

Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – Protocol

Title of project

Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis

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1 Plain English Summary

Two situations associated with a high risk of bleeding are trauma (including excessive bleeding after childbirth) and surgery. Bleeding can occur as a result of the surgery or injury itself or due to problems with the blood's clotting process. The risk of bleeding varies according to type of surgery with cardiac surgery, liver transplant, major vascular surgery, hip replacement, and obstetric interventions associated with a high risk of bleeding. Patients with bleeding usually require a blood transfusion and/or (re)-operation, both of which may lead to increased morbidity and mortality. It is therefore important to appropriately treat the cause of the bleed and reduce the blood loss. Knowledge of the exact cause of the bleed allows treatment to be tailored rather than replacing blood loss with transfusion.

ROTEM® Delta is a “viscoelastic” method developed to monitor the clotting process. It is performed near the patient during surgery and can help differentiate between surgical bleeding and a clotting disorder. A blood sample is placed in a disposable cup containing the reagent(s) and a sensor pin oscillates in the blood sample. As the blood starts clotting, the clot restricts the rotation of the pin with increasing resistance as the firmness of the clot increases. This is measured by the ROTEM® system and translated to the output which consist of graphical displays and numerical parameters. Other viscoelastic (VE) devices include thromboelastography (TEG®) and the Sonoclot® analyser. These have slight differences compared to ROTEM® in terms of whether it is the pin or the cup that oscillates and the direction in which the oscillation occurs. They also use different chemicals. However, they provide similar information on clot formation.

Standard laboratory clotting tests have a number of limitations for detecting problems with the clotting process. In general, they are only able to identify that the blood is not clotting properly, not what part of the clotting process is not working. They generally take between 40 and 90 minutes from taking the blood sample to give a result; this compares to less than 30 minutes for full results of VE testing methods which can give initial results in less than 10 minutes. VE can be repeatedly performed during and after surgery and so can provide a

dynamic picture of the clotting process. VE testing methods offer two key potential benefits over standard laboratory tests: the shorter timescale in which they are able to provide results and the additional information on the clotting process which they offer compared to standard tests. Additional information and quicker results mean requirements for specific blood products could be targeted and so the patient is not subjected to risks associated with unnecessary transfusion. Time in theatre, resource use, length of stay in a critical care unit, length of hospital stay, blood product usage, and the associated costs may therefore be reduced.

This assessment aims to determine the effectiveness of VE devices to assist with the diagnosis, management and monitoring of clotting disorders during and after surgery or trauma and may include information on the management of excessive bleeding post-childbirth. The assessment will consider both clinical effectiveness (improvement in patients' symptoms and adverse events) and cost effectiveness (cost of treatment). In addition, a cost effectiveness analysis of VE versus standard laboratory tests only will be conducted.

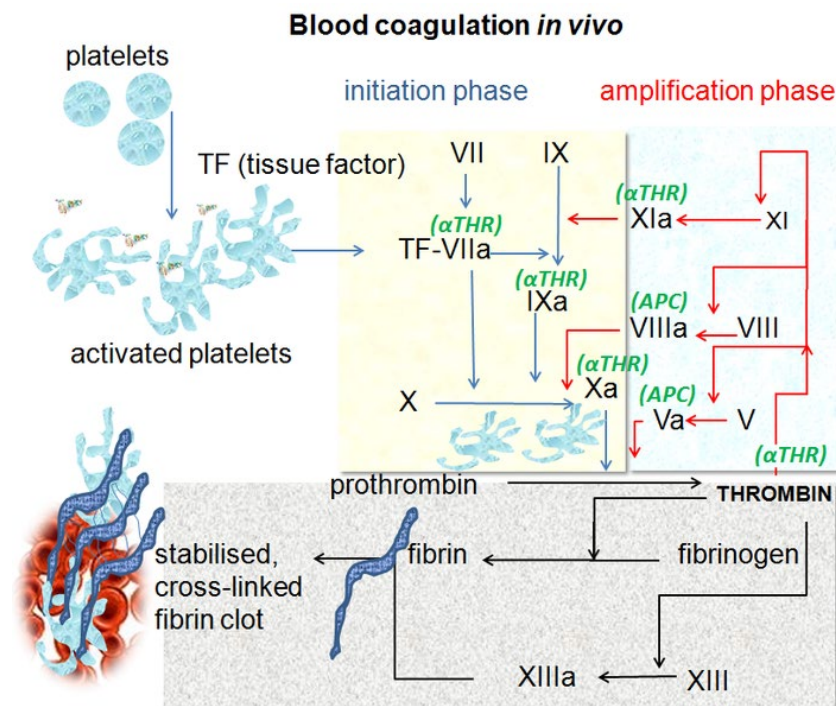
2 Decision problem

2.1 Population

There are two broad patient groups at high risk of bleeding: those who have experienced trauma (including post-partum haemorrhage) and those undergoing surgery. Patients undergoing surgery commonly present with bleeding complications which can have a negative impact on their clinical outcome in terms of increased peri-operative and post-operative morbidity and mortality. Bleeding can occur either as a result of the surgery/injury itself or due to perioperative or trauma induced coagulopathy. Coagulopathy occurs when the normal clotting mechanism (haemostasis) is interrupted impairing the blood's ability to clot. The normal clotting process starts with platelets which, combined with a number of clotting proteins, go through a series of steps to produce a solid fibrin clot (Figure 1). If any of these steps are interrupted this may result in prolonged or excessive bleeding. While coagulopathy can be caused by genetic disorders such as haemophilia it can also occur following injury as occurs in perioperative or trauma induced coagulopathy. The underlying mechanism of coagulopathy can include hyperfibrinolysis (markedly enhanced fibrinolytic activity), hypofibrinogenaemia (fibrinogen deficiency), thrombocytopenia (low levels of platelets), factor deficiency, and heparin effect.¹ There are several factors that increase the risk of coagulopathy during surgery. In cardiac surgery the use of heparin to prevent clotting whilst on cardiopulmonary bypass (CPB), preoperative anticoagulation medication, the dilution, activation and consumption of coagulation factors, and the use of cardiopulmonary bypass machines which may result in acquired platelet dysfunction, hypothermia (body temperature <35°C), and hyperfibrillation are all associated with an increased risk of coagulopathy.² In patients undergoing liver transplantation, advanced cirrhosis is associated with decreased levels of haemostatic proteins, low synthesis of anticoagulants, thrombocytopenia, and variations in levels of some clotting proteins.^{3, 4} Various stages of the liver transplant surgery itself, especially the anhepatic phase and immediately after organ reperfusion, can be associated with marked changes in haemostasis mainly in hyperfibrinolysis.⁴ In major trauma the following are associated with an increased risk of coagulopathy: consumption of coagulation factors and platelets during clot formation in an attempt to prevent loss of blood through damaged vessels; dilution of

whole blood as a consequence of red cell transfusion; hormonal and cytokine induced changes; hypoxia, acidosis and hypothermia which predispose to further bleeding; and ongoing bleeding.⁵

Figure 1 Blood coagulation *in vivo*⁶



The risk of bleeding varies according to type of surgery with cardiac surgery, liver transplant, major vascular surgery, hip replacement, and obstetric interventions associated with a high risk of bleeding. There were 36 702 cardiac surgery cases (based on Specialised Services National Definitions Set),⁷ 638 liver transplants, 72 542 hip replacements, and 175 997 obstetric operations in England and Wales in 2011-2012 based on Hospital Episode Statistics data.⁶ There are approximately 20 000 major trauma cases in England every year⁸ and injuries account for over 700 000 hospital admission each year.⁹ This assessment will focus on two patient groups identified by NICE as clinical priority areas: those undergoing cardiac surgery and trauma patients.

Patients with substantive bleeding usually require transfusion and/or re-operation. Table 1 summarises the number of patients undergoing various cardiac surgeries in Scotland over a

2 year period and shows the proportion of these patients who received a blood transfusion and the number of red blood cell units per episode transfused.¹⁰ Cardiothoracic surgery uses 5% of all donated blood in the UK, ¹¹ and the proportion of patients requiring re-operation for bleeding is estimated at 2-8% of cardiac surgery patients.¹² The increased morbidity and mortality associated with bleeding following surgery has been shown to be related to both blood transfusion and re-operation for bleeding. ¹² Patients with a diagnosis of trauma induced coagulopathy on admission to hospital have a 3 to 4 fold greater mortality risk and it is independently associated with increased transfusion requirements, organ injury, septic complications, and longer critical care stays.⁵ Trauma is the leading cause of death and disability in adults aged under 36 years around the world,¹³ and haemorrhage is the cause of 40% of all trauma deaths in the UK. ¹⁴

Red blood cell transfusion is independently associated with a greater risk of both infection and ischemic postoperative morbidity, hospital stay, increased early (30 day post-operative) and late mortality (up to 1 year post-operative), and hospital costs.¹⁵ It is therefore important to appropriately treat the coagulopathy and reduce the blood loss thus reducing the requirement for blood transfusion and reducing the risks of transfusion-related adverse events and saving costs.² Knowledge of the exact cause of the bleed allows treatment to be tailored to the cause of the coagulopathy rather than replacing blood loss with transfusion. For example, if thrombocytopenia is identified as the cause of the bleed this can be treated by platelet transfusion.¹⁶ Furthermore, the cost of donor blood and blood has increased and availability has reduced and there is also the risk of blood borne infection.¹¹

Table 1 Surgical blood use in 2005-6

Procedure	Number of episodes	% Episodes transfused	RBC units/episode transfused
Coronary replacement operations (minus revisions)	2 359	47.9	1.6
Heart and lung transplant	8	75.0	11.3
Revision coronary replacement operations	29	44.8	2.1

Valves and adjacent structures	758	54.5	2.5
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2.2 Intervention technology

The ROTEM® Delta point-of-care analyser

The ROTEM® Delta (trademark of TEM International GmbH; www.rotem.de) is a point-of-care (POC) analyser which uses thromboelastometry, a viscoelastic method, to test for haemostasis in whole blood. It is performed near the patient during surgery or when admitted following trauma. It is used to assist with the diagnosis, management and monitoring of haemostasis disorders during and after surgery associated with high blood loss. It is an integrated all-in-one system and analyses the coagulation status of a blood sample to differentiate between surgical bleeding and a haemostasis disorder.¹⁷ It uses a combination of five assays to characterise the coagulation profile of a citrated whole blood sample (Table 2). Initial screening is performed using the INTEM and EXTEM assays, if these are normal then it is an indication that surgical bleeding rather than coagulopathy is present. The use of different assays allows for rapid differential diagnosis between different haemostasis defects and anticoagulant drug effects.¹⁷ Training in use of the technology is required but specialist laboratory staff are not needed.

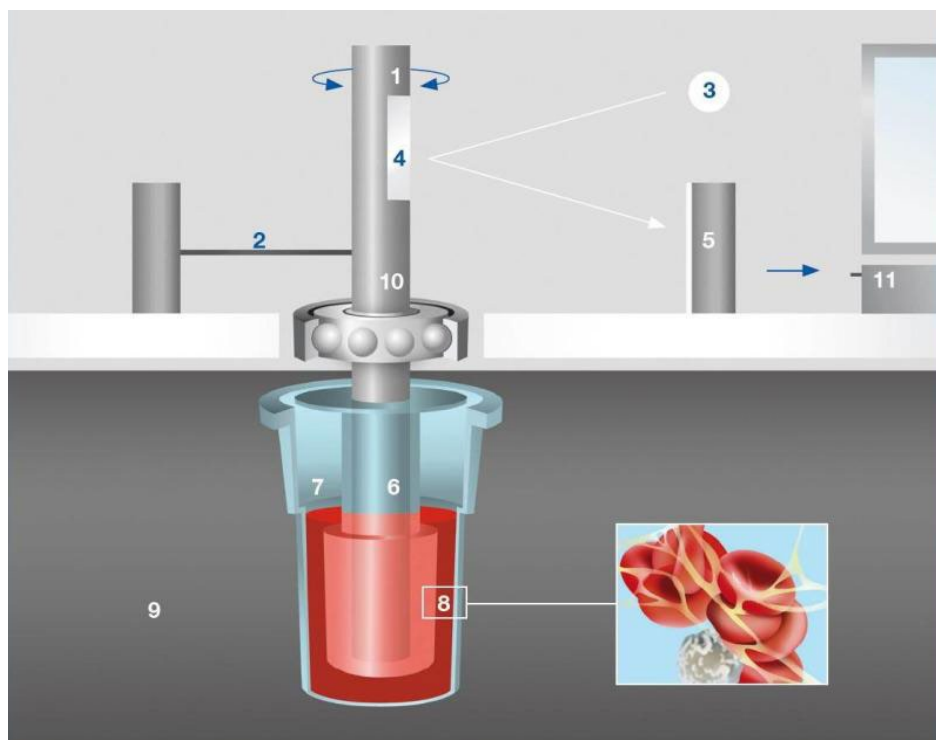
Table 2 Summary of ROTEM® Delta assays

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 heparinase; 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	In-vitro fibrinolysis inhibition: Fast detection of lysis when

	inhibitor (aprotinin)	compared to EXTEM.
Na-TEM	None	Non-activated assay. Can be used to run custom haemostasis tests.

Figure 2 shows the ROTEM® system. A 340 µl blood sample that has been anticoagulated with citrate is placed into the disposable cuvette (sample cup) (7) using an electronic pipette. A disposable sensor pin (6) is attached to the shaft which is connected with a thin spring (2) and slowly oscillates back and forth (1) suspended in the blood sample. The signal from the pin is transmitted via an optical detector system (3,4, 5). The test is started by adding the reagents described above. Although the typical test temperature is 37°C, different temperatures can be selected, for example for patients with hypothermia. Whilst the blood remains liquid the movement is unrestricted, as the blood starts clotting, the clot restricts the rotation of the pin with increasing resistance as the firmness of the clot increases. This is measured by the ROTEM® system and translated to the output which consist of graphical displays and numerical parameters.

Figure 2 ROTEM® system¹⁸



- 1 Oscillating axis
- 2 Counterforce spring
- 3 Light beam from LED

- 7 cuvette with blood sample
- 8 Fibrin strands & platelet aggregates
- 9 Heated cuvette holder

4 Mirror
5 Detector (electr. Camera)
6 Sensor Pin

10 Ball bearing
11 Data processing unit

The graphical output of results produced by the ROTEM® system is shown in Figure 3. A separate graphical display is produced for each reagent by an integrated computer (Appendix A). Numerical values for each of the following are also calculated and presented below the graph. Initial results are available within 5-10 minutes and full qualitative results are available in 20 minutes:

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

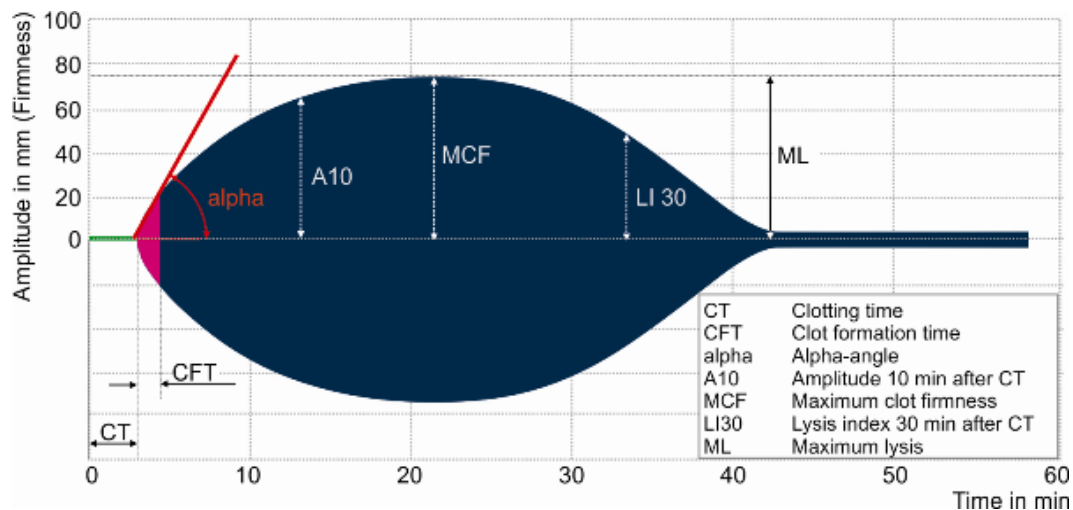
CFT: Clot formation time – time from CT until a clot firmness of 20 mm point has been reached and *a: Alpha angle* – angle of tangent between 2 and the curve. These measures indicate the speed at which the clot is forming and are mainly influenced by platelet function but are also affected by fibrinogen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

A10: Amplitude 10 minutes after CT – used to predict MCF 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.

Figure 3 ROTEM® Analysis and interpretation of results¹⁹



2.3 Alternative technologies

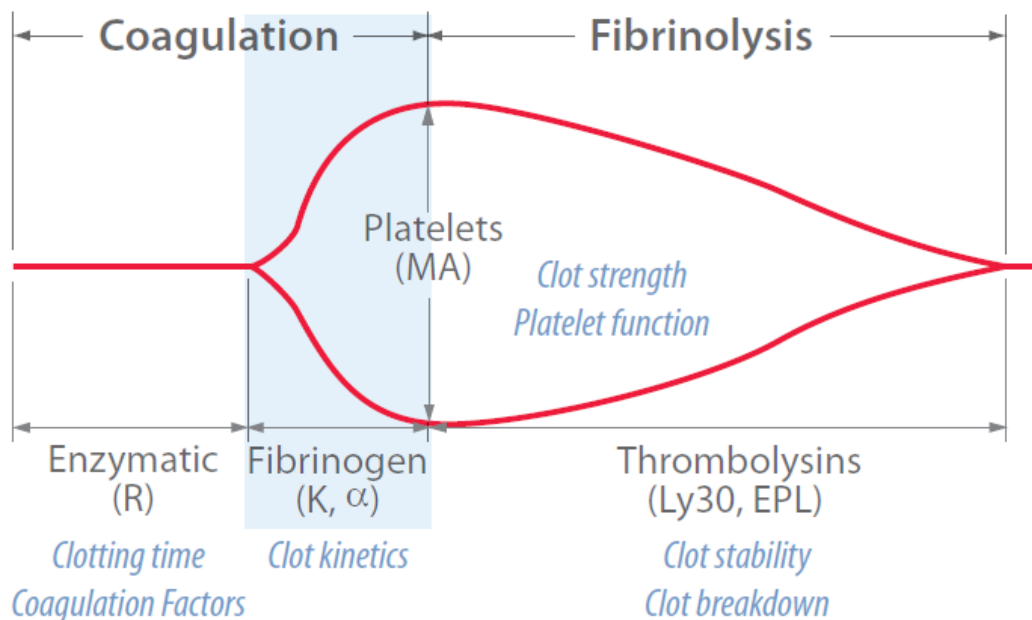
Thromboelastography

The ROTEM® system is a variant of the traditional thromboelastography (TEG®) method developed by Hartert in 1948.²⁰ The two techniques are generally considered as equivalent technologies and other recent reviews have evaluated them as a single intervention class.^{10, 21, 22} Like ROTEM®, thromboelastography is a viscoelastic method and provides a graphical representation of the clotting process. Thromboelastography is used in the TEG® 5000 analyser (trademark of Haemonetics Corporation, IL, USA; www.haemonetics.com). The rate of fibrin polymerisation and the overall clot strength is assessed.¹ Like ROTEM®, TEG® is able to provide an analysis of platelet function, coagulation proteases and inhibitors, and the fibrinolytic system within 30 minutes, or within 15 minutes if the rapid assay is used. The nomenclature used in TEG® differs from that used in ROTEM®; differences are summarised in Table 3. The practical differences between TEG® and ROTEM® are that TEG® uses a torsion wire rather than the optical detector used in ROTEM® to measure the clot formation, and while the movement in ROTEM® is initiated with the pin, with TEG® it is initiated from the cuvette.¹ The assays used in TEG® also differ (Table 3).^{3, 23} The platelet mapping function means that TEG® is able to measure platelet function which cannot be assessed using ROTEM®. Sample size requirements do not differ substantially between TEG® and ROTEM®; TEG® uses a 360µl blood sample compared to the 340µl sample used in ROTEM®.²³

Table 3 Summary of TEG® assays

Assay	Activator/Inhibitor	Role
Kaolin	Kaolin	Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway.
Heparinase	Kaolin + heparinase	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 4 TEG® Analysis and interpretation of results²⁴



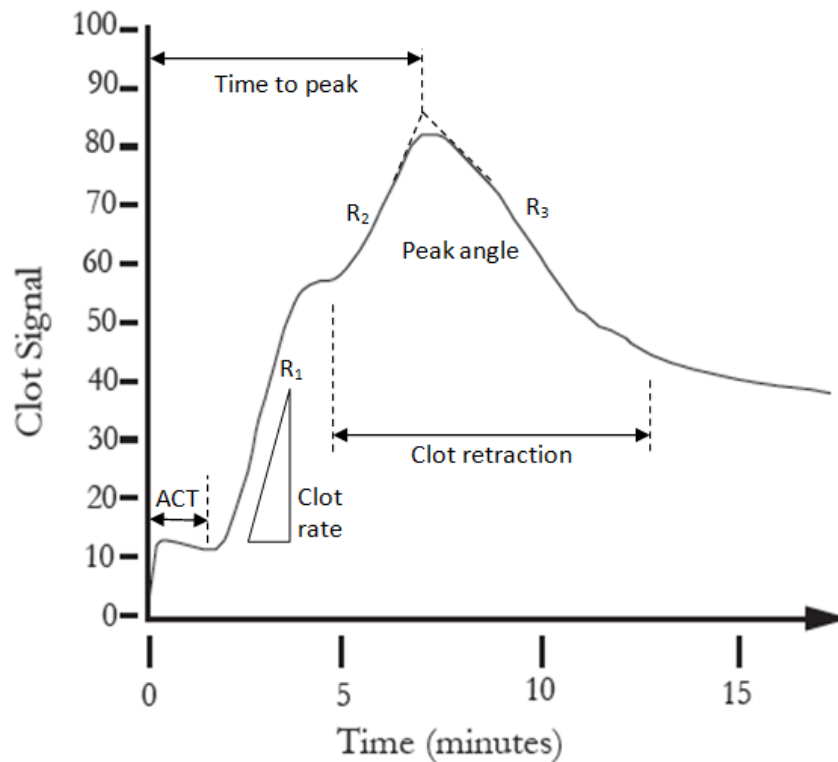
Sonoclot® Coagulation and Platelet Function Analyser

Another method that uses viscoelastometry to measure coagulation is the Sonoclot® coagulation and platelet function analyser (Sienco Inc., Arvada, CO). This analyser was first introduced in 1975 by von Kualla et al.²⁵ It provides information on the haemostasis process including coagulation, fibrin gel formation, fibrinolysis, and, like TEG®, is also able to assess platelet function. The Sonoclot® process is similar to ROTEM® and TEG®, although Sonoclot® is able to use either a whole blood or plasma sample, citrated blood samples can be used but are not required.²⁶ A hollow, open-ended disposable plastic probe is mounted on the transducer head. The test sample (blood or plasma) is added to the cuvette containing the reagents. A similar volume to ROTEM® and TEG® is used – 330 to 360 µl. As with ROTEM® it is the probe that moves within the sample, however, rather than moving horizontally the probe moves up and down along the vertical axis. As the sample starts to clot changes in impedance to movement are measured. Like TEG® and ROTEM®, Sonoclot® produces a qualitative graphical display of the clotting process and also produces quantitative results of activated clotting time, the clot rate and the platelet function (Figure 3, Table 4).³ However, the measure of activated clotting time (ACT) produced by Sonoclot® reflects initial fibrin formation whereas the equivalent measures produced by TEG® and ROTEM® reflects a more developed and later stage of initial clot formation.³ Most information on clot formation is available after 15 minutes. If details on platelet function are required this may take up to 20-30 minutes.²⁶

Table 4 Summary of Sonoclot® assays

Assay	Activator/Inhibitor	Role
SonACT	Celite	Large-dose heparin management without aprotinin
kACT	Kaolin	Large-dose heparin management with/without aprotinin
aiACT	Celite + Clay	Large-dose heparin management with aprotinin
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.

Figure 5 Sonoclot® Analysis and interpretation of results



Comparison of viscoelastic testing devices

We will refer to the three technologies, ROTEM®, TEG® and Sonoclot®, as a class as “viscoelastic testing point of care coagulation testing devices” or “VE devices,” however, data from each device will be analysed separately and the devices will not be treated as equivalent. Table 6 provides an overview of the different terms used by each device to refer to the different test outputs. This table also summarises the factors affecting clot formation at each stage and the different therapeutic options. A recent study comparing the costs of TEG® and ROTEM® found that TEG® was cheaper than ROTEM® based on costs provided by the manufacturers in 2008.²⁷ However, it should be noted that the platelet function assay costs £70 so if this assay is used the cost of TEG® is greatly increased. A detailed breakdown of costs is provided in Table 5. Similar costs were not available for Sonoclot®.

Table 5 Comparison of costs of TEG® and ROTEM® based on 2008 costs²⁷

Cost	TEG®	ROTEM®
List Price	£13 500 for 2 channel unit; £26 000 for 4 channel unit	£21 662 for standard 4 channel unit
Cost of reagents	Kaolin vials (for standard testing) £2.52 each, functional fibrinogen £8.33 each, platelet function £70 each.	Varies according to test: £0.29-£2.68
Cost of single test	£7.57 (only 1 cup/channel required for basic test)	£8.83 (2 cups channels required for basic test)
After care cost	£2000/year for 2 channel single unit; £1700 for each additional unit	£1400/year
Training	Minimum 2 days on-site with 24-h on call facility; as many follow-up training days as required in first 6 months; 1 day/month for next 6 months	Two days on site + 1 refresher day for 4 operators; any further training £1500/day plus expenses

Table 6 Stages of clot formation, factors affecting the clot, therapeutic options and terms used in TEG®, ROTEM® and Sonoclot®^{1, 3}

Development of clot	Factors affecting clot ²⁸	Therapeutic Options	ROTEM®	TEG®	Sonoclot®
Measurement period	NA	NA	RT	-	-
Initial clot/fibrin formation	Factor XII and X1 activity; reflective of intrinsic pathway if activators not used	Administration of plasma, coagulation factors, fibrinogen or platelets.	Clotting time (CT)	R	ACT
Development of clot or rapidity of clot formation	Factor II and VIII activity; platelet count and function, thrombin, fibrinogen, HCT		Clot formation time (CFT) and α angle (α)	Kinetics (k) and α angle (α)	CR
Maximum clot strength	Fibrinogen, platelet count and function, thrombin, factor XIII activity, HCT		Maximum clot firmness (MCF)	Maximum amplitude (MA)	Peak amplitude
Time to maximum clot strength			MCF-t	TMA	Time to peak
Amplitude (at set time)			A5, A10...	A (A5, A10..)	-
Clot elasticity			MCE	G	-
Maximum lysis	Fibrinolysis	Antifibrinolytic drugs and additional measures such as administration of fibrinogen or platelets.	ML	-	R ₃
Lysis at fixed time			LY30, LY45, LY60	CL30, CL45, CL60	
Time to lysis			CLT (10% from MCF)	TTL (2mm drop from MA)	
Maximum lysis			CLR	—	
Platelet function	Platelet function	Platelets	—	Platelet function	PF

2.4 Platelet function tests

VE tests are often performed in combination with platelet function tests in patients receiving antiplatelet drugs such as aspirin and clopidogrel. Whilst light transmission aggregometry in platelet rich plasma is the gold standard test for platelet function, a number of rapid near patient tests are available.²⁹ One of the most commonly used is the platelet function analyser (PFA) 100 (Dade-Behring, Marburg, Germany).³⁰ A more recently developed test which is commonly used in combination with ROTEM® is the Multiplate analyzer (Roche), a near patient test designed to detect platelet dysfunction.³¹ It uses whole blood and is based on the principle of impedance platelet aggregometry (IPA). It has a turnaround time of 10 minutes and can process up to 30 tests per hour. As mentioned above, both TEG® and Sonoclot® can run specific platelet mapping assays – the TEG® platelet mapping assay and gbACT+ assay for Sonoclot®. However, some centres prefer to use a separate platelet function test such as the Multiplate analyser instead of these assays.

2.5 Comparator

The comparator for this technology appraisal is a combination of clinical judgement and standard laboratory tests.

Standard laboratory tests for coagulopathy

Standard laboratory coagulation analyses include the following:

Prothrombin time – also used to derive measures *prothrombin ratio (PR)* and *international normalised ratio (INR)*. Measure of the extrinsic pathway of coagulation. It measures factors I (fibrinogen), II (prothrombin), V, VII, and X in blood plasma at 37°C. The sample is added to a test tube containing liquid sodium citrate and centrifuged, tissue factor is then added and the time the sample takes to clot is measured. The prothrombin ratio is the prothrombin time for a patient, divided by the result for control plasma. The INR is the ratio of a patient's prothrombin time to a normal (control sample) raised to the power of the ISI value for the analytical system used. The ISI value indicates how a particular batch of tissue factor compares to an international reference tissue factor.

Activated partial thromboplastin time (aPTT) – measures the “intrinsic” or contact activation pathway and the common coagulation pathway. An activated matrix (e.g. silica, celite, kaolin, ellagic acid) and calcium are mixed into the plasma sample and the time the sample takes to clot is measured.

Activated clotting/coagulation time (ACT) – based on ability of whole blood to form a visible fibrin monomer in a glass tube. Used to measure heparin anticoagulation.

Platelet count – In general a low platelet count is associated with an increased risk of bleeding. It is a purely quantitative measure and cannot detect pre-existing, drug-induced, or perioperatively acquired platelet dysfunction.²

Plasma fibrinogen concentration – a number of assays are available to assess plasma fibrinogen levels, the Clauss fibronigen assay is the most common and is based on the thrombin clotting time. Diluted plasma is clotted with a high concentration of thrombin at 37°C and the clotting time is measured. The result is compared with a calibration curve prepared by clotting a series of dilutions of a reference plasma sample of known fibrinogen concentration to give a result in g/L. Most laboratories use an automated method in which clot formation is considered to have occurred when the optical density of the mixture has exceeded a certain threshold.³²

These test have a number of limitations for prediction and detection of perioperative coagulopathy as they were not developed to predict bleeding or guide coagulation management in a surgical setting. In general, they are only able to identify that the 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°C which limits the detection of coagulopathies induced by hypothermia.² The aPTT and INR tests only affect the initial formation of thrombin in plasma without the presence of platelets or other blood cells. These tests are also not able to provide any 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 so long that it does not reflect the current state of the coagulation system when the results are reported.²

2.6 Care pathway

Current care pathway

The exact care pathway and use of standard coagulation testing before, during, and after surgery, will vary according to the specific type of surgery. Some centres routinely screen all patients pre-operatively for coagulation disorders using standard laboratory coagulation tests such as the PT and aPTT tests.³³ However, UK guidelines published in 2008 do not recommend routine coagulation tests to predict perioperative bleeding risk in unselected patients before surgery.³⁴ Instead, preoperative testing should only be considered in patients at risk of a bleeding disorder, for example those with liver disease, family history of inherited bleeding disorder, sepsis, diffuse intravascular coagulation, pre-eclampsia, cholestasis and those at risk of vitamin k deficiency.³³

It is generally recommended that patients stop taking anticoagulant medications (clopidogrel, warfarin, and aspirin) a number of days before surgery to reduce the risk of bleeding during surgery.^{11, 35} In the event of emergency surgery this may not be possible in which case coagulation testing should be performed.³³ If the surgery involves cardiopulmonary bypass (CPB) then heparin may be administered prophylactically to reduce the risk of clotting whilst on CPB.³⁵ It is essential to monitor heparin anticoagulation if this has been administered. An initial ACT test should be performed after the first surgical incision and be repeated at regular intervals during surgery.³⁶ Standard coagulation tests (platelet count, fibrinogen concentration, INR, PT, aPTT) are most commonly used to assess the coagulation status of patients who are experiencing high blood loss during surgery. However, these generally take too long to give a result that can inform treatment decisions. Instead decisions on how to treat the bleed have to be based largely on clinical judgement. The same tests are used after surgery to monitor coagulation status.

If bleeding occurs surgical intervention may be needed or packed erythrocytes are transfused if required. This is generally to maintain a haemoglobin concentration above 6g/dL during CPB and 8g/dL after CPV or according to other requirements as indicated by national guidelines. Other therapeutic options depending on laboratory test results include fibrinogen concentrate (bleeding patients with abnormal fibrinogen), fresh frozen plasma (if after transfusion of packed erythrocytes new laboratory results were not available and/or bleeding did not stop after fibrinogen administration), prothrombin complex concentrate (abnormal INR or aPTT), antithrombin concentrate (when ACT analyses not controlled by heparin alone), desmopressin (suspected platelet dysfunction), platelet concentrates (low platelet count).³⁵ If bleeding continues despite these treatments then additional treatment options include factor XIII concentrate and activated recombinant factor VII or factor VIIa.^{11,}
³⁵ Heparin dose adjustments may be made to try and control the bleeding.

Role of VE in the care pathway

VE can be repeatedly performed during and after surgery and so can provide a dynamic picture of the coagulation process during and after surgery. The role of VE in the care pathway is unclear. It could be used either as an *add-on* test in which case it would be performed as well as standard laboratory tests, or it could be as *replacement* test in which case standard laboratory tests would no longer be needed.

If VE does not prevent the need for standard laboratory tests and provides complementary findings then it should be performed in addition to any laboratory coagulation tests already recommended for specific populations. However, if the standard laboratory tests do not offer any supplementary information to that provided by VE then there should no longer be a need for standard tests and VE should replace some or all of the standard laboratory tests. VE offers two key potential benefits over standard laboratory tests: the shorter timescale in which they are able to provide results and the additional information on the clotting process which they offer compared to standard tests. It is hypothesised that by providing additional information and quicker results that requirements for blood products could be targeted and

so the patient is not subjected to risks associated with unnecessary transfusion. Time in theatre, resource use, length of stay in a critical care unit, length of hospital stay, blood product usage, and the associated costs may therefore be reduced.

3 Objectives

The overall objective of this project is to summarise the evidence on the clinical- and cost-effectiveness of VE devices to assist with the diagnosis, management and monitoring of haemostasis disorders during and after cardiac surgery or trauma induced coagulopathy.

We have defined the following research questions to address the review objective:

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?
 - a) If there are no data on one or more of the VE devices we will evaluate the accuracy of that or 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 (including post-partum haemorrhage) who are tested with VE devices compared to those who are not tested?
 - a) If there are no data on one or more of the VE devices we will evaluate the accuracy of that or those VE device(s) for the prediction of relevant clinical outcomes (e.g. transfusion requirement) in patients with trauma induced coagulopathy.
3. What is the cost-effectiveness of VE devices during or after cardiac surgery?
4. What is the cost-effectiveness of VE devices in patients with trauma induced coagulopathy? If sufficient data are available from the systematic review, scenario analyses may be run using data from the post-partum haemorrhage population in the trauma model. All analyses in trauma and post-partum haemorrhage populations will be limited to those outcomes (e.g. transfusion requirement) which are considered applicable to all included populations; this is a pragmatic approach adopted because any long term consequences are likely to differ widely both within a heterogeneous general trauma population and between general trauma and post-partum haemorrhage populations.

4 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care³⁷ and NICE Diagnostic Assessment Programme manual.³⁸

4.1 Inclusion and exclusion criteria

Inclusion criteria for each of the three clinical review questions are summarised in Table 7. Studies which fulfil these criteria will be eligible for inclusion in the review.

Table 7 Inclusion criteria

Question	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?	a) What is the accuracy of VE devices for the prediction of relevant clinical outcomes during or after cardiac surgery?	2. How do clinical outcomes differ among patients with coagulopathy induced by trauma (including post-partum haemorrhage) who are tested with VE devices compared to those who are not tested?	2a. What is the accuracy of VE devices for the prediction of relevant clinical outcomes in patients with coagulopathy induced by trauma (including post-partum haemorrhage)?
<i>Participants</i>	Adult (age ≥18 years) patients undergoing cardiac surgery		Adult (age ≥18 years) with clinically suspected coagulopathy induced by trauma (including post-partum haemorrhage). Studies in both military and civilian settings will be included.	
<i>Index test</i>	VE devices (ROTEM®, TEG® or Sonoclot®) alone or combined with platelet testing (e.g. multiplate test) or standard testing protocol, performed during or after surgery.	VE devices (ROTEM®, TEG® or Sonoclot®)	VE devices (ROTEM®, TEG® or Sonoclot®) or standard testing protocol	VE devices (ROTEM®, TEG® or Sonoclot®)
<i>Comparators</i>	No testing, standard testing protocol, or other VE device	Any other VE device or None	No testing, standard testing protocol, or other VE device	Any other VE device or None
<i>Reference standard</i>	NA	Patient relevant outcomes e.g. Massive transfusion, any transfusion	NA	Patient relevant outcomes e.g. Massive transfusion, any transfusion
<i>Outcomes</i>	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
<i>Study design</i>	Randomised controlled trials; if insufficient RCTs are available then	Diagnostic cohort studies	Randomised controlled trials; if insufficient RCTs are available then	Diagnostic cohort studies

	lower levels of evidence will be considered		lower levels of evidence will be considered	
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4.2 Clinical effectiveness search methods

Search strategies will be based on index test (ROTEM® Delta), as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care³⁷ and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.³⁹ Searches for studies for cost and quality of life will be developed separately.

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords associated with ROTEM®, thromboelastography and thromboelastometry will be adapted according to the configuration of each database.

The following databases will be searched for relevant studies from inception to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet)
<http://regional.bvsalud.org/php/index.php?lang=en>
- International Network of Agencies for Health Technology Assessment (INAHTA) Publication (Internet)

<http://www.inahta.org/>

- Biosis Previews (Web of Science)
- Conference Proceedings Citation Index – Science (Web of Knowledge)
- NIHR Health Technology Assessment Programme (Internet)

- Aggressive Research Intelligence Facility (ARIF) database (Internet)

<http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx>

- MEDION database (Internet)

<http://www.mediondatabase.nl/>

- PROSPERO (International Prospective Register of Systematic Reviews) (Internet)

<http://www.crd.york.ac.uk/prospero/>

Completed and ongoing trials will be identified by searches of the following resources (2000-present):

- NIH ClinicalTrials.gov (<http://www.clinicaltrials.gov/>)
- Current Controlled Trials (<http://www.controlled-trials.com/>)
- WHO International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictcp/en/>)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. We will also screen the website set up by the manufacturers of ROTEM® Delta which lists relevant studies.⁴⁰ References in retrieved articles and relevant systematic reviews will be checked.

No restrictions on language or publication status will be applied. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in Appendix 2; these will be adapted as necessary following consultation with clinical experts. It is anticipated that the core device terms strategy may be combined with additional facets to retrieve specific targeted topics, such as randomised controlled trials or studies of use in trauma care. Additional supplementary searches will be carried out as necessary. The main Embase strategy for each search will be

independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist.⁴¹ Identified references will be downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles will be checked for additional studies. The final list of included papers will also be checked on PubMed for retractions, errata and related citations.⁴²⁻⁴⁵

4.3 Review strategy

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following (where applicable): study design/details, participants, VE device, specific reagents used, clinical outcomes, accuracy for the prediction of clinical outcomes and test failure rates. Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.4 Quality assessment strategy

The methodological quality of included RCTs will be assessed using the Cochrane Risk of Bias Tool.⁴⁶ Diagnostic accuracy studies will be assessed for methodological quality using QUADAS-2.⁴⁷ Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Methods of analysis/synthesis

We will provide a narrative synthesis involving the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be

organised by research question addressed and VE device. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological limitations of the existing evidence base.

If sufficient data are available meta-analysis will be used to pool data. For studies comparing VE testing with no testing, summary estimates of treatment effect (e.g. hazard ratios, odds ratio, relative risks, weighted mean differences) together with 95% CIs will be estimated using DerSimonian and Laird random effects models. For diagnostic accuracy studies, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions will be calculated. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve.⁴⁸⁻⁵⁰ Forest plots will be used to display results from individual studies and summary estimates to allow visual assessment of heterogeneity. Heterogeneity will be assessed statistically using the τ^2 and I^2 statistics. If sufficient data are available, any observed heterogeneity will be investigated using meta-regression or stratified analysis. Variables that will be investigated as possible sources of heterogeneity include patient demographics (age, gender, surgery type), type of VE device (ROTEM®, TEG®, Sonoclot®), time point of surgery (during surgery only, during and after surgery, if sufficient data are available the time frame following surgery will also be investigated) and risk of bias domains.

5 Methods for synthesising evidence of cost-effectiveness

5.1 Identifying and reviewing published cost-effectiveness studies

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed. A review of published economic evaluations will be undertaken on the following databases, utilising a methodological study design filter where appropriate (see Appendix 2):

- MEDLINE (OvidSP)

- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (Wiley)
- Health Economic Evaluation Database (HEED (Wiley)
- EconLit (EBSCO)
- Research Papers in Economics (REPEC) (Internet)

<http://repec.org/>

Supplementary searches may be undertaken to focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses that study VE devices. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.^{38, 51} Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

5.2 Evaluation of costs, quality of life and cost-effectiveness

This project aims to assess the value of VE devices in two different patient populations: cardiac surgery patients and trauma patients with suspected coagulopathy. Therefore two separate economics models will be defined, constructed, analysed, and reported independently. Both models will evaluate the cost-effectiveness of ROTEM®, TEG®, and

Sonoclot® compared to no VE devices as described in section 3.1. If sufficient data are available from the systematic review, scenario analyses may be run using data from the post-partum haemorrhage population in the trauma model. The perspective will be that of the NHS and for the base case analysis a timeframe of one year will be used, as this time frame captures all relevant outcomes. Consequences will be expressed in quality adjusted life years (QALY) and potentially also the number of blood transfusions required. If evidence is found on any important mortality effects of transfusion reduction a lifetime time horizon will be explored in a separate scenario. All analyses in trauma and post-partum haemorrhage populations will be limited to those outcomes (e.g. transfusion requirement) which are considered applicable to all included populations; this is a pragmatic approach adopted because any long term consequences are likely to differ widely both within a heterogeneous general trauma population and between general trauma and post-partum haemorrhage populations. Any assumption used in the models and any parameter value will be based on the literature if possible and supplemented by clinical expert opinion as required.

Model structure

A Cochrane review of TEG® and ROTEM® showed that they are associated with a significant reduction in blood loss during cardiac surgeries. Blood loss can lead to complications such as stroke, renal dysfunction and re-operation to stop excessive bleeding. Also, due to blood transfusion following blood loss, complications such as febrile reaction, haemolytic transfusion reactions and transfusion-transmitted infections can occur. A study by Spalding et al. (2007) showed that the use of ROTEM® led to decreased costs for blood products in their hospital.⁵² Hence, it is important to model transfusion rate for each scenario, and relate blood loss and transfusion related complications to this. A possible structure is suggested by the HTA study done for the NHS Scotland in 2008,¹⁰ see Appendix 4. Input for this model was largely derived from a study by Davies (2006)⁵³ concerning the cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion. Where possible, more recent data sources will be investigated to populate the model.

Final choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts.

Issues relevant to analyses:

- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values and sources of assumptions will be documented.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model for the various health states. QALYs will be calculated from the economic modelling.

Costs

Resource utilisation will be estimated for the diagnostic tests, blood products and treatments related to complications and infections. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators.

6 Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 18/11/2013. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

7 Competing interests of authors

None

8 Timetable/milestones

Milestones	Completion data
Draft protocol	25/07/2013
Final protocol	21/08/2013
Progress report	18/11/2013
Draft assessment report	16/01/2014
Final assessment report	13/02/2014

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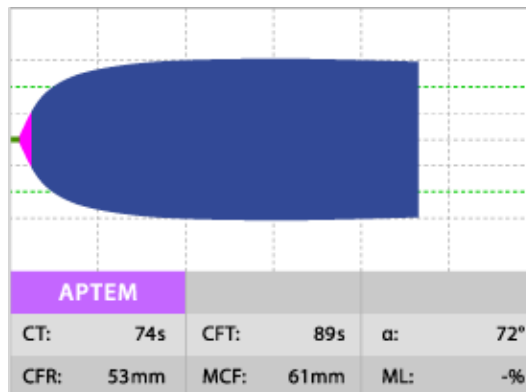
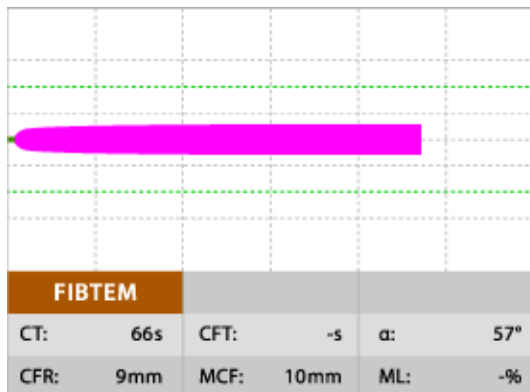
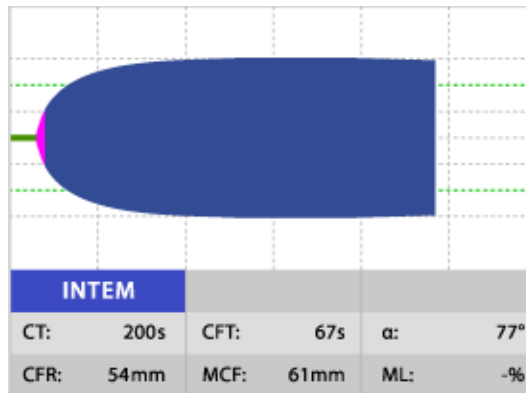
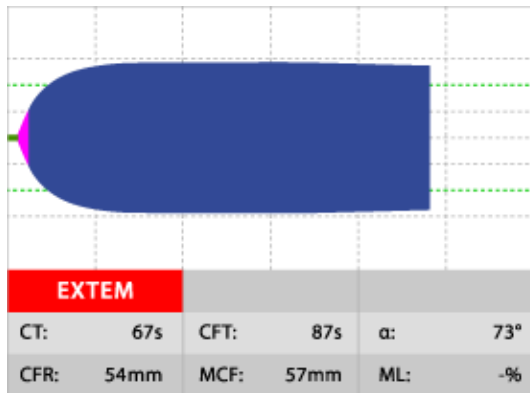
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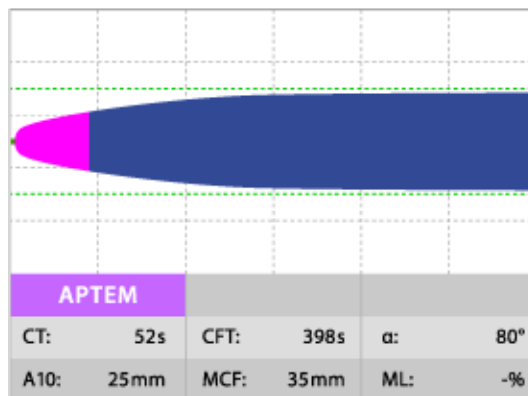
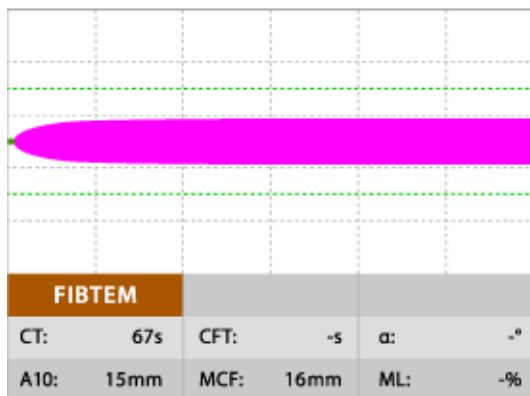
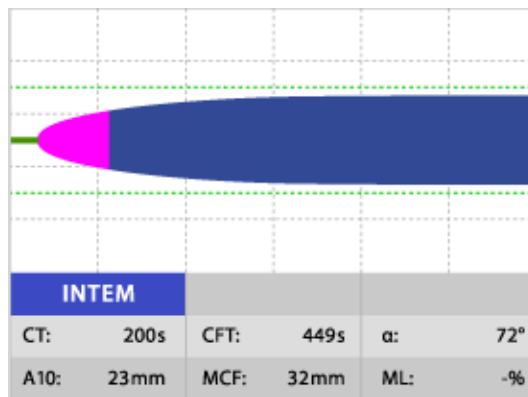
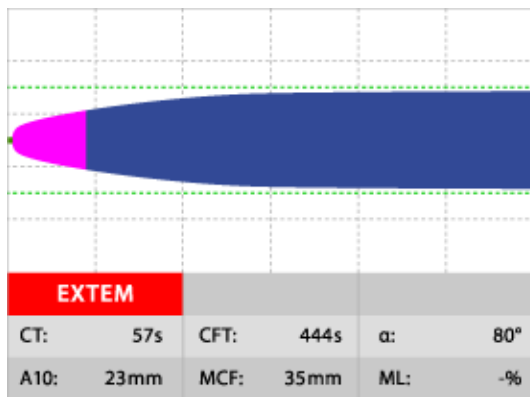
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Appendix 1: ROTEM® Result interpretation⁵⁴

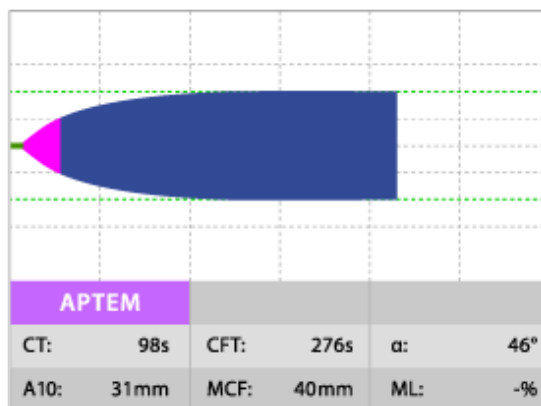
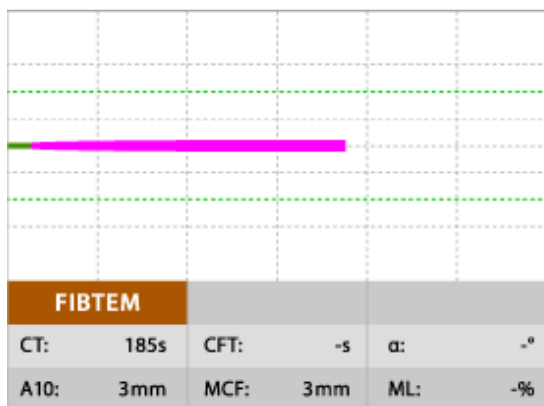
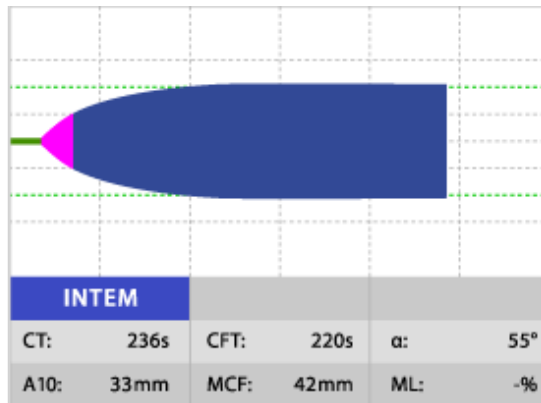
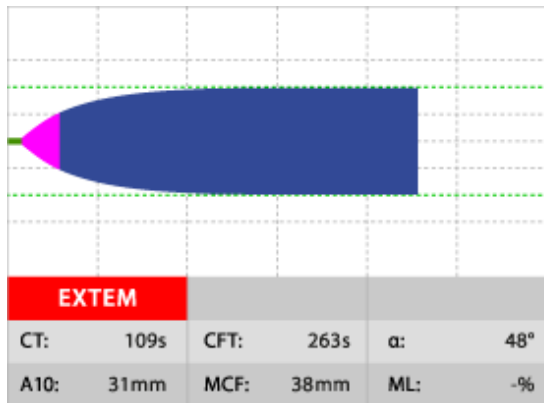
Normal Patient



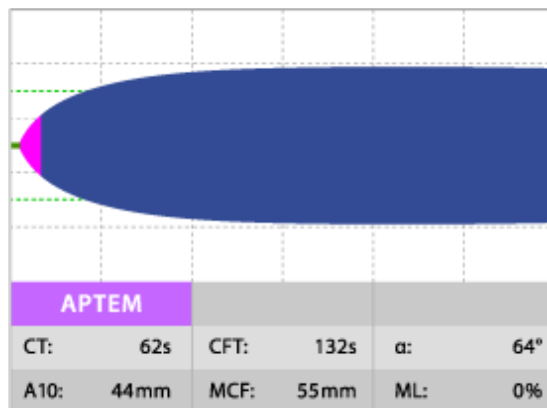
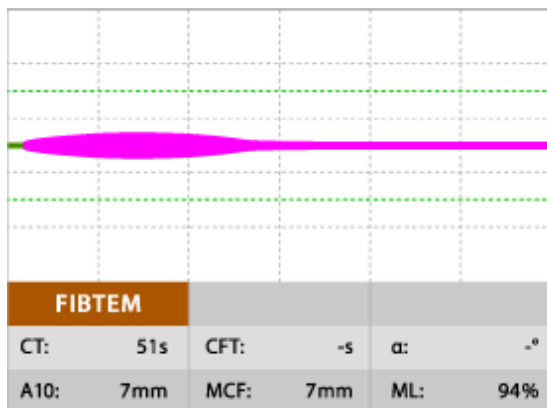
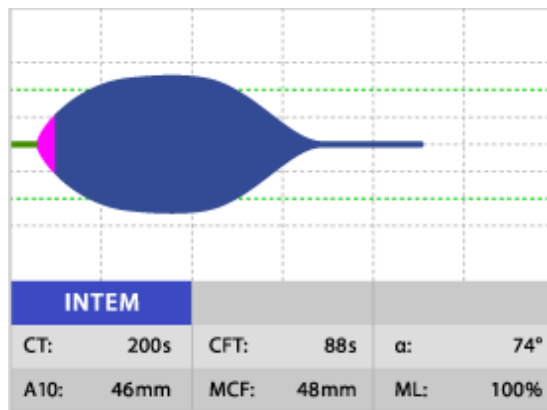
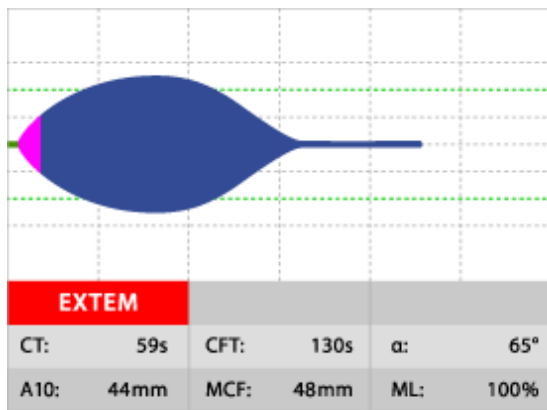
Platelet deficiency



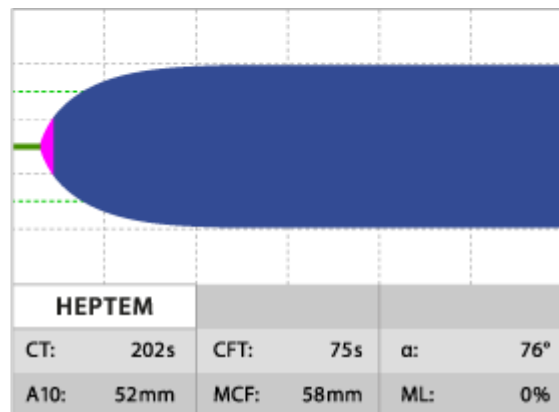
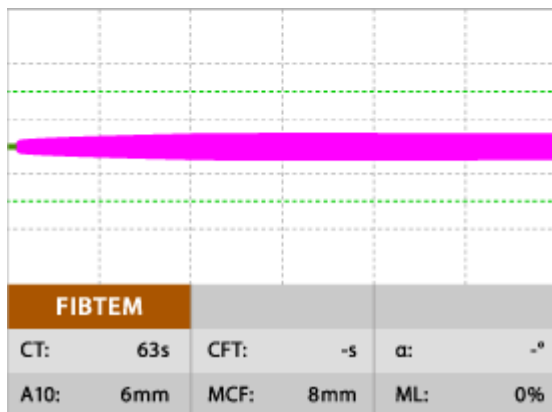
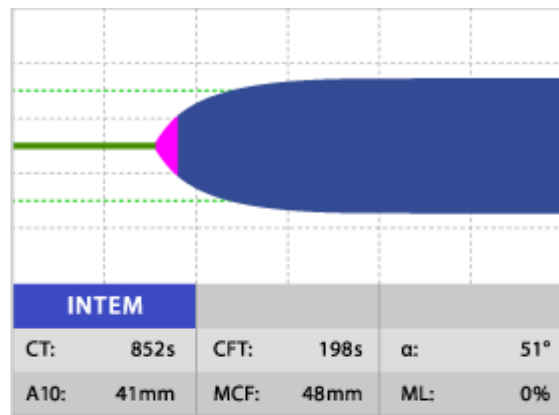
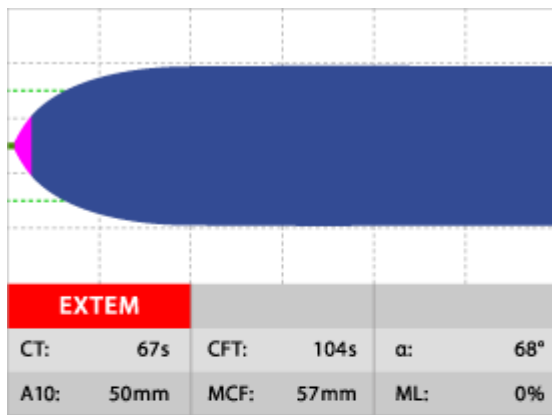
Fibrinogen deficiency



Hyperfibrinolysis



Heparin Influence



Appendix 2: Example search strategies

Clinical effectiveness search

Embase (OvidSP): 1974-2013/08/21

Searched 19.7.13

- 1 Random\$.tw. or clinical trial\$.mp. or exp health care quality/ (3173962)
- 2 animal/ (1884192)
- 3 animal experiment/ (1708883)
- 4 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5789666)
- 5 or/2-4 (5789666)
- 6 exp human/ (14881414)
- 7 human experiment/ (315546)
- 8 or/6-7 (14882855)
- 9 5 not (5 and 8) (4617774)
- 10 1 not 9 (3022408)
- 11 thromboelastography/ (4852)
- 12 (thrombo-elastogra\$ or thrombelastogra\$ or thrombelasto-gra\$).ti,ab,ot,hw,dv. (1536)
- 13 (thromb\$ adj2 elastogra\$).ti,ab,ot,hw,dv. (45)
- 14 (thromb\$ adj2 elasto-gra\$).ti,ab,ot,hw,dv. (2)
- 15 TEG.ti,ab,ot,dv. (1737)
- 16 (haemoscope\$ or hemoscope\$ or haemonetics or hemonectics).ti,ab,ot,hw,dv. (988)
- 17 whole blood h?emosta\$ system\$.ti,ab,ot,hw,dv. (2)
- 18 whole blood h?emo-sta\$ system\$.ti,ab,ot,hw,dv. (0)
- 19 (ROTEM\$ or ROTEG).ti,ab,ot,hw,dv. (758)
- 20 (thrombo-elastomet\$ or thrombelastomet\$).ti,ab,ot,hw,dv. (181)
- 21 (thromb\$ adj2 elastom\$).ti,ab,ot,hw,dv. (6)
- 22 (thromb\$ adj2 elasto?m\$).ti,ab,ot,hw,dv. (6)
- 23 (Sonoclot or sono-clot).ti,ab,ot,hw,dv. (158)
- 24 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system\$ or process or test or tests or analyz\$ or analys\$ or assay\$ or device\$ or measurement\$)).ti,ab,ot,hw,dv. (17)
- 25 or/11-24 (6973)
- 26 10 and 25 (1081)

Trials filter:

Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE (best sens). J Med Libr Assoc 2006;94(1):41-7.

Cost- effectiveness search

Embase (OvidSP): 1974-2013/08/21

Searched 19.7.13

- 1 health-economics/ (33085)
- 2 exp economic-evaluation/ (203646)
- 3 exp health-care-cost/ (195297)
- 4 exp pharmacoeconomics/ (168266)
- 5 or/1-4 (467212)
- 6 (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (581623)
- 7 (expenditure\$ not energy).ti,ab. (23068)
- 8 (value adj2 money).ti,ab. (1294)
- 9 budget\$.ti,ab. (23345)
- 10 or/6-9 (605163)
- 11 5 or 10 (874842)
- 12 letter.pt. (837410)
- 13 editorial.pt. (445235)
- 14 note.pt. (580574)
- 15 or/12-14 (1863219)
- 16 11 not 15 (789071)
- 17 (metabolic adj cost).ti,ab. (857)
- 18 ((energy or oxygen) adj cost).ti,ab. (3132)
- 19 ((energy or oxygen) adj expenditure).ti,ab. (19689)
- 20 or/17-19 (22873)
- 21 16 not 20 (784067)
- 22 exp animal/ (19202400)
- 23 exp animal-experiment/ (1712313)
- 24 nonhuman/ (4113850)
- 25 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4976072)
- 26 or/22-25 (20539135)
- 27 exp human/ (14881414)
- 28 exp human-experiment/ (315546)
- 29 27 or 28 (14882855)
- 30 26 not (26 and 29) (5657249)
- 31 21 not 30 (725363)
- 32 thromboelastography/ (4852)
- 33 (thrombo-elastogra\$ or thrombelastogra\$ or thrombelasto-gra\$).ti,ab,ot,hw,dv. (1536)
- 34 (thromb\$ adj2 elastogra\$).ti,ab,ot,hw,dv. (45)
- 35 (thromb\$ adj2 elasto-gra\$).ti,ab,ot,hw,dv. (2)
- 36 TEG.ti,ab,ot,dv. (1737)
- 37 (haemoscope\$ or hemoscope\$ or haemonetics or hemonectics).ti,ab,ot,hw,dv. (988)
- 38 whole blood h?emosta\$ system\$.ti,ab,ot,hw,dv. (2)
- 39 whole blood h?emo-sta\$ system\$.ti,ab,ot,hw,dv. (0)

- 40 (ROTEM\$ or ROTEG).ti,ab,ot,hw,dv. (758)
- 41 (thrombo-elastomet\$ or thrombelastomet\$).ti,ab,ot,hw,dv. (181)
- 42 (thromb\$ adj2 elastom\$).ti,ab,ot,hw,dv. (6)
- 43 (thromb\$ adj2 elasto?m\$).ti,ab,ot,hw,dv. (6)
- 44 (Sonoclot or sono-clot).ti,ab,ot,hw,dv. (158)
- 45 ((viscoelastic or visco-elastic) adj3 (detection or coagulation) adj2 (system\$ or process or test or tests or analyz\$ or analys\$ or assay\$ or device\$ or measurement\$)).ti,ab,ot,hw,dv. (17)
- 46 or/32-45 (6973)
- 47 31 and 46 (225)

Costs filter:

Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 17.3.11]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Appendix 3: Related NICE guidance

There is no related NICE guidance on this topic. We have screened all guidance related to blood and the immune system.

Appendix 4: Draft model structure

