

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 13 May 2014

THEMED COMMENTS

Comment number	Name and organisation	Section number	Comment	Response
<u>Technologies</u>				
1.	Royal College of Anaesthetists	4:1	There should be some discussion on the use of these technologies for diagnostic and for monitoring purposes. Clinically their major advantage is in trend analysis, identification of specific haemostatic defects, and assessing that there has been an appropriate response to a haemostatic intervention.	Thank you for your comment which the Committee considered. The use of the technologies for detecting, managing and monitoring haemostasis is described in sections 2, 3 and 4 of the guidance.
2.	Royal College of Anaesthetists	4.8	TEG assays Platelet mapping that assesses platelet function. It should be made quite clear that routine TEG/ROTEM tests, whilst giving some information on platelet function and number, cannot be used to determine the effect of antiplatelet drugs such as aspirin or clopidogrel, and specific reagents and tests need to be used, as in the platelet mapping technology, which gives the percentage platelet inhibition when tested with agonists such as AA or ADP. The ROTEM (at present) has no diagnostic test to assess platelet function when these common anti-platelet drugs are used, and consequently an additional POC machine will need to be used e.g. Multiplate, with the associated cost implications.	Thank you for your comment which the Committee considered. The Committee decided to change sections 4.3 and 4.8 of the guidance to include the use of platelet function analysers for ROTEM and platelet mapping for TEG.

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			<p>Rapid TEG: provides more rapid results than a standard kaolin assay.....this is true, BUT it only provides information on the MA, as the activation with tissue factor is so aggressive that it removes any useful information on the initial clot formation (R and K value).</p>	<p>The Committee considered this comment and decided to change section 4.8 to show that rapid TEG “<i>provides a more rapid measurement of the clot strength than a standard kaolin assay</i>”.</p>
3.	Royal College of Anaesthetists	4.15	<p>“turnaround time may be too long for the results to reflect the current coagulation status”...this is true, the information provided from these tests 60 minutes or more after sampling may be of no current relevance, and are often meaningless if there has been active ongoing bleeding and further deterioration in coagulation. As a consequence SLTs are often of no value in decision making if there is massive bleeding and early haemostatic intervention is required.</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The significant time delay in obtaining SLT results was considered in the assessment.</p>
4.	Royal College of Anaesthetists		<p>Has all the relevant evidence been taken into account? Our members have the following comments to make on the analysis carried out by the authors:</p> <p>A) The authors appear to have taken the RoTEM® as gold standard and the TEG® and Sonoclot® as adjunct devices. This does not reflect the history of the devices.</p> <p>A) Historically the TEG® was the first device to enter clinical practice with studies to investigate the potential for a hypercoagulable state in patients with malignant disease. (Caprini et al Thromb Res 1976 ;9(2):167-80) . The same group also showed that while the output from the thrombelastogram (also note there is no ‘o’ in the original spelling) showed a strong relationship with conventional laboratory test of coagulation the results were not interchangeable (Zuckerman et al Thromb Haaemost 1981;23(4):752-756).</p> <p>The first use in the operating theatre setting was in liver transplantation where the</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group informed the Committee that all devices were considered equally on the basis of available data. 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.</p>

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			<p>group in Pittsburgh were trying to assess the degree of hyperfibrinolysis and coagulopathy in patients having liver transplantation (Kang et al Anesth Analg 1985;64:888-896). Subsequent observational studies were recorded in cardiac surgical practice (Spiess et al J Cardiothorac Vasc Anesth 1995;9:168-173).</p> <p>The RoTEM® system was launched in Europe in 2003. It was originally 'marketed' by Pentapharm, Basel, Switzerland. Their approach was to give away the system to centres in Europe who performed cardiac and hepatic surgery. The RoTEM® system was taken over by TEM GMBH of Munich about 3 years ago. The system and its reagents gained approval from the FDFA in the United States about 2 years ago. This temporal and geographical difference in the use of the devices may explain why the TEG® is mainly used in North America and the UK and the RoTEM® in Europe.</p>	<p>Therefore, the External Assessment Group applied the summary relative risk for red blood cell transfusion in the model for ROTEM and TEG. Limited data suggested that the accuracy of Sonoclot in predicting clinical outcomes may be similar to that of TEG so the same relative risk was also applied in the model for Sonoclot. Under the assumptions made in the cost effectiveness analyses, that is, the clinical effectiveness of the 3 devices was comparable, ROTEM was dominated by TEG and Sonoclot because it was the most costly device. Therefore, the sensitivity analyses in the economics results section were performed using ROTEM because under the assumptions in the model, if ROTEM was cost-effective, the other 2 devices would also be cost-effective.</p>
<u>Transfusion</u>				
5.	Royal College of	5.12	Red blood cell transfusion. The reduction in RBC transfusions are probably the result of treatment algorithm driven changes to transfusion practice. The majority	Thank you for your comment which the Committee

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	Anaesthetists		of RCT's randomise patients to standard therapy (plasma and platelets) or an algorithm using factor or fibrinogen concentrates. The significant reduction in haemodilution may be the reason for the reduced RBC use. Fibrinogen concentrates are not widely available or licensed in the UK	considered. The Committee's consideration of using RBC transfusion as the main outcome in the model is described in section 6.11-9 of the guidance.
6.	Royal College of Anaesthetists	5.16	Fibrinogen transfusion In discussing these RCTs it is important to mention if these used ROTEM, where FIBTEM is routinely done, or TEG, where until quite recently, functional fibrinogen was not included in the routine battery of tests.	Thank you for your comment. The Committee considered this comment and decided to change section 5.15 of the guidance.
7.	Royal College of Anaesthetists	5.17	Platelet transfusion The same issues as above apply to studies that look at platelet transfusions. If these are based on transfusion because of a reduced MA/MCF, then there must be a means of differentiating thrombocytopenia from hypofibrinogaemia as the cause of a low MA/MCF.	Thank you for your comment. The Committee considered this comment and decided to change section 5.16 of the guidance.
8.	Royal College of Anaesthetists	5.35	Prediction of massive RBC transfusion It is not clear why these tests would be used to predict massive transfusion. Unless there is a gross abnormality one would not expect prediction to be high, these POC tests are tools to diagnose and manage coagulopathy.	Thank you for your comment which the Committee considered. The External Assessment Group informed the Committee that prediction studies were included in the assessment in cases where there were insufficient data from studies that evaluated differences in clinical outcomes between viscoelastometric-tested and untested populations.

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9.	TEM International	6.9	<p>Here, it is mentioned: “The Committee discussed the implications of using risk of red blood cell transfusion as the main outcome in the economic model. The Committee discussed 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 this decision was taken because most patients receiving any transfusion receive red blood cell, and no data were available to inform the probabilities of complications for red blood cell, platelet or fresh frozen plasma only, or any combination of these.”</p> <p>This statement is at least questionable since several publications point out the negative impact of FFP and platelet transfusion on morbidity and mortality (e.g., Spiess et al. Transfusion 2004; Dara et al. Crit Care Med 2005; Sarani et al. Crit Care Med 2008; Pereboom et al. Anesth Analg 2009; Shanwell et al. Vox Sanguinis 2009; Watson et al. J Trauma 2009; Inaba et al. J Am Coll Surg 2010; Inaba et al. Arch Surg 2010; Johnson et al. Arch Surg 2010; Murad et al. Transfusion 2010; Stanworth et al. Transfusion 2011; Tinmouth et al. Crit Care 2011; Bolton-Maggs et al. SHOT UK 2013; Bjursten et al. Intensive Care Med 2013; Hickey et al. Circulation 2013; Magee et al. Clinicoecon Outcomes Res 2013). Therefore, future models should consider the impact of fresh frozen plasma and platelet transfusion on morbidity and mortality, too.</p>	<p>Thank you for your comment which the Committee considered. The External Assessment Group informed the Committee that the data from the RCTs only provided information on the overall proportion of patients receiving transfusions with each blood product, not on the numbers of patients receiving combinations of products which meant this could not be modelled.</p>
<u>Evidence</u>				
10.	Royal College of Anaesthetists	3.2	<p>There is very little data reported on blood loss, the surrogates, transfusion and re-opening are used in the literature. Almost all the data is retrospective, relating blood loss, transfusion and reopening to mortality. Reported RCTs on transfusion do not report harm.</p>	<p>Thank you for your comment which the Committee considered. The uncertainties in the evidence are described in sections 5 and 6 of the guidance. The Diagnostics Assessment Report describes the evidence supporting this</p>

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				guidance in more detail and it can be found on the NICE website .
11.	TEM International	5.4-5.9	<ul style="list-style-type: none"> Has all of the relevant evidence been taken into account? <p>This question cannot be answered definitively since in section 5.4 to 5.9 it is not clearly stated whether additional reference listed in the comments of the stakeholders have been included in the systematic review. This document does not include a reference list which allows for that.</p>	Thank you for your comment which the Committee considered. All the additional references provided during consultation for the Diagnostics Assessment Report were reviewed by the External Assessment Group. The External Assessment Group's response was provided to the Committee and is currently available on the NICE website .
12.	TEM International	5.10	<p>Clinical effectiveness</p> <p>Does the statement "None of the studies reported follow-up of patients to assess the potential effects of different testing regimens on longer-term transfusion-related complications and mortality" referring to Sonoclot studies, solely?</p> <p>If so, this should be clearly stated in the text, since on the other hand, Weber et al. (Anesthesiology 2012) demonstrated a significant reduction in six-month mortality in the POC group (thromboelastometry (ROTEM) and impedance aggregometry (Multiplate)) compared to the control group (standard laboratory testing and clinical decision).</p>	Thank you for your comment which the Committee considered. The Committee decided to merge section 5.9 and 5.10 of the guidance to make it clear that the statement refers to Sonoclot studies only.
13.	TEM International	5.26	In this paragraph six-month mortality is not mentioned. Therefore, it is unclear whether the RCT published by Weber et al. (Anesthesiology 2012) is included in this analysis or not. Besides a significant reduction in six-month mortality (4	Thank you for your comment which the Committee considered. The Committee

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			vs. 20%; P = 0.013) this RCT demonstrated a significant reduction in the overall incidence of composite adverse events (acute renal failure, sepsis, thrombotic complications, and allergic reactions) in the POC group (ROTEM and Multiplate) compared with the conventional group (8 vs. 38%; P < 0.001).	decided to change section 5.25 of the guidance to make reference to the results of Weber et al (2012).
14.	TEM International	5.28	Which controlled clinical trial (rapid-TEG guided vs. standard transfusion protocol) reported as an abstract is referred to, here? The abstract published by Lendemans et al. 2013 (ROTEM-guided vs. standard transfusion protocol) seems to be not included in the analysis despite demonstrating a significant reduction in the incidence in-hospital mortality (20.9 vs. 38.3%; P = 0.012) as well as in multiple organ failure (36.3 vs. 66.7%; P = 0.00012).	<p>Thank you for your comment which the Committee considered.</p> <p>The full reference of the controlled clinical trial referred to in the guidance is stated in the Diagnostics Assessment Report:</p> <p><i>“Messenger BM, Craft RM, Carroll RC, Daley BJ, Enderson B, Snider CG. TEG-guided massive transfusion in trauma patients. Paper presented at the Annual Meeting of the International Anesthesia Research Society (IARS); 21-24 May 2011; Vancouver: Canada. Anesth Analg 2011;112(5 Suppl 1).”</i></p> <p>The External Assessment Group informed the Committee that Lendemans et al. 2013 did not fulfil the</p>

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			<p>One major criticism to the systematic review of the literature may be that on the one hand, RCTs and prospective observational (predictive) studies were included in this analysis, but on the other hand, retrospective cohort studies as well as before-and-after cohort studies have been excluded from this analysis. This is not in line with current systems to evaluate the evidence of the available literature for guidelines such as the SIGN or GRADE classification.</p>	<p>inclusion criteria for the assessment.</p> <p>The External Assessment Group informed the Committee that predictive accuracy studies were included in cases where data on clinical effectiveness were not available. All evidence was assessed in accordance with the Diagnostics Assessment Programme manual.</p>
15.	TEM International	6.15	<p>As mentioned in the comments to 5.10, Weber et al. (Anesthesiology 2012) demonstrated a significant reduction in six-month mortality in the POC group (thromboelastometry (ROTEM) and impedance aggregometry (Multiplate)) compared to the control group (standard laboratory testing and clinical decision). However, we agree that further research is needed to assess the potential effects of different testing regimens on longer-term transfusion-related complications and mortality.</p>	<p>Thank you for your comment which the Committee considered. The Committee decided to change section 5.25 of the guidance to make reference to the results of Weber et al (2012).</p>
16.	Royal College of Anaesthetists	6.9	<p>The committee has used out of date data for transfusion practice in the UK. We would suggest they use http://hospital.blood.co.uk/library/pdf/2011_Use_of_Blood_in_Adult_Cardiac_Surgery_report.pdf for a more accurate reflection if UK wide practice</p>	<p>Thank you for your comment which the Committee considered. The External Assessment Group considered this data and informed the Committee that this audit data does not provide information linking</p>

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				blood transfusion to outcomes and therefore, they considered the input values they used to be the more appropriate for the purpose of this assessment.
17.	Royal College of Anaesthetists:		<p>B) The authors have considered each of three systems give the same data output so can be used in an almost interchangeable way. This is not the case.</p> <p>The first use in the operating theatre setting was in liver transplantation where the group in Pittsburgh were trying to assess the degree of hyperfibrinolysis and coagulopathy in patients having liver transplantation (Kang et al Anesth Analg 1985;64:888-896). Subsequent observational studies were recorded in cardiac surgical practice (Spiess et al J Cardiothorac Vasc Anesth 1995;9:168-173)</p> <p>The RoTEM® system was launched in Europe in 2003. It was originally ‘marketed’ by Pentapharm, Basel, Switzerland. Their approach was to give away the system to centres in Europe who performed cardiac and hepatic surgery. The RoTEM® system was taken over by TEM GMBH of Munich about 3 years ago. The system and its reagents gained approval from the FDFA in the United States about 2 years ago. This temporal and geographical difference in the use of the devices may explain why the TEG® is mainly used in North America and the UK and the RoTEM® in Europe.</p> <p>B) There have been very few studies directly comparing the results from the TEG® and RoTEM®. However those that have been reported caution about the interchangeability of the data generated and also the recommendations as to guiding transfusion practice. This is my major concern with both the comparative efficacy and cost-benefit analysis outlined in the document for review.</p> <p>In brief the first study compared samples from patients having hepatic transplantation at the Royal Free Hospital in London (Coakley et al J Cardiothorac</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group informed the Committee that all devices were considered equally on the basis of available data. 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. Therefore, the External Assessment Group applied the summary relative risk for red blood cell transfusion in the model for ROTEM and TEG. Limited data suggested that the accuracy of Sonoclot in predicting clinical outcomes may be similar to that of TEG</p>

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			<p>Vasc Anesth 2006;20(4):548-553). The second was a laboratory based comparison in recalcified pooled plasma samples (Nielsen VG Blood Coag Fibrinolysis 2007;18(3):247-252) and the last in cardiac surgery patients operated in Groningen, Nederlands (Venema et al Anesth Analg 2010;111(2):339-344)</p> <p>In the liver transplant study the results for the two systems were compared and reported as the Cohen Kappa statistic (1 = perfect agreement, 0 is no agreement). There was moderate agreement between Clauss fibrinogen and fib-TEM assays about fulfilling fibrinogen transfusion criteria (kappa = 0.42, p ≤ 0.05). Agreement between TEG® and RoTEM® to transfuse platelets was fair (in-TEM v native heparinase TEG®, kappa = 0.33, in-TEM/kaolin heparinase TEG®, kappa = 0.28). There was moderate agreement between in-TEM and prothrombin time (kappa = 0.42), and poor agreement between other tests about the point to administer fresh frozen plasma.</p> <p>In the laboratory based assessment plasma (n = 8 per condition) was not activated (native) or was celite-activated in normal plasma, that made hypocoagulable plasma by dilution with hydroxyethyl-starch or hypercoagulable by addition of fibrinogen. The ROTEM® system generated significantly (P<0.05) shorter reaction time (mean ± SD, 459 ± 39 v. 788 ± 94 seconds) and greater angle (60.1 ± 5.3 versus 46.4 ± 4.6 degrees), maximum amplitude (27.6 ± 1.6 v.24.4 ±1.4 mm) with native plasma compared with the TEG®. Celite-activation tended to attenuate but not remove the differences between the two systems. The author concluded that comparison of the TEG® and the ROTEM® with similar samples demonstrated clinically significant differences in the data generated without exogenous activation. As there are differences in the proprietary activator used in each system then divergent results are expected, which may affect clinical decision-making.</p> <p>The study in a mixed cardiac surgery practice compared the TEG® in both native and kaolin activated samples with the data from the RoTEM® system using the inTEM (ellagic acid activated) or ExTEM (tissue factor activated) Each</p>	<p>so the same relative risk was also applied in the model for Sonoclot. Under the assumptions made in the cost effectiveness analyses, that is, the clinical effectiveness of the 3 devices was comparable, ROTEM was dominated by TEG and Sonoclot because it was the most costly device. Therefore, the sensitivity analyses in the economics results section were performed using ROTEM because under the assumptions in the model, if ROTEM was cost-effective, the other 2 devices would also be cost-effective.</p>

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			<p>measurement consisted of reaction time (R), coagulation time (K), maximum amplitude (MA), and angle (alpha).</p> <p>As with the data in recalcified plasma the R time of the kaolin TEG® was longer than that of the inTEM (mean±SD; 345±102 v. 179±74 seconds, P < 0.001) and the exTEM (55 ± 28 seconds, P < 0.001). The MA of the kaolin TEG® (71 ± 6.5 mm) was larger than the MCF of the inTEM (67 ± 5.2 mm, P < 0.02) but similar to that of the exTEM (69 ± 6.3 mm). The repeatability of the R and K times was poor in both devices, whereas the repeatability of the MA and alpha was sufficient for clinical purposes.</p> <p>In all of these reports the authors concluded that TEG® and RoTEM® measurements are not completely interchangeable, and the clinical interpretation of data from viscoelastic testing should be device specific and not generalised.</p> <p>Finally, the authors of the report under consideration suggest that there is no data to guide use of fibrinogen supplementation. This may be due to two confounding variables. First fibrinogen supplementation is licensed and available in many European countries. This, along with the geographical spread of the devices may explain why transfusion algorithms based on RoTEM® appear to frequently recommend fibrinogen (Schöchl et al Crit Care 2010;14(2): R55) while TEG® based algorithms appear to recommend plasma (Coakley et al J Cardiothorac Vasc Anesth 2006;20(4):548-553).</p> <p>The second potential problem of using viscoelastic tests of fibrinogen concentration to guide therapy may be due to the reports that the functional fibrinogen assay with the TEG® gives consistently higher readings (P<0.05) to that with the FibTEM (Solomon et al Anaesth Analg 2012;114(4):721-730).</p> <p>Finally, note should be taken that the normal reference ranges for all these devices are in young fit adults, not elderly patients with cardiac disease or other co-morbidities.</p>	
18.	Royal College of		The Kleijnen Systematic Review is comprehensive and well written. It is poorly referenced with many of the correctly cited papers incorrectly numbered in the	Thank you for your comment which the Committee

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	Anaesthetists		reference list. There is a lot of weight given how bad a blood transfusion is for a patient and in the UK this based on the retrospective data reported from Bristol by Murphy and colleagues. This data is just about to be superseded by the publication of the TITRE2 study a 2000 patient UK based RCT that will show alternative results to all the published retrospective data.	<p>considered.</p> <p>The Committee decided that the cost-effectiveness estimates are unlikely to be affected by the results of the TITRE2 trial. The Committee's consideration of the TITRE2 study is described in section 6.10 of the guidance.</p> <p>The External Assessment Group checked the references and could not find any errors. The External Assessment Group wondered whether the confusion may have been caused by the reference list to the protocol which was also included as an appendix in the Diagnostics Assessment Report.</p>
19.	TEM International		<p>Additional references, mentioned in the comments:</p> <p>The Scottish Intercollegiate Guidelines Network (SIGN). http://www.sign.ac.uk/index.html</p> <p>The Grading of Recommendations Assessment, Development and Evaluation (GRADE). http://www.gradeworkinggroup.org/index.htm</p>	Thank you for your comment which the Committee considered. All the additional references provided during consultation on the Diagnostics Assessment

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			<p>Spalding GJ, Hartrumpf M, Sierig T, Oesberg N, Kirschke CG, Albes JM. Cost reduction of perioperative coagulation management in cardiac surgery: value of "bedside" thrombelastography (ROTEM). Eur J Cardiothorac Surg. 2007 Jun;31(6):1052-7.</p> <p>Görlinger K, Dirkmann D, Weber CF, Rahe-Meyer N, Hanke AA. Algorithms for transfusion and coagulation management in massive haemorrhage. Anästhesiologie Intensivmedizin. 2011; 52:145-59.</p> <p>Görlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, Jakob H, Peters J. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology. 2011 Dec;115(6):1179-91.</p> <p>Larsen OH, Fenger-Eriksen C, Christiansen K, Ingerslev J, Sørensen B. Diagnostic performance and therapeutic consequence of thromboelastometry activated by kaolin versus a panel of specific reagents. Anesthesiology. 2011 Aug;115(2):294-302.</p> <p>Weber CF, Görlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, Cohn LH, Zacharowski K. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology. 2012 Sep;117(3):531-47.</p> <p>Görlinger K, Fries D, Dirkmann D, Weber CF, Hanke AA, Schöchel H. Reduction of fresh frozen plasma requirements by perioperative point-of-care coagulation management with early calculated goal-directed therapy. Transfus Med Hemother. 2012 Apr;39(2):104-113.</p> <p>Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, Fries D, Görlinger K, Haas T, Imberger G, Jacob M, Lancé M, Llau</p>	<p>Report were reviewed by the External Assessment Group. The External Assessment Group's response was provided to the Committee and is currently available on the NICE website.</p>

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			<p>J, Mallett S, Meier J, Rahe-Meyer N, Samama CM, Smith A, Solomon C, Van der Linden P, Wikkelsø AJ, Wouters P, Wyffels P. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2013 Jun;30(6):270-382.</p> <p>Esler C, Ghag S, Kirstenfeldt C, Fung YL, Pearse B, for the HSSA (Health Service Support Agency). Implementation of ROTEM® (Rotational thromboelastometry) in cardiac theatre reduces use of blood products. Abstract, HAA, Queensland, Australia, 2013.</p> <p>Lendemans S, Düsing H, Assmuth S, Hußmann B, Wafaisade A, Lefering R, Görlinger K, Marzi I. Die Einführung eines spezifischen Gerinnungsprotokolls (Point of Care) verbessert das Outcome beim blutenden Schwerverletzten -eine Subgruppenanalyse von 172 Patienten unter Beteiligung des Traumaregisters DGU (gefördert durch die DIVI). Deutscher Kongress für Orthopädie und Unfallchirurgie (DKOU 2013). Berlin, 22.-25.10.2013. Düsseldorf: German Medical Science GMS Publishing House; 2013. DocWI50-561. doi: 10.3205/13dkou367, urn:nbn:de:0183-13dkou3672. Published: October 23, 2013. http://www.egms.de/static/en/meetings/dkou2013/13dkou367.shtml</p>	
20.	TEM International		<p>Additional reference on the impact of FFP and platelet transfusion on patients' outcomes (see comment 16 on section 6.9):</p> <p>Spiess BD, Royston D, Levy JH, Fitch J, Dietrich W, Body S, Murkin J, Nadel A. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion. 2004 Aug;44(8):1143-8.</p> <p>Dara SI, Rana R, Afessa B, Moore SB, Gajic O. Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. Crit Care Med. 2005</p>	Thank you for your comment which the Committee considered. All the additional references provided during consultation on the Diagnostics Assessment Report were reviewed by the External Assessment Group. The External Assessment Group's response was

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			<p>Nov;33(11):2667-71.</p> <p>Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach JI, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med. 2008 Apr;36(4):1114-8.</p> <p>Pereboom IT, de Boer MT, Haagsma EB, Hendriks HG, Lisman T, Porte RJ. Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute lung injury. Anesth Analg. 2009 Apr;108(4):1083-91.</p> <p>Shanwell A, Andersson TM, Rostgaard K, Edgren G, Hjalgrim H, Norda R, Melbye M, Nyrén O, Reilly M. Post-transfusion mortality among recipients of ABO-compatible but non-identical plasma. Vox Sang. 2009 May;96(4):316-23.</p> <p>Watson GA, Sperry JL, Rosengart MR, Minei JP, Harbrecht BG, Moore EE, Cuschieri J, Maier RV, Billiar TR, Peitzman AB; Inflammation and Host Response to Injury Investigators. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma. 2009 Aug;67(2):221-30.</p> <p>Inaba K, Branco BC, Rhee P, Blackbourne LH, Holcomb JB, Teixeira PG, Shulman I, Nelson J, Demetriades D. Impact of plasma transfusion in trauma patients who do not require massive transfusion. J Am Coll Surg. 2010 Jun;210(6):957-65.</p> <p>Inaba K, Branco BC, Rhee P, Holcomb JB, Blackbourne LH, Shulman I, Nelson J, Demetriades D. Impact of ABO-identical vs ABO-compatible nonidentical plasma transfusion in trauma patients. Arch Surg. 2010 Sep;145(9):899-906.</p> <p>Johnson JL, Moore EE, Kashuk JL, Banerjee A, Cothren CC, Biffi WL, Sauaia A. Effect of blood products transfusion on the development of postinjury multiple</p>	<p>provided to the Committee and is currently available on the NICE website.</p>

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			<p>organ failure. Arch Surg. 2010 Oct;145(10): 973-7.</p> <p>Murad MH, Stubbs JR, Gandhi MJ, Wang AT, Paul A, Erwin PJ, Montori VM, Roback JD. The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. Transfusion. 2010 Jun;50(6):1370-83.</p> <p>Stanworth SJ, Grant-Casey J, Lowe D, Laffan M, New H, Murphy MF, Allard S. The use of fresh-frozen plasma in England: high levels of inappropriate use in adults and children. Transfusion. 2011 Jan;51(1):62-70.</p> <p>Tinmouth AT, McIntyre L. The conundrum of persistent inappropriate use of frozen plasma. Crit Care. 2011;15(3):160.</p> <p>Bjurstén H, Dardashti A, Ederoth P, Brondén B, Algotsson L. Increased long-term mortality with plasma transfusion after coronary artery bypass surgery. Intensive Care Med. 2013 Mar;39(3):437-44.</p> <p>Bolton-Maggs PHB (Ed), Poles D, Watt A, Thomas D and Cohen H on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2012 Annual SHOT Report (2013). Published July 2013. http://www.shotuk.org/wp-content/uploads/2013/08/SHOT-Annual-Report-2012.pdf</p> <p>Hickey M, Gatién M, Taljaard M, Aujnarain A, Giulivi A, Perry JJ. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. Circulation. 2013 Jul 23;128(4):360-4.</p> <p>Magee G, Zbrozek A. Fluid overload is associated with increases in length of stay and hospital costs: pooled analysis of data from more than 600 US hospitals. Clinicoecon Outcomes Res. 2013 Jun 26;5:289-96.</p>	

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<u>Cost of technologies</u>				
21.	TEM International	5.44-45	<p>Cost effectiveness</p> <p>Here it is stated: “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. The other 4 studies were cost-minimisation studies performed alongside a retrospective before and after study.”</p> <p>Since no RCT is mentioned here, it is questionable again whether the RCT in cardiac surgery published by Weber et al. (Anesthesiology 2012) has been included in this cost effectiveness analysis. Here, Weber reports: “Irrespective of any secondary costs of transfusion, analyses of the cumulative costs of hemostatic therapy showed that conventional coagulation management was nearly twice as expensive as POC-guided coagulation management. The mean costs of hemostatic therapy were on average 3,109 € per patient in the conventional group and 1,528 € per patient in the POC group (table 6).” Weber et al. reported in their RCT a detailed breakdown of cost savings in table 6.</p> <p>Furthermore, the authors stated in section 5.45 that only one study (Spalding et al. Eur J Cardiothorac Surg, 2007) reported a detailed breakdown of cost savings. However, besides in the before mentioned RCT published by Weber et al., a detailed calculation of costs has been performed in the before-and-after study in cardiac surgery published by Görlinger et al. (Anesthesiology 2011), too: “Calculation of costs was based on the price for blood products and coagulation factor concentrates in 2009: 1 U PRBC, 85 euros; 1 U FFP, 65 euros; 1 pooled platelet concentrate, 250 euros; 1g fibrinogen concentrate, 288 euros; 500 U PCC, 126 euros; 500 U AT, 44 euros; 1,250 U FXIII, 527 euros; and 4,8 mg rFVIIa, 3,203 euros. ... Overall costs for allogeneic blood products and coagulation factor concentrates per patient decreased by 6.5%, corresponding to a cost-saving of about 50,000 euros per year (table 5).”</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The Committee decided to change section 5.25 of the guidance to make reference to the results of Weber et al (2012).</p> <p>All the additional references provided during consultation on the Diagnostics Assessment Report were reviewed by the External Assessment Group. The External Assessment Group’s response was provided to the Committee and is currently available on the NICE website.</p>

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			<p>In addition, a detailed breakdown of cost savings in visceral and transplant surgery (University Hospital of Essen, Germany) has been reported by Görlinger et al. in Transfus Med Hemother in 2012 (page 110) and for the whole University Hospital Essen, Germany in Görlinger et al. Anästhesiologie in 2011 (page 155, figure 5). Cost effectiveness of POC testing has been analysed in the guidelines on the management of severe perioperative bleeding from the European Society of Anaesthesiology, too (Kozek-Langenecker et al. Eur J Anaesth 2013; chapter 7.3 Cost implications, page 306-8).</p> <p>Moreover, a recently published before-and-after study in cardiac surgery from Brisbane, Australia, reported detailed breakdown of cost savings of overall 928,998 AU\$ (48.3%) within 12 months after implementation of a ROTEM-based transfusion algorithm (Esler et al. HAA 2013).</p>	
22.	TEM International	5.71	<p>Cost of viscoelastic devices</p> <p>It is unclear whether the cost calculations of the devices themselves have been corrected according to the comments submitted in February to the NICE group (Klaus Görlinger, NICE DAR Comments, Febr 19th 2014, page 6f, comment 12).</p> <p>Costs for quality control seem still not be included.</p> <p>Furthermore, the cost calculation for the ROTEM and TEG tests performed in the cardiac and trauma model have not been corrected. In the cardiac model, a whole panel of ROTEM tests (INTEM, EXTEM, FIBTEM and HEPTM) is still compared to a basic kaolin and heparinase test in TEG. As explained in detail in the submitted comments to the NICE draft (Klaus Görlinger, NICE DAR Comments, Febr 19th 2014, page 5f, comment 10), on the one hand, INTEM and HEPTM are required only after heparin-reversal with protamine, and on the other hand, functional fibrinogen test in TEG is mandatory for discrimination between fibrinogen deficiency and low platelet count. As suggested in the</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group carried out additional sensitivity analyses to explore how the results would change if other combinations of assays are used in ROTEM and TEG. . The results of the analyses did not differ from that of the base case analysis; ROTEM and TEG remained cost-effective compared to standard laboratory tests.</p>

Comment number	Name and organisation	Section number	Comment	Response
			<p>submitted comments, comparable test combinations should be used for cost analysis in ROTEM and TEG (e.g., EXTEM, FIBTEM, INTEM and HEPTTEM vs. rapid-TEG, functional fibrinogen, kaolin-TEG and heparinase-TEG or INTEM and HEPTTEM vs. kaolin-TEG and heparinase-TEG). Furthermore, a heparinase cup is mandatory for all TEG tests performed during CPB, whereas EXTEM and FIBTEM reagents already include a heparin inhibitor. In the trauma model, costs for EXTEM and FIBTEM tests for ROTEM have to be compared to the costs for rapid-TEG and functional fibrinogen tests for TEG, accordingly (Klaus Görlinger, NICE DAR Comments, Febr 19th 2014, page 6, comment 11). Otherwise, a different diagnostic performance has to be assumed between ROTEM and TEG in both models (Larsen et al. Anesthesiology 2011) or you are just comparing apples and oranges in your cost-effectiveness analysis.</p>	<p>Results of the additional analyses were seen by the Diagnostics Advisory Committee and are now available on the NICE website.</p>
23.	Royal College of Anaesthetists	5.71	<p>Costs In terms of costs of the various assays, there are a few issues to consider: It is important to point out again that the ROTEM has 4 channels, whereas the TEG has only 2. For most scenarios where TEG is used, it will probably be necessary for hospitals to have two machines so that Kaolin, Kaolin heparinase and functional fibrinogen tests can be run simultaneously. Based on the old literature, it may be reasonable to assume that just two tests (K and KH) are required, but the data on the impact of low fibrinogen and association with massive haemorrhage is so convincing, that more clinicians will start to feel the necessity to run functional fibrinogen tests as well. The same applies for trauma patients. We do not think that just running a rapid TEG is adequate, and a functional fibrinogen would probably also be required. Many clinicians would also want a standard kaolin TEG to get information on the R and K times to inform decisions on FFP transfusion. It is not clear as to why it is assumed each trauma patient would routinely require testing 5 times. Cost of standard laboratory tests. A full blood count (to give platelet count) should be included with PT, PTT and fibrinogen.</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group carried out additional sensitivity analyses to explore how the results would change if other combinations of assays are used in ROTEM and TEG. The results of the analyses did not differ from that of the base case analysis; ROTEM and TEG remained cost-effective compared to standard laboratory tests. Results of the additional</p>

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				analysis were seen by the Diagnostics Advisory Committee and are now available on the NICE website .
24.	TEM International	6.10	<p>Here, it is stated: “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 are more effective and less costly than 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.”</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group carried out additional sensitivity analyses to explore how the results would change if other combinations of assays are used in ROTEM and TEG. . The results of the analyses did not differ from that of the base case analysis; ROTEM and TEG remained cost-effective compared to standard laboratory tests. Results of the additional analysis were seen by the Diagnostics Advisory Committee and are now available on the NICE website.</p>

Comment number	Name and organisation	Section number	Comment	Response
			<p>We agree, that viscoelastometric testing remains cost effective in any test combination when compared with standard laboratory testing. However, the authors clearly state in their cost-effectiveness analysis that ROTEM is the most expensive system but this depends on the test combination used. As mentioned in the comments to 5.77 and 5.78, costs for TEG tests are 2 to 2.9fold higher in cardiac and 2.8 to 3.9fold higher in trauma compared to ROTEM if similar test combinations are used. This is not reflected by the present cost-effectiveness analysis and may lead to misinterpretation in the cost-effectiveness between TEG and ROTEM in particular by decision-makers such as hospital administrators who are not familiar with the details of this viscoelastic test devices.</p>	<p>The Committee decided to change sections 5.83 and 5.84 of the guidance.</p>
<u>Cost-effectiveness results</u>				
25.	TEM International		<ul style="list-style-type: none"> • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? <p>Cost-effectiveness interpretations between the three different viscoelastic test devices are questionable due to the inequality of test combination selected for ROTEM and TEG.</p> <p>Statements such as “ROTEM – the most expensive device” may lead to misinterpretation in the cost-effectiveness between TEG and ROTEM in particular by decision-makers such as hospital administrators who are not familiar with the details of this viscoelastic test devices. This cost-effectiveness analysis does not reflect that costs for TEG tests are 2 to 2.9fold higher in cardiac</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The Committee decided to change sections 5.83 and 5.84 of the guidance.</p>

Comment number	Name and organisation	Section number	Comment	Response
			and 2.8 to 3.9fold higher in trauma compared to ROTEM if similar test combinations are used. Therefore, cost-effectiveness seems to be more dependent on the test combination than on the device , used. However, this may have not only an impact on costs but on clinical effectiveness, too. This should be pointed out clearly in the conclusions and summary.	
26.	TEM International	5.72 and 5.74	<p>Base-case results</p> <p>Due to the inequality of test combinations for ROTEM and TEG used in both models, cardiac and trauma (see comment above and Klaus Görlinger, NICE DAR Comments, Febr 19th 2014, page 5-7, comment 10-12), the calculated differences in cost savings between ROTEM and TEG are highly questionable. This may lead to misinterpretation of the whole cost-effectiveness analysis.</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group carried out additional sensitivity analyses to explore how the results would change if other combinations of assays are used in ROTEM and TEG. . The results of the analyses did not differ from that of the base case analysis; ROTEM and TEG remained cost-effective compared to standard laboratory tests. Results of the additional analysis were seen by the Diagnostics Advisory Committee and are now available on the NICE website.</p>
27.	TEM International	5.77-78	Probailistic analysis results	Thank you for your comment which the Committee

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			<p>Here, it is stated: "...the probability of cost effectiveness for each of the 3 viscoelastometric technologies compared to standard laboratory tests was 0.79 for ROTEM (the most expensive device), 0.82 for TEG and 0.87 for Sonoclot (the cheapest device)."</p> <p>Here again, the inequality of test combination between ROTEM and TEG results in a falsification of the cost-effectiveness analysis. As demonstrated in the submitted comments to the NICE group (Klaus Görlinger, NICE DAR Comments, Febr 19th 2014, page 5f, comment 10-11) costs for TEG tests are 2 to 2.9fold higher in cardiac and 2.8 to 3.9fold higher in trauma compared to ROTEM if similar test combinations are used. This should be considered in the cost calculation in order to avoid a falsification of the cost-effectiveness analysis.</p>	<p>considered.</p> <p>The External Assessment Group carried out additional sensitivity analyses to explore how the results would change if other combinations of assays are used in ROTEM and TEG. . The results of the analyses did not differ from that of the base case analysis; ROTEM and TEG remained cost-effective compared to standard laboratory tests. Results of the additional analyses were seen by the Diagnostics Advisory Committee and are now available on the NICE website.</p>
28.	TEM International	5.79	<p>Scenario analysis results</p> <p>Again, this calculation is based on the assumption that 12 ROTEM tests (3x 4) have to be performed per patient in the cardiac model. This assumption is not in line with the algorithms used in recently published studies (e.g., Görlinger et al. AnästH Intensivmed 2011; Görlinger et al. Anesthesiology 2011; Weber et al. Anesthesiology 2012; Esler et al. HAA 2013).</p> <p>However, based on the assumption that 12 ROTEM tests are performed in each</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group carried out additional sensitivity analyses to explore how the results would change if other combinations of</p>

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			cardiac patient, ROTEM analysis would result in cost savings in hospitals dealing with more than 27 ($326 : 12 = 27.2$) cardiac patients with bleeding per year. If the number of tests per patient can be reduce (e.g., to 7 tests; see Klaus Görlinger, NICE DAR Comments, Febr 19th 2014, page 5f, comment 10), cost savings can be achieved already with 16 bleeding cardiac patients per year.	assays are used in ROTEM and TEG. . The results of the analyses did not differ from that of the base case analyses; ROTEM and TEG remained cost-effective compared to standard laboratory tests. Results of the additional analysis were seen by the Diagnostics Advisory Committee and are now available on the NICE website .
29.	TEM International	5.81, 5.83-84	Similar financial considerations have to be done in the trauma model (see comments on 5.71, 5.74, 5.78, and 5.79) .	Thank you for your comment which the Committee considered. The External Assessment Group carried out additional sensitivity analyses to explore how the results would change if other combinations of assays are used in ROTEM and TEG. The results of the analyses did not differ from that of the base case analysis; ROTEM and TEG remained cost-effective

Comment number	Name and organisation	Section number	Comment	Response
				<p>compared to standard laboratory tests. Results of the additional analyses were seen by the Diagnostics Advisory Committee and are now available on the NICE website.</p>
<u>Trauma and post-partum haemorrhage population</u>				
30.	Haemonetics	1.3	<p><u>“Despite the several prospective studies available to date, 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).”</u></p> <p>We felt there is value in mentioning that there remains recommendation from several associations at current levels of evidence for the use of VE in Trauma and Massive hemorrhage. This level of evidence was used by the American College of Surgeons (2013) to recommend the use of VE (TEG and ROTEM) for the management of trauma patients.</p> <p>To name a few, the Danish Society of Blood Banking/Clinical Immunology (2014) recommended current new guidelines that TEG or ROTEM should be used in bleeding patients including trauma and PPH.</p> <p>In addition, the Association of Anaesthetists of Great Britain and Ireland (2010) have recommended TEG or ROTEM if available, should be used in the management of massive haemorrhage, and , Obstetric Anaesthetists’ Association (OAA) and Association of Anaesthetists of Great Britain and Ireland (AAGBI)</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group reviewed the evidence considered in guidance from other organisations. The External Assessment Group informed the Committee that most of the studies considered in guidance from other organisations did not meet the inclusion criteria for this assessment.</p> <p>The Committee concluded that the evidence is currently insufficient to recommend the routine adoption of viscoelastometric point-of-</p>

Comment number	Name and organisation	Section number	Comment	Response
			<p>'Guidelines for Obstetric Anaesthesia Services' (2012) recommend TEG or ROTEM as essential equipment for efficient functioning of the obstetric anaesthetic service.</p> <p>Finally, the European Society of Anaesthesiology (2013) recommends the use of VE in the management of severe perioperative bleeding.</p>	<p>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”.</p>
31.	Royal College of Anaesthetists		<p>Are the summaries of clinical and cost effectiveness reasonable interpretation of the evidence?</p> <p>The ESA guideline committee gave a 1C recommendation that perioperative POC coagulation monitoring with TEG/ROTEM, in conjunction with transfusion algorithms, should be used for cardiac surgery, major trauma and liver transplant surgery. It was felt that more research was required before a recommendation could be made for obstetric haemorrhage.</p> <p>Accepting that whilst there are only a limited number of RCTs to provide high grade evidence, large observational cohort studies strongly indicate that the use of TEG/ROTEM facilitates the optimal management of excessive bleeding and reduce transfusion by enabling goal directed tailored haemostatic therapy, and allows differentiation of microvascular and surgical bleeding. The potential reductions in allogeneic blood product transfusions and re-exploration rates have important implications for overall patient safety and health care costs.</p>	<p>Thank you for your comment which the Committee considered.</p> <p>The External Assessment Group reviewed the evidence considered in guidance from other organisations. The External Assessment Group informed the Committee that most of the studies considered in guidance from other organisations did not meet the inclusion criteria for this assessment.</p> <p>The Committee concluded that the evidence is currently insufficient to recommend the routine adoption of viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems) in the</p>

Comment number	Name and organisation	Section number	Comment	Response
				NHS to help detect, manage and monitor haemostasis in the emergency control of bleeding after trauma and during postpartum haemorrhage”.
<u>Implementation</u>				
32.	Royal College of Anaesthetists		<p>Are the provisional recommendations sound and a suitable basis for guidance in the NHS?</p> <p>There is no discussion or guidance on:</p> <ul style="list-style-type: none"> • Quality control testing of machines and logs • Training of non-laboratory staff users, ongoing training and use of training logs • The use of IT to ensure that results available to staff remote from the machine and the results being part of the patient record. • The above are in place for standard laboratory tests 	Thank you for your comment. The Committee considered this comment and decided to change section 6.20 and add section 1.3 to the guidance. NICE’s Health Technology Adoption Programme provides support for the adoption of guidance and will consider these points in its work.
<u>Factual check</u>				
33.	Royal College of Anaesthetists	3.13	Standard tests of coagulation determine the time to clot of platelet poor plasma in vitro.	Thank you for your comment which the Committee considered. The Committee decided to change section 3.13 of the guidance.
34.	Royal College of Anaesthetists	3.14	Allogeneic haemostatic transfusion therapy (platelets, FFP or cryo) may be given to improve haemostatic potential. These are not drugs per se. The only drugs are the antifibrinolytics, DDAVP and the recombinants.	Thank you for your comment which the Committee considered. The Committee decided to change section 3.14 of the guidance.

Comment number	Name and organisation	Section number	Comment	Response
35.	Royal College of Anaesthetists	3.15	Fibrinogen level is <u>greater</u> than 1g/dl should be corrected to <u>less</u> than.	Thank you for your comment which the Committee considered. The Committee decided to change section 3.15 of the guidance.
36.	Royal College of Anaesthetists	3.16	Complications: should include TACO.	Thank you for your comment which the Committee considered. The Committee decided to change section 3.16 of the guidance.
37.	Royal College of Anaesthetists	4.8	Functional fibrinogen assay “which divides clot strength into contributions from platelets and from fibrin”. This sentence is not quite right. In the functional fibrinogen assay the platelet contribution to the MA is removed. The MA of the fibrin clot gives a result with close correlation to Clauss fibrinogen.	Thank you for your comment which the Committee considered. The Committee decided to change section 4.8 of the guidance.
38.	Royal College of Anaesthetists	4.8	The comparator: In regard to SLTs the point should also be made that SLT are performed on plasma samples, with the platelets and other blood cells removed and therefore they do not reflect the true physiological clotting process (cell based model of haemostasis).	Thank you for your comment which the Committee considered. The Committee decided to change section 4.14 of the guidance.
39.	TEM International	5.18	Evidence on outcomes “Prothrombin transfusion” must be changed to “Prothrombin complex concentrate transfusion”	Thank you for your comment which the Committee considered. The Committee decided to change section 5.17 of the guidance.
40.	Royal College of Anaesthetists	5.19	Bleeding: not clear if this is bleeding or postoperative chest drain loss.	Thank you for your comment which the Committee considered. The External Assessment Group informed the Committee that the

Comment number	Name and organisation	Section number	Comment	Response
				sentence refers to both bleeding and postoperative chest drain loss (but mainly measured as mediastinal tube drainage).
<u>Other</u>				
41.	Royal College of Anaesthetists	3.1	<p>Clinical need and practice</p> <p>Why is there no mention of liver transplant surgery? This is the area that has the longest experience of TEG/ROTEM. Over 700 liver transplants are performed annually in the UK, with many of these patients requiring massive transfusions.</p> <p>The problem addressed: The need for POC tests in the setting of complex major surgery with bleeding needs to be highlighted. Turnaround times for standard laboratory tests (SLT) of coagulation are of the order of 60-90 minutes. As a consequence much of our current transfusion practice is empirical, and means that some patients will, as a consequence, receive unnecessary or inappropriate haemostatic interventions. This in a large part accounts for the enormous variability in transfusion practice between institutions, and is part of the explanation as to why POC coagulation monitoring has been shown to reduce transfusions compared to standard care. In addition SLT are not able to diagnose fibrinolysis or hypercoagulability.</p> <p>Cardiac surgery is occasionally associated with high blood loss. It is more commonly associated with coagulaopathy related to cardiopulmonary bypass and pre-operative medications.</p>	Thank you for your comment which the Committee considered. Liver surgery is outside the scope of this assessment.
42.	TEM International	5.52	<p>Cost-effectiveness model</p> <p>The assumption “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</p>	Thank you for your comment which the Committee considered. The Committee concluded that, based on the available evidence, more evidence is needed on the

Comment number	Name and organisation	Section number	Comment	Response
			applied in the Sonoclot model” is still questionable .	clinical effectiveness of the Sonoclot system and recommended its use for research only.
43.	LINC Medical		No Comments to make	Thank you for your comment.
44.	TEM International		Thank you again for considering our comments.	Thank you for your comment.