NICE National Institute for Health and Care Excellence

NICE guidance

Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems)

HealthTech guidance
Published: 20 August 2014

www.nice.org.uk/guidance/htg348

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces DG13.

1 Recommendations

Cardiac surgery

1.1 The ROTEM system and the TEG system are recommended to help detect, manage and monitor haemostasis during and after cardiac surgery.

1.2 The Sonoclot system is only recommended for use in research to help detect, manage and monitor haemostasis during and after cardiac surgery. Research is recommended into the clinical benefits and cost effectiveness of using the Sonoclot system during and after cardiac surgery (see section 7.1).

1.3 Healthcare professionals using the ROTEM system and the TEG system during cardiac surgery should have appropriate training and experience with these devices.

Emergency control of bleeding

1.4 There is currently insufficient evidence to recommend the routine adoption of viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems) in the NHS to help detect, manage and monitor haemostasis in the emergency control of bleeding after trauma and during postpartum haemorrhage. Research is recommended into the clinical benefits and cost effectiveness of using viscoelastometric point-of-care testing to help in the emergency control of bleeding after trauma or during postpartum haemorrhage (see section 7.2).

2 The technologies

2.1 Three viscoelastometric point-of-care testing devices (ROTEM, TEG and Sonoclot systems) used to help detect, manage and monitor haemostasis were included in this assessment. Additional details of the ROTEM, TEG and Sonoclot devices are provided in section 4.

3 Clinical need and practice

The problem addressed

3.1 Viscoelastometric point-of-care testing may be used to determine whether bleeding is a result of coagulopathy (when the blood's ability to clot is impaired) or a surgical bleed. It is mainly used in people who are having major surgery that is associated with high blood loss, such as cardiac surgery, or in people who need emergency control of bleeding caused by trauma or post-partum haemorrhage. Viscoelastometric testing helps guide the clinician to select the most appropriate treatment to stop the bleeding.

3.2 High blood loss is associated with a marked rise in mortality in hospital. Bleeding is a potential complication of any surgical procedure, and the risk of bleeding is proportional to the size and complexity of the surgery.

3.3 The purpose of this assessment is to evaluate the clinical and cost effectiveness of viscoelastometric testing (using the ROTEM, TEG or Sonoclot systems) to detect, manage and monitor haemostasis in cardiac surgery, and in the emergency control of bleeding after trauma and during postpartum haemorrhage.

The condition

3.4 Haemostasis is the term used to describe the process of blood clotting and the subsequent dissolution of the clot after the injured tissue has been repaired. During haemostasis, 4 steps occur in a rapid sequence. First, blood vessels constrict to reduce blood loss. Second, 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 after rupture of the endothelial lining of vessels, and the plug covers the break in the vessel wall. The third step is coagulation or blood clotting. This reinforces the platelet plug with fibrin threads that act as a 'molecular glue'. Finally, the clot must dissolve for

normal blood flow to resume after tissue repair. This happens through the action of plasmin. Abnormalities, in any of these 4 haemostasis steps, either acquired, or of a genetic origin, can lead to bleeding (during and after surgery) or thrombosis.

3.5 The fibrinolysis system is responsible for removing blood clots. During surgery, the body's normal process for managing clots can become severely disrupted, leading to a condition known as 'acquired hyperfibrinolysis'. Acquired hyperfibrinolysis has been observed in a variety of clinical scenarios including liver transplantation, cardiac surgery, vascular surgery, postpartum haemorrhage and severe trauma. 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.

3.6 Coagulopathy is characterised by severe bleeding in the patient. It is not easy to detect by laboratory testing because the classical coagulation tests such as prothrombin time and activated partial thromboplastin time are not sensitive for coagulopathy. However, failure to recognise and treat it can lead to uncontrollable bleeding.

3.7 For 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 surgery. Mortality may be greatly increased when severe bleeding occurs during the operation.

The population

3.8 Two population groups were included in this assessment. These were adult patients (18 years and older) having cardiac surgery, and those who need emergency control of bleeding after trauma and during postpartum haemorrhage.

3.9 Excessive bleeding (more than 2 litres) is encountered in 5% to 7% of people having cardiac surgery. If conventional methods (see section 3.15) to stop bleeding fail, reoperation (in 3.6% to 4.2% of cases) may be needed. Major blood loss is linked to adverse outcomes and associated with an 8-fold increase in the likelihood of death. More than 30,000 people have heart surgery in the UK each

year and adult cardiac surgery accounts for approximately 15% of all allogeneic red cell and allogeneic blood coagulation transfusions.

3.10 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 traffic 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, which may not meet the precise definition of major trauma, are cared for in the same way. People with major trauma often need complex reconstructive surgery.

3.11 Major obstetric haemorrhage occurs in approximately 6.7 per 1,000 births in the UK 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 difficult to quantify because of dilution with amniotic fluid. Also, the physiological changes of pregnancy may mask the normal clinical signs of decrease in blood plasma volume (hypovolaemia).

The diagnostic and care pathways

3.12 There is no NICE clinical guideline on managing blood coagulation during cases of major bleeding.

3.13 Most patients who have elective surgery have normal coagulation but if their history includes any haemostatic disorders then blood coagulation and fibrinogen tests are carried out. If there is no history of abnormal bleeding, British Committee for Standards in Haematology guidelines (2008) do not recommend preoperative coagulation testing. However, some clinicians choose to order coagulation testing that includes prothrombin time, activated partial thromboplastin time, platelet count and international normalised ratio tests. These tests look at specific areas of the clotting cascade and help determine how quickly the blood will clot during some surgical procedures, such as cardiac surgery. The tests are performed on platelet-poor plasma (blood plasma with very low number of platelets) in vitro.

3.14 During some types of elective cardiac surgery, it may be important that the blood does not clot as quickly as normal. In such cases drug treatment (such as

heparin) may be given to slow the clotting time. Conversely, if the patient's blood does not clot quickly enough, drug treatment with antifibrinolytics (like tranexamic acid) and, desmopressin or allogeneic blood transfusion using platelets, fresh frozen plasma or cryoprecipitate, may be used to speed up the clotting process. Coagulation testing in most NHS hospitals takes at least 45 minutes.

3.15 To manage bleeding, early and sufficient blood product support can be given to patients with major blood loss and to those with dilutional coagulopathy. Supportive care with fresh frozen plasma and platelets can be given to patients with severe coagulopathy while the underlying condition is being treated. People with haematological disorders such as myelodysplasia or factor VIII inhibitors will need specialist care. Pharmacological agents such as prothrombin complex concentrate, fibrinogen concentrate and recombinant VIIa can be used to increase haemostatic capacity. The British Committee for Standards in Haematology guidelines on management of major haemorrhage currently state that, during major haemorrhage, prothrombin time and activated partial thromboplastin time should be maintained at less than 1.5 times baseline, platelet count should be maintained at greater than 75 times 10^9 platelets per litre, and fibrinogen level should be maintained at greater than 1.0 g per litre. Transfusion of fresh frozen plasma, platelet and cryoprecipitate should be considered when the levels fall below these figures.

3.16 Complications related to transfusion include transfusion-associated graft-versus-host disease, administration of an incorrect blood component, haemolytic transfusion reaction, transfusion-related acute lung injury, febrile reaction, transfusion associated circulatory overload, acute respiratory distress syndrome, multiple organ failure and infections such as HIV, hepatitis A, B and C, and malaria.

3.17 Surgical reintervention may be necessary to find out the cause of postoperative bleeding. It involves reopening the surgical site and is associated with increased morbidity and mortality. As such, it is only used after all other interventions have failed to, or are deemed unlikely to stop the bleeding.

4 The diagnostic tests

The interventions

The ROTEM system (TEM International)

4.1 The ROTEM system is a point-of-care device used to help detect, manage and monitor haemostasis associated with high blood loss. The device uses thromboelastometry, a viscoelastometric method, to test for haemostasis in whole blood including the initiation of clotting, platelet count, fibrinogen and fibrinolysis.

4.2 During and after surgery, ROTEM is intended to be used to help identify the probable cause of bleeding and to help the clinician determine whether bleeding is a result of a coagulopathy or a surgical bleed.

4.3 ROTEM uses a combination of 5 assays (INTEM, EXTEM, FIBTEM, APTEM and HEPTEM) to characterise the coagulation profile of a sample of whole blood. Initial testing using the INTEM and EXTEM assays can indicate whether there is a clotting factor deficiency. If the initial test results appear normal, this indicates that surgical bleeding rather than coagulopathy is present. Additional assays include FIBTEM, which can indicate a fibrinogen deficiency; APTEM, which can indicate hyperfibrinolysis; and HEPTEM, which can indicate whether coagulopathy is due to the presence of residual heparin. Platelet function analysers may be used in conjunction with ROTEM to test platelet function when patients are taking antiplatelet drugs such as aspirin or clopidogrel.

4.4 The ROTEM analysis is generally done with citrated whole blood near the patient during the surgery, although the device may be positioned in the laboratory. A blood sample is taken from the patient and placed in a cuvette. A cylindrical pin is then immersed and 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. As the clot becomes firmer, it increasingly restricts the rotation of the pin.

4.5 The manufacturer claims that a complete set of results from ROTEM will determine the presence and type of coagulopathy, indicate a need for fibrinogen or platelet administration, and facilitate the monitoring of heparin and protamine. ROTEM also provides information on the qualitative aspect of clot formation by looking at the elasticity of a clot to determine how well certain parameters of the sample are forming.

4.6 Initial results are available within 5 to 10 minutes and full qualitative results are available in 20 minutes. Some results, such as for the diagnosis of fibrinolysis, may take more than 20 minutes.

The TEG system (Haemonetics)

4.7 The thromboelastography (TEG) system is a 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. 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; and a mechanical-electrical signal is relayed through a computer interface where real-time analysis is displayed.

4.8 The TEG assays include:

- a kaolin-activated test, which assesses clot formation, fibrin polymerisation and fibrinolysis
- a kaolin with heparinase test, which assesses clot formation in people who have been given heparin
- a functional fibrinogen assay, which measures the fibrinogen impact on the clot strength (made possible by the suppression of the platelet contribution factor)

- platelet mapping that assesses platelet function and monitors antiplatelet therapy
- a rapid TEG, which provides a more rapid measurement of the clot strength than a standard kaolin assay and is used mainly in emergency situations such as trauma.

4.9 Like ROTEM, TEG measures and graphically displays the changes in viscoelasticity at all stages of the developing and resolving clot. These include the time until initial fibrin formation, the kinetics of fibrin formation and clot development, the ultimate strength and stability of the fibrin clot, and fibrinolysis.

The Sonoclot system (Sienco Inc.)

4.10 The Sonoclot system is also a viscoelastometric device used for measuring coagulation and platelet function. It provides information on haemostasis including coagulation, fibrin gel formation, clot retraction (platelet function) and fibrinolysis.

4.11 The Sonoclot test is performed by placing whole blood into a pre-warmed cuvette in which a vertically vibrating probe is suspended. As the blood clots, increased viscosity causes changes in the mechanical impedance that is exerted on the probe. Clot formation is displayed in real time on a computer which is connected to the device via USB. The Sonoclot device generates both a qualitative graph known as the Sonoclot signature, and quantitative results on the clot formation time (activated clotting time and the rate of fibrin polymerisation or clot rate). These help to identify coagulopathies including platelet dysfunction, factor deficiencies, anticoagulant effect, hypercoagulable tendencies and hyperfibrinolysis.

4.12 The Sonoclot assays include:

- SonACT, which measures large-dose heparin management without aprotonin
- kACT, which measures large-dose heparin management with or without aprotonin

- aiACT, which measures large-dose heparin management with aprotonin
- gbACT+, which measures overall coagulation and assesses platelet function in non-heparinised patients
- H-gbACT+, which measures overall coagulation and assesses platelet function in the presence of heparin.

The comparator

4.13 The comparator for this assessment is a combination of clinical judgement and standard laboratory tests. Standard laboratory coagulation analyses include prothrombin time which is also used to measure prothrombin ratio and international normalised ratio, activated partial thromboplastin time, activated clotting/coagulation time, platelet count and plasma fibrinogen concentration.

4.14 Standard laboratory tests were not developed to predict bleeding or guide coagulation management. They are able to identify when blood is not clotting properly, but they are not able to identify what part of the clotting process is disrupted. Standard laboratory tests are performed on platelet-poor plasma (blood plasma with low number of platelets) and therefore do not reflect the true physiological clotting process. Moreover, they are performed at 37°C, which limits the detection of coagulopathies induced by hypothermia. Standard laboratory tests are unable to provide information on clot formation over time or on fibrinolysis, and so cannot detect hyperfibrinolysis.

4.15 After a blood sample is taken, standard laboratory tests usually take between 40 and 90 minutes to give a result. This turnaround time may be too long for the results to reflect the current coagulation status of the patient.

5 Outcomes

The diagnostics advisory committee considered evidence from several sources.

How outcomes were assessed

5.1 The assessment was performed by an external assessment group and consisted of a systematic review and development of a decision analytical model for viscoelastometric point-of-care testing to help detect, manage and monitor haemostasis.

5.2 The systematic review was carried out to provide evidence on the clinical effectiveness, and the decision analytical model was developed to assess the cost effectiveness.

Clinical effectiveness

5.3 The purpose of the review was to find out how clinical outcomes differ among people who are tested with viscoelastometric devices during or after surgery compared with those who are tested with standard laboratory tests alone. Cardiac surgery, trauma and management of postpartum haemorrhage were included in the assessment. When there were no data on a viscoelastometric device, the accuracy of the device in predicting relevant clinical outcomes (for example, need for transfusion) during or after surgery was evaluated.

5.4 In total, 39 publications of 33 studies were included in the systematic review: 11 randomised controlled trials (RCTs; 14 publications) evaluating ROTEM and TEG and 3 prediction studies that evaluated Sonoclot (because no RCTs evaluating Sonoclot were identified) in cardiac surgery patients; 1 ongoing RCT, 1 controlled clinical trial and 15 prediction studies (18 publications) in trauma patients; and 2 prediction studies (1 publication) in women with postpartum haemorrhage.

Cardiac surgery

5.5 The external assessment group included 11 RCTs (n=1,089, range 22 to 228; 14 publications) for the assessment of viscoelastometric devices in patients having cardiac surgery. Of these RCTs, 6 assessed TEG, 4 assessed ROTEM and 1 assessed ROTEG (an early version of ROTEM). Information on 2 RCTs was only available as abstracts. The RCTs were conducted in Australia, Austria, Germany, Spain, Turkey, the UK and the USA. Most included patients having surgery irrespective of whether or not they had a bleeding event; 2 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 of transfusion procedures. One RCT was restricted to patients having aortic surgery, 2 included patients having coronary artery bypass graft and the remainder included patients having mixed cardiac surgery.

5.6 Mean or median age, when reported, ranged from 53 to 72 years and the proportion of men ranged from 56% to 90%. Most studies did not place any restriction on entry based on anticoagulation use, but 1 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, 2 combined TEG with standard laboratory tests, 2 combined ROTEM with platelet function testing (point-of-care in 1), and 1 combined ROTEM with clinical evaluation. The timing of the viscoelastometric test varied across studies.

5.7 All studies except 1, which performed TEG on arrival at the intensive care unit, administered multiple viscoelastometric tests. Timing included baseline or before bypass or anaesthesia, after cardiopulmonary bypass, after protamine administration, on admission to intensive care unit and up to 24 hours post-cardio-pulmonary bypass in 1 study. Four studies only performed viscoelastometric testing after surgery in patients who were continuing to bleed. Four studies used an algorithm based on standard laboratory tests in the control group; all other studies stated that control groups included combinations of clinical judgement and standard laboratory tests.

5.8 There were a number of methodological issues with the RCTs included in this assessment. Only 3 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 at 'high' risk of bias on at least 50% of the assessed criteria.

5.9 The external assessment group included 3 prediction studies conducted in Switzerland and the USA, which evaluated Sonoclot, because no RCTs were available. Two of these also evaluated TEG and so provided a direct comparison between the 2 devices. Mean or median age, when reported, ranged from 63 to 65 years and the proportion of men ranged from 61% to 69%. All of the studies included patients having mixed cardiac surgery irrespective of whether or not they had a bleeding event. Patients with a known coagulopathy were excluded in 1 study and another study excluded patients with abnormal preoperative coagulation. Both studies excluded patients receiving anticoagulants and 1 also excluded patients on antiplatelet treatment. None of the 3 studies reported follow-up of patients to assess the potential effects of different testing regimens on longer-term transfusion-related complications and mortality.

5.10 The external assessment group assessed the risk of bias and the applicability of the 3 studies. The main areas of concern were the patient selection process, which was unclear in all cases, and whether the way in which viscoelastometric testing was applied was applicable to the objectives of the assessment. Two of the studies were rated as having 'high' applicability concerns for the intervention because they assessed the predictive ability of selected individual parameters of viscoelastometric testing, rather than the device as a whole, or reporting data for all assays and parameters measured by the device.

Evidence on outcomes

Red blood cell transfusion

5.11 Eight RCTs evaluated red blood cell transfusion within 24 to 48 hours as a continuous outcome. All 8 RCTs reported lower volume of red blood cell transfusion in the viscoelastometric algorithm group compared with the control group but this was only statistically significant in 3 RCTs (2 of ROTEM and 1 of TEG). One RCT, which assessed ROTEM, did not report on the statistical significance of the difference. Six RCTs provided dichotomous data (having 2

possible values) on the number of patients who received red blood cell transfusion in each intervention group. The summary relative risk was 0.88 (95% confidence interval [CI] 0.80 to 0.96) suggesting a significant beneficial effect of the viscoelastometric testing algorithm in reducing the number of patients who received red blood cell transfusion. There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to viscoelastometric device: relative risk 0.86 (95% CI 0.72 to 1.02) for the 3 RCTs that evaluated TEG and 0.88 (95% CI 0.78 to 1.00) for the 3 RCTs that evaluated ROTEM and ROTEG.

Any blood transfusion

5.12 Three RCTs evaluated any blood product transfusion as a continuous outcome. All 3 reported lower volume of any blood product transfusion in the viscoelastometric algorithm group compared with the control group. This was statistically significant in 2 (1 ROTEM and 1 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 to 1.02) and the other assessed TEG (relative risk 0.63, 95% CI 0.44 to 0.92). The summary relative risk was 0.79 (95% CI 0.57 to 1.08) suggesting a beneficial effect of the viscoelastometric testing algorithm in reducing the number of patients who received any blood product transfusion. However, this effect did not reach statistical significance. There was some evidence of heterogeneity across studies (I^2=64%).

Factor VIIa transfusion

5.13 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 to 1.17) suggesting a beneficial effect of the ROTEM testing algorithm. However, this difference did not reach statistical significance. There was no evidence of heterogeneity across studies (I^2=0%).

Fresh frozen plasma transfusion

5.14 All the included RCTs evaluated fresh frozen plasma transfusion either as a continuous or dichotomous outcome. Fresh frozen plasma transfusion within 24 to 48 hours was evaluated as a continuous outcome in 10 RCTs. All but 2 RCTs reported lower volume of fresh frozen plasma transfusion in the viscoelastometric algorithm group compared with the control group. This was statistically significant in 6 RCTs (2 of ROTEM and 4 of TEG); 3 did not report on the statistical significance of the difference. Dichotomous data on the number of patients who received fresh frozen plasma transfusion in each intervention group were reported in 5 RCTs. The summary relative risk was 0.47 (95% CI 0.35 to 0.65), suggesting a significant beneficial effect of the viscoelastometric testing algorithm in reducing the number of patients who received a fresh frozen plasma transfusion. There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to viscoelastometric device; relative risk 0.52 (95% CI 0.20 to 1.35) for the 3 RCTs that evaluated TEG and 0.46 (95% CI 0.34 to 0.63) for the 2 RCTs that evaluated ROTEM.

Fibrinogen concentrate transfusion

5.15 Fibrinogen concentrate transfusion was evaluated as a continuous outcome in 3 RCTs which used ROTEM as the intervention. All 3 reported no difference in the volume of fibrinogen concentrate transfused between the viscoelastometric algorithm group and the control group. Dichotomous data on the number of patients who received a fibrinogen concentrate transfusion in the intervention group were also provided in 2 RCTs. The summary relative risk was 0.94 (95% CI 0.77 to 1.14) suggesting no difference between the treatment groups.

Platelet transfusion

5.16 All the included RCTs evaluated platelet transfusion as either a continuous or dichotomous outcome. Platelet transfusion within 24 to 48 hours was evaluated as a continuous outcome in 8 RCTs (4 used TEG and 4 used ROTEM as the intervention). All reported lower volume of platelet transfusion in the

viscoelastometric algorithm group compared with the control group but this was only statistically significant in 5 (2 of ROTEM and 3 of TEG). Statistical significance of the difference was not reported in 2 RCTs. Dichotomous data on the number of patients who received a platelet transfusion in each intervention group were reported in 6 RCTs (3 used TEG and 3 used ROTEM as the intervention). The summary relative risk was 0.72 (95% CI 0.58 to 0.89) suggesting a significant beneficial effect of the viscoelastometric testing algorithm in reducing the number of patients who received a platelet transfusion. There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to viscoelastometric device; relative risk 0.56 (95% CI 0.36 to 0.86) for the 3 RCTs that evaluated TEG and 0.78 (95% CI 0.60 to 1.00) for the 3 RCTs that evaluated ROTEM and ROTEG.

Prothrombin complex concentrate transfusion

5.17 Prothrombin complex concentrate transfusion was evaluated as a continuous outcome in 3 RCTs. All 3 reported lower volume of prothrombin complex concentrate transfusion in the viscoelastometric algorithm group compared with the control group but this was only statistically significant in 1 RCT while a second did not report on the statistical significance of the difference. Dichotomous data on the number of patients who received a prothrombin complex concentrate transfusion in each intervention group were reported in 2 of the 3 RCTs. The summary relative risk was 0.39 (95% CI 0.08 to 1.95) suggesting no difference between the treatment groups.

Bleeding

5.18 Bleeding was evaluated as a continuous outcome in 9 RCTs. Most reported less bleeding in the viscoelastometric intervention group; however, only 2 reported a statistically significant difference in bleeding between the 2 groups.

5.19 The 3 predictive studies that evaluated Sonoclot provided data which allowed calculation of odds ratios for predicting bleeding in patients who tested positive on a particular test or test parameter (Sonoclot, TEG or standard laboratory tests) compared with those who tested negative. Positive results on standard

laboratory 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 the parameters investigated, with the exception of 1 TEG and 1 Sonoclot parameter, were associated with a statistically significant increased risk of bleeding. Two of the standard laboratory tests (prothrombin time and activated partial thromboplastin time) showed higher odds ratios than other parameters, but confidence intervals overlapped with other standard laboratory tests and TEG and Sonoclot parameters.

5.20 Another study evaluated each test class as a whole (that is, 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, performed in 1989, 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.

Reoperation

5.21 Dichotomous data on the number of patients who needed reoperation to investigate bleeding in each intervention group were reported in 7 RCTs. The summary relative risk was 0.72 (95% CI 0.41 to 1.26), suggesting a beneficial effect of the viscoelastometric testing algorithm in reducing the number of patients needing reoperation. However, this difference was not statistically significant. There was no evidence of heterogeneity across studies (I^2=0%). Summary estimates were similar when stratified according to viscoelastometric device; relative risk 0.75 (95% CI 0.31 to 1.83) for the 5 RCTs that evaluated TEG and 0.69 (95% CI 0.33 to 1.44) for the 2 RCTs that evaluated ROTEM.

Surgical source of bleeding identified on reoperation

5.22 Dichotomous data on the number of patients in whom a surgical source of bleeding was identified on reoperation was reported in 4 RCTs. The summary relative risk was 1.04 (95% CI 0.42 to 2.57) suggesting no difference between the

groups. 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 to 2.87). The summary estimate for the 3 RCTs assessing TEG was similar at 0.99 (95% CI 0.18 to 5.36).

Length of intensive care unit stay

5.23 The length of intensive care unit stay was evaluated as a continuous outcome in 4 RCTs. All reported shorter stays in the viscoelastometric group compared with the control group but this difference was only statistically significant in 1 study.

Length of hospital stay

5.24 The length of hospital stay was evaluated as a continuous outcome in 4 RCTs. All reported similar durations of stay in the viscoelastometric and standard laboratory test groups.

Mortality

5.25 Dichotomous data on the number of deaths (within 24 hours, 48 hours, in hospital or 'early mortality') in each intervention group were reported in 4 RCTs. The summary relative risk was 0.87 (95% CI 0.35 to 2.18) suggesting no difference between the intervention groups. 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 to 2.87) and the summary estimate for the 3 RCTs assessing TEG was similar at 0.88 (95% CI 0.21 to 3.66). An additional RCT provided data on 6-month mortality. This study reported statistically significantly reduced mortality in the viscoelastometric testing group at 6 months compared with the standard laboratory test group (relative risk 0.20, 95% CI 0.05 to 0.87).

Trauma

5.26 The external assessment group identified 1 ongoing RCT that is comparing the

TEG (rapid assay) with standard laboratory testing (international normalised ratio, fibrinogen, D-dimer) in adults with blunt or penetrating trauma who are likely to need a transfusion of red blood cells within 6 hours from admission as indicated by clinical assessment. The study authors provided the external assessment group with additional information on the trial (in the form of a study protocol). The outcomes being evaluated in this study include quality and quantity of blood products transfused, patterns of transfusion ratios of red blood cell, fresh frozen plasma, bleeding-related deaths classified as very early mortality (less than 2 hours post-injury),early mortality and late mortality, cessation of coagulopathic bleeding and multiple organ failure. Results from this study are not yet available.

5.27 Because no other RCTs were identified, the external assessment group considered lower levels of evidence. One controlled clinical trial reported as an abstract was included. This study compared a rapid-TEG guided protocol with a standard transfusion protocol in adult trauma patients needing massive transfusion (defined as more than 12 red blood cell units in 24 hours, or more than 4 red blood cell units in 4 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, systemic inflammatory response syndrome, multiple organ failure, sepsis, deep vein thrombosis, stroke, acute coronary syndrome, or days to discharge. There was a statistically non-significant trend towards reduced pneumonia, days on the ventilator and intensive care unit days, and a statistically significant trend towards increasing platelet use in the group tested with TEG. No other studies with a concurrent control group were identified for the trauma population.

5.28 There were insufficient data from studies that evaluated differences in clinical outcomes between viscoelastometric-tested and untested populations, and the external assessment group therefore included lower levels of evidence. Fifteen prediction studies (18 publications; n=4,217) were included. Nine studies evaluated TEG of which 4 also evaluated standard laboratory tests. The other 6 studies evaluated ROTEM of which 4 also evaluated standard laboratory tests. No studies of Sonoclot were identified. None of the studies evaluated both TEG and ROTEM in the same patients.

5.29 The prediction studies in trauma patients were conducted in the UK, the USA,

Switzerland, Netherlands, Denmark and Austria. Most included mixed trauma patients but 3 were restricted to patients with blunt trauma and 2 were restricted to patients with traumatic brain injury. One study excluded patients with traumatic brain injury, and 1 excluded patients with isolated head injury. None of the studies restricted inclusion based on bleeding. One study excluded patients who had previously taken anticoagulants and another excluded patients who had recently taken clopidogrel or warfarin. The mean or median age, when reported, ranged from 33 to 49 years. The proportion of men ranged from 59% to 82%. Mean injury severity score, reported in 11 studies, ranged from 12 to 34. Mean Glasgow Coma Scale scores ranged from 11 to 14 but were only reported in 6 studies.

5.30 Outcomes assessed in the studies included any blood product transfusion, fresh frozen plasma transfusion, massive transfusion, massive transfusion of cryoprecipitate, massive transfusion of plasma, massive transfusion of platelets, plasma transfusion, platelet transfusion, red blood cell transfusion, bleeding, neurosurgical intervention and death. Six studies used multiple logistic regression models to estimate odds 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 cell transfusion, age, sex, mechanism of injury, trauma or injury severity, haemoglobin levels and race.

5.31 The main areas of concern with regard to these studies were the process of patient selection and whether the way in which viscoelastometric testing was applied was applicable to the objectives of the assessment. With 2 exceptions, all studies were rated as being at 'high' or 'unclear' risk of bias in the patient selection process. Ten 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 viscoelastometric 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, when the reference standard was 1 or more measure(s) of transfusion requirements, because it was unclear whether or not the decision to transfuse was informed by viscoelastometric testing results. This also resulted in an 'unclear' risk of bias rating with respect to the reference

standard. The remaining 5 studies were rated as 'low' applicability concerns because they reported objective reference standards (for example mortality).

Evidence on outcomes

Red blood cell transfusion

5.32 The ability of viscoelastometric devices to predict red blood cell transfusion was evaluated in 3 studies (2 of TEG, 1 of ROTEM and standard laboratory tests). One study used an end point of any red blood cell transfusion within 12 hours, 1 used an end point of transfusion within 6 hours and 1 did not specify the time point. A positive result (indicating a need for red blood cell transfusion) on each of the parameters assessed, with the exception of CT on ROTEM, was associated with an increased risk of red blood cell transfusion. There were no clear differences between ROTEM parameters or ROTEM and standard laboratory tests in the 1 study that reported multiple evaluations.

Any blood transfusion

5.33 The ability of viscoelastometric devices to predict any blood product transfusion was evaluated in 3 studies (2 of TEG, 1 of ROTEM and standard laboratory tests). 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 result suggesting that the patient's blood was hypercoagulable was associated with a decreased risk of transfusion (odds ratio 0.14, 95% CI 0.03 to 0.76). There were insufficient data to calculate confidence intervals in 1 of the studies so the significance of the odds ratios from this study could not be assessed. The other 2 studies both reported statistically significant associations for all parameters assessed. An overall TEG result indicating that the patient's blood was hypocoagulable was found to be associated with the greatest increased risk of transfusion, but confidence intervals were very wide (odds ratio 180.00, 95% CI 14.15 to 2,289.13). Odds ratios for individual TEG, ROTEM or standard laboratory tests were much smaller, ranging from 2.50 to 15.26.

Massive transfusion

5.34 The ability of viscoelastometric devices to predict massive red blood cell transfusion was evaluated in 6 studies (3 of TEG and 3 of ROTEM). All but 1 also evaluated standard laboratory tests. All used a threshold of 10 units or more of red blood cells 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 odds ratios for at least 1 of the viscoelastometric test components. A further study provided data that permitted calculation of odds ratios. The other 2 studies only provided data on area under the curve together with 95% confidence intervals. 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. Areas under the curve, when reported, were between 0.70 and 0.92 with no clear differences between ROTEM, TEG or standard laboratory tests.

Mortality

5.35 The association of viscoelastometric devices with mortality was evaluated in 7 studies (5 evaluated TEG, 2 evaluated ROTEM and 3 also evaluated standard laboratory tests). Two studies provided data as adjusted odds ratios and 3 further studies provided data that permitted calculation of odds ratios and associated confidence intervals. The other 2 studies only provided data on area under the curve with 95% confidence intervals. These data were also reported in 1 of the studies that reported adjusted odds ratios. A positive result was associated with a statistically significant increased risk of death for most parameters assessed. The only exceptions were 2 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 to 6.20) and an overall TEG result suggesting that a patient's blood was hypocoagulable (odds ratio 0.23, 95% CI 0.03 to 1.91). Three studies that evaluated a ROTEM or TEG result indicating the presence of hyperfibrinolysis showed the strongest association with death with odds ratios ranging from 25 to 147, although confidence intervals were wide. Areas under the curve were

between 0.63 and 0.93 with no clear differences between ROTEM, TEG or standard laboratory tests.

Management of postpartum haemorrhage

5.36 No studies were identified that compared clinical outcomes among patients with postpartum haemorrhage who were tested with viscoelastometric devices compared with those who were not tested.

5.37 Because no studies evaluated differences in clinical outcomes between viscoelastometric-tested and untested populations, the external assessment group included lower levels of evidence. Two prediction studies, reported only as abstracts, were included in the review (n=245). Both studies were conducted in the UK. The outcomes evaluated in the studies varied: 1 assessed the prediction of coagulopathy needing treatment, fresh frozen plasma transfusion and platelet transfusion; the other assessed the prediction of red blood cell transfusion and invasive procedures. One included women with postpartum haemorrhage defined as more than or equal to 1,000 ml blood loss, and the other included women with major obstetric haemorrhage defined as equal to or more than 1,500 ml blood loss.

5.38 The main area of concern with regard to the 2 prediction studies conducted in patients with postpartum haemorrhage was whether the way in which viscoelastometric testing was applied was applicable to the objectives of the assessment.

5.39 Both studies provided data that allowed calculation of odds ratios for predicting outcomes in patients who tested positive on ROTEM compared with those who tested negative. The study that evaluated ROTEM and standard laboratory tests only reported data in a format that allowed calculation of odds ratios for the ROTEM parameter (maximum clot firmness based on FIBTEM analysis) for the prediction of red blood cell transfusion of at least 4 units. There was a strong positive relationship between this parameter and red blood cell transfusion (odds ratio 41.54, 95% CI 9.01 to 191.59).

5.40 The other study reported that a positive ROTEM result was associated with

coagulopathy needing treatment (odds ratio 168.0, 95% CI 15.6 to 1,814.7). This study also evaluated fresh frozen plasma transfusion and platelet transfusion. Data were available to calculate odds ratios for these outcomes but not associated confidence intervals. The ROTEM results were also predictive of both these outcomes but the significance of the association was unclear. The size of the odds ratio was smaller than for the association with coagulopathy needing treatment (76 for fresh frozen plasma transfusion and 19 for platelet transfusion).

Cost effectiveness

5.41 The aim of the external assessment group's economic analysis was to identify the cost-effectiveness of ROTEM, TEG and Sonoclot compared with standard laboratory tests to help detect, manage and monitor haemostasis in patients having cardiac surgery and trauma surgery who have suspected coagulopathy. The cost-effectiveness of viscoelastometric devices was not assessed in the management of postpartum haemorrhage because of the lack of evidence in the clinical effectiveness review.

Review of existing economic analyses

5.42 Searches were carried out to identify cost-effectiveness studies of viscoelastometric point-of-care testing. The searches identified 331 records of which 5 studies fulfilled the inclusion criteria. Two were only available as conference abstracts; 3 were conducted in cardiac patients, 1 in patients having liver transplant and 1 in both cardiac and liver transplant patients.

5.43 One study was a formal cost-effectiveness analysis of viscoelastometric devices in cardiac and liver transplant patients. This study was conducted for the Scottish NHS.

5.44 The other 4 studies were cost-minimisation studies performed alongside a retrospective before and after study. All 4 studies compared the volume and costs of blood transfused before and after the introduction of a viscoelastometric device. Three studies evaluated ROTEM and 1 evaluated TEG. All 4 found that costs were reduced as a result of the introduction of a viscoelastometric device.

Only 1 of the 4 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 by 32%).

Cost-effectiveness model

5.45 For both the cardiac and trauma models, the external assessment group adopted the model structure used in the health technology assessment carried out 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). However, the external assessment group used more recent data sources whenever possible to update the input parameters of the model.

5.46 The models were based on a decision tree that started with the choice of strategy to be followed, that is, viscoelastometric device (ROTEM, TEG or Sonoclot) or standard laboratory tests. Within each strategy, patients then either did or did not receive a transfusion. Transfusion, when it occurs, may be associated with adverse events or complications. Complications were categorised as being related to surgery and/or transfusion, or related to transfusion alone.

5.47 Complications related to surgery and/or transfusions included in the model were: renal dysfunction, myocardial infarction, stroke, thrombosis, excessive bleeding needing reoperation, 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, transfusion-related acute lung injury and febrile reaction.

5.48 In addition, the external assessment group assumed that patients may also experience transfusion-transmitted infections. Transfusion-transmitted infections include bacterial contamination, variant Creutzfeldt–Jakob disease, malaria, human T-cell lymphotropic virus, HIV and hepatitis A, B and C.

5.49 The models' time horizons were set to 1 month and 1 year because the benefits of

a reduction in red blood cell transfusion were considered to have occurred within this time frame. At 1 month, the models reflect the period of hospitalisation and accordingly capture 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), 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 models, a time horizon of 1 year was considered more appropriate, because these infections do not usually appear immediately.

5.50 Costs were estimated from the perspective of the NHS and personal social services. 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. Discounting was not necessary since the longest time horizon was set at 1 year.

Model inputs (cardiac and trauma models)

Red blood cell transfusion

5.51 For the cardiac model, the baseline risk of having a transfusion was estimated based on the number of red blood cell transfusions in the standard laboratory tests group in 4 of the cardiac surgery trials included in the effectiveness review. Since the effectiveness review did not find evidence of a difference in the relative risk of red blood cell transfusion between studies that assessed ROTEM and those that assessed TEG, the external assessment group applied the summary relative risk for red blood cell 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 external assessment group therefore assumed that this summary relative risk could be applied in the Sonoclot model. A beta and a normal distribution were assigned for the probabilistic sensitivity analyses.

5.52 For the trauma model, the baseline risk of red blood cell 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 red blood cell transfusion. A random effects model was used to estimate the mean proportion of patients who received red blood cell transfusion. As there were no data comparing the proportion of transfused patients in a trauma population who received viscoelastometric testing with those who received standard laboratory tests, the external assessment group applied the same relative risk as in the cardiac surgery population.

Complications related to surgery

5.53 Reoperation 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 external assessment group assumed that there was no difference in the direct risk of having a complication between those tested with viscoelastometric devices and those tested with standard laboratory tests. The same assumption was made in Davies et al. (2006). The risk of complications in each testing strategy was influenced indirectly by the different red blood cell transfusion rates associated with each strategy. The probability of experiencing septicaemia was obtained from 1 study. However, the population in this study was not representative of the population in the assessment because it only included patients who received 4 or more units of red blood cell within 1 day of surgery (that is, patients with massive bleed). The external assessment group judged this estimate to be too high and reduced the estimate by an arbitrary factor of 0.5.

5.54 For the trauma model, 2 complications were included: acute respiratory distress syndrome and multiple organ failure. Estimates for the incidence of acute respiratory distress syndrome were obtained from a study of 14,070 trauma patients conducted in the USA, which reported an overall incidence of 4.6%. The same study was used to calculate the proportion of patients with acute respiratory distress syndrome among those who received a transfusion as 15.5%. For multiple organ failure, no studies were found that either provided estimates or allowed direct calculation of incidence for those transfused. However, based on the overall incidence of multiple organ failure being 3 to 5 times higher than that of acute respiratory distress syndrome, the external assessment group considered that a multiple organ failure incidence rate of 30% was a realistic

assumption.

Transfusion-related complications

5.55 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 a UK Serious Hazards of Transfusion report, which collects and analyses anonymised information on adverse events and reactions in blood transfusions from all relevant healthcare organisations in the UK. The observations from the report were corrected for participation in the UK Serious Hazards of Transfusion survey (98%). The external assessment group assumed that the total number of transfused patients per year is around 800,000.

5.56 For the trauma model, the probability of transfusion-related complications was assumed to be the same as that for the cardiac surgery patients. The external assessment group considered this likely to be an underestimation given that people with trauma on average receive more units of blood than cardiac surgery patients, which increases the exposure to various donors.

Transfusion-transmitted infections

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

5.58 For the trauma population, the probability of transfusion-transmitted infections was assumed to be the same as that for the cardiac surgery population. The external assessment group acknowledged that this is likely to be an underestimation, because patients with trauma receive on average more units of blood than cardiac surgery patients, which increases the exposure to various donors.

Mortality

5.59 For the cardiac model, the estimated risk of mortality in the standard laboratory tests group at 1 month was estimated based on the number of deaths reported in 1 study. This study was based on a large sample (n=8,598) of a population that matched the target population for the assessment. It reported a 1-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 gave an overall 1-month mortality of 2.7%.

5.60 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 in the transfused group, the external assessment group used a calibration procedure, meaning that when reliable estimates were available, 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), 1-month mortality was assumed to be zero because it was assumed that these infections appeared after the hospitalisation period. Mortality for various transfusion-related complications and bacterial contamination were derived from the UK serious hazards of transfusion survey, unless they were lower than the calibrated mortality value. Those complications with mortality lower than 4.3% were included in the calibration procedure.

5.61 In order to estimate the mortality associated with the use of viscoelastometric testing, the external assessment group assumed that any mortality benefit from viscoelastometric testing resulted from fewer patients receiving a transfusion. This meant that the 1-month mortality for each group (not transfused, transfused without complications, and transfused with complications) in the viscoelastometric group was assumed to be the same as in the standard laboratory tests group.

5.62 At 1 year, the mortality in the standard laboratory tests group was estimated using data from a study which reported 1-year mortality of 1.2% for non-transfused patients and 7.8% for transfused patients. For the non-transfused

patients, 0.4% mortality at 1 month and 1.2% mortality at 1 year gave a mortality of 0.8% for between 1 and 12 months. Similarly, for the transfused patients, mortality for between 1 and 12 months was calculated as 3.66%. The 1-year mortality for each subgroup of patients in the viscoelastometric group was assumed to be the same as in the standard laboratory tests group.

5.63 For the trauma population, the external assessment group used a random effects model to estimate mortality at 1 month based on the studies included in the effectiveness review. In the standard laboratory tests group, the mean 1-month mortality was 15.7% (95% CI 11.7% to 20.1%). The external assessment group assigned 1-month mortality to transfused and non-transfused patients, such that the overall mortality would be equal to 15.7%. One study was retrieved that showed that mortality was 3.3 times higher among patients who received a transfusion. Therefore, the goal was to estimate mortality such that the weighted average of these gave an overall mortality of 15.7%, the mean mortality in the standard laboratory tests group derived from the systematic review. From this it follows that mortality was 9.1% in patients who did not receive a transfusion and 29.8% in those who did.

5.64 Mortality for the 2 trauma and/or transfusion-related complications acute respiratory distress syndrome and multiple organ failure were estimated from other sources. The probability of mortality was estimated from a trial in acute respiratory distress syndrome patients that reported a mortality of 83 of 385 (21.6%). Data from 2 studies were pooled to estimate the mortality in patients with multiple organ failure, giving an overall mortality of 26.2%.

5.65 One-month mortality rates for transfusion-related complications and transfusion-transmitted infections were derived when possible from the Serious Hazards of Transfusion survey, and, as in the cardiac surgery population, it was assumed that all infections apart from bacterial contamination would only appear after 1 month, implying zero mortality in the first month. As in the cardiac population, the 1-month mortality for each subgroup of patients in the viscoelastometric group was assumed to be the same as in the standard laboratory tests group, implying that any mortality benefit in the viscoelastometric group was due to fewer patients being transfused.

5.66 Few data were available for mortality between 1 and 12 months after trauma. One

study was identified, which reported 3% mortality for this period, but no information was identified on how this mortality was distributed over transfused and non-transfused patients. The external assessment group therefore applied the same ratio as for 1-month mortality (3.3). This gave a mortality of 1.7% in non-transfused patients and 5.7% in transfused patients. These values were assumed to apply to both the standard laboratory tests and the viscoelastometric group.

Health benefits

5.67 Health benefits were expressed in terms of life years and QALYs gained at 1 month and 1 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 external assessment group used utility values from the 1996 Health Survey for England.

5.68 For the trauma model, the external assessment group 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 (standard error 0.016) 12 to 18 months after the trauma. No studies reporting utilities for the period of hospitalisation and shortly afterwards were identified. The external assessment group therefore assumed the same utility for the period of hospitalisation as for the cardiac population during hospitalisation.

5.69 For patients with acute respiratory distress syndrome, the external assessment group used the results of a prospective cohort study that measured quality-adjusted survival in 200 patients in the first year after acute respiratory distress syndrome. This study reported utilities of 0.60 (standard error 0.01) and 0.64 (standard error 0.01) at 6 months and 1 year after onset of acute respiratory distress syndrome respectively. The external assessment group applied a value of 0.60 to the period of 1 month, and 0.64 to the period between months 1 and 12. Similar data were unavailable for patients with multiple organ failure, so the external assessment group applied the same utilities as for patients with acute respiratory distress syndrome based on the assumption that both complications are similar in severity. For patients with transfusion-related complications, the

external assessment group assumed that after discharge, as in the cardiac population, the utility would be equivalent to patients without complications.

Costs (cardiac and trauma models)

5.70 Short-term (1 month) and long-term (1 year) costs were considered in both the cardiac and trauma models. Preoperative and perioperative costs of transfusion were taken from Davies et al. (2006) and inflated to 2013 costs.

5.71 Three types of blood products were included in the model. The respective prices for standard red blood cells, adult platelets and clinical fresh frozen plasma were £122.09, £208.09, and £27.98, as obtained from the NHS blood and transplant price list 2013/14. Data on units of blood transfused were obtained from 1 study. In the trauma population, data from 2 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 patient needing a transfusion.

5.72 The total cost of the different viscoelastometric devices consisted of the costs of the devices themselves, the costs of extra items (only those that were available and comparable for the 3 devices) and after-care and training costs. 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.

5.73 The external assessment group assumed that cardiac surgery patients will be tested 3 times. Therefore, for ROTEM a basic test would consist of INTEM, EXTEM, FIBTEM and HEPTEM; for TEG a basic kaolin and heparinise test; and for Sonoclot, gbACT and kACT. The external assessment group 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 Sonoclot patients would just receive an H-gbACT+ test. Each patient was assumed to be tested 5 times.

5.74 The total cost per set of standard laboratory tests inflated to 2013 prices was taken from the Scottish health technology assessment and was equal to £26 for

fibrinogen concentration, prothrombin time, activated clotting/coagulation time and activated partial thromboplastin time combined. This cost was applied to both the cardiac and trauma models.

5.75 The average length of hospital stay for the cardiac model was sourced from the Hospital Episode Statistics 2012/13, which reports a mean stay of 10.53 days per patient having 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 statistically significant differences between viscoelastometric and standard laboratory test groups in terms of length of hospital stay, so the external assessment group assumed equal average length of hospital stay for each of the different strategies. Costs of intensive care unit stay were not considered.

5.76 For the trauma model, data on length of hospital stay were taken from the only 2 trauma studies included in the effectiveness review that reported on this parameter. The average length of stay in hospital was 10.55 days, 4.9 of which were spent in the intensive care unit. Based on the National Schedule of Reference Costs, intensive care unit stay was valued at £1,173 per day. For hospital stay after intensive care unit, the external assessment group was unable to define a cost per day because of the wide variability in trauma injuries, and assumed the same per-day costs as for the cardiac surgery model.

5.77 The external assessment group used the following estimated lengths of stay for the different complications, based on the available evidence:

- For acute respiratory distress syndrome, the external assessment group used data from a study that reported an intensive care unit length of stay of 18.8 days and hospital length of stay of 26.8 days.
- For multiple organ failure, a study reported an intensive care unit length of stay of 19.1 days. However, there were no data for overall stay, so the external assessment group assumed that amount of time spent in hospital after intensive care unit discharge is equal to the time spent by people with acute respiratory distress syndrome (8 days).
- For patients without acute respiratory distress syndrome or multiple organ failure, the lengths of intensive care unit and hospital stay were estimated to

be 2.2 days and 7.4 days respectively, in order to achieve the averages of 10.55 days and 4.9 days for all patients.

- For people with transfusion-related complications and bacterial infection, the external assessment group assumed the same length of stay as for cardiac surgery patients and the same unit costs per day. While patients stayed in the intensive care unit, no additional hospital costs were applied for complications because the external assessment group 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 intensive care unit, the same per-day costs applied for the cardiac model were applied.

5.78 Long-term costs (costs between hospital discharge and 1 year after surgery) included those related to the other transfusion-transmitted infections, specifically variant Creutzfeldt-Jakob disease, malaria, human T-cell lymphotropic virus, HIV, hepatitis A, B and C.

Base-case results (cardiac and trauma models)

5.79 For the cardiac model, all the viscoelastometric devices dominated (that is, were more effective and less costly than) standard laboratory tests. The external assessment group assumed the same treatment effects for each viscoelastometric testing device (QALY=0.8773). The cost of Sonoclot was lower than that of ROTEM and TEG, and the device was associated with greater cost savings (£132) than either TEG (£79) or ROTEM (£43).

5.80 For the trauma model, all the viscoelastometric 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).

5.81 The results of other outputs from both the cardiac and trauma models showed that, compared with standard laboratory tests, the use of viscoelastometric devices is associated with lower mortality, a reduced probability of experiencing complications, and lower transfusion and hospitalisation costs. The probability of

experiencing transfusion-transmitted infections was very low (almost zero) in both groups but lower in the viscoelastometric group.

Probabilistic analysis results (cardiac and trauma models)

5.82 The impact of statistical uncertainties regarding the models input parameters was explored through probabilistic sensitivity analysis.

5.83 For the cardiac model, the scatter plot of the probabilistic sensitivity analysis outcomes in the cost-effectiveness plane was not very informative because the model only assumed a difference in costs between the technologies. The probabilistic sensitivity analysis confirmed that using standard laboratory tests is the strategy with the lowest probability of being cost effective. If the maximum acceptable incremental cost-effectiveness ratio (ICER) was £30,000 per QALY gained, the probability of cost effectiveness for each of the 3 viscoelastometric technologies compared with standard laboratory tests was 0.79 for ROTEM, 0.82 for TEG and 0.87 for Sonoclot. When the maximum acceptable ICER was higher than £30,000 per QALY gained, the cost-effectiveness probabilities converged to around 0.80 for all technologies.

5.84 Probabilistic sensitivity analysis results for the trauma model were similar to the cardiac model. The analysis confirmed that using standard laboratory tests was the strategy with the lowest probability of being cost effective. 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. As the ceiling ratio increased, the cost-effectiveness acceptability curve for ROTEM converged to 0.87. A similar pattern was observed for TEG and Sonoclot.

Scenario analysis results

5.85 For the cardiac model, all scenario analyses suggested that ROTEM remained cost saving. The only exception was the number of tests run on each device per year. If the number of tests run on each device were reduced to 200, ROTEM no longer dominated standard laboratory tests, and ICER was £16,487 per QALY gained. The external assessment group estimated, using iterative analysis, that if

all other parameters in the model remained 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 per QALY gained. If the number of tests per year were reduced to 152, the ICER would be around £30,000 per QALY gained.

5.86 Additional scenario analyses for cardiac surgery suggested that when viscoelastometric testing is carried out in conjunction with standard laboratory testing, TEG was more effective and less costly (-£1) than standard laboratory testing alone and that the ICER for ROTEM and standard laboratory testing alone was £7,487 per QALY gained. When the number of tests and type of assays used were varied, viscoelastometric testing dominated standard laboratory testing alone.

5.87 For the trauma model, all scenario analyses suggested that ROTEM remained cost saving. 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 per QALY gained. When the number of tests per year was reduced to 65, the ICER was approximately £30,000 per QALY gained.

5.88 Additional scenario analyses for trauma surgery suggested that when viscoelastometric testing is carried out in conjunction with standard laboratory testing, ROTEM and TEG dominated (-£558 and -£591 respectively) standard laboratory testing alone. When the number of tests and type of assays used were varied, viscoelastometric testing dominated standard laboratory testing alone.

5.89 For the trauma model, threshold analysis on the combined effect of a reduction in the percentage of patients transfused and the blood volumes transfused (assuming that equal volumes of blood were transfused in the viscoelastometric testing and standard laboratory test groups) showed that, at a relative risk of transfusion of 0.9822 or more, ROTEM was no longer cost saving (with an ICER of £0 per QALY gained). When the relative risk of transfusion increased to 0.9874, the ICER of ROTEM compared with standard laboratory tests was £30,000 per QALY gained.

5.90 Reducing baseline transfusion risk in the standard laboratory test group

(assuming that equal volumes of blood were transfused in the viscoelastometric testing and standard laboratory test groups) showed that ROTEM was no longer cost saving at a transfusion rate of 5%, and that the ICER was £30,000 per QALY gained for a transfusion rate of 4%. This compares with a transfusion rate of 32% used in the base-case analysis. When the analysis was repeated with an increased relative risk of red blood cell transfusion (from 0.88 to 0.95), the ICER was above £30,000 per QALY gained 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.

6 Considerations

6.1 The diagnostics advisory committee reviewed the evidence available on the cost effectiveness of viscoelastometric testing to help detect, manage and monitor haemostasis in cardiac surgery and in the emergency control of bleeding after trauma and during postpartum haemorrhage.

6.2 The committee considered whether the ROTEM, TEG and Sonoclot systems included in this assessment could be considered equivalent for the purpose of this assessment. It noted that each device has different measures and includes different assays. The committee also noted that although none of the 11 randomised controlled trials (RCTs) included in the systematic review provided a direct comparison between TEG and ROTEM, the summary estimates for all outcomes were similar when stratified by viscoelastometric device. There was also no evidence to indicate a difference in effectiveness between the 2 devices. The committee also considered the results of the 3 prediction studies, which did not suggest a significant difference in the ability of Sonoclot and TEG to predict bleeding. The committee noted that equivalent clinical effectiveness had been assumed in the modelling but concluded that the level of evidence available for the Sonoclot system was not sufficient for the device to be considered equivalent to the ROTEM and TEG systems. The committee noted that the ROTEM and TEG systems comprise different tests and although both systems can be used to detect, manage and monitor haemostasis, the data from each system are not interchangeable. The committee therefore concluded that, based on the available evidence, TEG and ROTEM could be considered equivalent to each other but more evidence was needed on the clinical effectiveness of the Sonoclot system.

6.3 The committee considered the clinical evidence on the use of viscoelastometric testing in managing postpartum haemorrhage. It noted that the review did not identify studies that compared clinical outcomes among women with postpartum haemorrhage who were tested with viscoelastometric devices and those who were not. It also noted that lower levels of evidence in the form of 2 prediction studies, available only as abstracts, were included in the clinical effectiveness review. The committee agreed with the external assessment group's judgement that the available data are insufficient for constructing an economic model to assess the cost effectiveness of viscoelastometric devices in this population. The

committee considered whether the nature of bleeding in postpartum haemorrhage is identical to that in trauma. Clinical experts informed the committee that such an assumption should be interpreted with caution because of the difference in clotting mechanisms. The committee concluded that more evidence is needed on the use of viscoelastometric devices in the management of postpartum haemorrhage.

6.4 The committee discussed the clinical evidence on the use of viscoelastometric testing in trauma patients. It noted that the review identified 1 ongoing RCT and a clinical trial that did not report numerical or statistical outcome data. It also noted that because of insufficient data from studies that evaluated differences between viscoelastometric-tested and untested populations, 15 prediction studies were included in the review. The committee noted that the external assessment group had to assume similar probabilities of red blood cell transfusion (relative risk: 0.88), transfusion-related complications and transfusion-transmitted infections in trauma surgery as in cardiac surgery because data on how clinical outcomes vary in patients tested with viscoelastometric compared with conventional testing were not available to inform the economic model for trauma patients. The committee deliberated whether these assumptions are reasonable. Clinical experts informed the committee that the nature of coagulopathy is different in the 2 populations and that patients having trauma surgery are likely to have higher blood loss; they therefore have greater blood transfusion needs than those having cardiac surgery. The committee concluded that it is not appropriate to assume similar probabilities of red blood cell transfusion, transfusion-related complications and transfusion-transmitted infections in trauma surgery as in cardiac surgery.

6.5 The committee discussed the clinical evidence on the use of viscoelastometric testing in cardiac surgery. It noted that pooled estimates derived from the meta-analyses of 6 RCTs that evaluated the ROTEM and TEG systems in cardiac surgery indicated that viscoelastometric testing is associated with a significant reduction in the numbers of patients receiving red blood cell transfusion (relative risk: 0.88, 95% confidence interval [CI] 0.80 to 0.96). The committee concluded that there is sufficient evidence to demonstrate the clinical effectiveness of using the ROTEM and TEG systems in cardiac surgery.

6.6 The committee considered the lack of a formal assessment of publication bias in

the systematic review. The external assessment group advised the committee that for RCTs, the number of studies was too small for such an assessment to be meaningful and that for prediction studies, there is no reliable method of assessing publication bias. The committee noted that the external assessment group's 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 1 ongoing RCT.

6.7 The committee discussed the cost-effectiveness modelling on the use of viscoelastometric testing in trauma patients. The committee considered the areas of uncertainty in the economic model produced by the external assessment group. It heard that the structure of the model may not be appropriate because the model is driven by a decrease in transfusion rather than outcomes and mortality. The committee therefore interpreted the results of the cost-effectiveness analysis in trauma patients with caution, and concluded that more evidence is needed on the clinical effectiveness of viscoelastometric testing in the management of trauma.

6.8 The committee discussed the results of the base-case analysis on the use of viscoelastometric testing in cardiac surgery. It noted that viscoelastometric testing dominated standard laboratory tests (that is, was more effective and less costly) producing more quality-adjusted life years (QALYs); 0.0047 and costing less (-£43 for ROTEM and -£79 for TEG). The committee also noted that results of other outputs from the model show that the use of viscoelastometric devices is associated with lower mortality, a reduced probability of experiencing complications, and less transfusion and hospitalisation. Based on the level of clinical evidence, the committee did not consider that the Sonoclot system was of equivalent clinical effectiveness to the ROTEM and TEG systems. The committee did not therefore consider the results of the cost-effectiveness analysis for the Sonoclot system to be robust. The committee concluded that the use of the ROTEM and TEG systems to help detect, manage and monitor haemostasis in cardiac surgery is cost effective when compared with standard laboratory tests alone.

6.9 The committee discussed the implications of using risk of red blood cell transfusion as the main outcome in the economic model and considered whether other types of transfusion such as fresh frozen plasma and platelet transfusion

should have been included in the model. The external assessment group informed the committee that it used these outcomes in the model because most patients receiving any transfusion receive red blood cell, and no data were available to inform the probabilities of complications from red blood cell, platelet or fresh frozen plasma transfusions individually, or any combination of these. In addition, the studies included in the review do not indicate what combination of blood products patients received, or in what percentage. The external assessment group stated that this approach is consistent with the only cost-effectiveness study in the field, the Scottish Health Technology Assessment, and is also consistent with the study by Davies et al. (2006), on which the Scottish Health Technology Assessment was based. The committee noted that relative risk for mortality in patients receiving red blood cell transfusions compared with non-transfused patients, obtained from data from a large cohort study in a UK setting (Murphy, 2007), was almost identical to the pooled estimate obtained from studies that reported short-term mortality included in the clinical-effectiveness review. The committee therefore agreed with the external assessment group's approach of using red blood cell transfusion as the main outcome in the economic model and concluded that including other types of transfusion would not significantly affect the results of the cost-effectiveness analyses.

6.10 The committee was informed of a recently completed UK-based multicentre RCT, named TITRE2, which assessed the impact of changing the haemoglobin level threshold at which red blood cell transfusion is performed. The external assessment group informed the committee of the results of the unpublished study which are considered academic in confidence by the authors and therefore cannot be reported here. The committee discussed the relevance of the results to this assessment and concluded that the impact of changing the haemoglobin level threshold represents a different clinical scenario to using viscoelastometric testing to guide transfusion decisions. The committee therefore concluded that the cost-effectiveness estimates are unlikely to be affected by the results of the TITRE2 trial.

6.11 The committee discussed the external assessment group's decision to model the type of assays and number of tests for viscoelastometric testing 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. The

committee was informed that each device is available with different numbers of channels and runs different assays that are not directly comparable between devices. The committee considered whether the results found in the trials would also be applicable to different assay combinations and numbers of tests used in clinical practice. It noted that the results of the scenario analyses showed 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 – that is, ROTEM and TEG continued to dominate standard laboratory tests. The committee concluded that when the combination of assays and numbers of tests is varied, viscoelastometric testing with the ROTEM or TEG system remains cost effective when compared with standard laboratory tests.

6.12 The committee considered the assumption in the base case that 500 tests would be run on each viscoelastometric device per year. It noted that, although the length of time for which a device is used and the average number of tests run per machine per year influences the material cost of a test, the number of tests had to be very low before viscoelastometric testing was no longer cost effective. The committee noted that in the scenario analyses the incremental cost-effectiveness ratio (ICER) of viscoelastometric testing compared with standard laboratory testing is around £30,000 per QALY gained when the number of tests per year is reduced to 152 (from 500 tests per device per year in the base case). Clinical experts informed the committee that 600 to 800 tests could be run per device per year. The committee considered that it was likely that on average more than 152 tests would be run on each viscoelastometric device per year and therefore concluded that using viscoelastometric testing would be cost effective in routine practice when compared with standard laboratory tests.

6.13 The committee discussed the 1-year time horizon used in the model. It heard from the external assessment group that because the ROTEM and TEG systems were shown to be both more effective and cheaper than standard laboratory tests at 1 year (with a probability of at least 0.68 of being cost effective), effectiveness would only increase and costs would be likely to decrease over a lifetime. The committee acknowledged that the expected increase in effectiveness is based on minimising long-term complications such as stroke, which is likely to be avoided by fewer transfusions, and would also imply lower cost. The committee concluded that the 1-year time horizon used in the model was appropriate.

6.14 The committee discussed the use of viscoelastometric testing as an add-on, or as a replacement for, standard laboratory tests in cardiac surgery patients. It noted that 3 of the RCTs (2 of TEG and 1 of ROTEM) included in the systematic review reported the effectiveness of using viscoelastometric testing and standard laboratory tests together, compared with using standard laboratory tests alone. For all outcomes assessed, the results of these studies were similar regardless of whether viscoelastometric testing was used alone or in combination with standard laboratory tests. The committee concluded that performing standard laboratory tests in addition to viscoelastometric testing is unlikely to give further benefit over that provided by viscoelastometric testing alone. However, the committee heard from clinical experts that standard laboratory tests provide additional information such as prothrombin time and fibrinogen levels, which are useful when deciding on the dose of prothrombin complex concentrate or fibrinogen concentrate to be administered. The committee noted that the external assessment group had only used the viscoelastometric testing alone scenario in the economic model and discussed whether the additional cost of standard laboratory tests would affect the cost-effectiveness results. It noted that additional scenario analyses carried out by the external assessment group showed that using viscoelastometric testing in addition to standard laboratory tests is cost effective when compared with standard laboratory tests alone. Viscoelastometric testing with the ROTEM system and standard laboratory tests resulted in an ICER of £7,487 per QALY gained compared with standard laboratory tests alone. Viscoelastometric testing with the TEG system and standard laboratory tests dominated standard laboratory tests alone. The committee concluded that viscoelastometric testing should be used in conjunction with standard laboratory tests in cardiac surgery.

6.15 The committee discussed whether viscoelastometric testing should be carried out intraoperatively, postoperatively or both during cardiac surgery. It noted that, although the timing of the viscoelastometric test varied across the 11 RCTs included in the review, the clinical effectiveness of viscoelastometric testing did not vary according to the time the viscoelastometric test was administered. The committee concluded that viscoelastometric testing should be used both intraoperatively and postoperatively.

6.16 The committee considered the potential effects of different testing regimens on longer-term transfusion-related complications and mortality. It noted that none of

the studies included in the clinical-effectiveness review reported follow-up of patients to assess these effects. The committee concluded that further research is needed to assess the potential effects of different testing regimens on longer-term transfusion-related complications and mortality.

6.17 The committee heard from some of its expert members that the most cost-effective use of viscoelastometric testing in cardiac surgery could be in people considered at high risk of haemostatic instability. The committee discussed the possible population subgroups that could be classified as higher risk and concluded that further research is needed to understand the characteristics of patients at high risk of haemostatic instability in whom viscoelastometric testing may be most cost effective.

6.18 The committee noted that the ROTEM and TEG systems need maintenance and quality control procedures to be in place to ensure the clinical effectiveness of the systems in use.

7 Recommendations for further research

7.1 The committee recommended further research to demonstrate the utility of the Sonoclot system in detecting, managing and monitoring haemostasis in cardiac surgery.

7.2 The committee recommended further research in using viscoelastometric testing in the emergency control of bleeding after trauma and during postpartum haemorrhage to assess its effectiveness compared with standard laboratory testing. The committee recommended that outcomes should include, but may not be limited to, bleeding outcomes, mortality, duration of hospital or intensive care unit stay, transfusion rates and volumes transfused.

7.3 The committee recommended further research comparing the clinical effectiveness of all 3 viscoelastometric devices (ROTEM, TEG and Sonoclot systems) in cardiac surgery and in the emergency control of bleeding after trauma and during postpartum haemorrhage. In particular, the committee recommended research to determine which of the parameters included in the viscoelastometric testing systems are the most significant in changing clinical decision-making and improving clinical outcomes. The degree of change needed in these parameters to affect clinical decision-making and clinical outcomes should also be considered.

7.4 The committee recommended that future trials should include longer-term follow-up, beyond the initial hospital episode, with a view to informing the cost-effectiveness modelling and reducing uncertainty.

7.5 The committee recommended further research to understand the characteristics of patients at high risk of haemostatic instability in whom viscoelastometric testing may be most cost effective.

8 Implementation

8.1 NICE will support this guidance with a range of activities to promote the recommendations for further research. This will include incorporating the recommendations for research in section 7 into the NICE guidance research recommendations database and highlighting these recommendations to public research bodies. The research proposed will also be put forward to NICE's Medical Technologies Evaluation Programme research facilitation team for consideration of the development of specific research protocols.

9 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Professor Adrian Newland
Chair, Diagnostics Advisory Committee

Dr Mark Kroese
Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Ron Akehurst
Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Professor Paul Collinson
Consultant Chemical Pathologist and Professor of Cardiovascular Biomarkers, St George's Hospital

Dr Sue Crawford
General Practitioner (GP) Principal, Chillington Health Centre

Professor Ian A Cree
Senior Clinical Advisor, NIHR Evaluation Trials and Studies Coordinating Centre, University of Southampton

Professor Erika Denton
National Clinical Director for Diagnostics, NHS England, Honorary Professor of Radiology,

University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards
Head of Health Technology Assessment, BMJ Evidence Centre

Mr David Evans
Lay Member, Safety Engineer and Occupational Hygienist

Dr Simon Fleming
Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Professor Chris Hyde
Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Professor Noor Kalsheker
Professor of Clinical Chemistry, University of Nottingham

Mr Matthew Lowry
Director of Finance and Infrastructure, Doncaster and Bassetlaw Hospitals NHS Foundation Trust

Dr Michael Messenger
Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

Dr Peter Naylor
General Practitioner (GP), Chair Wirral Health Commissioning Consortia

Dr Dermot Neely
Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Richard Nicholas
Consultant Neurologist; Honorary Senior Lecturer, Heatherwood and Wexham Park Hospitals

Dr Gail Norbury
Consultant Clinical Scientist, Guys Hospital

Dr Diego Ossa
Director of Market Access Europe, Novartis Molecular Diagnostics

Professor Mark Sculpher
Professor of Health Economics at the Centre for Health Economics, University of York

Dr Steve Thomas
Consultant Vascular and Cardiac Radiologist at Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger
CEO, DiaSolve Ltd, London

Mr Christopher Wiltsher
Lay Member

Specialist committee members

Dr. Seema Agarwal
Consultant in Cardiac Anaesthesia and Intensive Care, Liverpool Heart and Chest Hospital

Mr Simon Davidson
Clinical Scientist, Royal Brompton & Harefield NHS Foundation Trust

Dr Laura Green
Consultant Haematologist, Barts Health NHS Trust and NHSBT

Dr. Sarah Haynes
Autologous Transfusion Co-ordinator, University Hospital of South Manchester

Dr. Niall O'Keeffe
Consultant in Cardiac Anaesthesia and Intensive Care, Central Manchester and Manchester Children's University Hospital Trust

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Farouk Saeed
Topic Lead

Dr Sarah Byron
Technical Adviser

Robert Fernley
Project Manager

10 Sources of evidence considered by the committee

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

Whiting P, Al M, Westwood ME et al. (2014) 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.

Registered stakeholders

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

Manufacturers/sponsors:

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

Professional/specialist and patient/carer groups:

- British Society for Haematology
- Healthcare Improvement Scotland
- Royal College of Anaesthetists

- Royal College of Nursing
- Royal College of Paediatrics and Child Health.

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government.

Update information

Minor updates since publication

December 2025: Diagnostics guidance 13 has been migrated to HealthTech guidance 348. The recommendations and accompanying content remain unchanged.

ISBN: 978-1-4731-7361-3