National Institute for Health and Care Excellence

IP1243 – Ultrasound enhanced catheter-directed thrombolysis for pulmonary embolism
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 1 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 pulmonary embolism (PE). 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 PE 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 PE 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 PE are complex, yet well established 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. A further literature search undertaken on December 19th 2014 based on the search criteria used did not result in any further significant data or studies being identified. No further information meeting the search criteria is available.	Thank you for your comment. The consultee agrees with main recommendation. They have also undertaken a further literature search and did not find any new studies. 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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2	Consultee 4 NHS Professional British Thoracic Society	**1**	The main recommendations appear to concentrate on comparing ultrasound-assisted versus standard catheter-directed thrombolysis. This clearly misses the point as the role of neither catheter-directed approach to thrombolysis in the management of either intermediate or high-risk PE is clear.	Thank you for your comment. The Interventional Procedures Programme at NICE assesses the safety and efficacy of new interventional procedures. The Committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. The Committee does not have a remit to determine the placement of a procedure in the pathway of care for a disease or condition. Section1.3 *encourages further research into ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism.*
3	Consultee 4 NHS Professional British Thoracic Society	**1.3**	We would argue that the important question is not whether ultrasound-enhanced or standard catheter-directed thrombolysis is better, but rather: a. Whether catheter-directed techniques are superior/safer than peripheral thrombolysis and/or surgical embelectomy in high-risk/massive PE b. Whether catheter-directed techniques are superior (and as safe) in improving longer-term outcomes in patients with well-defined intermediate/submassive (and especially in the intermediate-high risk group defined in the 2014 ESC PE guidelines) PE.	Thank you for your comment. The Interventional Procedures Programme at NICE assesses the safety and efficacy of new interventional procedures. The Committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. The Committee does not have a remit to determine the placement of a procedure in the pathway of care for a disease or condition.

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4	Consultee 4 NHS Professional British Thoracic Society	**2.2**	The major issue seems to be a lack of understanding of standard management of acute PE with poor appreciation of the importance of risk-stratifying patients into high (massive) and intermediate (sub-massive) risk patients. Currently, reperfusion is recommended for "high-risk (ESC definition)" or "massive (AHA definition)" PE. High-risk/Massive status is defined by low bp/shock and by far the commonest method of reperfusion is thrombolysis using peripherally administered tPA (most commonly alteplase at a dose of 1.5/mg/kg over 2 hrs including an upfront 10mg bolus). The alternative methods of reperfusion (surgical embelectomy or catheter assisted techniques) are less commonly used and in the UK are reserved for patients with clear contraindications to thrombolysis. There is ongoing debate about the management of "intermediate risk (ESC - especially the high-intermediate risk group)" or "submassive (AHA definition)" PE with no clear or definite role for peripheral thrombolysis, mainly because the benefit of reperfusion can easily be outweighed by the bleeding risk associated with peripheral thrombolysis.	Thank you for your comment. Section 2.2 in the guidance has been amended in line with existing NICE clinical guideline on management of venous thromboembolic diseases CG144 (2012).
5	Consultee 4 NHS Professional British Thoracic Society	**2.2 & lay description**	The draft NICE document seems very confused about standard management of high-risk/massive PE with the following on the front-page summary: " For severe PE, thrombolysis is sometimes used: a catheter (tube) is inserted into a blood vessel (usually in the groin), moved into the artery in the lungs and used to deliver clot-busting drugs to dissolve the clot (thrombolysis). " Although section 2.2 does appear to recognise the use of peripheral thrombolysis it again fails to distinguish between reperfusion in high risk/massive and intermediate risk/sub-massive PE.	Thank you for your comment. Both section 2 and the lay description (front page summary) are intended to be brief summaries of the way the procedure is typically done. The list of current treatments and alternatives in section 2.2 is not intended to be definitive. Section 2.2 in the guidance has been amended in line with existing NICE clinical guideline on management of venous thromboembolic diseases CG144 (2012).

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6	Consultee 4 NHS Professional British Thoracic Society	**4 & 5**	The data reviewed is, as acknowledged in the draft document, of quite low quality consisting mainly of 1 systematic review and 1 RCT of ultrasound assisted catheter-directed thrombolysis compared with heparin alone in intermediate risk/submassive PE (ULTIMA trial).	Thank you for your comment. As there is limited evidence, recommendation in 1.1 states that 'the procedure should only be used with special arrangements for clinical governance, consent and audit or research'.
7	Consultee 1 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 study is not yet published. Adverse events (i.e, death and bleeding) presented in this study have already been reported in the guidance. Efficacy data that have not been published or accepted for publication by peer review are not normally selected for presentation to the Committee. Therefore, the study will not be included in table 2 of the overview. IPAC may review the guidance upon publication of new evidence in peer reviewed journals.

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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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			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

	N	Mean	StdDev	Median	Min	Max	p-value*	p-value**
RV/LV Ratio at Baseline	123	1.55	0.39	1.54	0.76	3.28		
RV/LV Ratio Post-Procedure	116	1.13	0.21	1.14	0.68	1.76		
Post-Procedure - Baseline	115	-0.42	0.36	-0.36	-2.34	0.25	<0.0001	<0.0001
Percent Change	115	-24%	17%	-24%	-71%	21%		
Estimate of mean Change in RV/LV – Historical Change in RV/LV	115	-0.22	0.37	NA	NA	NA	<0.0001	<0.0001

*Two-sided t-test
**Two-sided Wilcoxon Signed Rank test
Source SEATTLE II Clinical Study Report Table 11.4

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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

Source SEATTLE II Clinical Study Report Tables 11-5 and 11-6

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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.	
8	Consultee 2 Consultant Interventional Radiologist	**General**	The [redacted] system is a technically straightforward and safe device for administering catheter directed thrombolysis. Whilst systemic thrombolysis remains the mainstay in clinical practise, in those patients with high risk of bleeding complications, for e.g. recent surgery, GI haemorrhage or stroke, the use of [redacted] may reduce the dose of lytic agent required to achieve a successful clinical outcome.	Thank you for your comment.

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9	Consultee 3 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. The Committee noted your views and experiences in their deliberations.
10	Consultee 4 NHS Professional British Thoracic Society	**General**	We would all agree that the use of lower doses of thrombolytic agents in reperfusion of high and intermediate-risk PE needs further investigation and the seemingly low incidence of major bleeding in catheter-directed techniques is encouraging. It should be noted that either catheter-based technique is extremely time-consuming and dependent on significant expertise and experience. It should also be acknowledged that half-dose peripheral thrombolysis as used in the MOPPET study also appeared to be associated with low rates of significant bleeding.	Thank you for your comment.

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11	Consultee 1 Manufacturer	**General**	**Draft PE guidance:** For entry into “corrections” relating to the following pages: Page 7 - Quintana paper - the numbers should all be moved one field to the left. Then in the left most column, the numbers 20.8 (12-49) should be added. In the second table, also for the Quintana paper, the RV/LV ratio “before” is listed as 20.8 (12-49). This field should contain “NR”. Page 23 – “FDA approval in 2008 for infusion of thrombotic drugs into the pulmonary arteries.” This statement is not the correct indication statement. The FDA approval is for ultrasound facilitated, controlled and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism. The CE mark in the EU is approved for: the treatment of pulmonary embolism patients with ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25 mmHg) or echocardiographic evaluation.	Thank you for your comment. The Consultee highlighted some errors in the overview. These have been amended.