update the input parameters of the model.

The model is based on a decision tree (figure 4) that starts with the choice of strategy to be followed, i.e. VE device (ROTEM, TEG, or Sonoclot) or standard laboratory tests. Within each strategy, patients then either do or do not receive a transfusion. RBC transfusion, where it occurs, may be associated with adverse events or complications. Complications were categorised as either complications related to surgery and/or transfusion or transfusion-related complications.

Complications related to surgery and/or transfusions, included in the model were: renal dysfunction, myocardial infarction, stroke, thrombosis, excessive bleeding requiring re-operation, wound complications and septicaemia.

Transfusion-related complications included transfusion-associated graft versus host disease, complications related to the administration of an incorrect blood component, haemolytic transfusion reactions (acute or delayed), post-transfusion purpura (PTP), transfusion-related acute lung injury (TRALI) and febrile reaction.

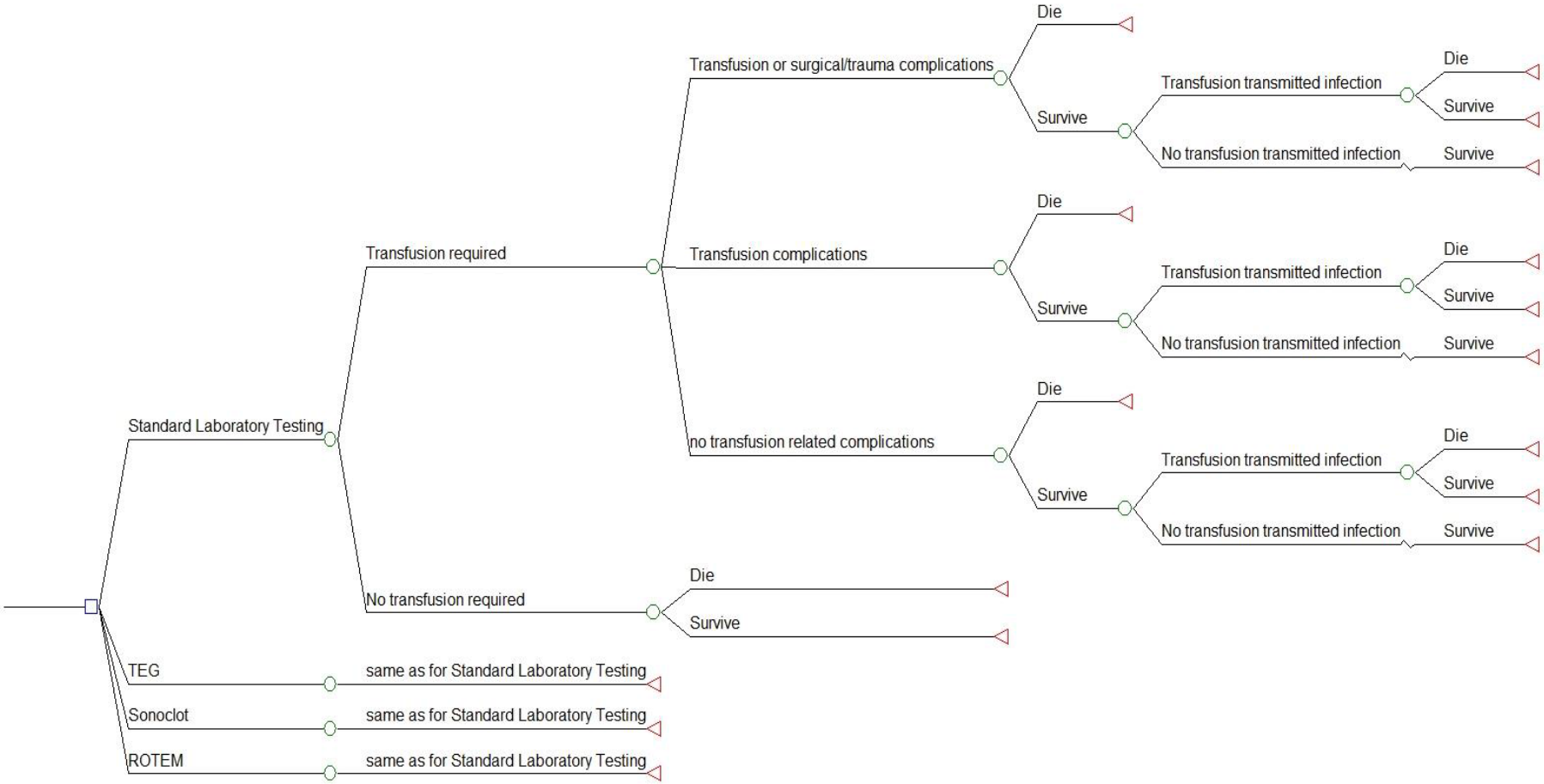
In addition, the EAG assumed that patients may also experience transfusion-transmitted infections. Transfusion-transmitted infections include bacterial contamination, variant Creutzfeldt - Jakob disease (vCJD), hepatitis A virus

(HAV), malaria, human T-cell lymphotropic virus (HTLV), Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).

The model's time horizons were set to one month and one year because the benefits of a reduction in RBC transfusion were considered to have occurred within this timeframe. At one month, the model reflects the period of hospitalisation and accordingly captures the impact of complications related to surgery and blood loss, transfusion-related complications and infection caused by bacterial contamination. It should be noted that, as in Davies et al (2006) [xv], bacterial contamination is the only transfusion-transmitted infection that was assumed to occur during the hospitalisation period. For other transfusion-transmitted infections included in the model, a time horizon of one year was considered more appropriate, as these infections do not usually manifest themselves immediately.

Discounting was not necessary since the longest time horizon was set at one year. Costs were estimated from the perspective of the NHS and PSS. Consequences were expressed in life years gained and quality adjusted life years (QALYs). QALY weights (utilities) were assigned to adverse events to express their consequences.

Figure 4: Decision tree



c) Model inputs

RBC transfusion

For the cardiac model, the baseline risk of having a transfusion was estimated based on the number of transfusions in the standard laboratory tests group in four of the cardiac surgery trials included in the effectiveness review.

Table 5: Probability of RBC transfusion for the cardiac model

Technology	Mean value	Distribution	Distribution parameters	Source
Baseline risk of RBC transfusion in Standard laboratory tests group	Base case: 0.592	Normal (prob. of RBC transfusion)	μ =0.592; σ = 0.03	Section 3.2.1.3 of the DAR
RR: ROTEM, TEG and Sonoclot	Base case RR=0.88	Normal	μ =0.88; σ =0.04	Section 3.2.1.3 of the DAR

Since the effectiveness review did not find evidence of a difference in the relative risk of RBC transfusion between studies that assessed ROTEM and those that assessed TEG, the EAG applied the summary relative risk for RBC transfusion estimated for all studies for the ROTEM and TEG models. Limited data suggested that the accuracy of Sonoclot in predicting clinical outcomes may be similar to that of TEG. The EAG therefore assumed that this summary relative risk could be applied in the Sonoclot model. A beta and a normal distribution, respectively, were assigned for the PSA.

For the trauma model, the baseline risk of RBC transfusion for the standard laboratory tests group was also estimated using data from those studies that reported data on the proportion of patients who received an RBC transfusion. A random effects model was used to estimate the mean proportion of patients who received an RBC transfusion. As there were no data comparing the proportion of transfused patients in a trauma population who received VE testing compared to those who received standard laboratory tests, the EAG applied the same relative risk as in the cardiac surgery population.

Table 6: Probability of RBC transfusion for the trauma model

Technology	Mean value	Distribution	Distribution parameters	Source
Baseline risk: Standard laboratory tests	Base case: 0.321	Normal (prob. of RBC transfusion)	μ =0.321; σ = 0.056	Estimated
Relative risk: ROTEM, TEG and Sonoclot	Base case RR=0.88	Normal	μ =0.88; σ =0.08*	Section 3.2.1.3 of the DAR & assumption

*This is 0.04 in the cardiac surgery model. The EAG doubled it in order to account in the PSA for the uncertainty about the assumption that the RR for the cardiac surgery population is also valid for trauma.

Complications related to surgery and transfusion

Re-operation to investigate bleeding is the only complication among those included in the model that was evaluated by the RCTs included in the effectiveness review. Data on the other complications were limited so the EAG assumed that there was no difference in the direct risk of having a complication between those tested with VE devices and those tested with standard laboratory tests. The same assumption was made in Davies et al. The risk of complications in each testing strategy was influenced indirectly by the different RBC transfusion rates associated with each strategy.

The probability of experiencing septicaemia was obtained from one study[xiv]. However, the population in this study was not representative of the population in the assessment since it only included patients who received four or more units of RBC within one day of surgery (i.e. patients with massive bleed). The EAG judged this estimate to be too high and reduced the estimate by an arbitrary factor of 0.5.

Table 7: Probability of experiencing complications related to surgery and blood loss in people undergoing cardiac surgery

Type of complication	Mean value	Distribution	Distribution parameters[1]	Source
Renal dysfunction	0.03	Normal	μ =0.03; σ =0.003	Davies et al. 2006
Myocardial infarction	0.03	Normal	μ =0.03; σ =0.003	Davies et al. 2006
Stroke	0.01	Normal	μ =0.01; σ =0.001	Davies et al. 2006
Thrombosis	0.03	Normal	μ =0.03; σ =0.003	Davies et al. 2006
Excessive bleeding re-operation Baseline risk Standard laboratory tests Relative Risk VE devices	0.053 0.72	Normal Log-Normal	μ =0.053; σ =0.019 μ =0.72; σ =0.285	Section 3.2.1.2 of the DAR
Wound complications	0.07	Normal	μ =0.07; σ =0.007	Davies et al. 2006
Septicaemia	0.0207 (0.0414 from Karkouti et al. 2006)	Beta	α =38; β =917	Karkouti et al. 2006 and assumption

For the trauma model, two complications (ARDS and MOF) were included. Estimates for the incidence of ARDS were obtained from a study[xv] of 14,070 trauma patients conducted in the USA. This study reported an overall incidence of ARDS of 4.6%. The same study was used to calculate the proportion of patients with ARDS among those who received a transfusion as 15.5%. For MOF, no studies were found that either provided estimates or allowed direct calculation of incidence for those transfused. The EAG considered that a MOF incidence rate of 30% is a realistic assumption.

Transfusion-related complications

The trials included in the clinical effectiveness review did not report data on transfusion-related complications; therefore data on the probabilities of experiencing transfusion-related complications were based on reports from the UK Serious Hazards of Transfusion (SHOT). The SHOT observations

were corrected for the participation in the SHOT survey (98%). The EAG assumed that the total number of transfused patients per year is around 800,000

Table 8: Probability of experiencing transfusion related complication in cardiac and trauma surgery

Type of complication	Mean value	Distribution	Distribution parameters*	Source
Transfusion-associated graft versus host disease	0.00000021	Normal	μ=0.00000021; σ=0.000000022	UK Serious Hazards of Transfusion (SHOT).
Incorrect blood component	0.0003	Normal	μ=0.00030; σ=0.00003086	
Haemolytic transfusion reactions – acute	0.000011	Normal	μ=0.000011; σ=0.00000112	
Haemolytic transfusion reactions – delayed	0.00004	Normal	μ=0.00004; σ=0.000004125	
PTP	0.0000015	Normal	μ=0.0000015; σ=0.000000156	
TRALI	0.000023	Normal	μ=0.000023; σ=0.0000024	
Febrile reaction	0.0003	Normal	μ=0.0003; σ=0.000030751	

***Only mean values are reported in the SHOT report**

For the trauma model, the probability of transfusion-related complications was assumed to be the same as that for the cardiac surgery patients.

Transfusion-transmitted infections

The probabilities of experiencing transfusion-transmitted infections were also taken from the UK SHOT report using the same method of calculation as for transfusion-related complications. These were also reported as the risk per patient transfused.

Table 9: Probability of transfusion-transmitted infections in cardiac and trauma surgery

Type of complication	Mean value	Distribution	Distribution parameters*	Source
Transfusion-associated graft versus host disease	0.00000021	Normal	μ=0.00000021; σ=0.000000022	UK Serious Hazards of Transfusion (SHOT).
Incorrect blood component	0.0003	Normal	μ=0.00030; σ=0.00003086	
Haemolytic transfusion reactions – acute	0.000011	Normal	μ=0.000011; σ=0.00000112	
Haemolytic transfusion reactions – delayed	0.00004	Normal	μ=0.00004; σ=0.000004125	
PTP	0.0000015	Normal	μ=0.0000015; σ=0.000000156	
TRALI	0.000023	Normal	μ=0.000023; σ=0.0000024	
Febrile reaction	0.0003	Normal	μ=0.0003; σ=0.000030751	

***Only mean values are reported in the SHOT report**

For the trauma population, the probability of transfusion-transmitted infections was assumed to be the same as that for the cardiac surgery. The EAG acknowledges that this is likely to be an underestimation, as patients with trauma receive on average more units of blood than cardiac surgery patients (see Table 26 and 33, pages 109 and 119 of the DAR), increasing the exposure to various donors.

Mortality

At one month, the estimated risk of mortality in the standard laboratory tests group was estimated based on the number of deaths reported in one study. This study was based on a large sample (n=8,598) of a population that matched our target population. It reported a one month mortality of 0.4% for non-transfused patients and 4.3% for transfused patients. Using the transfusion percentage applied in the current model (59.2%), this would yield an overall (transfused or not) one month mortality of 2.7%.

Several different complications can occur. Even though mortality may vary by complication, it was assumed that the mortality of all transfused patients (essentially the sum of mortalities due to each complication and no complication) was fixed at 4.3%. Therefore, in order to obtain a 4.3% mortality rate in the transfused group, the EAG used a calibration procedure.

What this meant is that where reliable estimates were available or some assumption necessary, a specific mortality estimate was applied to each complication. For the rest and for no complications the mortality value was calculated so that the total mortality added up to 4.3%. This mortality value was calculated to be 4.28%.

For the transfusion-transmitted infections (except bacterial contamination), the one month mortality was assumed to be zero since these infections were assumed to manifest themselves after the hospitalisation period. Mortality rates for various transfusion-related complications and bacterial contamination were derived from the SHOT survey.

In order to estimate the mortality associated with the use of VE testing, the EAG assumed that any mortality benefit from VE testing resulted from fewer patients receiving a transfusion. This meant that the one month mortality for each group (not transfused, transfused without complications, transfused with complications) in the VE group was assumed to be the same as in the standard laboratory tests group.

At one year, the mortality in the standard laboratory tests group was estimated using data from the same study which reported a one year mortality of 1.2% for non-transfused patients and 7.8% for transfused patients. For the non-transfused patients, a 0.4% mortality at one month and a 1.2% mortality at one year yielded a mortality rate for between one and 12 months of 0.8%. Similarly, for the transfused patients a mortality rate for between one and 12 months was calculated as 3.66%. The one year mortality for each sub-group of patients in the VE group was assumed to be the same as in the standard laboratory tests group.

For the trauma population, the EAG used a random effects model to estimate mortality at one month based on the studies included in the effectiveness review. In the standard laboratory tests group, the mean one month mortality was 15.7% (95%CI 11.7%-20.1%). The EAG assigned one month mortality rates to transfused and non-transfused patients such that the overall mortality

rate would be equal to 15.7%. One study was retrieved which showed that mortality was 3.3 times higher among patients who received a transfusion. Therefore the goal was to estimate mortality rates such that the weighted average of these yielded an overall mortality of 15.7%, the mean mortality in the standard laboratory tests group derived from the systematic review; i.e. 32% Mort $_{trans}$ + 68% Mort $_{not\ trans}$ = 15.7%. From this it follows that mortality was 9.1% in patients who did not receive a transfusion and 29.8% in those that did.

Mortality for the two trauma and/or transfusion related complications; ARDS and MOF were estimated from other sources. The probability of mortality in patients with ARDS was estimated from a trial[xvi] in ARDS patients which reported a mortality rate of 83/385 = 21.6%. Data from two studies were pooled to estimate the mortality rate in patients with MOF yielding an overall mortality rate of 26.2%.

One month mortality rates for transfusion-related complications and transfusion-transmitted infections were derived when possible from the SHOT survey, and, as in the cardiac surgery population, it was assumed that all infections apart from bacterial contamination would only manifest themselves after one month, implying a zero mortality rate in the first month. As in the cardiac population, the one month mortality for each sub-group of patients in the VE group was assumed to be the same as in the standard laboratory tests group, thus implying that any mortality benefit in the VE group was due to fewer patients being transfused.

For mortality between one and 12 months after trauma little data were available. One study was identified, which reported 3% mortality for this period. However, no information was identified on how this mortality is distributed over transfused and non-transfused patients. The EAG therefore applied the same ratio as for 1 month mortality (3.3). Solving 32% $Mort_{trans}$ + 68% $Mort_{not\ trans}$ = 3.0% yielded a mortality in the non-transfused of 1.7% and mortality in the transfused of 5.7%. These values were assumed to apply to both the standard laboratory tests and VE group.

Health benefits

Health benefits were expressed in terms of life years and quality-adjusted life years (QALYs) gained at one month and one year. For the calculation of the life years, patients were assumed to die in the middle of the period where death occurred. Life years were then valued with different utilities depending on the health state of the patient. Except for stroke, the EAG used utility values from the 1996 Health Survey for England. For the cardiac population the utilities used are summarised in Table 12 below.

Table 10: Utilities per health state and time period for the cardiac population

Health states	Mean value	Distribution	Distribution parameters
From surgery to hospital discharge			
All patients	0.64	Beta	α = 0.7898; β = 0.4443
From hospital discharge to 1 month			
All patients except stroke	0.88	Beta	α = 2.9799; β = 0.4063
Stroke patients	0.64	Normal	μ=0.64; σ= 0.0653
Month 1 to 12 (after surgery and hospital discharge)			
All patients except stroke and transmitted infections	0.93	Beta	α = 5.6187; β = 0.4229
Stroke	0.64	Normal	μ=0.64; σ= 0.0653
Transmitted infections	0.88	Beta	α = 2.9799; β = 0.4063

For the trauma model, the EAG identified a study that collected EQ-5D utilities 12 to 18 months after trauma. This study included patients with severe trauma and reported a mean utility of 0.69 (SE 0.016) in these patients 12 to 18 months after the trauma. No studies reporting utilities for the period of hospitalisation and shortly afterwards were identified. The EAG therefore assumed the same utility for the period of hospitalisation as for the cardiac population during hospitalisation.

For ARDS patients the EAG used the results of a prospective cohort study that measured quality adjusted survival in 200 patients in the first year after ARDS. This study reported utilities of 0.60 (SE 0.01) and 0.64 (SE 0.01) at six months and one year after onset of ARDS respectively. The EAG applied the value of 0.60 to the period of one month, and 0.64 to the period between months 1 and 12. Similar data were unavailable for patients with MOF, so the EAG applied the same utilities as for patients with ARDS based on the assumption that both complications are similar in severity. For patients with transfusion related complications, the EAG assumed that after discharge, as in the cardiac population, the utility would be equivalent to patients without complications.

Table 4: Utilities per health state and time period (trauma population).

Health states	Mean value	Distribution	Distribution parameters	Source
During hospitalisation				
All patients except transfusion and trauma complications	0.64	Beta	$\alpha = 0.7898$; $\beta = 0.4443$	Assumed same as cardiac population
Transfusion and trauma Complications	0.60	Normal	$\mu = 0.60$; $\sigma = 0.091$	Angus et al. 2001[xvii]
From hospital discharge to 1 month				
All patients except transfusion and trauma complications	0.69	Normal	$\mu = 0.69$; $\sigma = 0.1056$	Holtslag et al.[xviii]
Transfusion and trauma Complications	0.60	Normal	$\mu = 0.60$; $\sigma = 0.091$	Angus et al. 2001
Month 1 to 12 (after surgery and hospital discharge)				
All patients except transfusion and trauma complications or transfusion transmitted infection	0.69	Normal	$\mu = 0.69$; $\sigma = 0.1056$	Holtslag et al.
Transfusion and trauma Complications	0.64	Normal	$\mu=0.64$; $\sigma= 0.0979$	Angus et al. 2001
Transfusion transmitted infection	0.69*0.88=0.61	Normal	$\mu = 0.61$; $\sigma = 0.0933$	Holtslag et al. and Davies et al. 2006

Costs

Short (one month) and long-term (one year) costs were considered in the model. Short-term costs included the following four groups: (1) pre- and peri-operative costs of transfusion, (2) costs of blood products, (3) test costs for the identification of patients at risk of bleeding during or after transfusion and (4) costs related to complications due to surgery and blood loss, transfusion-related complications and infections due to bacterial contamination. Long-term costs included those related to the other transfusion-transmitted infections, i.e. vCJD, HAV, malaria, HTLV, HIV, HBV and HCV, and disabling stroke.

The following short term costs were included in the cardiac and trauma models:

i. For both the cardiac and trauma models, pre-operative and peri-operative costs of transfusion were taken from the Davies report and inflated to 2013.

Table12: Pre and peri-operative costs associated with transfusion.

Type of service	Cost	Source
Pre-operative costs of allogeneic blood per transfusion	£27.97	Davies et al. 2006.
Peri-operative costs of transfusion services: Additional allogeneic blood match Use of transfusion sets	 £0.65 £3.21	Davies et al. 2006.

ii. Cost of blood products: Three types of blood products were included in the model. The prices for standard red blood cells, adult platelets and clinical FFP were obtained from the NHS Blood and Transplant price list 2013-2014101 and these are £122.09, £208.09, and £27.98, respectively. Data on units of blood transfused were obtained from one study[xix].

In the trauma population, data from two trauma studies included in the effectiveness review that reported volumes of blood products used

were used to estimate the average number of units transfused per transfused patient.

iii. Cost of VE devices: The total costs of the different VE devices consisted of the costs of the devices themselves, the costs of extra items in addition to the device (only those that were available and comparable for the three devices) and after-care and training costs.

Table 13: Comparison of costs of ROTEM, TEG and Sonoclot based on 2013 costs.

Cost component	ROTEM	TEG	Sonoclot
4 channel device	£24,950	£20,000	£14,950
Connectivity kit	£4,078	Included in device cost	Included in device cost
Software/ Database commander	£2,415		
Printer	£126		
Trolley	£1,015		£750
Total Device Cost	***£32,584***	***£20, 000***	***£15,700***
Years of use	3	3	3
Total cost ROTEM + Extras per year	£10,861	£6,667	£5,233
After care cost per year	£1,750	£2,000	£933
Training cost per year (advanced)	£725	£0	£0
Total cost ROTEM per year	£13,336	£8,677	£6,633
Number of tests per year with the 4 channel device	500	500	500
Material cost per test	***£26.67***	***£17.33***	***£13.27***

The differences in costs in terms of device, between the cardiac and trauma models, were in the types of assays used to define a basic test and in the number of tests run. The EAG assumed that trauma patients would not be tested using the heparin assays. Therefore for ROTEM, a basic test would consist of INTEM, EXTEM and FIBTEM; for TEG, the regular kaolin test would be replaced by the rapid TEG and for Sonoclot patients would just receive a basic glass bead activated test.

Table 14: Comparison of costs of ROTEM, TEG and Sonoclot basic test.

Basic Test Cost (cardiac)	
ROTEM intem	£1.13
ROTEM extem	£1.22
ROTEM fibtem	£2.22
ROTEM heptem	£2.43
Cup and pin (x4)	£3.15 x 4
Equipment cost	£26.67
Total cost ROTEM test	£46.27
Kaolin vial	£2.72
Heparinase cup and pin	£8.75
Plain cup and pin	£5.45
Equipment cost	£17.33
Total cost TEG test	£34.25
gbACT	£2.20
kACT	£2.20
Equipment cost	£12.33
Total cost Sonoclot test	£16.73
Basic Test Cost (trauma)	
ROTEM intem	£1.13
ROTEM extem	£1.22
ROTEM fibtem	£2.22
Cup and pin (x3)	£3.15 x 3
Equipment cost	£26.67
Total cost ROTEM test	£40.69
Rapid TEG	£11.25
Plain cup and pin	£5.45
Equipment cost	£17.33
Total cost TEG test	£34.03
gbACT	£2.20
Equipment cost	£12.33
Total cost Sonoclot test	£14.53

iv. Cost of standard laboratory tests: The total cost per set of standard laboratory tests inflated to 2013 prices was taken from the Scottish HTA and was equal to £26 for fibrinogen concentration, PT, PC, ACT and APTT combined. This cost was applied to both the cardiac and trauma models.

v. Hospitalisation costs: The average length of hospital stay was sourced from the Hospital Episode Statistics 2012/2013 which reports a mean stay of 10.53 days per patient undergoing cardiac surgery. The cost per day (inflated to 2013 prices) was £198 for patients without complication, according to Davies et al. 2006. None of the studies included in the effectiveness review reported significant differences between VE groups and standard laboratory tests in terms of length of hospital stay so the EAG assumed equal average length of hospital stay for each of the different strategies. Costs of ICU stay were not considered.

For the trauma model, data on length of hospital stay were taken from the only two trauma studies included in the effectiveness review that reported on this parameter. The average length of hospital stay was 10.55 in-hospital days and 4.9 of these days were spent in the ICU. Based on National Schedule of Reference Costs, ICU stay was valued at £1,173 per day. For hospital stay after ICU, the EAG were unable to define a cost per day due to the wide variability in trauma injuries, and assumed the same per-day costs as for the cardiac surgery model.

For ARDS, the EAG used data from a study that reported an ICU length of stay of 18.8 days and hospital length of stay was 26.8 days. For MOF, a study reported an ICU length of stay of 19.1 days but there was no data for overall stay so the EAG assumed that amount of time spent in hospital after ICU discharge is equal to the time spent by people with ARDS (8 days). For patients without ARDS or MOF, lengths of ICU and hospital stays were estimated to be 2.2 days and 7.4 days respectively.

For people with transfusion related complications and bacterial infection the EAG assumed the same length of stay as for cardiac surgery patients and the same unit costs per day. While patients stayed in the ICU, no additional hospital costs were applied for complications because the EAG assumed that the level of care was already such that the marginal resource use due to complications was relatively small. Once patients were out of the ICU, the same per day costs applied for the cardiac model were applied.

vi. Costs between hospital discharge and one year after surgery: Long-term costs (during month 1 and 12 after cardiac surgery) due to all transfusion-transmitted infections with the exception of bacterial contamination were included in both the cardiac and trauma models. Table 30, page 114 of the DAR summarises the length of stay (in days) and associated costs per day of transfusion-transmitted infections (excluding bacterial contamination) during month 1 and 12 after the hospitalisation period.

Assumptions made in the model

The following assumptions were made in the model.

General
1. ROTEM, TEG and Sonoclot were assumed to be equally effective.
2. Complications related to surgery and/or transfusion, transfusion-related complications and infection caused by bacterial contamination were assumed to occur during the hospitalisation period.
3. For the transfusion-transmitted infections (except bacterial contamination), one month mortality was assumed to be zero since these infections were assumed to manifest themselves after the hospitalisation period.
4. Patients were assumed to die in the middle of the period where death occurred.
5. The EAG assumed that four channel VE devices were used.
6. Only those extra items that were available (and comparable) for the three devices, were included in the acquisition costs. After-care and training costs were also included.
7. The EAG assumed 3 years of machine usage.
8. The EAG assumed that, on average, 500 tests were performed per machine per year.
9. The EAG assumed equal average length of hospital stay for the VE and Standard laboratory tests groups.
10. For HAV, HBV, HCV and HIV the EAG assumed two acute hospitalisations and three outpatient visits during the first 12 months after surgery. For malaria and HTLV the EAG assumed two acute hospitalisations with no outpatient visits.
Cardiac surgery population
11. The EAG assumed that there was no difference in the risk of having a complication between those tested with VE devices and those tested with standard laboratory tests (except for the probability of re-operation), except due to transfusion.
12. The probability of experiencing septicaemia was sourced from Karkouti et al. 2006 but reduced by an arbitrary factor of 0.5 because the original estimate was deemed to be too high.
13. The mortality associated with 'Incorrect blood component', 'delayed haemolytic transfusion reactions', 'febrile reaction', all surgery and/or transfusion complications, and patients with transfusion but without complications was estimated using the calibration procedure described in Section 4.3.1.5, page 104 of the DAR.
14. The EAG assumed that any mortality benefit from VE testing resulted from fewer patients receiving a transfusion, which meant that the one month mortality for each patient group (not transfused, transfused without complications, transfused with complications) in the VE group was assumed to be the same as in the standard laboratory tests group.
15. The one year mortality for patients in each category (not transfused, transfused without complications, transfused with complications) for the VE group was assumed to be the same as in the standard laboratory tests group.
16. A basic test for ROTEM was defined as a combination of the INTEM,

EXTEM, FIBTEM and HEPTEM assays. A basic test for TEG was defined as a standard Kaolin and a heparinise assays. A basic test for Sonoclot was a combination of the gbACT and kACT would be used for this population.
17. It was assumed that each patient is tested 3 times in total during and after surgery.
18. For parameters where standard errors were not reported, estimates for the PSA assumed a 95% CI with limits deviating 20% from the mean.
Trauma population
19. For the proportion of patients who received VE testing compared to the ones who received standard laboratory tests, The EAG applied the same RR as in the cardiac surgery population.
20. A MOF incidence rate of 30% was assumed.
21. The probability of transfusion-related complications and the probability of transfusion-transmitted infections were assumed to be the same as for cardiac surgery patients.
22. The ratio between mortality for transfused and non-transfused was assumed to be the same as in the Bochicchio et al. study.
23. The EAG assumed that all complication mortality rates that were below the overall mortality rate for transfused were part of a calibration, resulting in equal probabilities.
24. The one month and one year mortality for patients in each category (not transfused, transfused without complications, transfused with complications) for the VE group was assumed to be the same as in the standard laboratory tests group.
25. For the period of hospitalisation and the period from discharge to 1 month The EAG assumed the same utility as for the cardiac population during hospitalisation.
26. The EAG applied the same pre-operative and peri-operative costs of transfusion as for the cardiac surgery population.
27. To estimate the number of units of blood transfused for the VE testing strategy, the EAG estimated the ratio of units transfused in the VE group and the units transfused in the standard laboratory tests group found in the cardiac group, and applied this to the standard laboratory tests trauma volumes.
28. A basic test for ROTEM was defined as a combination of the INTEM, EXTEM and FIBTEM assays. The rapid TEG assay was considered as the basic test for TEG. A basic test for Sonoclot was the gbACT assay
29. The EAG assumed that each patient was tested 5 times.
30. For parameters where standard errors were not reported, estimates for the PSA assumed a 95% CI with limits deviating 30% from the mean.

Base case results

a) Cardiac model results

For the cardiac model, all the VE technologies dominated standard laboratory tests. As the same treatment effects were assumed for each VE testing device, effectiveness was the same for each device (QALY=0.8773). The cost of Sonoclot was lower than that of ROTEM or TEG and so this device was associated with greater cost-savings (£132) compared to TEG (£79) or ROTEM (£43).

Table15: Cardiac surgery model outputs (base case)

	Standard laboratory tests	ROTEM	TEG	Sonoclot
LY	0.9624	0.9660	0.9660	0.9660
QALY	0.8726	0.8773	0.8773	0.8773
Cost	£2,631	£2,588	£2,552	£2,499
Incr. QALYs vs. Standard laboratory tests		0.0047	0.0047	0.0047
Incr. costs vs. Standard laboratory tests		-£43	-£79	-£132

The results of other outputs from the model show that compared with standard laboratory tests, the use of VE devices is associated with less mortality, a reduced probability of experiencing complications and less transfusion and hospitalisation costs. The probability of experiencing transfusion-transmitted infections was very low (almost zero) in both groups but was lower in the VE group.

Table16: Cardiac surgery additional model outputs (base case)

Outcome	VE	Standard laboratory tests
One month mortality	2.4%	2.7%
One year mortality	4.6%	5.1%
Percentage surgery and/or transfusion complications	11.9%	14.4%
Percentage transfusion-related complications	0.04%	0.04%
Percentage transfusion-transmitted infections	0.00%	0.00%
Transfusion costs	£231	£290
Hospitalisation costs	£2,174	£2,213

b) Trauma model results

For the trauma model, all the VE technologies dominated standard laboratory tests. The effectiveness of the devices was the same (QALY=0.5713). The cost of Sonoclot was lower than that of ROTEM or TEG and so this device was associated with greater cost-savings (£818) than TEG (£721) or ROTEM (£688).

Table17: Trauma model outputs (base case)

	Standard laboratory tests	ROTEM	TEG	Sonoclot
LY	0.8343	0.8425	0.8425	0.8425
QALY	0.5644	0.5713	0.5713	0.5713
Cost	£7,661	£6,973	£6,940	£6,842
Incr. QALYs vs. Standard laboratory tests		0.0069	0.0069	0.0069
Incr. costs vs. Standard laboratory tests		-£688	-£721	-£818

The results of other outputs from the model show that compared with standard laboratory tests, the use of VE devices is associated with less mortality, a reduced probability of experiencing complications and less transfusion and hospitalisation costs. The probability of experiencing transfusion-transmitted infections was very low (almost zero) in both groups but was lower in the VE group.

Table18: Coagulopathy induced by trauma additional model outputs (base case)

Outcome	VE device	Standard laboratory tests
One month mortality	14.9%	15.7%
One year mortality	17.3%	18.2%
Percentage trauma and/or transfusion complications	12.9%	14.6%
Percentage transfusion-related complications	0.02%	0.02%
Percentage transfusion-transmitted infections	0.00%	0.00%
Transfusion costs	£1,045	£1,491
Hospitalisation cots	£5,724	£6,040

Probabilistic sensitivity analysis

The impact of statistical uncertainties regarding the model's input parameters was explored through probabilistic sensitivity analysis (PSA).

For the cardiac model, the scatter plot of the PSA outcomes in the cost-effectiveness (CE) plane was not very informative because the model only assumed the difference in costs between the technologies. The PSA confirmed that using standard laboratory tests is the strategy with the lowest probability of being cost-effective (Figure 32, page 132 of the DAR). The CEACs in Figures 33 to 35, (page 133-134 of the DAR) illustrate the difference between ROTEM, TEG or Sonoclot and standard laboratory tests in terms of the probability of being cost effective. At a cost-effectiveness threshold of £30,000 per QALY, the probability of cost-effectiveness for each of the three VE technologies was 0.79 for ROTEM, (the most expensive device), 0.82 for TEG and 0.87 for Sonoclot (the cheapest device). At higher thresholds, the cost-effectiveness probabilities converged to around 0.8 for all technologies.

PSA results for the trauma model were similar to the cardiac model. The PSA confirmed that using standard laboratory tests was the strategy with the lowest probability of being cost-effective (Figure 38, page 139 of the DAR). A comparison of ROTEM with standard laboratory tests found a cost effectiveness probability equal to 0.96 for ROTEM for a ceiling ratio equal to £0 (Figure 39 page 139 of the DAR). As the ceiling ratio increased, the CEAC for ROTEM converged to 0.87. A similar pattern was observed for TEG and Sonoclot.

Scenario analysis

For the cardiac model, all scenario analyses suggested that ROTEM remained cost saving (Table 40, page 136 of the DAR). The only exception was the number of tests run on each device per year. If the number of tests run on each device is reduced to 200, ROTEM (the most expensive of the three devices) no longer dominated standard laboratory tests, and an ICER of

£16,487 is found (Table 40 and Figure 36 pages 135-136 of the DAR). The EAG estimated, using iterative analysis, that if all other parameters in the model remain unchanged, the costs of ROTEM and standard laboratory tests would be equal if 326 tests were run on ROTEM each year. At this level the ICER would be £0. If number of tests per year is reduced to 152 then the ICER is around £30,000.

For the trauma model, all scenario analyses suggested that ROTEM remained cost saving (Table 43, page 141 of the DAR). The iterative analysis performed to estimate the number of tests per year such that ROTEM would still be cost-saving suggested a break-even value of 81 tests per year; at this level the ICER was £0. When the number of tests per year was reduced to 65 the ICER was approximately £30,000.

For the trauma model, threshold analysis on the combined effect of a reduction in the percentage transfused and the blood volumes transfused (assuming that equal volumes of blood were transfused in the VE testing and standard laboratory tests groups) showed that at a relative risk of transfusion of 0.9822 or more, ROTEM was no longer cost-saving (ICER was zero). When the relative risk of transfusion increased to 0.9874, the ICER of ROTEM versus standard laboratory tests was £30,000.

Reducing baseline transfusion risk in the standard laboratory tests group, (assuming that equal volumes of blood were transfused in the VE testing and standard laboratory tests group) showed that ROTEM was no longer cost-saving at a transfusion rate of 5% and the ICER was £30,000 for a transfusion rate of 4%. This compares to a transfusion rate of 32% used in the base case analysis. When the analysis was repeated with an increased relative risk of RBC transfusion, from 0.88 to 0.95, the ICER was above £30,000 for a transfusion rate of 8% or less. After reducing the probability of complications related to trauma and/or transfusion, transfusion-related complications and

transfusion related-infection to zero ROTEM remained cost-saving with a reduction in costs of £372.

Expected value of perfect information (EVPI) analysis

For the trauma model, the EAG explored the value of information associated with the model uncertainty by estimating the expected value of perfect information (EVPI), which is the amount the decision-maker should be willing to pay to eliminate all uncertainty in the decision. The decision is made based on the expected net monetary benefit given current information, i.e. the technology with the highest expected net monetary benefit is chosen as optimal. The EVPI per patient was calculated as the average of the maximum net benefits across all PSA outcomes (expected net benefit of perfect information) minus the maximum average net benefit for the different technologies (expected net benefit given current information).
Additional research might be justified when the expected net benefit for future patients, defined as the population EVPI, exceeds the expected costs of additional research. Therefore the per person EVPI is multiplied by the population size to give the population EVPI. This is then summed over the lifetime for which the research recommendation is expected to be valid, discounted at 3.5% to give the net present value. The EAG selected a period of five years for this value. For the trauma model a potential population of 16,825 adult patients in the UK was assumed based on data from the National Audit Office. This provides an upper limit of the potential population, as standard laboratory tests and VE testing will probably not be indicated for the whole trauma population. The EAG distinguished two approaches to the population EVPI depending on whether the problem to be addressed was which of the four different strategies should be recommended, or whether to recommend VE testing (e.g. ROTEM) instead of standard laboratory tests. In the former case, all four technologies were included in the EVPI estimation. For the latter situation the EAG only compared ROTEM as it the most expensive strategy.

Results of the population EVPI (defined as the expected net benefit for future patients) are presented in Figure 40 (page 140 of the DAR). This shows that, at a cost-effectiveness threshold of £30,000 per QALY, the population EVPI when all four technologies are considered was £25,017,471, whilst the population EVPI when only ROTEM and standard laboratory tests were compared was more than 22 times lower at £1,263,131.

4. Issues for consideration

1. At the start of this assessment the role of VE testing in the care pathway was considered to be unclear; it could be used either as an add-on to, or replacement for standard laboratory tests. Three of the RCTs included in the systematic review compared the effectiveness of VE testing combined with standard laboratory tests (two studies using TEG and one using ROTEM) to standard laboratory tests alone. These studies provided data on the add-on value of VE testing. For all outcomes assessed, the results of these studies were consistent with those of studies which compared VE testing alone with standard laboratory tests. These findings indicate performing standard laboratory tests in addition to VE testing is unlikely to give further benefit over that provided by VE testing alone. If recommended by the committee, VE testing could therefore be regarded as a replacement for standard laboratory tests. During scoping however, clinical opinion suggested that in current practice, standard laboratory tests are performed alongside VE testing.

2. None of the included RCTs provided a direct comparison between TEG and ROTEM. However, summary estimates were similar when stratified by VE device; thus, there was no evidence to indicate a difference in effectiveness between the two devices. None of the RCTs evaluated Sonoclot, so the EAG included lower evidence data for this device. Three prediction studies, two of which also evaluated TEG and standard laboratory tests, enabled a direct comparison between Sonoclot and TEG and between the two VE devices and standard laboratory tests. The

limited data available do not suggest a significant difference in the ability of Sonoclot and TEG to predict bleeding, however, there were insufficient data to rule out a difference in the overall clinical effectiveness of these two devices. In the absence of data suggesting a difference between the three devices, the EAG concluded that the summary relative risk could be applied to all 3 devices and in effect, considered all 3 devices to be equivalent to each other.

3. With the exception of one small, non-randomised controlled trial, all studies conducted in trauma patients or women with post-partum haemorrhage included in the systematic review were prediction studies. These studies evaluated the predictive accuracy of different VE device parameters, some also assessed standard laboratory tests with a reference standard consisting of clinical outcome or measure of transfusion requirements. These studies generally found that a positive result on each of the TEG or ROTEM parameters or on standard laboratory tests was associated with an increased risk of transfusion (RBC, any blood product and massive transfusion) and death. There was no clear difference between ROTEM, TEG or standard laboratory tests. However, none of the studies provided a direct comparison between TEG and ROTEM. An overall TEG result suggesting that a patient was hypocoaguable was the strongest predictor of any blood product transfusion. The presence of hyperfibrinolysis was the strongest predictor of mortality. No studies of the Sonoclot device were identified that fulfilled inclusion criteria for either the trauma or PPH populations.

4. Publication bias was not formally assessed in the review because, for RCTs, the number of studies was too small for such an assessment to be meaningful and, for prediction studies, there is no reliable method of assessing publication bias. However, the search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts and the identification of one ongoing RCT.

5. The cost-effectiveness of VE devices was assessed in two key populations: people undergoing cardiac surgery and people with trauma acquired coagulopathies. There were insufficient data from the clinical effectiveness review to construct a model to assess the cost-effectiveness of VE devices in women with post-partum haemorrhage.

6. There were no data on the clinical effectiveness of Sonoclot so the EAG assumed that the TEG- and ROTEM-based estimates used in the model would also be applicable to Sonoclot; thus the same health effect estimates were used for all three VE devices.

7. The time horizon used in the model is one year. This is because at one year all VE devices where shown to be both more effective and cheaper than standard laboratory tests and with little uncertainty (probabilities of at least 0.68 of being cost effective); effectiveness would only increase and costs would be likely to decrease over a lifetime. The expected increase in effectiveness is based on the avoidance of transfusions. In addition, long term complications such as stroke, which are likely to be avoided by fewer transfusions, would also imply lower cost.

8. Each device is available with different numbers of channels and runs different assays which are not directly comparable between devices. The EAG decided which assays and number of tests to model based on the combination of assays and numbers of tests used in the trials so that the costs included in the model correspond to the source of the effectiveness data. However, it is unclear whether the results found in the trials would also be applicable to different assay combinations and numbers of tests used in clinical practice. The EAG found that varying the number of tests, which could also be a proxy for assay combinations, did not alter the conclusions in terms of cost-effectiveness. The length of time that a machine is used for and the average number of tests run per machine per year influences the material cost of a test. However, scenario analysis showed that the number of tests had to be very low before VE testing was no longer cost-effective.

9. The main outcome used in the economic models was the proportion of patients at risk of RBC transfusion. From this, it was possible to impute other effects such as units of blood transfused, adverse events, complications, changes to quality of life, and overall survival. This is consistent with the only cost-effectiveness study in the field, the Scottish HTA report and is also consistent with the study by Davies et al.(2006), on which the Scottish HTA was based.

10. In order to estimate the mortality for VE testing, the EAG assumed that any mortality benefit from VE testing resulted only from fewer patients receiving RBC transfusion. It should be noted that differential mortality between VE and standard laboratory tests could result from reasons other than differential rates of transfusion, such as reduced volume transfused or differential transfusion of other blood products e.g. FFP and platelets. However, the EAG validated the method of only using mortality data associated with RBC transfusion by comparing the estimated RR of mortality (VE versus standard laboratory tests) with the results of the systematic review. This showed a relative risk of mortality for ROTEM and TEG of 0.90 which was almost identical to the relative risk estimated in the systematic review (0.87).

11. There were no data on the clinical effectiveness of any of the VE devices in trauma patients. The EAG therefore assumed equivalent clinical effectiveness to the cardiac surgery population. Clinically, patients undergoing (elective) cardiac surgery are likely to differ from trauma patients which may affect the relative effectiveness of the VE devices. Trauma patients are likely to have higher blood loss and therefore have greater blood transfusion requirements. The EAG estimated the baseline risk of RBC transfusion in trauma patients from the predictive accuracy studies included in the systematic review, but these studies could not inform the relative risk of transfusion in patients who were and were not tested with a VE device. Scenario analysis indicated that if the relative risk of RBC transfusion was as high as 0.98, VE testing would still be cost-

saving in this population. This compares to a value of 0.88 derived from the systematic review of cardiac surgery patients and used in the base case analysis.

12. Where possible, the EAG used cardiac and trauma specific utility and cost estimates in the models. However, for some of the short term utility parameters trauma specific data were not found. The EAG thus assumed that during the first month, the trauma population would have the same utility as the cardiac population. Given that many trauma patients spent quite some time in ICU, often being ventilated, the true utility is likely to be lower. In addition, there were no good data on costs of a hospital stay once trauma patients leave the ICU. This is related to the fact that these patients may go to a wide variety of departments, depending on the type of trauma (e.g. brain trauma or mainly orthopaedic trauma). The EAG therefore made the assumption that costs per day would also be the same as for cardiac patients; it is unclear whether this is an over- or underestimation. However, given that these utilities and costs only apply to a very short time period they are unlikely to have influenced whether VE testing was cost-effective.

13. EVPI analysis was conducted for the trauma population. This showed that it may be worth spending money on further primary research given that, when comparing all four technologies (ROTEM, TEG, Sonoclot, and standard laboratory tests) the population EVPI was around £25 million for an ICER of £30,000. However, the EVPI should be interpreted with caution given that the value, when comparing only a single VE device (ROTEM) with standard laboratory tests, was 22 times lower at just over £1.25 million. This would suggest that there is relatively little uncertainty as to whether ROTEM would be cost-effective in comparison to standard laboratory tests.

14. None of the RCTs included in the review assessed Sonoclot. As the only difference in the models was the costs of the devices, and Sonoclot was the cheapest device, Sonoclot was the most likely to be cost-effective.

15. Other issues for consideration are outlined in the section detailing the key model assumptions.

5. Equality considerations

No equality considerations were identified during scoping. The population for this assessment did not include children below the age of 18 years. In addition, pregnancy and maternity are protected characteristics.

6. Implementation issues

1. Training in the use of these devices may be required to ensure their clinical effectiveness. A 2010 published report of studies undertaken by the UK National External Quality Assessment Scheme (NEQAS) for Blood Coagulation on the use of TEG and ROTEM devices in operating theatres indicated that there may be variation in practice with regard to the use of these devices. The published article reported the results of a series of four quality assurance studies, with up to 18 TEG users and 10 ROTEM users involved in testing two samples per study. Some centres returned results that were judged to be sufficiently different from those obtained by other participants to predict alterations in patient management decisions. Based on these findings it would seem that staff training requirements are likely to be an important consideration for the implementation of these devices.

2. Preliminary anecdotal evidence from the NICE Health Technologies Adoption Programme (HTAP) suggests that:

    a. Sonoclot is not used anywhere in the UK at this point in time although, the device is currently being used in informal clinical evaluations to compare against TEG or ROTEM.

    b. In all the sites visited by HTAP, VE testing is used in conjunction with standard laboratory tests.

c. VE testing appears to be very helpful to surgeons in Camp Bastion for management of blood products and for deciding whether to re-operate.

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Appendix A: Sources of evidence considered in the preparation of the overview

The diagnostics assessment report for this assessment was prepared by Kleijnen Systematic Reviews:

Whiting P, Al M, Westwood ME, Corro Rammos I, Ryder S, Armstrong N, Misso K, Ross J, Severens JL, Kleijnen J. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. A Diagnostic Assessment Report. Kleijnen Systematic Reviews Ltd, 2014.

The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers/sponsors:

- Haemonetics
- LINC Medical systems
- TEM UK Ltd.
- Framar Hemologix
- Roche

Professional/specialist and patient/carer groups:

- Healthcare Improvement Scotland
- Royal College of Nursing
- Royal College of Paediatrics and Child Health

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