Norfolk and Norwich University Hospitals NHS Foundation Trust

James Paget University Hospitals NHS Foundation Trust

Management of Acute Pulmonary Embolism (PE) in Adults (≥18)

Document Control:

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	All medical and nursing staff		
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Management of Acute Pulmonary Embolism (PE) in Adults (>18)	23/4/23

Distribution Control

Printed copies of this document should be considered out of date. The most up to date version is available from the Trust Intranet.

Consultation

The following were consulted during the development of this document:
All respiratory consultants, the Thrombosis & Thromboprophylaxis Committee and IRU and Critical Care leads.

Monitoring and Review of Procedural Document

The document owner is responsible for monitoring and reviewing the effectiveness of this Procedural Document. This review is continuous however as a minimum will be achieved at the point this procedural document requires a review e.g. changes in legislation, findings from incidents or document expiry.

Relationship of this document to other procedural documents

This document is a clinical guideline applicable to NNUH please refer to local Trust's procedural documents for further guidance, as noted in Section 5.

Contents

Quick Reference

1. Introduction

Pulmonary embolism is defined as an obstruction within the pulmonary vasculature caused by clot, air, tumour or fat.

A saddle PE is defined as a clot found in the main pulmonary artery that crosses into the right and left main pulmonary arteries, saddle PE is often associated with a higher clot burden and RV dysfunction but this does not necessarily correlate to a higher mortality (1). It is more appropriate to term PEs as high risk, intermediate risk and low risk with respect to mortality in 30 days rather than in terms of clot burden, as this will help guide treatment modalities.

Diagnosed pulmonary embolism has been reported to have an annual incidence of approximately 3-4 per 10 000 people in the U.K (2). Each year between 2005 and 2008 pulmonary embolism was mentioned on the death certificates of 12 000-13 000 people in the U.K (3). Untreated the risk of death from PE is around 30% (1). Pulmonary embolism is also the 2nd most common cause of maternal death in the U.K (4).

1.1. Rationale

In patients presenting with PE, treatment with heparin and/or oral anticoagulant reduces the risk of death in normotensive patients. However, where patients have high risk pulmonary embolism, associated with cardiovascular instability, the risk of death has been quoted as more than 50% (5). In other centres this has resulted in the development of PERT (pulmonary embolism response team) who are called when PE patients are admitted to aid decision making. At the Norfolk and Norwich we do not have a PERT, however, we do have access to on call respiratory, ITU, interventional radiology and haematology consultants, and therefore these specialties may all be consulted where there is no clear cut “correct” answer in the optimal patient management.

1.2. Objectives

This guideline is written to aid decision making regarding the initial treatment, particularly thrombolysis, of adult patients presenting with acute pulmonary embolism. It will also discuss risk stratification of patients with pulmonary emboli.

1.3. Scope

This document is not designed for the paediatric population where PE is incredibly rare. It does not cover the outpatient management of PE, specific anticoagulation strategies or follow up as these are addressed in other trust guidance.

1.4. Glossary

ACB	Acute Care Bay
AMU	Acute Medical Unit
ARC	Acute Respiratory Care
BP	Blood Pressure
CDT	Catheter Directed Thrombolysis
CPR	Cardiopulmonary resuscitation
CTPA	Computed Tomography Pulmonary Angiogram
CTEPH	Chronic Thromboembolic pulmonary hypertension

DVT	Deep Vein Thrombosis
HDU	High Dependency Unit
ICH	Intracranial haemorrhage
IRU	Interventional Radiology Unit
ITU	Intensive Care Unit
JPUH	James Paget University Hospitals NHS Foundation Trust
LMWH	Low molecular weight heparin
LV	Left Ventricle
NEWS2	National Early Warning Score 2
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
PE	Pulmonary Embolus
PEITHO	Pulmonary Embolism thrombolysis
PERT	Pulmonary Embolism Response Team
PESI Score	Pulmonary embolism severity index score
RV	Right Ventricle
sPESI score	Simplified Pulmonary embolism severity index score

2. Responsibilities

Dr Gray drafted the original document and in 2023 it was reviewed and amended in line with new evidence regarding risk stratification and catheter directed therapies.

3. Policy Principles

3.1. High Risk Pulmonary Embolism Definition

High risk PE can be defined as follows (6):

1. Patient requires cardiopulmonary resuscitation (CPR)
2. Systolic BP<90mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status AND End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)
3. Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis.

3.2. High risk PE Prognosis

The International Cooperative Pulmonary Embolism Registry (ICOPER) found the 90-day mortality rate for patients with acute PE and systolic blood pressure of less than 90 mm Hg at presentation was 52.4% compared with 14.7% in those with a higher systolic pressure (5). For this reason international guidelines suggest thrombolytic therapy for the treatment of high risk PEs (7–9).

3.3. High Risk PE Management

Figure 1 suggests a management algorithm for suspected PE associated with shock or significant hypotension. Where the patient is stable enough to be transferred to the radiology

department and undergo CTPA, this is the preferred investigation (9), if the patient is too unstable for transfer, echocardiography may help rule PE out as a cause for haemodynamic instability, provided there is no evidence of right heart dysfunction.

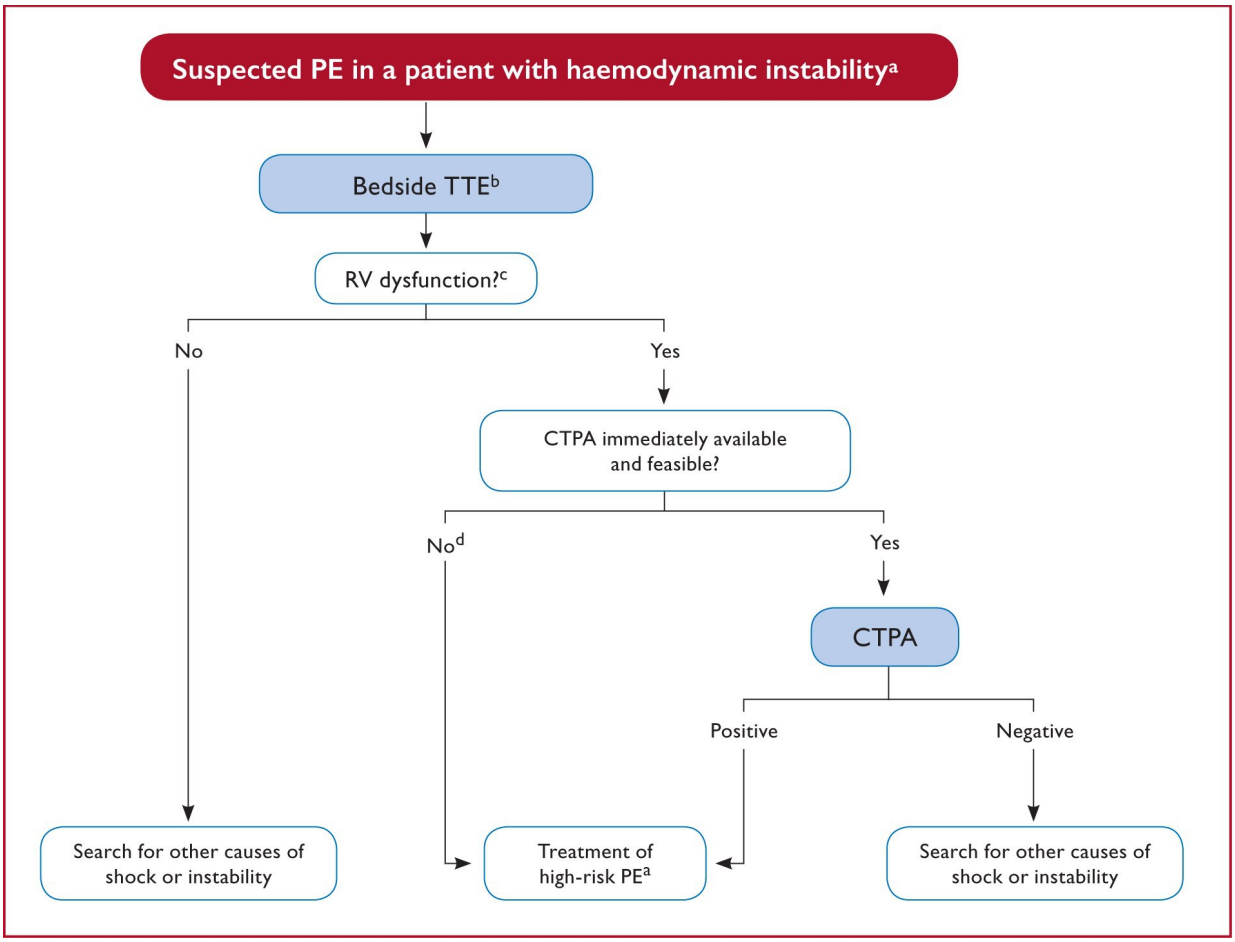
Echocardiography alone cannot confirm the diagnosis of acute PE in the absence of other tests. Every effort should be made to confirm a diagnosis (10). Where this is not possible thrombolysis should be considered on a case by case basis and discussed with senior doctors where time allows.

Patients with high risk PE should undergo thrombolysis as described in section 11 unless there are contraindications.

Patients with oxygen saturations <90% should receive supplemental oxygen (6). High flow oxygen therapy and non invasive ventilation (in a level 2 setting) may be considered. Intubation and ventilation in patients with RV dysfunction may result in severe hypotension and should only be done if other treatment modalities have failed (6).

Acute RV failure leading to low systemic output is the leading cause of death in high risk PE. ESC recommendations for acute RV failure are highlighted in figure 2.

3.4. Figure 1. Management of suspected High Risk PE (6).



Other bedside modalities that may guide treatment include compression ultrasonography to exclude DVT

3.5. Figure 2. Treatment of RV failure in acute high risk PE

Strategy	Principles	Cautions
Volume optimisation		
Cautious volume loading, saline, or Ringer's lactate, ≤500 mL over 15–30 min	Consider in patients with normal–low central venous pressure (due, for example, to concomitant hypovolaemia)	Volume loading can over-distend the RV, worsen ventricular interdependence, and reduce CO
Vasopressors and Inotropes		
Norepinephrine, 0.2–1.0 μg/kg/min	Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient	Excessive vasoconstriction may worsen tissue perfusion
Dobutamine, 2–20 μg/kg/min	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor; may trigger or aggravate arrhythmias

Adapted from ESC guidelines 2019 (6)

3.6. Intermediate Risk Pulmonary Embolism Definition

These patients are normotensive but have risk factors that mean their mortality risk is higher than patients in low-risk categories.

Specific scoring systems to risk stratify normotensive patients with confirmed pulmonary emboli have been developed based on this mortality risk (11). PESI (Pulmonary Embolism Severity Index) and sPESI (simplified Pulmonary Embolism Severity Index) scores are supported by the most evidence (11).

Residual proximal DVT after a PE diagnosis raises the possibility of further embolic events and should be considered when assessing patients risk (12). Elevated lactate and raised creatinine may indicate poor cardiac output and are associated with a higher mortality (13). There does not seem to be a significant relationship between mortality and pulmonary artery clot burden, suggesting the extent of clot on CT doesn't correlate with perfusion (13).

3.7. Risk Stratification of PE

Pulmonary Embolism Severity Index (PESI) scores
shows both the original and simplified PESI scores. PESI scores may then be used to estimate 30 day mortality. This can also be used as a tool to determine who can be safely managed as an outpatient and who should be considered for admission. (14).

Figure 4: 30 day mortality as assessed by PESI and sPESI shows the 30 day mortality as determined by the PESI and sPESI scores respectively.

Figure 3: Original and Simplified PESI score

Parameter	Original	Simplified
Age	Age in years	1 (If age >80 years)
Male Sex	+ 10	
Cancer	+ 30	1
Chronic heart failure	+ 10	1
Chronic pulmonary disease	+ 10	
Pulse rate ≥ 110bpm	+ 20	1
Systolic BP < 100 mmHg	+ 30	1
Respiratory rate > 30 breaths/min	+ 20	
Temperature < 36°C	+ 20	
Altered mental status	+ 60	
Arterial oxyhaemoglobin saturation <90%	+ 20	1

Adapted from European society of cardiology guideline 2014 (9).

Figure 4: 30 day mortality as assessed by PESI and sPESI

Original			Simplified	
Class	Points	30 day mortality (%)	Class	30 day mortality
I	≤65	0-1.6	0	1% (95% CI 0-2.1%)
II	66-85	1.7-3.5		
III	86-105	3.2-7.1		
IV	106-125	4-11.4	≥ 1	10.9% (95% CI 8.5-13.2)
V	>125	10-24.5		

Adapted from European society of cardiology guideline 2019 (6).

After a PESI score patients can then be risk stratified according to figure 5. The intermediate-low risk group can be considered for admission and anticoagulated appropriately as per Trust guidelines. PESI scores in admitted patients can be recalculated at 48 hours, which may help aid discharge planning. Moores et al discussed re-evaluating PESI scores at 48 hours and found that those who had moved from class III to II or I had a lower 30 day mortality than those who had no change in their PESI score (1.2% vs 11.3%) (15).

Figure 5: Risk Stratification of Pulmonary Emboli

Early Mortality Risk		Risk Parameters and Scores			
		Shock or hypotension	PESI class III-V or sPESI ≥ 1	Signs of RV dysfunction on an imaging test	Cardiac biomarkers
High		+	(+)	+	(+)
Intermediate	High	-	+	Both positive	
	Low	-	+	Either 1 or none positive	
Low		-	-	Assessment optional if assessed both negative	

European Society of Cardiology guideline 2019 (6)

3.7.1. Acute Right Ventricular dysfunction

Right ventricular impairment may be detected on imaging modalities despite haemodynamic stability. RV dysfunction on echocardiography is associated with an elevated risk of short-term mortality in patients who appear haemodynamically stable at presentation, but positive predictive value for PE-related death was <10% in a meta-analysis (6). Echo is not mandatory in normotensive patients. CTPA may suggest evidence of pulmonary hypertension when the right ventricle or main pulmonary artery is enlarged. These patients have a higher risk of short

term mortality even in the absence of haemodynamic compromise, but its positive predictive value is low and shouldn't be used in isolation to risk stratify patients or to implement thrombolysis (9,16). An increased RV/LV ratio of ≥1.0 on CT was associated with a 2.5-fold increased risk for all-cause mortality a five-fold risk for PE-related mortality (6).

3.7.2. Cardiac Biomarkers

Troponin is a marker of myocardial injury and has been associated with an increase in mortality in patients admitted with a PE (9,17,18). High-sensitivity troponin T concentrations <14 pg/mL had a negative predictive value of 98% for excluding an adverse in-hospital clinical outcome in patients with PE (6). In addition NT-proBNP a marker of "myocardial stretch", may also be elevated in patients with a large clot burden and may be used to help risk stratify patients (9,16). Similar to troponin, a low NT-proBNP (< 500pg/ml) is less likely to be associated with unfavourable early outcomes.

3.7.3. Serum Lactate

Lactate is a marker of the adequacy of tissue perfusion and correlates with disease severity in a number of different kinds of shock. The PERGO study found that a venous lactate of >2.3mmol/L was associated with an adverse hospital outcome (vasopressor treatment, CPR, PE mortality) and a venous lactate of >3.3mmol/L was associated with an increase in all-cause mortality (19). When venous lactate is used in combination with the ESC 2019 risk stratification guidelines a lactate of <2.3mmol/L in intermediate low risk patients excludes adverse outcomes with a negative predictive value of greater than 99%. Conversely in intermediate high risk patients a lactate of >3.3mmol/L was able to identify a subgroup of patients at risk of adverse outcomes (19).

In a different study of 496 normotensive patients with acute PE, the combination of elevated lactic acid, RV dysfunction, and elevated troponin was associated with a 17.9% incidence of in-hospital mortality or nonfatal hemodynamic collapse (20).

3.8. Management

Intermediate-high risk patients pose a significant management challenge. The largest double blind randomised controlled trial to date looking at thrombolysis in "sub massive" PEs (PEITHO 2014) showed **no mortality benefit with thrombolysis**, mortality was low in both groups, however. The group receiving Tenecteplase showed a significant reduction in haemodynamic decompensation at 7 days, 1.6% vs 5%. However, in the Tenecteplase group there was an increased incidence of both intracranial haemorrhage (2% vs 0.2%) and extracranial haemorrhage (6.3% vs 1.2%) (21). Major bleeding (as defined in figure 6).

Figure 6: Definition of Major Bleeding during the PEITHO study

	Type of Bleed
1	Fatal
2	Symptomatic: in a critical area or organ such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, pericardial OR intramuscular with compartment syndrome
3	A fall in Hb of 20g/L or more leading to transfusion of 2 or more units of blood.

Adapted from Schulman et al (22)

Interestingly after 2 years of follow up there was no effect on long term mortality, dyspnoea, RV dysfunction or Chronic Thromboembolic Pulmonary Hypertension (CTEPH) in the thrombolysis group (18,23). **Routine thrombolysis of intermediate risk PEs cannot be recommended**.

However, each case should be considered on an individual basis and the high- intermediate risk group should be managed in a high acuity setting (ACB, ARC on Hethel or HDU), **have hourly observations for at least 24 hours and be closely monitored for deterioration, even if their National Early Warning score (NEWS2) suggests less frequent monitoring is required**. **They should also have daily senior reviews, where risk and benefit of thrombolysis should be considered**.

If thrombolysis is being considered this decision should be made in conjunction with the AMU/respiratory consultant in charge of the patient's care (or the on call consultant out of hours) and ITU. Thrombolysis should be initiated in a level 2 environment, where time allows, but in life threatening emergencies can be administered immediately; assuming prompt transfer for ongoing monitoring is arranged post thrombolysis.

4. Thrombolysis

4.1. Thrombolysis for High Risk PE

Patients with haemodynamic compromise and confirmed pulmonary embolism should receive thrombolysis, but despite this recommendation there have been few studies comparing the dose and duration of this treatment. The European Society of Cardiology guidelines specifically suggests Alteplase 100mg IV infused peripherally over 2 hours (6,9,13), pulmonary embolism is a licensed indication for Alteplase and is approved by the trust. Alteplase is also recommended by the British Thoracic Society for the management of massive pulmonary embolism (24). See Appendix 1.

Prior to thrombolysis an arterial line for BP monitoring should be considered. Patients should be verbally consented for thrombolysis where possible, and this should be documented in the notes. Particular reference should be made to bleeding (approx. 10-15%)(17,25), especially intracranial bleeds (approx. 2%) and death (17).

4.2. Reperfusion in Intermediate High-Risk PE

If reperfusion therapy is being considered in a patient with intermediate high risk PE then in general management is the same as with high risk PEs, as outlined in Appendix 1.

However the PEITHO study found that in patients over the age of 75 the bleeding risk was higher (25), so this must be considered in the risk benefit analysis. The administration of LMWH should not be delayed whilst the decision about thrombolysis is made. The default position is to give a therapeutic dose of LMWH.

Previous guidance suggested consideration of half dose thrombolysis with 50mg alteplase instead of 100mg (26), especially where there were concerns about bleeding or patient frailty. A meta-analysis by Zhang et al confirmed that the half dose treatment appeared to be effective with fewer bleeding events, but there was not enough evidence to change practice. However, a recent study comparing 3768 patients receiving 50 mg versus full-dose 100 mg of alteplase for PE demonstrated that half-dose systemic thrombolysis was ineffective, with an increased frequency of treatment escalation (53.8%vs. 41.4%;p< 0.01), driven largely by secondary thrombolysis (25.9% vs. 7.3%;p< 0.01) and Catheter Directed Thrombolysis (14.2% vs. 3.8%;p< 0.01), with similar rates of in-hospital mortality and ICH(13% vs. 15%, and 0.5% vs. 0.4%, respectively (27).

Half dose thrombolysis may be considered in the frail, elderly or small patients, or those with relative contraindications to full dose thrombolysis (28). However, given the more recent evidence this may not be effective and this should be considered.

There is no one-size fits all approach when considering thrombolysis dose or indeed when to give it, in this group of patients. This should be discussed with the respiratory physician on call and ITU consultant (if ITU support is required) +/- AMU consultant depending on the location of the patient.

4.3. Monitoring and Observation post thrombolysis

Post thrombolysis patients should be monitored in a Level 2 environment and will require a cardiac monitor and continuous pulse and oxygen saturation monitoring. If an arterial line is in place BP may also be continuously monitored. If there is no arterial line BP recording should be undertaken and documented at least every 15minutes for the first 2 hours. Providing this is improving and the clinician is satisfied this can then move to every 30 minutes for the next 2 to 6 hours and then hourly for the next 12 hours.

4.4. Exclusion Criteria for thrombolysis

4.4.1. Absolute Contraindications

- Haemorrhagic stroke at any time
- Ischaemic stroke within 6 months
- CNS damage or neoplasia
- Recent major trauma/surgery/head injury within 2 months
- Genital/urinary tract bleeding within 2 months
- Haematology abnormalities OR coagulopathy (INR>1.7(relative if 1.4-1.7), APTT>40, or platelets <100,000mm^3), or on direct oral anticoagulants (e.g. Dabigatran, Rivaroxaban, Apixaban, Edoxaban).
- Allergy to Alteplase
- Aortic dissection

Absolute contraindications may well become relative in life threatening PEs.

4.4.2. Relative Contraindications

- Active pulmonary disease with cavitation
- Acute pancreatitis

- Aneurysm
- Bacterial endocarditis
- Oesophageal varices
- Pericarditis
- Recent symptoms of possible peptic ulceration
- Pregnancy or within 4 weeks post-partum
- Arterial puncture at non-compressible site within last 7 days

4.5. Catheter Directed thrombolysis (CDT)

This is not current routinely available at NNUH. The most extensively studied CDT technique is ultrasound-facilitated, catheter-directed thrombolysis with the EKOSonic system. The EKOS device infuses low-dose Alteplase directly through the pulmonary clot, in combination with ultrasound impulsions. The local delivery means a lower dose of thrombolytic agent is required, with the goal of reducing bleeding. In the ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) trial 2014, 59 patients with PE and RV dysfunction were randomized to receive either heparin alone (n = 29) or heparin plus catheter-directed thrombolysis (10–20 mg Alteplase) facilitated by ultrasound (n = 30). The primary endpoint, the difference in RV/LV ratio from baseline to 24 h, was significantly improved in the CDT group compared to heparin alone (0.30 ± 0.20 vs. 0.03 ± 0.16; $p < 0.001$). Several other non-randomized, noncomparative studies including hemodynamically unstable PE patients or hemodynamically stable PE with RV dysfunction found comparable results in terms of the improvement in RV function (27). Major bleeding rates ranged between 0% to 16.6% and ICH rates between 0% to 2.4% (27). In the subsequent dose-ranging OPTALYSE PE trial, four accelerated-dosing regimens (8 mg/2 h, 8 mg/4 h, 12 mg/6 h, and 24 mg/6 h) for ultrasound-facilitated, catheter-directed thrombolysis were evaluated in 101 patients with intermediate-risk PE. Across all four arms, which used a shorter delivery duration and lower-dose Alteplase, there was improved RV function and reduced clot burden compared with baseline. So far none of the studies have looked at mortality/morbidity benefit and they focus on surrogate end points, however this area does look promising and we may be able to offer this option in the future. The HI-PIETHO study is awaited and may provide some much needed evidence.

5. Related Documents

IVC filter insertion Please see click for clots website on the intranet Trustdocs Id: 1252
ALS protocol Trustdocs Id 10535

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7. Audit of the process

Compliance with the process will be monitored through the following:

Key elements	Process for Monitoring	By Whom (Individual / group /committee)	Responsible Governance Committee /dept	Frequency of monitoring
Review of relevant guideline	Review of Literature	T and T Committee	Clinical Safety Effectiveness Sub-Board	3 yearly

The literature review results are to be discussed at relevant governance meetings (T & T Committee) to review the results and recommendations for further action. Then sent to (Clinical Safety Effectiveness Sub-Board) who will ensure that the actions and recommendations are suitable and sufficient.

8. Appendix 1: Thrombolysis Regimes

8.1. High Risk PE with haemodynamic instability

- Reconstitute 100mg Alteplase (each vial is 50mg) with 50ml of water for injection
- 10mg IV bolus (5ml) over 1-2 minutes (BNF)
- 90mg IV (45ml) as an infusion via a syringe driver over 2 hours
- Do not give more than 1.5mg/kg in patients who weigh less than 65Kg
- On completion of the Alteplase infusion, check APTT and again at 4 hours and start unfractionated heparin infusion at 1000 units/ hr when APTT < 2.0. A bolus of UFH heparin 5000/5ml should be given and the infusion should be adjusted to maintain APTT at 1.5 to 2.5.
- Guidelines on initiation and monitoring of heparin infusions can be found on trust docs Trustdocs Id: 1707.
- If a patient has received LMWH before thrombolysis is administered then UFH should be delayed until 8 hours following the last dose of LMWH.
- Heparin infusion may be stopped when the patient is stable, as assessed by the clinician and may include
    - Blood pressure greater than 100mmHg,
    - Saturations greater than 92% on air
    - Heart rate is less than 100bpm
- LMWH should be administered once UFH infusion has been off for 1-2 hours.
- When the patient is being considered for discharge anticoagulation with either Warfarin or a DOAC should be considered. This will be determined by individual patient factors and decisions may be guided using the Click for Clots information page on the trust intranet.

8.2. Half dose thrombolysis

- Reconstitute 50mg Alteplase with 25ml of water for injection
- 10mg IV bolus (5ml) over 1-2 minutes (BNF)
- 40mg IV (20ml) as an infusion via a syringe driver over 2 hours

8.3. Peri-arrest/arrested patients with suspected PE

- Reconstitute Alteplase with 25ml of water for injection
- Administer a bolus of Alteplase 50mg IV.
- In patients who subsequently arrest commence CPR as per ALS guidelines
- In patients who were undergoing CPR at the time of Alteplase administration, continue CPR as per ALS guidelines for 60-90mins post administration (at clinician's discretion).

9. Equality Impact Assessment (EIA)

Type of function or policy	Existing

Division	Medicine	**Department**	
Name of person completing form	Dr N Gray	**Date**	23/4/23

Equality Area	**Potential Negative Impact**	**Impact Positive Impact**	**Which groups are affected**	**Full Impact Assessment Required YES/NO**
Race				No
Pregnancy & Maternity				No
Disability				No
Religion and beliefs				No
Sex				No
Gender reassignment				No
Sexual Orientation				No
Age				No
Marriage & Civil Partnership				No
EDS2 – How does this change impact the Equality and Diversity Strategic plan (contact HR or see EDS2 plan)?		This policy does not discriminate		

- **A full assessment will only be required if: The impact is potentially discriminatory under the general equality duty**
- **Any groups of patients/staff/visitors or communities could be potentially disadvantaged by the policy or function/service**
- **The policy or function/service is assessed to be of high significance**

IF IN DOUBT A FULL IMPACT ASSESSMENT FORM IS REQUIRED

The review of the existing policy re-affirms the rights of all groups and clarifies the individual, managerial and organisational responsibilities in line with statutory and best practice guidance.