NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

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

Final scope

August 2013

1 Introduction

The ROTEM system is manufactured by Tem international. The Medical Technologies Advisory Committee identified the ROTEM system as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note that included a description of the purpose of the technology as detailed in section 2.1. A glossary of terms is provided in appendix B.

2 Description of the technology

This section describes the properties of the diagnostic technology based on the manufacturer's notification to NICE. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

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

ROTEM is intended for use during surgery to help identify the probable cause of intraoperative bleeding. The results help to guide the clinician in selecting

the correct therapy. It is also intended for use in the immediate post-operative period to help guide the clinician in determining whether bleeding is a result of a coagulopathy (when the blood's ability to clot is impaired) or a surgical bleed.

2.2 Product properties

ROTEM uses a combination of five assays (INTEM, EXTEM, FIBTEM, APTEM and HEPTEM) to characterise the coagulation profile of a whole blood sample. Initial testing is performed using the INTEM and EXTEM assays which can indicate whether a clotting factor deficiency is present. When used during surgery, if initial test results appear normal, it is an indication that surgical bleeding may be present. Additional assays include FIBTEM which can indicate a fibrinogen deficiency, APTEM which can indicate hyperfibrinolysis or HEPTEM which neutralises the effects of heparin therefore indicating whether the coagulopathy is due to residual heparin. The APTEM test, a tissue factor activated, heparin insensitive test performed in the presence of aprotinin (fibrinolysis inhibitor), confirms hyperfibrinolysis by comparing the TEM result of this assay with the EXTEM test (same activator, but without aprotinin).

Table 1: ROTEM assays

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

The ROTEM analysis is generally performed with citrated whole blood near the patient during the surgery although the instrument may be positioned in the laboratory. A blood sample is taken from the patient and is placed into a cuvette. A cylindrical pin is then immersed and is oscillated by a spring to the

right and the left. The movement of the pin is unrestricted as long as the blood is liquid but encounters resistance as the blood begins to clot. The clot increasingly restricts the rotation of the pin with rising clot firmness.

It is claimed that the complete results of ROTEM will:

- Determine the presence and type of coagulopathy.
- Indicate a requirement for fibrinogen or platelet administration, and facilitate heparin and protamine monitoring.

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

The results are calculated by an integrated computer and reproduced in graphical format (figure 1). The device produces a graph of coagulation against a time axis. A prolonged clotting time can indicate a coagulation disorder. The first results are available within 5-10 minutes for quick therapy decisions and full qualitative results are available in 20 minutes

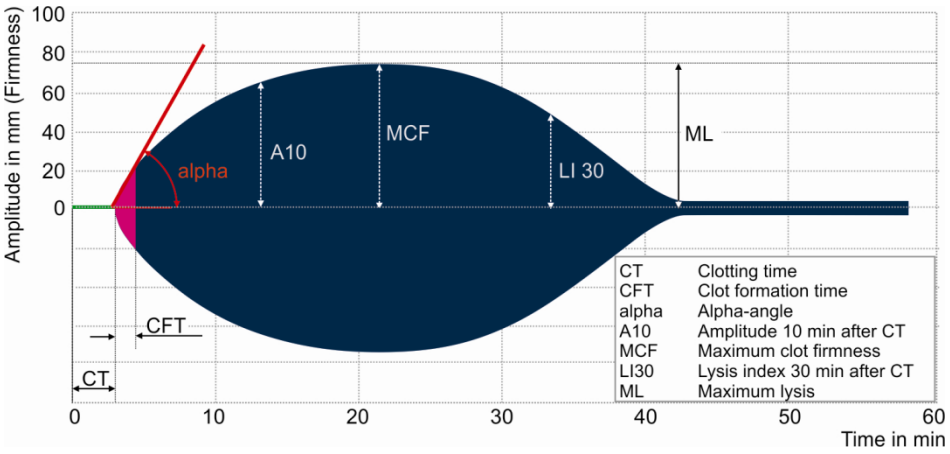

Figure 1: ROTEM graphical format

2.3 Alternative technologies

a) Thromboelastography (TEG) system (Haemonetics): This is a non-invasive device that is designed to monitor and analyse clot formation in a blood sample. It can be used for POC or laboratory testing.

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

Similar to TEM, TEG measures and graphically displays the changes in viscoelasticity at all stages of the developing and resolving clot (figure 2). These include the time until initial fibrin formation (reaction time), the kinetics of fibrin formation and clot development (kinetics, α angle [α]), the ultimate strength and stability of the fibrin clot (maximum amplitude [MA]), and clot lysis (fibrinolysis).

With the use of a specific kit, the TEG can also be used to monitor the effect of antiplatelet drugs such as aspirin and clopidogrel. This can be useful for monitoring their therapeutic effect and also postoperatively where these drugs can increase the risk of perioperative bleeding.

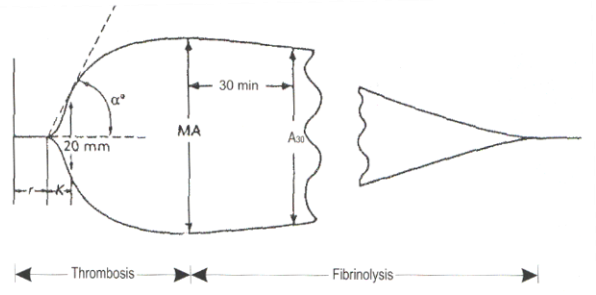

Figure 2: TEG graphical format

b) <u>The Sonoclot Coagulation and Platelet Function Analyser (Sienco, Inc.):</u>
This is also a viscoelastic monitor used for measuring coagulation and platelet function. It provides information on the haemostasis process

including coagulation, fibrin gel formation, clot retraction (platelet function) and fibrinolysis.

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

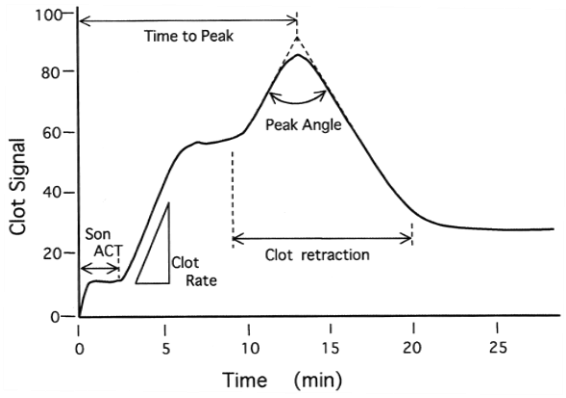

Figure 3: Sonoclot signature

3 Target conditions / indications

Viscoelastometric point-of-care testing is intended for use:

- During surgery to identify the probable cause of intraoperative bleeding by discriminating between poor platelet function and poor clotting. The results allow the clinician to select the correct therapy.
- In the immediate post-operative period to help control haemostasis and help guide the clinician to determine whether bleeding is a result of a coagulopathy or a surgical bleed.

3.1. Background

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

The population groups included in this assessment are:

- Cardiac surgery
- Emergency bleeding (such as in trauma and post-partum haemorrhage)

Cardiac surgery

Although mortality is low for most surgical procedures, ranging from less than 0.1% for most routine surgery to 1% to 2% for cardiac surgery and 5% to 8% for elective vascular cases, the low mortality may be greatly increased when severe bleeding occurs during the operative procedure (Marietta *et al,* 2006).

Cardiac surgery is often associated with profuse bleeding. Excessive bleeding (greater than 2 litres) is encountered in 5% to 7% of patients. It may require reoperation in 3.6% to 4.2% of patients if conventional methods fail to arrest the bleed (Marietta *et al,* 2006). Major blood loss is linked to adverse outcomes and is associated with an eightfold increase in the odds of death.

More than 30,000 people have heart surgery in the United Kingdom each year and adult cardiac surgery accounts for approximately 15% of all allogeneic red cell and allogeneic blood coagulation transfusions (NHS Blood and Transplant Hospitals and Science, 2012).

In cardiac patients (who are frequently on antiplatelet medication such as aspirin or clopidogrel) platelet function analysers are routinely used in

conjunction with viscoelastometric testing. Platelet function analysers are designed to perform platelet function testing in whole blood samples in near-patient or laboratory settings. During early scoping, clinical opinion suggested that they are used in theatres across the UK to look specifically at platelet function.

Trauma surgery

Major trauma describes serious and often multiple injuries where there is a strong possibility of death or disability. In England, the most common cause is a road accident. There is an estimated minimum of 20,000 cases of major trauma each year in England resulting in 5,400 deaths and around a further 28,000 cases which, although not meeting the precise definition of major trauma, would be cared for in the same way. Major trauma patients often require complex reconstructive surgery. Burns are the fourth most common type of trauma worldwide, following traffic accidents, falls, and interpersonal violence (National Audit Office, 2010).

Post-partum haemorrhage

Major obstetric haemorrhage is a common cause of maternal morbidity and mortality and occurs in approximately 6.7 per 1000 births in the UK (RCOG, 2001). The recognition of major obstetric haemorrhage can be challenging. Blood loss may be concealed and can be difficult to quantify due to dilution with amniotic fluid. In addition the physiological changes of pregnancy may mask the normal clinical signs of hypovolaemia (decrease in volume of blood plasma).

3.2 Haemostasis

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

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

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

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

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

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

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

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

including liver transplantation, postpartum haemorrhage, cardiac surgery, vascular surgery and severe trauma.

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

Table 2: Causes of intraoperative and postoperative bleeding

Intraoperative	• Disseminated intravascular coagulation • Heparin overdose • Hyperfibrinolysis
Early postoperative (days 0–2)	• Structural/technical defects • Thrombocytopenia • Inherited or acquired platelet disorders • Mild to moderate inherited coagulation disorder
Delayed postoperative (days 2–7)	• Thrombocytopenia • Acquired platelet disorders (aspirin or NSAID) • Vitamin K deficiency • Multiorgan failure • Antibodies to factor V following use of bovine thrombin in fibrin glue

3.3 Diagnostic pathway

Pre-surgery

If the patient's history includes any haemostatic disorders then blood coagulation and fibrinogen tests are completed. Most patients who undergo elective surgery have normal coagulation. In the absence of a history of abnormal bleeding, UK guidelines (Chee *et al,* 2008) do not recommend pre-operative coagulation testing. However some clinicians choose to order coagulation testing (which includes Prothrombin Time (PT), Partial Thromboplastin Time (PTT), Platelet Count and International Normalised Ratio (INR) tests). These tests look at specific areas of the clotting cascade and help determine how quickly the blood clots when carrying out some surgical procedures, particularly cardiac, where it is important that the blood does not clot as quickly as normal and medications may be given to slow the clotting time. In other cases, the patient's blood may not clot quickly enough, and steps may be taken to speed up the clotting process. A blood sample is taken from the patient and sent to the nearest laboratory. The quickest estimated time for the results to be returned is 45 minutes. According to expert opinion, this method is currently used in most NHS hospitals.

During and after surgery

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

Using laboratory-based tests during and immediately after surgery has been questioned as this can cause delays of about 45 to 60 minutes from blood sampling to obtaining results (Ganter and Hofer, 2008). Moreover, laboratory rests are carried out on plasma rather than whole blood and at a standard temperature of 37^{o} rather than patient temperature. During early scoping, Clinical Expert Advisers state that, for cardiovascular and liver surgeries, TE may be used by some hospitals in conjunction with or instead of standard laboratory tests. TE is the term used to associate the detection principles of TEG and TEM (please see glossary for details).

Treatment

Targeted therapy includes surgical intervention, blood and blood products, factor concentrates, protamine and anti fibrinolytics.

The following management of bleeding has been recommended (Baglin, 2010):

- Early and sufficient blood product support should be given to patients with major blood loss and to those with dilutional coagulopathy.

- Supportive care with judicious use of Fresh Frozen Plasma (FFP) and platelets should be given to patients with severe coagulopathy whilst the underlying condition is being treated.

- Patients with overt haematological disorders such as myelodysplasia, or factor VIII inhibitors will require specialist care. Pharmacological agents can be used to increase haemostatic capacity but should be used by

clinicians with appropriate experience. Such drugs include DDAVP, tranexamic acid, and off-licence use of drugs such as recombinant factor VIIa. Aprotonin was used extensively in the past but is now used with caution because of thrombotic complications, including death, and renal impairment.

Complications related to transfusion include:

- Transfusion-associated graft versus host disease
- Complications related to the administration of an incorrect blood component
- Haemolytic transfusion
- Transfusion-related acute lung injury
- Febrile reaction
- Infections (HIV, Hepatitis A, B and C, Malaria etc).

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

3.1.1 Patient issues and preferences

Some of the benefits of using this technology include:

- Decreased time in critical care unit
- Shortening of hospitalisation time
- Reduction in complications from blood transfusion

4 Scope of the evaluation

Table 3: Scope of the evaluation

Decision question	What is the clinical and cost effectiveness of using viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems) for detecting, managing and monitoring haemostasis during and after surgery and in emergency management of major bleeding?
Population	• Adults undergoing cardiac surgery • Emergency management of major bleeding in adults (for example, trauma and post-partum haemorrhage).
Interventions	Alone or in addition to standard coagulation testing: • ROTEM System (TEM International.) • TEG System (Haemonetics) • Sonoclot (Sienco, Inc.) For adults receiving antiplatelet therapy who are undergoing cardiac surgery, the interventions may be used in conjunction with platelet function analysis.

Comparator	Routine and standard practice for detecting, managing and monitoring haemostasis during and after surgery, without the use of viscoelastometric testing:
	• Clinical judgement alone or in conjunction with
	  • Coagulation tests (for instance prothrombin time [PT], partial thromboplastin time [PTT, platelet count, international normalised ratio [INR] tests)
	  • fibrinogen testing

Healthcare setting	Secondary care
Outcomes	Intermediate measures for consideration may include: • Test accuracy • Test failure rate • Waiting time for tests results • Proportion of patients requiring blood transfusion • Cumulative use of blood products • Proportion of patients experiencing complications related to surgery or blood transfusion • Proportion of patients requiring surgical re-intervention
	Clinical outcomes for consideration may include:

	• Non-fatal and fatal bleeding • Transfusion-related complications • Thrombotic or thromboembolic events • Mortality (from any cause) • Adverse events related to testing • Health related quality of life
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • The pre-operative and peri-operative costs of transfusion • The costs of the tests and associated consumables • Costs related to complications due to surgery or transfusion and transfusion-related complications • Operating theatre and resource use • Costs associated with critical care unit stay • Staff training costs
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

5 Modelling approach

The aim and structure of the economic model will depend upon the final scope.

5.1 Existing models

Davies *et al* (2006) constructed a model which aimed to assess the cost effectiveness of cell salvage transfusion when compared with allogenic transfusion and other interventions to either reduce surgical blood loss or to minimise the use of peri-operative allogenic blood. An adapted version of this model was used in assessing the clinical and cost effectiveness of TEM/TEG in the 2008Health Technology Assessment Report 11 by NHS Quality Improvement Scotland.

5.2 Modelling possibilities

If no end-to-end studies are identified, a linked evidence approach to modelling will be the most likely scenario. The intermediate measures and direct outcomes of the diagnostic strategies employed will need to be related to changes in final health outcomes.

Possible questions to be addressed by modelling include the variability in practice regarding the use of viscoelastometric point-of-care testing, specifically whether the tests are used alone or in addition to standard coagulation testing

6 Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No equality issues were raised at the scoping workshop and the assessment subgroup meeting.

7 Implementation issues

Support tools are developed by the implementation team at NICE. The implementation team does not get involved in developing the guidance recommendations but works alongside the guidance-producing programme, the communications team and field based teams to, amongst other things, ensure intelligent dissemination of NICE guidance to the appropriate target audiences.

Appendix A Glossary of terms

Activated Partial Thromboplastin Time (aPTT): is a test that can be used where someone has unexplained bleeding or clotting. Along with the PT test (which evaluates the extrinsic and common pathways of the coagulation cascade), the aPTT is often used as a starting place when investigating the cause of a bleeding or thrombotic (blood clot) episode. The aPTT and PT tests are also sometimes used as pre-surgical screens for bleeding tendencies, although numerous studies have shown that they are not useful for this purpose. The aPTT is also used to monitor heparin anticoagulant therapy.

Coagulopathy: Any disorder of blood coagulation in which blood is either too slow or too quick to coagulate (clot).

Haemostasis: The stoppage of bleeding or haemorrhage by the physiological properties of vasoconstriction and coagulation or by surgical/therapeutic means.

Hyperfibrinolysis: describes a situation with markedly enhanced fibrinolytic activity, resulting in increased, sometimes catastrophic bleeding. Hyperfibrinolysis can be acquired or arise congenitally. Congenital hyperfibrinolysis can occur if a person has certain medical conditions such as haemophilia. Acquired hyperfibrinolysis can occur during surgical procedures.

International sensitivity index (ISI): Quick values measured with different thromboplastins cannot be directly compared with one another. To render coagulation times as comparable as possible, in 1983 the World Health Organization (WHO) approved a standard thromboplastin. Every manufacturer of thromboplastin must calibrate it against the WHO standard (2 references exist: one for human recombinant-based thromboplastins, one for rabbit brain-based ones). The value obtained is known as the International Sensitivity Index (ISI). This enables the various sensitivities of the thromboplastins to be ascertained.

International normalised ratio (INR): Globally recommended unit for measuring thromboplastin time, which renders different measurements comparable despite the different thromboplastins used. It is calculated as:

INR = (Patient's PT / Normal mean PT) x ISI

For example: The PT of a patient receiving oral anticoagulant is 64 seconds (= 18% Quick). The prothrombin time of a normal plasma is 22 seconds (= 100% Quick). The ISI of the thromboplastin used is 0.93. Substituting this value in the formula above gives the following INR:

(64) / (22) 0.93 = 2.7 INR

This signifies a coagulation time that is 2.7 times longer than the standard. The longer the patient's coagulation time, the higher the INR.

Prothrombin Time (PT) test: is used to check the blood for its ability to clot. Often done to check how well anticoagulant treatment is working or before surgery to evaluate how likely the patient is to have a bleeding or clotting problem during or after surgery. Normal PT Values are 10-12 seconds (this can vary slightly from lab to lab). Common causes of a prolonged PT include vitamin K deficiency, hormone drugs including hormone replacements and oral contraceptives, disseminated intravascular coagulation, liver disease, and the use of the anti-coagulant drug warfarin. Additionally, the PT result can be altered by a diet high in vitamin K, liver, green tea, dark green vegetables and soybeans.

Partial Thromboplastin Time (PPT) test: determines if heparin therapy (for blood thinning) is effective. It can also be used to detect the presence of a clotting disorder. It does not show the effects of low molecular weight heparins. A normal PTT values are 30 to 45 seconds (this can value slightly from lab to lab). Extended PTT times can be a result of anticoagulation therapy, liver problems, lupus and other diseases that result in poor clotting.

Thromboelastometry (TEM): The ROTEM device uses thromboelastometry (TEM), which is a viscoelastometric method for haemostasis testing of multiple risk factors including initial clotting, platelet interaction and fibrinolysis in a sample of whole blood. Whole blood is pipetted into a warmed disposable cup; a disposable pin is then lowered into the fluid blood. TEM uses kinetic torsion detection, in which the pin rotates on a fixed steel axis, and employs the light refraction detection principle.

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

TE: A term used to associate to both detection principles (thromboelastography and thromboelastometry). TEG and TEM are product names not a principle.

Appendix B Related NICE guidance

None

Appendix C References

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