National Institute for Health and Care Excellence

IP1219 – Ultrasound enhanced catheter-directed thrombolysis for deep vein thrombosis
Consultation Comments table

IPAC date: Thursday 12 March 2015

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 3 NHS Professional British Society of Interventional Radiology (BSIR)	**1**	Agree with recommendations in the consultation document. No additional comments.	Thank you for your comment. The consultee agrees with main recommendation.

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2	Consultee 5 Manufacturer	**1**	Thank you for providing the opportunity for [redacted] as manufacturer, to provide feedback on the draft NICE guidance relating to ultrasound-enhanced, catheter-directed thrombolysis (UE CDT) for deep vein thrombosis (DVT). At [redacted] we want our products to deliver positive outcomes in the right patient populations, and are committed to collaborating with NHS organisations to achieve this. The draft NICE guidance on the use of UE CDT for DVT is a concise and accurate reflection of the existing data sets. We support the conclusion that UE CDT should be used in the UK as part of an audit or further study. Considering the significant morbidity and mortality of DVT as well as its financial burden on the NHS, we believe gaining a better understanding of this diverse patient group would be beneficial. The treatment pathways for patients with venous thrombo-embolism (VTE) are complex, and gaining a better understanding would be advantageous. Accurately determining which patients would benefit most from each treatment would ensure the best possible patient outcomes, and most appropriate use of NHS resources. [redacted] would welcome engaging in a dialogue with NICE and the NHS on how such audits or studies should look.	Thank you for your comment. The consultee agrees with main recommendation. Section 1.3 in the guidance encourages further research and states that 'patient selection should be explicitly documented, including the duration and extent of thrombosis. The dose of thrombolytic agent used and the duration of thrombolysis should be reported, together with all complications. Outcome measures should include the success of thrombolysis (complete, partial or failed) and long-term sequelae'. The Committee noted comments on the interest shown in engaging with NICE in identifying relevant audit criteria and developing an audit tool that will be available when guidance is published.

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3	Consultee 2 NHS Professional	**General**	There is a significant amount of patient data on the use of USE-CDT available in literature, in three fields, intra-arterial; Pulmonary Embolus and DVT. The guidance doesn't review the safety and efficacy findings in other fields and as such may miss important findings in these other areas of treatment. The papers reviewed fail to answer the specific question of whether the additional expense of USE-CDT changes the outcome for patients. There has been significant progression made in the treatment of chronic and acute DVT, with surgical thrombectomy largely being discounted as a treatment option. With the advent of better technology in venous stenting. Total lysis is no longer the endpoint for ~80% of patients. A further study should take place to look at whether the endpoint of the episode changes significantly which may include stenting early ~80% or total lysis ~20% in modern practice. For USE-CDT to show cost effectiveness it would have to provide a significant reduction in timeframe over modern low dose CDT alone, as stenting is the normal outcome for DVT lysis.	Thank you for your comment. Ultrasound enhanced catheter directed thrombolysis (USE-CDT) for pulmonary embolism (PE) and intra-arterial thrombosis falls outside the scope of this guidance. Guidance on use of ultrasound enhanced CDT for PE is currently under development and will be published with the deep vein thrombosis (DVT) guidance. Cost-effectiveness analysis is not within the remit of the IP Programme. If USE-CDT receives normal arrangements IP guidance in the future, it could be referred to the Medical Technologies Evaluation Programme for cost-effectiveness consideration.

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4	Consultee 2 NHS Professional	**General**	The panel should be careful when considering comparative data that doesn't represent modern practice in CDT, which has optomised total lysis dosage and thus complication well below what is reported in the comparative data presented, which may give a false. Venous stenting has become such an important part of DVT treatment that using historical data which represent this may give a false impression of benefit over traditional CDT. There is no evidence of any safety concerns with the use of USE-CDT. There is no strong evidence of a efficacy benefit with the use of USE-CDT over modern CDT when stenting is utilised.	Thank you for your comments. The Committee were presented with all evidence available on this procedure. The BERNUTIFUL randomised controlled trial (NCT01482273) comparing ultrasound-enhanced thrombolysis against standard catheter directed thrombolysis for Ilio-femoral deep vein thrombosis has been published. This study has been added to table 2 in the overview. As there is limited evidence on efficacy, recommendation in 1.1 states that 'the procedure should only be used with special arrangements for clinical governance, consent and audit or research'.
5	Consultee 1 NHS Professional	**General**	There is a clear realisation internationally that the treatment of acute and chronic venous disease can save significant morbidity and loss of working contribution from patients. The disease is complex to treat and [redacted] certainly has a role within the treatment regime of these patients to reduce risk and improve outcomes.	Thank you for your comment.
6	Consultee 4 NHS Professional Consultant Interventional Radiologist	**General**	Catheter directed thrombolysis is effective in treating iliofemoral DVT with good outcomes reported, albeit in small scale studies. The additional benefit of ultrasound acceleration remains to be established. Subgroup of patients with extensive thrombosis, for e.g. involvement of the IVC may be those cases where the additional benefit may exist.	Thank you for your comment. Section 1.3 encourages further research on this procedure.

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7	Consultee 5 Manufacturer	**General**	The NICE draft guidance regarding use of ultrasound-enhanced, catheter-directed thrombolysis for DVT is a well-balanced and accurate reflection of the existing data sets relating to the use of this technology for this indication. We can confirm that as of December 19th 2014 no further information meeting the search criteria is available. For entry into “corrections” relating to the following pages: Page 11 - the summary of the Engelberger paper. The results table indicates that 2 patients experienced late thrombosis. The paper itself indicates there were 3 such patients. The 3% rate noted in the paper is correct, however the actual number of patients should have been 3 instead of 2. Page 15 - there is a missing parenthesis. [trauma 94)] Page 16 - results table indicates that 14 of 26 patients had complete clot lysis. The paper itself states 13 of 26 for 50%. Page 16 – a parenthesis is missing and a 9 appears in its place. [11.5 93/26)] Page 17 – a parenthesis is missing [(National venous thrombolysis registry] Page 26 - states that evidence is mainly from 2 retrospective comparative case series and 4 small retrospective case series, utilising reference sources 5-8. However, reference 5, Dumantepe 2013 and reference 8, Grommes 2011 are actually prospective studies. Page 31 - the ACCESS PTS study is discussed. The draft guidance states that the primary endpoint is the Villalta score at one year. However, the study actually has a primary efficacy endpoint of the Villalta score at 30 days and the secondary efficacy endpoint is the Villalta score at 1 year. Additionally, there is a technical endpoint of patency. Page 32 - Reference 4: the title of the paper is incorrect. “and…experience.” should be deleted.	Thank you for your comment. The Consultee highlighted some errors in the overview. These have been amended.

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8	Consultee 6 Patient	**General**	I would like to give evidence regarding this and DVT related guidances. I have recently suffered my third pelvic venous thrombus and would be a candidate for this therapy. I have observations regarding how current practice impedes emergency access to this therapy. I would be happy to answer questions that might lead to solutions to problems relating to: emergency triage, access to treatment and compression therapy, and venous thrombus research. Treatment and research in the UK appears to lag behind our international comparators. Research in 2007 found that; "Iliofemoral deep venous thrombosis (DVT) is associated with serious short-term and long-term physical, social, and economic sequelae for patients." Anthony J. Comerota, MD, Marilyn H. Gravett, MFA, Journal of Vascular Surgery Volume 46, Issue 5, November 2007, Pages 1065â€“1076. I would like to help to improve outcomes by sharing my experience with NICE.	Thank you for your comment. This comment was submitted for PE public consultation (IP1243) but also relevant to DVT consultation (IP1219). The Committee noted your views and experiences in their deliberations.

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9	Consultee 5 Manufacturer	**4&5**	A further literature search undertaken in January 2015, based on the inclusion criteria for identification of relevant studies, identified the “BERNUTIFUL” randomized controlled trial mentioned on page 31 of IP 1219 as published in Circulation: Cardiovascular Interventions 2015 ref E8:e002027. 1. This trial reinforces the need to undertake further studies on efficacy. 2. In this trial, patients diagnosed with ilio-femoral DVT had an [redacted] catheter placed and a thrombolytic (rt-PA) infusion administered. Patients were then randomised to either the [redacted] ultrasound ‘turned on’ (US) or ‘turned off’ (NON-US). Based on prior studies (Comerota et al, 2011), catheter based therapies for deep vein thrombosis are typically delivered until a target endpoint of >90% lysis of thrombus is achieved. In BERNUTIFUL, treatment to a fixed time point (15 hours) was selected as the primary efficacy endpoint, yielding incomplete thrombolysis in 46% of the NON-US group and 29% of the US group, as evidenced by the need to administer additional treatments. 3. The difficulties in quantifying venous thrombus burden have long plagued the study of endovascular thrombus therapies. For example, correctly identifying identical segments between baseline and follow-up images and the conversion of 2-dimensional imaging into a volumetric estimation can be troublesome.	Thank you for your comment. The BERNUTIFUL randomised controlled trial (NCT01482273) comparing ultrasound-enhanced thrombolysis against standard catheter directed thrombolysis for Ilio-femoral deep vein thrombosis has been published. This study has been added to table 2 in the overview.

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			4. In the present study, Engelberger et al. took advantage of the radiopaque ultrasound transducers on the [redacted] catheter to address the difficulty of correctly comparing identical venous segments imaged at baseline and at follow-up. Although the presence and visibility of the transducers do in fact address this issue, the measurement technique did not address the difficulty of determining volume from a 2-dimensional image. 5. The safety results of this study were consistent with previous trials, supporting NICE's initial observation that there are no major safety concerns. In summary, while this study collected much of the data as recommended in the draft NICE guidance (patient selection, duration and extent of thrombus, thrombolytic dose and duration of infusion, complications and outcomes), further research is needed. The difficulties highlighted by this study should further inform the data collection for future registries or audits using this system. We continue to support the conclusion that UE CDT should be used in the UK as part of an audit or further study (e.g. as part of the NHS Commissioning through Evaluation programme) and welcome the opportunity to partner with NICE to more fully evaluate [redacted]' place in the treatment of DVT.	

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10	Consultee 5 Manufacturer	**4 & 5**	In addition we would like to submit the following to further support the safety profile of UECDT (study not yet published). SEATTLE II Clinical Study Summary SEATTLE II Study Design Submassive and Massive Pulmonary Embolism Treatment with Ultrasound Accelerated Thrombolysis Therapy (SEATTLE II) is a prospective single arm trial in which 150 patients with sub-massive or massive pulmonary embolism were treated with 12-24 mg of rt-PA and the [redacted] Endovascular System. Study Inclusion and Exclusion Criteria Study inclusion criteria were: 1. CT evidence of proximal PE (filling defect in at least one main or segmental pulmonary artery) AND 2. Age ≥ 18 years AND 3. PE symptom duration ≤14 days AND 4. Informed consent can be obtained from subject or Legally Authorized Representative (LAR) AND 5. Massive PE (syncope, systemic arterial hypotension, cardiogenic shock, or resuscitated cardiac arrest) OR 6. Submassive PE (RV diameter-to-LV diameter ≥ 0.9 on contrast-enhanced chest CT)	Thank you for your comment. This is an unpublished study on ultrasound enhanced CDT for pulmonary embolism (PE). The patient population in this study does not match the indication under remit in this guidance. Normally, efficacy outcomes from non peer-reviewed studies are not presented to the Committee, unless they contain important safety data. Safety profile might be different for DVT and PE. Adverse events (i.e, death and bleeding) reported in this paper have already been reported in the DVT guidance.

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			Study exclusion criteria were: 1. Stroke or transient ischemic attack (TIA), head trauma, or other active intracranial or intraspinal disease within one year 2. Recent (within one month) or active bleeding from a major organ 3. Hematocrit < 30% 4. Platelets < 100 thousand/μL 5. INR > 3 6. aPTT > 50 seconds on no anticoagulants 7. Major surgery within seven days of screening for study enrollment 8. Serum creatinine > 2 mg/dL 9. Clinician deems high-risk for catastrophic bleeding 10. History of heparin-induced thrombocytopenia (HIT) 11. Pregnancy 12. Catheter-based pharmacomechanical treatment for pulmonary embolism within 3 days of study enrollment 13. Systolic blood pressure less than 80 mm Hg despite vasopressor or inotropic support 14. Cardiac arrest (including pulseless electrical activity and asystole) requiring active cardiopulmonary resuscitation (CPR) 15. Evidence of irreversible neurological compromise 16. Life expectancy < 30 days 17. Use of thrombolytics or glycoprotein IIb/IIIa antagonists within 3 days prior to inclusion in the study 18. Previous enrollment in the SEATTLE study	

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			SEATTLE II Patient Population Patients between the ages of 21 and 90 years with confirmed pulmonary embolism and symptoms for 14 days or less and a right to left ventricular end diastolic diameter ratio (RV/LV ratio) of ≥ 0.9 on CT angiogram were enrolled in the study. One hundred nineteen (79%) patients presented with sub-massive pulmonary embolism while thirty-one (21%) presented with massive pulmonary embolism (syncope or prolonged hypotension). SEATTLE II Study Endpoints The primary efficacy endpoint was change in RV/LV ratio from baseline to 48 hours on CT angiography. The secondary efficacy endpoints were change in pulmonary systolic pressure at end of study treatment and at 48 hours after initiation of study treatment, symptomatic recurrent PE and all-cause mortality within 30 days of study treatment. The primary safety end point was major bleeding within 72 hours after initiating study treatment and the secondary safety endpoint was technical procedural complications during the study procedure. SEATTLE II Results and Discussion Subjects received either one or two [redacted] Endovascular Devices depending on thrombus location. Study drug was delivered at 1mg/hr per device with a target dose of 24 mg per patient. Bilateral infusion lasted 12 hours and unilateral infusion lasted 24 hours. CT Angiography was repeated 48 ± 8 hours after the initiation of treatment.	

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<tr><td></td><td></td><td></td><td>The mean RV/LV ratio was reduced by 0.42 (SD = 0.36), from 1.55 (SD = 0.39) to 1.13 (SD = 0.21). When compared using a two-sided t-test, the p-value is <0.0001. The RV/LV reduction was also compared to a hypothetical reduction of 0.2, which is the expected improvement in patients treated with anticoagulation alone. When the hypothetical reduction of 0.2 was compared to the actual reduction of 0.44, the p-value remained <0.0001.
Table 1: RV/LV Ratio
<table>
<tr><th></th><th>N</th><th>Mean</th><th>StdDev</th><th>Median</th><th>Min</th><th>Max</th><th>p-value*</th><th>p-value**</th></tr>
<tr><td>RV/LV Ratio at Baseline</td><td>123</td><td>1.55</td><td>0.39</td><td>1.54</td><td>0.76</td><td>3.28</td><td></td><td></td></tr>
<tr><td>RV/LV Ratio Post-Procedure</td><td>116</td><td>1.13</td><td>0.21</td><td>1.14</td><td>0.68</td><td>1.76</td><td></td><td></td></tr>
<tr><td>Post-Procedure - Baseline</td><td>115</td><td>-0.42</td><td>0.36</td><td>-0.36</td><td>-2.34</td><td>0.25</td><td><0.0001</td><td><0.0001</td></tr>
<tr><td>Percent Change</td><td>115</td><td>-24%</td><td>17%</td><td>-24%</td><td>-71%</td><td>21%</td><td></td><td></td></tr>
<tr><td>Estimate of mean Change in RV/LV – Historical Change in RV/LV</td><td>115</td><td>-0.22</td><td>0.37</td><td>NA</td><td>NA</td><td>NA</td><td><0.0001</td><td><0.0001</td></tr>
</table>
*Two-sided t-test
**Two-sided Wilcoxon Signed Rank test</td><td></td></tr>
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			Pulmonary artery systolic pressure was measured directly via endovascular catheter at baseline and at the conclusion of the study infusion. Pulmonary artery systolic pressure at 48 hours was estimated using transthoracic echocardiography. The mean baseline pulmonary artery systolic pressure was 51.4 (SD = 16) mmHg. The mean post infusion pulmonary artery systolic pressure was 37.5 (SD = 11.9) mmHg and at 48 hours, the mean estimated pulmonary artery systolic pressure was 37.1 (SD = 14.5) mmHg. When compared to baseline using a two-sided t-test, the reduction in pulmonary artery systolic pressure at the end of the study treatment had a p-value <0.0001. There was no significant change in pulmonary artery systolic pressure between end of study treatment and 48 hours.	

Table 2: Systolic Pulmonary Artery Pressure – Baseline and End of Treatment

	N	Mean	StdDev	Median	Min	Max	p-value**
Baseline PA Systolic Pressure (mmHg)	150	51.4	16	49.5	8	95	
Post Infusion PA Systolic Pressure(mmHg)	147	37.5	11.9	37	13	81	
Post Infusion - Baseline	147	-14	15	-13	-69	48	<0.0001
48 Hour PA Systolic Pressure (mmHg)	115	37.1	14.5	34	15	92	
48 hours – Baseline	115	-14.8	15.9	-15	-51	18	<0.0001

*48-hour value is from the Core Lab. Baseline and post-infusion values are from the sites

**two-sided t-test

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			Thrombus burden was measured on CT angiography at baseline and 48 hours after initiation of the study treatment. Thrombus burden was calculated using the modified Miller score. The mean baseline Miller score was 22.98 (SD = 5.97) and the post-procedure mean score was 15.65 (SD = 6.01). When compared using a two-sided t-test, the p-value was <0.0001.	

Table 3: Modified Miller Thrombus Score

	N	Mean	StdDev	Median	Min	Max	p-value*	p-value**
Modified Miller Score at Baseline	147	22.98	5.97	23.00	4.00	40.00		
Modified Miller Score Post-Procedure	143	15.65	6.01	18.00	1.00	29.00		
Post-Procedure - Baseline	140	-7.39	6.49	-6.00	-28.00	8.00	< 0.0001	< 0.0001
Percent Change	140	-30%	27%	-28%	-97%	73%		

*two-sided t-test
**two-sided Wilcoxon Signed Rank test
Source SEATTLE II Clinical Study Report Table 11-8

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			Four subjects died in the study period. All deaths occurred in sub-massive pulmonary embolism patients. One patient decompensated hemodynamically and died during placement of the [redacted] Endovascular Devices. Three patients died following treatment. Their deaths were adjudicated as not related to the study procedure or device. Bleeding events were reported in 36 patients. Fifteen major bleeds (GUSTO moderate or severe) were reported. However, one of these bleeds occurred >72 hours after the initiation of study treatment. Six (43%) of the major bleeds occurred in subjects presenting with co-morbidities that increase the risk of adverse events associated with the infusion of the study drug. There were no intracranial hemorrhages, fatal bleeds or bleeds with permanent sequelea. There were no reported vascular injuries such as dissection or perforation, or damage to heart valves or other cardiac structures.	