

Assessment & treatment of patients with suspected or confirmed pulmonary embolism (PE)

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August 2018 - Entire document re-written and updated to include management of PE across in-patient settings. Document re-named.

Keywords:

PE, Pulmonary Embolism, VTE, Ambulatory, DOAC, Rivaroxaban, Apixaban

1 INTRODUCTION

This document sets out the University Hospitals of Leicester (UHL) NHS Trust's Policy and Procedures for the investigation and treatment of suspected or confirmed pulmonary embolism (PE)

- a) in an ambulatory (outpatient) setting.
- b) as an inpatient

1.1 Policy Aim/statement of intent

The aim of this document is to:

- a) Define the inclusion/exclusion criteria for the investigation and treatment of pulmonary embolism as an outpatient.
- b) Outline the assessments and investigations to be undertaken for suspected pulmonary embolism.
- c) Describe the treatment and follow up for patients with confirmed pulmonary embolism, managed in both an ambulatory setting and as inpatients.

2 POLICY SCOPE

2.1 This policy applies to:

- a) Adults with suspected or confirmed PE who meet the criteria to be investigated/treated in an outpatient setting
- b) Adult patients with suspected or confirmed PE who require in-patient management

It does not include patients who are pregnant, who should be discussed/managed by the obstetric team in the first instance. See UHL policy C5/2001 Investigation and management of VTE in pregnancy and puerperium.

It does not apply to patients on renal replacement therapy or those with CrCl <30 who should be discussed with the renal team in the first instance. The renal team can make a referral for investigation by the respiratory team in CDU if deemed clinically appropriate or can provide advice regarding management for current in-patients at any UHL site.

3 DEFINITIONS AND ABBREVIATIONS

Ambulatory care – care delivered in an outpatient setting.

Provoked Pulmonary Embolism (PE) - associated with acquired risk factors, either transient or persistent [1]

Unprovoked/Idiopathic Pulmonary Embolism (PE) - associated with no apparent clinical risk factors [1]

Venous thromboembolism (VTE) – clot formation in the veins, incorporates DVT, PE and DVT+PE

AMBULATORY

All clinical staff within UHL that are involved in the management of the Ambulatory PE clinic need to be aware of this policy and ensure the guidelines are followed.

4.1 Responsibilities within the organisation

The medical director is the executive lead for this policy. Ambulatory treatment of PE is initially the responsibility of the ambulatory PE service which is in the Respiratory Service, RRCV (CMG). Responsibilities of the team whilst the patient is undergoing treatment include the following:

- Administration of outpatient care programme
- Commencement and control of anticoagulant therapy
- Liaison with community agencies (appendix 1)
- Patient information and education including advice and phone numbers if worsening symptoms
- Referral for thrombophilia testing where appropriate

Prescription of LMWH and oral anticoagulants is the responsibility of the medical team on CDU/short stay unit, or the Specialist ambulatory PE nurse prescriber at the time of diagnosis.

The clinical lead of the ambulatory PE service is responsible for overseeing and managing the service. The clinical lead is a Respiratory consultant appointed by the Respiratory Head of Service. The clinical responsibility for the patients who are managed by the ambulatory pulmonary embolism service is held by the on call respiratory consultant on the day they are seen.

Urgent clinical problems are the responsibility of the on call respiratory team. The Haemostasis and thrombosis team will deal with specific haematological queries.

Haemostasis & thrombosis referrals:

- All patients requiring thrombophilia screens or with known thrombophilia defects will be referred to Haematology via a referral

All other PE patients (i.e. those not requiring thrombophilia screens or specialist haemostasis and thrombosis advice) will attend a general respiratory clinic (under the CDU consultant responsible for their care) for follow up at 3 months (for Provoked PE) and 4 to 6 months (for Unprovoked PE).

All patients with negative tests will be referred back to their GP unless they require admission.

Nurses who undertake the role of ambulatory pulmonary embolism nurse specialists must:

- Be level 1 Registered Nurse
- Be registered with NMC
- Have completed the education and training programme and hold a valid statement of competence
- Be assessed as competent and hold a Statement of Competence to assess patients and adjust warfarin treatments as defined in this policy.
- Be familiar with the following documents:
 - i) NMC Code of Professional Conduct – NMC 2015
 - ii) The Scope of Professional Practice – UKCC 1992

The UHL Trust will accept vicarious liability for the action of the ambulatory pulmonary embolism Nurse Specialists. The ambulatory pulmonary embolism Nurse Specialist will adhere to the guidelines and policies identified.

4.2 Responsibilities of and communication with stakeholders

All patients discharged from the ambulatory PE clinic should have a typed/ICE letter sent to their GP stating diagnosis and any change in management and follow up plans.

All patients started on anticoagulation should have an anticoagulation discharge letter completed and sent to the GP.

IN-PATIENTS

All clinical staff within UHL that are involved in the management of in-patients with confirmed PE need to be aware of this policy and ensure the guidelines are followed.

4.3 Responsibilities within the organisation

The medical director is the executive lead for this policy. Inpatient treatment of PE is the responsibility of the relevant medical/surgical consultant and their team. Responsibilities of the team whilst the patient is undergoing treatment include the following:

- Administration of inpatient care programme
- Commencement and control of anticoagulant therapy
- Prescribe and monitor DOAC's
- Liaison with community agencies (via ICE discharge letter and ICE anticoagulation discharge letter)
- Patient information and education including advice and phone numbers if worsening symptoms
- Referral for thrombophilia testing where appropriate
- Referral for Respiratory clinic follow up where appropriate

4.4 Responsibilities of and communication with stakeholders

All patients discharged with a confirmed PE should have a typed ICE letter sent to their GP stating diagnosis and any change in management and follow up plans.

All patients started on anticoagulation should have an anticoagulation discharge letter completed and sent to the GP.

5 POLICY IMPLEMENTATION – WHAT TO DO AND HOW TO DO IT

5.1 Introduction

Suspected pulmonary embolism is a common cause of presentation to hospital and ranges in severity from small emboli with few or no symptoms through to massive, life threatening pulmonary embolism. Over the last decade there has been an attempt to characterize a group of low risk patients who may be able to receive treatment for their pulmonary embolism outside of a traditional inpatient setting. Studies have sought to identify what proportion of patients may be considered low risk. The figures range from 37%-43.6% of patients with confirmed PE who may be considered suitable for home treatment [2,3,4,5]. Furthermore, with the introduction of Direct Oral Anticoagulants (DOACS), the out-patient management of PE has become more straightforward. This policy sets out the keys steps to investigate and diagnose PE and then identify those patients suitable for out-patient management. The policy additionally sets out the steps required to manage patients with confirmed PE both in an ambulatory (out-patient) setting and as an inpatient from diagnosis to outpatient follow up.

5.2 Diagnosis of PE - Patient Care Pathway

5.2.1 Assessment & Diagnosis

Assessment and diagnosis falls under the responsibility of:

- a) For ambulatory patients - the ambulatory PE service which is based in CDU at Glenfield Hospital
- b) For inpatients – the responsible medical team

The diagnostic process is facilitated by validated clinical probability scores and second generation D-dimer assays. This may allow the discharge of a subgroup of patients without further radiological investigation i.e. low clinical probability of PE and normal D-dimers.

Assessment of patients with possible venous thromboembolism (VTE) either de novo presentation or possible recurrence involves the following:

- **Clinical probability** in all patients
- **D-dimers** in selected patients dependent on the clinical probability
- **Radiology** in selected patients dependent alone on the clinical probability if high and dependent on clinical probability in conjunction with raised D-dimers if the clinical probability is low or intermediate (see UHL guideline C1/2006 - The imaging of suspected pulmonary emboli)

Other responsibilities of the team whilst the patient is undergoing assessment and diagnosis include the following:

- Provision of appropriate analgesia
- Assessment of patients with confirmed PE for outpatient care
- Assessment of patients with confirmed PE for associated pathology using malignancy proforma (appendix 8)
- Follow up arrangements for patients with a confirmed PE
- Liaison with general practitioners regarding outcomes

5.2.2 PE assessment protocol

- All patients presenting with signs or symptoms of pulmonary embolism (PE), must have an assessment of their general medical history, a physical examination and a chest X-ray to exclude other causes.
- All patients should have an assessment of provoking risk factors for VTE:
 - Prior VTE
 - Stasis and endothelial injury - indwelling venous devices, major surgery in preceding 6 weeks, fractures of hip/pelvis/long bones, multiple trauma/burns, long haul travel (>4 hours), paralysis (including anaesthesia for >30mins), varicose veins
 - Thrombophilia – look for family history VTE in a first degree relative
 - Medical conditions - active malignancy, MI, CCF, stroke, obesity, inflammatory bowel disease, nephrotic syndrome, thyroid dysfunction
 - Drugs - Combined oral contraceptive, HRT, Tamoxifen, chemotherapy
 - Age – over the age of 40 the risk doubles with each decade
 - Smoking
 - Physical inactivity
- If PE is suspected, use the two-level PE Wells score (see table below) to estimate the clinical probability of PE.

- Investigations should then include:
 - INR
 - D-Dimer (if Wells score ≤ 4)
 - FBC, U&E, LFT
 - CXR
 - ECG
 - BNP should not be checked routinely but is indicated in any patient in whom right heart strain is suspected (tachycardia, hypotension, hypoxia, history of collapse, central embolus on CT scan). Patients with a positive BNP must be treated as in-patients.

5.2.3 D-Dimers

This measures cross-linked fibrin broken down by plasmin. **D-dimer levels are usually elevated with DVT and/or PE**

- **Normal levels can help to exclude VTE but**
- **Elevated D-dimer levels are non-specific and have low positive predictive value.**

A number of studies have shown the value of D-dimers for the **exclusion** of venous thromboembolism [7,8]. When a clot is formed, fibrin monomers are cross-linked to each other in the region of the D domains of the molecules. After lysis the D domains remain cross-linked giving rise to D-dimers, which can be detected by commercial assay. They are, therefore, sensitive to clot formation. At present the Leicester hospitals are using the automated, immunoturbidimetric assay. The normal range is $<0.5 \mu\text{g/ml}$ FEU. Negative D-dimer results, in the presence of a low clinical probability score can exclude a PE in 99.8% of cases [9,10,11] . However, there are many causes for a raised D-Dimer other than VTE and therefore **the test cannot be used to support the diagnosis but only to exclude the diagnosis in patients with a low clinical probability score.**

Specificity of D-dimers decreases with aging and with co-morbid illnesses such as cancer, infection, inflammation, vasculitis, pregnancy, trauma, haemorrhage and post-surgical states. All of these can cause a positive D-dimer test. Consequently D-dimer testing may have limited value as a diagnostic test for VTE in hospitalized patients (more false positive results) and is unhelpful in the early postoperative period.

Normal D-dimers in a patient on vitamin K antagonist treatment such as warfarin must be interpreted with caution as the anticoagulant therapy may normalise this despite acute thrombus being present. These patients should be discussed on an individual basis.

5.2.4 Two-level PE Wells Score

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified scores	
PE likely	More than 4 points
PE unlikely	4 points or less

Adapted from Wells PS et al. (2000) Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer [10].

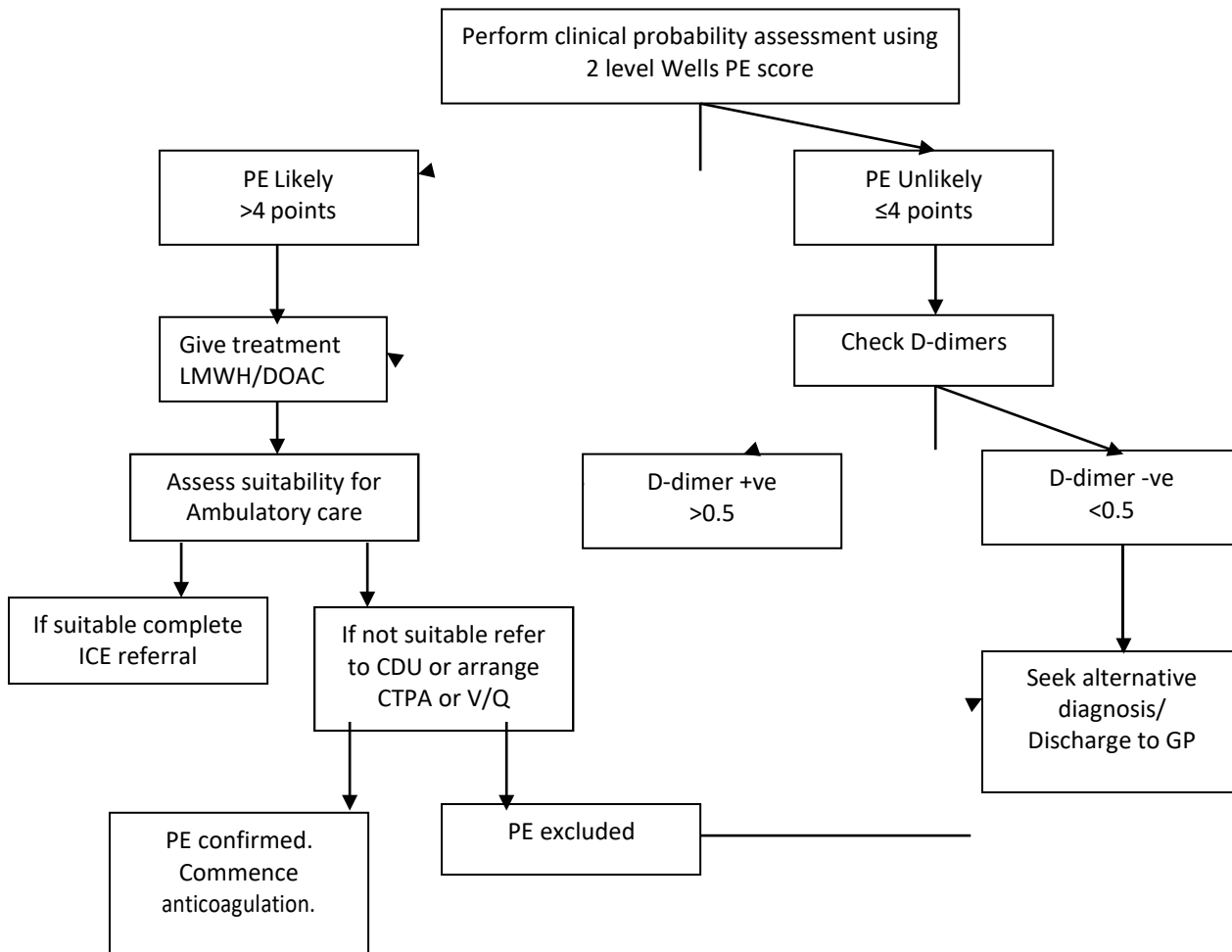
Wells clinical probability score unlikely and D-Dimer <0.5 µg/ml FEU

If the patient has a low clinical probability and normal D-dimers (<0.5 µg/ml FEU) there is a low probability of venous thromboembolism and an alternative diagnosis should be sought or discharge back to the GP should be considered.

Wells clinical probability score likely or clinical probability unlikely but raised D-Dimers:

- 1) Patients should be given an interim therapeutic dose of anticoagulation if diagnostic investigations are suspected to take longer than 1 hour (PE) or 4 hours (DVT). The options are:
 - single therapeutic dose of LMWH - will provide 24 hours of cover
 - DOAC pre-pack, if available.
 - No anticoagulant: if the risk of such interim therapy is felt to outweigh the benefit. This decision should be documented in the medical notes.
- 2) Assess suitability for Ambulatory care (see 5.3 below)
- 3) If suitable for Ambulatory care referral should be made on ICE. Patients must have baseline **CXR, U&Es, LFTs, FBC and INR**. It is not considered good medical practice for patients to be treated on this presumptive basis for more than 24 hours as for many patients this would involve unnecessary treatment [2]. Therefore if the patient cannot be seen in the ambulatory clinic within 24 hours (see opening times below) investigation and treatment should remain with the assessing team or referral made to CDU. For the outpatient therapy programme to be effective it is important that there should be no undue delay in the diagnosis of the patient. There are currently 3 dedicated CTPA slots each working week day for the diagnosis of patients with suspected PE who might then be suitable for outpatient care.
- 4) If not suitable for ambulatory care consider admission to GH CDU or, for current in-patients, arrange CTPA or V/Q
For patients who have an allergy to contrast media; or who have significant renal impairment; or whose risk from irradiation is high (e.g. women under 40 years of age) assess the suitability of a ventilation/perfusion scan, as an alternative to CTPA.

5.2.5 Flow chart for clinical assessment of suspected PE



5.3 Ambulatory Care

In the recent 2018 publication of the BTS Guidelines for the initial outpatient management of pulmonary embolism [2], the review of evidence states that in a selected low risk population the out-patient management of acute PE is non-inferior in terms of recurrent VTE, risk of major bleeding, and PE related death compared to in-patient care. In addition, management of low risk PE in an outpatient setting results in a reduction in length of stay in hospital which may be associated with healthcare related cost savings.

In the largest RCT, Aujesky *et al* randomised 344 selected low risk patients (based on PESI score and pre-defined exclusion criteria based on clinical and social factors) with confirmed pulmonary embolism to either inpatient treatment (n=172) or outpatient treatment (n=172) with low molecular weight heparin and vitamin K antagonist [5]. The study showed non-inferior outcomes for recurrent VTE at 14 and 90 days with no recurrences in either group at 14 days and one recurrence (0.6%) at 90 days in the outpatient group. At 14 days, major bleeding outcomes were non-inferior in the outpatient group with two intramuscular bleeds compared with none in the inpatient group. There was no difference in mortality (1 death in each arm). Ninety-five percent of patients in the outpatient arm were managed entirely as outpatients, with a mean length of inpatient stay (LOS) of 0.5 days from randomisation compared with 3.9 days in the inpatient arm. There was no significant difference between the 2 groups in terms of other health care utilization (hospital readmissions, emergency department visits and outpatient visits to a doctor's office within 90 days). Patient satisfaction was very high.

Identifying a low risk population, suitable for ambulatory management

Accurate risk stratification and identification of those at low risk of morbidity and mortality following a diagnosis of pulmonary embolism (PE) can influence management strategies and facilitate outpatient management or early discharge in those deemed appropriate. There are several studies both deriving and validating various prediction scores [2]. The most frequently used and most validated scores are the Pulmonary Embolism Severity Score Index (PESI) score and simplified PESI (sPESI) scores.

Simplified Pulmonary Embolism Severity Index Score - s-PESI score

A simplified version of the PESI score (s-PESI) was derived by Jiménez *et al* [6] and externally validated using data from a large International Registry (RIETE). A score of zero is classified as low risk. The s-PESI score was shown to be non-inferior to the PESI score in predicting 30 day mortality. Thirty day mortality in the low risk group (sPESI =0) was 1.0% (95% CI 0.69-0.80). There was a low incidence of major bleeding and recurrent VTE in those classified as low risk by s-PESI of $\leq 1.5\%$ at 30 days in both the derivation and validation groups. One potential criticism of the s-PESI score for use in an ambulatory decision setting in PE is that age and a history of cancer are not subject to change during the course of an admission or assessment. The loose term 'cancer' also may mean different things and could be interpreted differently depending on the setting and the desire for the clinician and/or patient to undergo outpatient treatment.

sPESI Score

Parameter	Score	Risk class	Total points
Age > 80 years	1	Low High	0 ≥ 1
Cancer	1		
Chronic cardiopulmonary disease	1		
Pulse ≥ 110 bpm	1		
SBP < 100mmHg	1		
Arterial blood oxygen saturation < 90%	1		

5.3.1 Criteria for outpatient management

Risk assessment

Only those patients with a sPESI score of 0 will be considered suitable for outpatient management by the ambulatory pulmonary embolism service. Those who score 1 because of one of the following factors (age >80, cancer or chronic cardiopulmonary disease may be considered for ambulatory treatment, only following discussion with a senior clinician – Respiratory SpR or Consultant and following a full explanation of the risks of outpatient management with the patient). Those with a HR ≥ 110 or a systolic BP <100mmHg or an Arterial blood oxygen saturation <90% are absolutely contraindicated from management in the ambulatory setting and must be admitted to hospital.

Parameter	Score	Risk class	Total points
Age > 80 years	1	Low High	0 ≥ 1
Cancer	1		
Chronic cardiopulmonary disease	1		
Pulse ≥110 bpm	1		
SBP < 100mmHg	1		
Arterial blood oxygen saturation < 90%	1		

Additional Exclusion Criteria

There are several exclusion criteria that can additionally identify patients not suitable for outpatient management of acute pulmonary embolism. To be treated as an outpatient the patient must:

- Be able to understand the treatment instructions or have home support or carer to understand instructions and carry them out (must have access to telephone)
- Appreciate the importance of full compliance with treatment
- Have the ability to attend hospital for treatment
- Have no social reasons that prevent the ability to return home – no fixed abode, inadequate care, lack of telephone communication, pose concerns over compliance (e.g. memory impairment, illicit drug abuse)
- Not be perceived as having a high bleeding risk e.g. liver disease, active peptic ulcer disease
- Have no contra-indications to anticoagulants
- Not have respiratory distress (RR<30)
- Not require iv analgesia
- Not have inter-current illness or other co-morbidity requiring admission/in-patient management
- Not have an eGFR <30
- Be an Adult (18 years and above).
- Not be pregnant

Patients with an active cancer diagnosis can be assessed for outpatient investigation and treatment on an individual basis in order to improve quality of life (treatment close to home rather than in hospital) but it must be acknowledged that this group of patients has a higher risk of mortality and morbidity due to the underlying malignancy than those patients who do not have cancer. If there is any doubt about the safety of outpatient treatment or if they do not meet the criteria outlined above, they should be admitted to hospital for investigation and treatment of their suspected pulmonary embolism.

Thrombotic indications for in-patient management

Measurement of RV:LV ratio measurement on CT or assessment of RV function on echocardiography is not indicated for the identification of low-risk patients for outpatient management. Routine measurement of cardiac biomarkers (BNP, Troponin) is not indicated for the identification of low risk patients.

Where RV dilatation has been identified on CT scanning in patients who are suitable for outpatient management (sPESI of 0 *and* no clinical exclusion criteria), a normal laboratory cardiac biomarker (BNP) may be used to identify low risk patients. Those with an elevated troponin or BNP in the presence of possible right heart strain either on echo or CT should be managed as in patients.

Bleeding indications for in-patient management

- Patients with active bleeding
- Known heparin allergy or heparin associated thrombocytopenia
- Patients at significant risk of bleeding
 - Active peptic ulceration
 - Liver disease (PT>2s beyond normal range)
 - Uncontrolled hypertension (diastolic >110mmHg, Systolic >200mmHg)
 - Angiodysplasia
 - Recent eye or CNS surgery or recent haemorrhagic stroke (within 1 month)
 - Thrombocytopenia (platelet count below $100 \times 10^9 /l$)
 - Renal Failure (CrCl <30 ml/min)

5.3.2 Patients requiring in-patient management

Patients requiring in-patient management due to immobility, transport difficulties, co-existing medical pathology or social reasons should be referred to CDU.

Patients admitted via this route should be clerked by the on call team and it is their responsibility to prescribe all the regular medication and any other medication required e.g. analgesia, anticoagulants etc.

All admitted PE patients that are commenced on an oral anticoagulant should be referred to the Anticoagulation Service via ICE.

5.3.3 Aims of the ambulatory PE service

- To investigate and treat suspected PE patients safely as an outpatient and prevent these patients being admitted to hospital enabling them to lead a normal life style.
- Free admission beds for more acutely ill patients.
- To accelerate assessment, imaging, diagnosis and commencement of treatment.
- To educate patients/carers in ongoing treatment and future preventative care.
- To provide telephone support and advice to patients/carers.
- To provide follow up support and follow up appointments
- To improve the investigation and management of suspected PE and improve adherence to UHL guidelines.
- To act as a resource for other wards, staff, junior doctors and GP's.
- To refer patients back to primary care providers of anticoagulation, UHL anticoagulation service and GPs.

5.3.4 Ambulatory PE service referral

Patients can be referred to the Ambulatory PE service at GH by:

- GPs
- Accident and Emergency
- Glenfield Clinical Decisions Unit
- Glenfield Short Stay Unit
- LRI Medical Assessment Unit
- LRI GPAU

Ambulatory PE Service Working timetable

	Weekdays	Weekends	Bank Holidays
Base	Ambulatory Care, CDU, GH		
Hours	08:30-4:30	Currently no service	Currently no service
Consultant	Respiratory Consultant on call has overall clinical responsibility		
Junior doctors	CDU medical staff		
Nursing staff	Elaine Bailie, Nisha Parmar, Ambulatory Pulmonary Nurse Specialists		

In the absence of the Ambulatory Nurse Specialist, patients remain the responsibility of the assessing medical team.

5.4 Treatment of PE – patient care pathway

5.4.1 Negative Imaging

- Ambulatory Patients who have negative imaging and have no other medical problems are referred back to GP with a letter.
- The Ambulatory PE Nurse Specialist is to use Discharge Protocol (Appendix 1).
- A copy of the discharge letter should be filed in patients notes.
- In patient care remains under the responsible consultant.

5.4.2 Positive Imaging – Ambulatory Care Treatment and Discharge Check-list

- Patients who are diagnosed with PE must fit criteria for ambulatory out-patient treatment as per protocol.
- PE Ward Attender Proforma to be completed each time patient attends clinic/has phone consultation. All information collected and advice given to be documented, signed and filed in patient's notes.
- Specialist Ambulatory PE nurse or doctor on CDU to follow 'Confirmed PE pathway' (Appendix 10).
- Patient education and counselling to decide preferred anticoagulation (Appendix 9).
- Complete anticoagulation initiation checklist: Appendix 2 for Warfarin or Appendix 3 for Rivaroxaban/Apixaban.
- Doctor in CDU or an independent prescriber must prescribe anticoagulant therapy on drug prescription chart.
- TTO's to be prescribed by doctor or independent prescriber and supplied to patient.
- WARFARIN: If commenced on warfarin a yellow anticoagulation booklet is supplied and explained. An anticoagulation discharge letter will be completed and faxed to the GP. Following the initiation of warfarin patients will be seen at Day 5 (Appendix 7) for repeat INR/review of side effects/symptoms following which INR monitoring will be done in GP anticoagulation clinics (N.B. stabilisation no longer takes place in UHL service).
- DOAC: If commenced on a DOAC an Orange anticoagulant therapy booklet, UHL Rivaroxaban medicine leaflet/UHL Apixaban Medicine Leaflet, anticoagulant alert card will be supplied (Appendix 4). The patient will be contacted by telephone at one week after commencement of DOAC to check compliance/side effects.
- Educate and provide patient information leaflets (see section 5.7.10).
- Complete malignancy screen for idiopathic/unprovoked PE (Appendix 8).
- Supply contact numbers.
- Complete letter to GP and anticoagulation discharge letter on ICE
- Request out-patient appointment on ICE letter in 'follow up arrangements'. This appointment should be with the on call consultant for CDU on the day of confirmed PE. An appointment should be requested for 3 months for provoked PE and 4 to 6 months for unprovoked/idiopathic PE.
- Request GP to do follow up FBC/U&E/LFTs in 4 weeks and thereafter as per LMSG guidance

5.4.3 Positive Imaging – In Patient Treatment and Discharge Check-list

- Ward medical team to follow 'Confirmed PE pathway' (Appendix 10).
- Patient education and counselling to decide preferred anticoagulation (Appendix 9).
- Complete anticoagulation initiation checklist: Appendix 2 for Warfarin or Appendix 3 for Rivaroxaban/Apixaban.
- Refer via ICE to anticoagulation team.
- Anticoagulant therapy must be prescribed on drug prescription chart.
- TTO's to be prescribed by doctor or independent prescriber and supplied to patient.
- WARFARIN: If commenced on warfarin a yellow anticoagulation booklet is supplied and explained. Following the initiation of warfarin – patients can be referred to GP's anticoagulation clinics to continue monitoring of their INRs as long as they are dosed for 4 working days (N.B. stabilisation no longer takes place in UHL service so an anticoagulation discharge letter needs to be completed).

- DOAC: If commenced on a DOAC an Orange anticoagulant therapy booklet, UHL Rivaroxaban medicine leaflet/UHL Apixaban Medicine Leaflet, anticoagulant alert card will be supplied (Appendix 4).
- Educate and provide patient information leaflets (see section 5.7.10).
- Complete malignancy screen for idiopathic/unprovoked PE (Appendix 8).
- Supply contact numbers.
- Complete letter to GP and anticoagulation discharge letter on ICE.
- Where clinically appropriate, request a respiratory out-patient appointment on ICE letter in 'follow up arrangements'. For Respiratory in-patients this should be with the consultant responsible for their care and for non-respiratory ward this should be in general respiratory clinic. An appointment should be requested for 3 months for provoked PE and 4 to 6 months for unprovoked/idiopathic PE - Please see section 5.7.7.
- Request GP to do follow up FBC/U&E/LFTs in 4 weeks and thereafter as per LMSG guidance:
 - https://267lv2ve190med3l1mgc3ys8-wpengine.netdna-ssl.com/wp-content/uploads/2017/08/Primary-care-warfarin-guidance_LMSG.pdf
 - <https://www.lmsg.nhs.uk/guidelines/health-community/new-oral-anticoagulants>

5.4.4 Anticoagulation for confirmed PE

All patients newly diagnosed with PE require to be commenced on anticoagulation. Patients presenting with massive PE and haemodynamic compromise should be managed as per the UHL policy: Guideline for Thrombolysis Therapy in Pulmonary Embolism B24/2016

General contraindications to anticoagulation

The following substantially increase the risk of major bleeding and appropriate specialist(s) should be consulted in the decision to anticoagulate or not, and to consider other options for management (e.g. IVC filter):

- Current or recent gastrointestinal ulceration
- Presence of malignant neoplasm at high risk of bleeding
- Recent brain or spinal injury
- Recent brain, spinal or ophthalmic surgery
- Recent intracranial haemorrhage
- Known or suspected oesophageal varices
- Arteriovenous malformation
- Vascular aneurysms, major intraspinal or intracerebral vascular abnormalities

ORAL ANTICOAGULATION

NICE recommends Warfarin and 4 direct oral anticoagulants (DOAC) for treatment of Pulmonary Embolism in the absence of active cancer. The 4 DOACs are: Rivaroxaban, Apixaban, Endoxaban and Dabigatran.

NICE guidelines CG144 (<https://www.nice.org.uk/guidance/CG144>)

NICE TA287 (<https://www.nice.org.uk/Guidance/TA287>)

NICE TA341 (<https://www.nice.org.uk/Guidance/TA341>)

NICE TA354 (<https://www.nice.org.uk/Guidance/TA354>)

NICE TA327 (<https://www.nice.org.uk/Guidance/TA327>)

Patients commenced on oral anticoagulation should be referred on ICE to the anticoagulation team

WARFARIN

Warfarin is still the anticoagulant of choice in the following circumstances:

- 1) Patients at risk of bleeding (after consultation with specialists)
- 2) Renal failure: creatinine clearance <30 ml/min (always discuss with renal team)
- 3) Liver failure (always discuss with gastroenterology)
- 4) Extremes of body weight: <50kg or >120kg
- 5) Patient preference for warfarin
- 6) Patients with poor compliance to medication where INR monitoring is beneficial
- 7) In the context of some known prothrombotic conditions (e.g. antiphospholipid syndrome)

Initiation of Warfarin

When initiating warfarin bridge with LMWH. All newly diagnosed patients to start LMWH for at least 5 days until INR greater than (>) 2.0 for 2 consecutive days as recommended by supplier. Upon initiation patients should be referred via ICE to the anticoagulation service.

Patients to have standard induction of Warfarin - Tait and Sefcick scale (Appendix 5). Warfarin dosed as per INR to keep within range as per anticoagulation protocol. Check INR on days 1 and 5 (if discharged arrange for community based anticoagulation services to check INR and dose). N.B. patients can be referred to GP anticoagulation clinics to continuing monitoring of INR as long as they are dosed for 4 working days (INR stabilisation no longer takes place in UHL service so an anticoagulation discharge letter must contain detailed information for the GP to follow)

If discharged, administration of LMWH is to be undertaken by the patient. If patient unwilling or unable, arrange administration by district nurse/community nurse.

For ambulatory clinic only - document LMWH dose and INR results day 1 and 5 as per Appendix 7.

For more information on warfarin dosing see UHL Guidelines on Oral anticoagulation with warfarin and coumarins B44/2016

DIRECT ORAL ANTICOAGULANTS

The advantages are: quick onset of action, no need for heparin therapy at start-up (Apixaban & Rivaroxaban only); availability of specific antidote (Dabigatran only); and no need for frequent monitoring.

The choice of DOAC depends upon number of factors including:

- Patient choice
- Age
- Renal function
- Compliance with once/twice daily dosing
- Risk of bleeding

DOAC	Inhibits	Initial heparin	Reversal agent
Apixaban	Factor (F) Xa	No	No
Rivaroxaban	F Xa	No	No
Edoxaban	F Xa	Yes	No
Dabigatran	F II (thrombin)	Yes	Yes

Overall, the DOACs are similar to warfarin in efficacy, and have an advantage in reducing bleeding complications. Rivaroxaban (but not Apixaban) has an **increased** risk of GI bleeding compared with warfarin.

General caution is advised for extremes of body weight (<50kg or >120kg). Warfarin is preferred where creatinine clearance is <30. Please consult a Haematologist if intending to use a DOAC in either scenario.

The expert panel report and guideline for antithrombotic therapy for VTE published in March 2016 highlights the preferential use of direct anticoagulants over warfarin for VTE (12).

The efficacy and safety of DOAC compared to standard treatment with warfarin is summarised in the table below:

Outcomes in DOAC trials for initial/short-term treatment				
DOAC (vs Warfarin)	Efficacy	Major Bleeding	CRNM Bleeding	GI bleeding
Apixaban	→	↓	↓	↓
Rivaroxaban	→	↓	→	↑
Edoxaban	→	→	↓	--
Dabigatran	→		↓	--
Because of differing characteristics & study design, cross DOAC comparisons cannot be made. Data shown only for illustration of trial outcomes in comparison with warfarin (in the respective trials).				
CRNM clinically relevant non-major; GI gastro-intestinal				

Apixaban and Rivaroxaban are recommended first line above the other two DOACs, and are approved for use without the need for a Shared Care Agreement (SCA) - **SIMPLE AMBER**. The key practical advantage of these two drugs is that they do not need heparin therapy at start-up.

Dabigatran and Edoxaban are not recommended as first line, and require a SCA for use - **AMBER (SCA needed)**. Please ensure discussion with a consultant specialist before initiating these medications

Heparin therapy for 5 days is required at start-up. Specific situations where these may be used:

- lactose intolerance (Apixaban and Rivaroxaban have lactose as a constituent)
- where the bleed risk is high and an agent with an antidote (Dabigatran) is felt to be more appropriate

Dosing regimes

	Initial*	Short term (up to 3-6m)	Long term (>6m)
Apixaban	10mg bd x7d	5mg bd	2.5mg bd
Rivaroxaban	15mg bd x21d	20mg od (15mg od low dose)	10mg od (20mg od high VTE risk)
Edoxaban	Heparin x5d	60mg od (30mg od low dose)	---
Dabigatran	Heparin x5d	150mg bd (110mg bd low dose)	---
*Please note differing initial dose periods and dosing regimes Dose adjustment may be needed – please refer to BNF			

Reversal

There is currently no specific reversal agent for Factor Xa inhibitors: Rivaroxaban, Apixaban, Edoxaban. Treatment cessation and supportive therapy are advised.

For **moderate to severe** anticoagulant-related bleeding, please consult the on call Haematologist for consideration of blood products and PCC.

FOR DABIGATRAN ONLY, use of a specific antidote (Idarucizumab) is available but should be discussed with haematology.

The protocol for the management of bleeding on Rivaroxaban/Apixaban can be found on INsite <http://insitetogether.xuhl-tr.nhs.uk/SP2007/Medicines%20Information/Management%20of%20Bleeding%20Complications%20in%20patients%20on%20Apixaban%20and%20Rivaroxaban.pdf>

Effect on coagulation tests

A coagulation profile is recommended for all anticoagulant-related bleeding. Currently, there is limited clinical value of these results in the context of DOAC therapy. Any local guidance for specific situations should be followed.

If the PT and/or APTT are prolonged, levels are likely to be significant but a normal PT and APTT do not exclude significant drug levels (especially with Apixaban).

Drug levels can be measured with a specific assay as part of an agreed pathway (in consultation with Haematology).

Concomitant Antiplatelet therapy

Discontinue the antiplatelet during the initial & short term treatment (up to 6 months), unless there is a history of recent (<12 months) acute coronary syndrome (&/or coronary intervention) or stroke/TIA.

If longer term anticoagulant treatment planned (beyond 6 months)

- please review the risk-benefit balance with regards to resuming antiplatelet therapy
- if concomitant antiplatelet therapy is warranted, consider using the low dose anticoagulant option (if available – see table: dosing regimens).

RIVAROXABAN (XARELTO)

Rivaroxaban is an oral direct factor Xa inhibitor with 80-90% bioavailability but must be taken with food. It is licensed and has NICE approval for the treatment of PE/DVT and the prevention of recurrence of VTE in adults.

It is given as a fixed dose and has no specific food interactions like warfarin. The half life is 5-13 hours but anti Xa activity persists for 24 hours. This drug disrupts thrombin generation and clot development. The factor Xa inhibition is dose dependent. Renal clearance is approximately 35%.

There is no specific antidote for rivaroxaban and the absence of monitoring makes non compliance more difficult to detect compared with warfarin. Counselling and follow up is required to avoid a situation where recurrent VTE becomes the first sign of non-compliance.

Contra-indications to Rivaroxaban:

- 1) Liver disease with coagulopathy or severe hepatic impairment
- 2) Pregnancy and Breastfeeding. Women of child-bearing age should be counselled to avoid getting pregnant while on treatment
- 3) Concomitant treatment with any other anticoagulant
- 4) Lesion or condition considered to be a significant risk for major bleeding
- 5) Active clinically significant bleeding
- 6) Allergy/hypersensitivity to the active substance
- 7) Creatinine clearance <30 ml/min or undergoing dialysis (discuss with renal team any patient with CrCl <30 ml/min). CrCl should be calculated using the Cockcroft Gault calculation not eGFR.

Drug interactions:

Rivaroxaban should not be used in patients taking:

- CYP3A4 inhibitors: azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, posaconazole and isavuconazole), HIV protease inhibitors (e.g. Ritonavir)
- CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbitone, and St John's Wort)
- Macrolide antibiotics e.g. clarithromycin
- Tacrolimus
- Dronedarone
- Use with caution in patients receiving other drugs affecting haemostasis (e.g. NSAIDs, clopidogrel, aspirin). See 'concomitant antiplatelet therapy' above)

More information can be found at: <https://www.medicines.org.uk/emc/> and www.bnf.org

Initiation and dosing of Rivaroxaban:

Dose: Day 1 to 21 – 15mg twice daily (42 tablets)

Day 22 onwards – CrCl >50 ml/min 20mg once daily. Consider dose reduction to 15mg once daily if CrCl 30-49/ml and risk of bleeding outweighs risk of recurrent PE/DVT. Provide further 7 days tablets then GP to take over supply for remainder of the duration of anticoagulation.

Consider dose reduction to 10mg od after 6 months for secondary prevention of recurrent VTE (EINSTEIN-CHOICE) [13]. A dose reduction for extended anticoagulation is only appropriate for patients where the need for anticoagulation is in 'clinical equipoise'. Those in whom the risk of recurrent VTE is felt to be high should remain on full dose anticoagulation.

Missed doses

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take the missed dose immediately and take the next dose on time (if the next dose is due, two 15mg doses are recommended i.e. 30mg). After 21 days, the dose should not be doubled within the same day to make up for a missed dose.

Monitoring

Routine monitoring of drug levels or coagulation tests is not necessary.

It is recommended that the patient's GP repeat FBC, U&E, LFTs one month after initiation and then checks renal function (CrCl) at least once a year, or more frequently as clinical circumstances dictate when it is suspected that the renal function could deteriorate.

APIXABAN (ELIQUIS)

Apixaban is also an oral direct factor Xa inhibitor with similar efficacy to Rivaroxaban. Half-life is 12 hours and renal excretion is lower at approx. 25%. It does not require to be taken with food. Similar to Rivaroxaban there is no current licenced antidote. Dosing is twice daily throughout treatment course – compliance must therefore be taken into consideration.

Apixaban may be the DOAC of choice in:

- patients with dyspepsia or a history of previous gastrointestinal bleeding (trial data suggests lower GI bleeding risk with Apixaban; Journal of Thrombosis and Haemostasis, 12: 320–328)
- patients who present with unprovoked PE or recurrent PE in whom extended treatment (no scheduled stop date) may be indicated due to the lowest overall bleeding risks. (AMPLIFY-EXT [14] - Apixaban 2.5mg bd significantly reduces the risk of recurrent VTE without increasing bleeding risk)
- Patients with CrCl between 30 and 49 ml/min (no dose reduction necessary for Apixaban due to less renal excretion).
- Females of childbearing age: our own local experience suggests a smaller increase in menstrual bleeding compared to Rivaroxaban

Contraindications and drug interactions are the same as for Rivaroxaban

Initiation and dosing of Apixaban:

Dose: Day 1 to 7 – 10mg twice daily (28 tablets)

Day 7 onwards – 5mg twice daily. Provide 21 days (42 tablets) then GP to take over supply for remainder of the duration of anticoagulation.

Missed doses

If a dose is missed, the patient should take the dose immediately and then continue with twice daily intake as before.

Monitoring

Routine monitoring of drug levels or coagulation tests is not necessary.

It is recommended that the patient's GP repeats FBC, U&E, LFTs one month after initiation and then checks renal function (CrCl) at least once a year, or more frequently as clinical circumstances dictate when it is suspected that the renal function could deteriorate.

LOW MOLECULAR WEIGHT HEPARIN (LMWH)

Enoxaparin is the first line LMWH of choice within UHL and Dalteparin is second line.

Guidance on dosage can be found on INsite and Appendix 6:

[http://insitetogether.xuhl-tr.nhs.uk/pag/pagdocuments/Treatment%20of%20Deep%20Vein%20Thrombosis%20and%20Pulmonary%20Embolism%20Administration%20Guide%20\(Inhixa%20AE\)%20UHL%20Guideline.pdf](http://insitetogether.xuhl-tr.nhs.uk/pag/pagdocuments/Treatment%20of%20Deep%20Vein%20Thrombosis%20and%20Pulmonary%20Embolism%20Administration%20Guide%20(Inhixa%20AE)%20UHL%20Guideline.pdf)

Indications

- LMWH is the gold standard for both treatment and prevention of cancer-related VTE. There remains lack of clarity as to when cancer is 'active' and 'inactive' for purposes of use of alternative oral anticoagulant, and such decisions should be made at consultant level.
- Patients deemed with an active cancer diagnosis should be prescribed low molecular weight heparin (LMWH) and this should be extended therapy (no scheduled stop date). The need for ongoing treatment should be reviewed, at a minimum, every 6 months by a secondary care physician.
- LMWH may also be appropriate as a bridge to oral anticoagulation in the context of acute medical illness.
- Women who are pregnant or in the puerperium – these patient must be discussed and/or managed by the obstetric department.
- Some intravenous drug abusers.

Monitoring

- Baseline FBC, PT/INR
- FBC 5 to 7 days after commencing LMWH
- Anti Xa levels to assess potential accumulation or inadequate dosing. Levels should be taken 3 to 5 hours post-dose (peak level) for patients with: significant renal impairment, morbid obesity (weight >120kg), underweight (weight <45kg), pregnancy.

Shared care agreement

A full shared care agreement must be completed

5.4.5 Follow up

BTS and NICE recommend follow up for patients post pulmonary embolism [2,15]. Follow up should address 3 issues:

1. Resolution of symptoms. The incidence of CTEPH after acute PE is in the region of 0.5 to 3% [16]. Risk factors for CTPEH include initial high burden of clot/proximal clot at diagnosis, unprovoked PE, recurrent PE, and CT evidence of RHS at presentation. Patient symptoms and risks factors for CTPEH should be assessed and further investigations performed as needed. **Routine Echocardiogram after PE is NOT recommended.** Patients that remain symptomatic at around 6 months post PE should then have ECG, spirometry and echocardiogram. If these suggest pulmonary hypertension with no other significant cardiopulmonary disease then V/Q should be performed.
2. To determine duration of anticoagulation. Patients with provoked PE should be treated for at least 3 months and unprovoked PE 6 months. Long term treatment will be considered for recurrent thrombosis, patients with an on-going risk factor, or unprovoked PE. It may be possible to decide on finite (3-6 months) or indefinite anticoagulation when treatment is started but many patients (e.g. those with a first unprovoked proximal DVT or PE) will need to be reviewed at three to six months to decide whether or not to stop anticoagulation, and the need for further tests to identify any underlying haematological conditions. (see advice on 'Duration of Anticoagulation' below)
3. Need for thrombophilia screening. There is no need to routinely screen a patient that going to remain on long term anticoagulation. In people with an unprovoked PE, consider antiphospholipid testing (anti-cardiolipin and anti-beta glycoprotein antibodies) before stopping anticoagulants. In people with an unprovoked PE who have a first-degree relative who has had a DVT or PE, consider referral to haematology to arrange hereditary thrombophilia testing (factor V Leiden mutation, Prothrombin gene mutation antithrombin, protein C, and protein S testing).

Follow up should be requested on the ICE discharge letter.

- All patients with a first unprovoked PE should be reviewed in General Respiratory Clinic between 4 to 6 months after discharge. A judgement of the perceived benefits of this review for patients with significant co-morbidity or who are already under medical follow up should be made by the consultant in charge of their care.
- Patients with recurrent PE or symptoms/imaging (echo/CT) suggestive of CTEPH should be referred to General Respiratory Clinic.
- All patients with a first provoked PE should be reviewed in clinic at 3 months. Clinic review this should be with the team responsible for the patient's care. Clinic review should address the 3 points above.
 - If the patient remains symptomatic continue anticoagulation and refer to General Respiratory Clinic for investigation of chronic emboli.
 - If the patient is well and the provoking risk factor has resolved stop anticoagulation and provide advice regarding reducing risk of recurrent VTE.
 - If the provoking risk factor has not resolved continue anticoagulation and review again at an appropriate timescale
 - If thrombophilia screening is needed the patient should be referred to the Haemostasis and Thrombosis team.

5.4.6 Screening for malignancy

Screening for underlying undiagnosed malignancy should be performed in all patients presenting with an unprovoked PE [15]. **Please use Appendix 8.**

NICE Jan 2015 recommends:

- A full history and physical examination to look for evidence of malignancy
- A chest X-ray
- Blood tests including a full blood count, serum calcium, and liver function tests
- Urinalysis
- *Consider* referral for further investigations for cancer with an abdomino-pelvic CT scan (and mammogram in women) in all people over 40 years with a first unprovoked PE who do not have features of cancer based on the initial investigations above

The relationship between unprovoked VTE and occult malignancy was initially identified in the 1800s by Trousseau [17]. Numerous clinical studies and trials have shown that patients presenting with VTE are 'high-risk' for occult malignancy or for developing malignancy shortly after the initial diagnosis of VTE, with up to 10% of patients diagnosed with malignancy within a year of the initial diagnosis of unprovoked VTE.

However the evidence base for this is limited and recent studies and a local radiology audit of >900 patients have shown that very few patients are diagnosed with cancer on an abdomino-pelvic CT scan post unprovoked VTE [18-20]. In our local cohort all the patients diagnosed with occult malignancy as a cause for unprovoked VTE had clinical signs, symptoms or red flags for underlying cancer.

Another assumption of the above NICE recommendation is that abdomino-pelvic CT is a sensitive screening tool. However, it is well documented that abdomino-pelvic CT is not sensitive at identifying early cancers particularly in the stomach, colon, pancreas and female reproductive tract. **Thus abdomino-pelvic CT is not a screening tool for malignancy and potentially may give false reassurance.**

We recommend the following investigation algorithm for patients post unprovoked VTE:

All patients should have a documented senior clinical review (CT/ST3/ANP and above) to include:

- Focused clinical examination guided by patient history
- A CXR
- Blood tests (FBC, Bone profile & LFTs)
- Near patient urinalysis

Patients with abnormal routine blood tests must be investigated and followed up after commencement of anticoagulation. Patients with anaemia must have repeat FBC one and 4 weeks after commencement of anticoagulation.

Further investigations should be guided by the patient's history and examination as elicited in Appendix 8. Specialist investigations are based on the 'Assessing and Referring Adult Cancers' algorithm ([adult cancer NICE graphic](#)). Patients with 'red-flags' should be referred under the 2-week wait cancer pathway for appropriate locally agreed investigations.

No further imaging is recommended in patients post-unprovoked PE out of the above algorithm or agreed 2 week wait guidelines. Any requests for imaging which do not fulfil the guidelines will be returned to the referrer for further consideration.

5.4.7 Prescription of medication

Prescription of LMWH and oral anticoagulants is the responsibility of the medical team or the Specialist Ambulatory PE nurse prescriber at the time of diagnosis.

TTOs

Please ensure an adequate supply of anticoagulant medication (4 weeks) to avoid missed doses. Provide clear instructions to ensure GP follow up within that time window. An ICE Anticoagulation Discharge Letter should be completed for all inpatient discharges. Clear instructions for GP are required e.g. duration of therapy and/or plan for clinic review.

The following is a guide as to how to complete the discharge letter medications for the different anticoagulants

RIVAROXABAN tablets– 15mg bd for 3 weeks, then 20mg od.

APIXABAN tablets – 10 mg bd for 7 days then 5mg bd.

WARFARIN - 3 boxes of 1mg tablets x 28 tablets per box

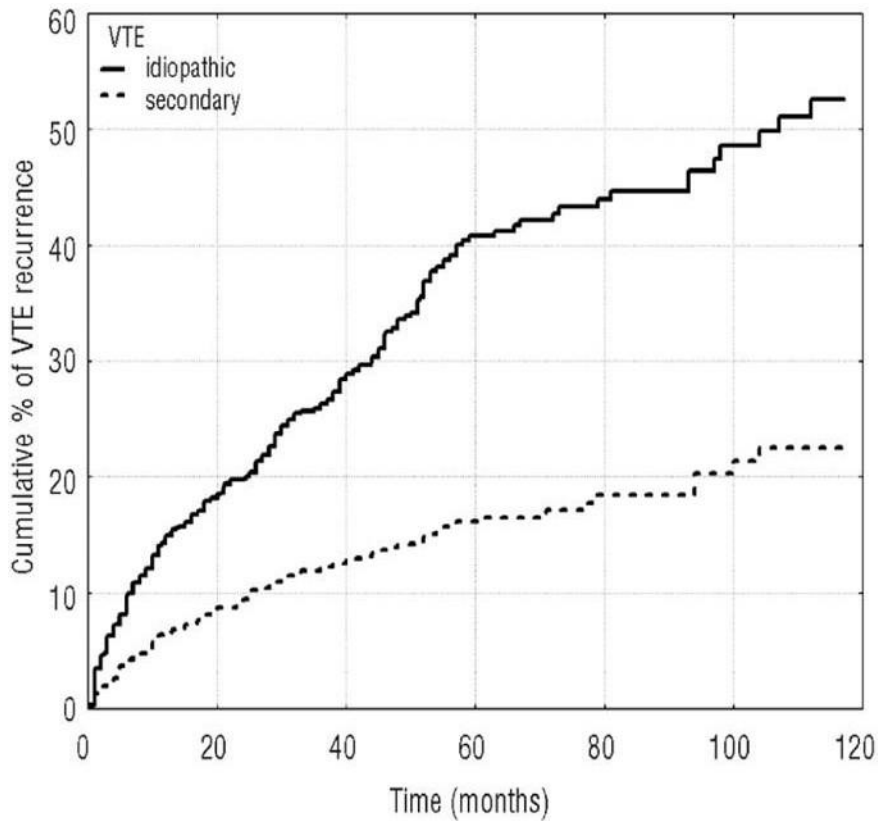
Patients informed to get further supplies from GP

LMWH – weight based dosage in pre filled syringes is administered on site when the patients attend for daily monitoring blood tests. In the circumstance of District Nurse administration or self-administration the weight based dosage in pre filled syringes is supplied (along with a sharps box for self-administration).

5.4.8 Duration of Anticoagulation

The decision regarding the duration of anticoagulation should be made at a senior level (consultant/GP).

- Offer LMWH to patients with active cancer and confirmed PE, and continue the LMWH as extended therapy (no scheduled stop date). Every 6 months, assess the risks and benefits of continuing anticoagulation. There is increasing evidence for the use of DOACs in cancer associated thrombosis [21,22] but further studies are awaited. The benefits and risks of either changing to a DOAC or treating from the outset with a DOAC should be discussed with the patient.
- Commence DOAC/warfarin in patients with confirmed PE within 24 hours of diagnosis.
- Anticoagulation for the first episode of provoked PE should be a minimum of 3 months. After 3 months patient review is necessary to determine if the provoking factor has resolved and to assess risk of CTEPH. Complex lower limb fractures often require a longer duration of anticoagulation due to revision surgery/reduced mobility/physiotherapy. Patients in whom the provoking factor has been non-orthopaedic surgery/long haul travel/combined oral contraceptive/HRT can usually stop at 3 months. Consider referral to haemostasis and thrombosis team if PE has been life-threatening due to a provoked event.
- All patients with a first unprovoked PE should receive anticoagulation for a minimum of 6 months and be reviewed in clinic at 4 to 6 months to consider benefits/risks of extended anticoagulation. The risk of recurrent VTE, after stopping anticoagulation, for a first unprovoked event is approximately 10% within the first year, rising to 40% by 5 years and 50% by 10 years [23].



Idiopathic VTE				Secondary VTE		
months	N. of VTE	Cum Incid (%)	95% CI	N. of VTE	Cum Incid (%)	95% CI
6	85	10.0	8.0-12.0	32	4.2	2.8-8.7
12	39	15.0	12.6-17.4	17	6.6	4.8-8.4
36	74	26.3	23.0-29.6	34	12.3	9.8-14.8
60	56	40.8	36.5-45.1	14	16.1	13.0-19.2
96	9	46.4	41.1-51.8	6	20.3	15.8-24.8
120	5	52.6	45.6-59.5	2	22.5	17.2-27.8

The rate of recurrence is increased by certain risk factors such as male gender, ethnicity (Caucasian/African American), obesity, antiphospholipid syndrome, increasing age [24]. Of note, patients presenting with PE rather than proximal DVT are 3 times more likely to represent with recurrent PE than with DVT. Given the risk of fatality of PE this must be considered carefully. There are a number of validated risk scores for predicting recurrent VTE including the DASH score and the Vienna predication model [24]. There are additionally a number of bleed risk scores but predicative power for all of them are low [25]. There is only one developed for use in PE – RIETE score [26]. Bleeding risk in the principal studies suggests rates of major bleeding are lowest for Apixaban.

	AMPLIFY Warfarin	AMPLIFY-EXT APIX 5mg bd	AMPLIFY-EXT APIX 2.5mg bd	AMPLIFY-EXT PLACEBO	EINSTEIN CHOICE RIVA 20mg od	EINSTEIN CHOICE RIVA 10mg od	EINSTEIN CHOICE Aspirin 100mg od
Major Bleeding	1.8%	0.1%	0.2%	0.3%	0.5%	0.4%	0.3%
CRNM bleeding	8.1%	4.2%	3.0%	2.3%	2.7%	2.0%	1.8%

Bleeding risk is lowered by reducing DOAC dose after initial 6 months treatment and should be considered [13,14]. Additionally, risk of recurrent VTE does fall over time so the decision to continue long-term anticoagulation means the risks/benefits should be reviewed as need arises.

- If a decision for extended anticoagulation is made for patients on Rivaroxaban, the dose should remain at 20mg once daily for a total of 6 months. Beyond 6 months consider dose reduction to 10mg once daily for the prevention of recurrent VTE. A dose reduction for extended anticoagulation is only appropriate for patients where the need for anticoagulation is in 'clinical equipoise'. Those in whom the risk of recurrent VTE is felt to be high should remain on full dose anticoagulation.
- If a decision for extended anticoagulation is made for patients on Apixaban the dose should remain at 5 mg twice daily for a total of 6 months. Beyond 6 months consider a dose reduction to 2.5mg twice daily for prevention of recurrent VTE. A dose reduction for extended anticoagulation is only appropriate for patients where the need for anticoagulation is in 'clinical equipoise'. Those in whom the risk of recurrent VTE is felt to be high should remain on full dose anticoagulation.
- If a patient presents with a second or subsequent PE/DVT, treatment should be lifelong unless bleeding risk is deemed high - see UHL Guidelines on Oral anticoagulation with warfarin and coumarins B44/2016

5.4.9 Transfer of care for anticoagulation monitoring

Rivaroxaban and Apixaban do not require blood monitoring.

Patients commenced on warfarin, can be referred to a GP community based anticoagulation services for stabilisation (INR does not have to be within therapeutic range). Referral must be done via the anticoagulation discharge letter and patients must be dosed for a minimum of 4 working days.

For the ambulatory PE service, patients commenced on warfarin, can be referred from day 5 for stabilisation (INR does not have to be within therapeutic range). Duration of warfarin treatment must be clearly documented in the notes, on anticoagulation prescription and in front of the yellow booklet as per national consensus.

5.7.10 Patient Information

Patients having anticoagulation treatment will be given verbal and written information about:

- how to use anticoagulants
- duration of anticoagulation treatment
- possible side effects of anticoagulant treatment and what to do if these occur
- the effects of other medications, foods and alcohol on oral anticoagulation treatment
- monitoring their anticoagulant treatment
- how anticoagulants may affect their dental treatment
- taking anticoagulants if they are planning pregnancy or become pregnant
- how anticoagulants may affect activities such as sports and travel
- when and how to seek medical help

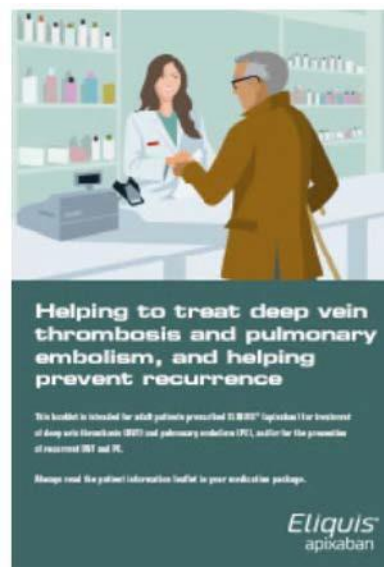
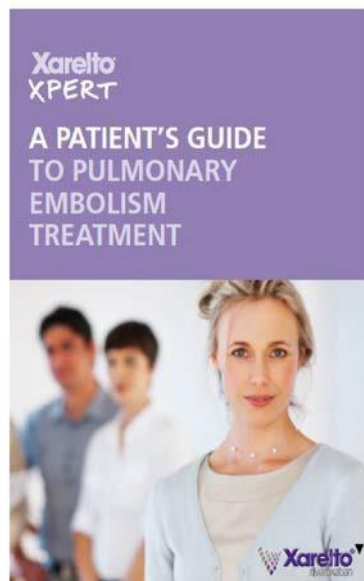
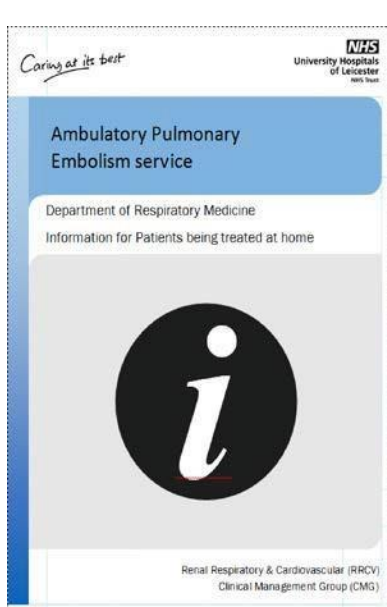
Ensure the initiation of anticoagulation checklist has been completed and signed then filed in patient case notes (Appendix 2 warfarin, Appendix 3 and 11 rivaroxaban/apixaban).

There are several sources of written information for patients:

<https://www.blf.org.uk/support-for-you/pulmonary-embolism>

<http://xarelto-info.co.uk/static/documents/pe-patient-brochure.pdf>

<https://www.eliquis.co.uk/hcp/resources/patient-materials/patient-information-booklets-dvt-pe>



5.4.10 Surgical procedures

Elective surgery is not advised in the first 3-6 months following VTE diagnosis. For patients undergoing elective surgery, rivaroxaban and apixaban should be discontinued at least 24 hours before the surgery is planned and for high bleeding risk surgery this should be 48-72 hours. Decisions regarding peri-operative care are the responsibility of the operating surgeon, and advice on bridging can be sought from the Haematologists (Dr Gooding / Dr Myers).

For emergency situations, please consult the on call Haematologist for advice.

6 EDUCATION AND TRAINING REQUIREMENTS

There are no current education and training requirements needed to implement this policy. The nurse specialists that run the Ambulatory PE clinic have been fully trained and have been in post for a substantial period of time prior to this policy update. Doctors and Nurse Practitioners assessing patients should be made aware of this policy in the same manner they are signposted to all UHL guidelines (e.g. INsite and Local Induction)

7 PROCESS FOR MONITORING COMPLIANCE

Element to be monitored	Lead	Tool	Frequency	Reporting arrangements
Audit of referrals made to Ambulatory PE Clinic in CDU to ensure patients meet established criteria	Elaine Bailie (Ambulatory specialist nurse)	Continuous excel database	Reporting monthly	Data report submitted quarterly to CDU Ambulatory Consultant Lead Respiratory Physician and data shared at CDU operational meeting
Review of all complaints/Datix submitted involving the Ambulatory PE Clinic	Ambulatory Consultant Lead Respiratory Physician	Reports will be gathered from the RRCV patient safety team	Monthly	Report to be shared at the monthly CDU operational meeting and quarterly data at Respiratory Specialties Board.
Ambulatory Specialist Nurse Competency	Sue Mason (Head of Nursing)	Appraisal	Annual	Appraisal documentation
Audit of Adherence to confirmed PE policy	Ambulatory Consultant Lead Respiratory Physician	Retrospective Audit of case notes (50 sets minimum)	Annual	Data to be shared at CDU operational meeting and presented at Trust Audit meeting or Respiratory Audit meeting

8 EQUALITY IMPACT ASSESSMENT

8.1 The Trust recognises the diversity of the local community it services. Our aim is therefore to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.

8.2 As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified

1. **Gjonbrataj E et al.** Risk factors associated with provoked pulmonary embolism. **Korean J Intern Med** 2017; **32(1)**:95-101
2. **Howard LSGE et al.** BTS Guideline for Initial outpatient management of pulmonary embolism. **Thorax** 2018;**73 Suppl 2** (<https://www.brit-thoracic.org.uk/document-library/clinical-information/pulmonary-embolism/op-pe/bts-guidelines-for-the-outpatient-management-of-pulmonary-embolism/>)
3. **Elf JE et al.** Home treatment of patients with small to medium sized acute pulmonary embolism. **Journal of Thrombosis and Thrombolysis** 2015;**39(2)**:166-72
4. **Davies CWH et al.** Early discharge of patients with pulmonary embolism: a two-phase observational study. **European Respiratory Journal** 2007;**30(4)**:708-14
5. **Aujesky D et al.** Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. **Lancet** 2011;**378(9785)**:41-48
6. **Jimenez D et al.** Simplification of the Pulmonary Embolism Severity Index for Prognostication in Patients With Acute Symptomatic Pulmonary Embolism. **Archives of Internal Medicine** 2010;**170(15)**:1383-89
7. **Bounameaux H et al.** Plasma measurement of D dimer as diagnostic aid in suspected venous thromboembolism: an overview. **Thromb Haemost** 1994;**71(1)**:1-6
8. **Janssen M et al.** Rapid D-dimer assays to exclude deep vein thrombosis and pulmonary embolism: current status and new developments **Seminars in Thrombosis and Haemostasis** 1998;**24(4)**:393-40
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10. **Wells PS et al.** Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. **Thromb Haemost** 2000; **83(3)**:416-20
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18. **Carrier M et al.** Screening for Occult Cancer in Unprovoked Venous Thromboembolism. *New England Journal of Medicine.* **N Engl J Med** 2015; 373:697-704
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20. **Hussain T et al.** Unprovoked venous thromboembolism (VTE) – are we over investigating? **Clinical Radiology.** Volume 70, S13
21. **Mantha S et al.** Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. **J Thromb Thrombolysis** 2017;43(2):166–171
22. **Kahale LA et al.** Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. **Cochrane Database Syst Rev.** 2018;Jun 19;6:CD006650.
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27. **Nieto J et al.** Validation of a score for predicting fatal bleeding in patients receiving anticoagulation for venous thromboembolism. **Thrombosis research**2013;132:175-179

Additional guidance documents:

C5/2001 Investigation and management of VTE in pregnancy and puerperium
 Oral anticoagulation with warfarin and coumarins B44/2016
 Prothrombin Complex Concentrate (PCC – Octaplex or Beriplex P/N) Clinician pack
 C265/2016
 Massive haemorrhage – UHL policy C263/2016
 Guideline for Thrombolysis Therapy in Pulmonary Embolism B24/2016
 The imaging of suspected pulmonary emboli C1-2006
 Management of bleeding on Rivaroxaban and Apixaban
<http://insitetogether.xuhl-tr.nhs.uk/SP2007/Medicines%20Information/Management%20of%20Bleeding%20Complications%20in%20patients%20on%20Apixaban%20and%20Rivaroxaban.pdf>

10 PROCESS FOR VERSION CONTROL, DOCUMENT ARCHIVING AND REVIEW

This policy should be reviewed in 2 years or before if new national guidance becomes available which indicates a need to change process. The policy will be reviewed by the Respiratory Consultant with clinical responsibility for the Ambulatory PE clinic as determined by the Respiratory Head of Service.

The updated version of the policy will then be uploaded and available through INsite Documents and the Trust's externally-accessible Freedom of Information publication scheme. It will be archived through the Trusts PAGL system.

APPENDIX 1:

NURSE LED DISCHARGE FOR PATIENTS REFERRED TO AMBULATORY PE CLINIC WITH SUSPECTED PE

It has been agreed by the ambulatory PE team that if the criteria listed below has been achieved then the patient can be referred back to their GP:

- All patients have been assessed using the clinical probability score.
- All patients have had routine bloods taken (FBC, U&E, LFTs, Calcium, INR, D-dimer unless high clinical probability)
- If patients have a low or intermediate clinical probability and D-Dimers are <0.5 µg/ml.
- If imaging has been performed it is negative for PE.
- If no other diagnosis has been identified by imaging.
- Patients have been advised what to do if their condition worsens or they have new symptoms.
- They have no other conditions that require admission.
- A letter has been sent to the GP.
- Events have been clearly documented in the patients' notes.
- A copy of the GP letter is filed into the notes.
- If patients have a PE they are referred to clinic for follow up.

Undertaken only by ambulatory PE Nurse Specialist

APPENDIX 2: ANTICOAGULATION WITH WARFARIN. INITIATION CHECKLIST, INITIATION SCHEDULES AND REFERRALS FOR MONITORING

ANTICOAGULATION THERAPY CHECK LIST FOR NEW POSITIVE PATIENTS UHL

Diagnosis:

Seen by:

Date:

Please tick each point once the patient has been informed of the following:

1. Clinical need for anticoagulation	
2. How heparin works (if applicable)	
3. How warfarin works	
4. Need for regular INR monitoring.	
5. Using a calendar to remember dose adjustments / appointments	
6. Obtaining supply of medication from: <ul style="list-style-type: none"> • Hospital initially • Repeat prescriptions from GP 	
7. Discuss current drug therapy and the need to inform clinic of change of medication.	
8. Discuss over the counter medication and herbal remedies.	
9. To ask their local pharmacist for advice on medications and possible interactions	
10. Advice on alcohol consumption <ul style="list-style-type: none"> • Need for moderation (no more than 2 units per day) • Not to 'binge' • Effects of warfarin combined with alcohol 	
11. Aware of possible side effects of therapy eg bleeding, bruising.	
12. For women only, contraception, periods, pregnancy and HRT.	
13. Dietary advice given, especially regarding avoidance of crash diets.	
14. Yellow anticoagulant treatment book given.	
15. Lifestyle issues discussed, smoking, exercise, weight control and work	
16. Contact numbers given.	
FOR PATIENTS WITH DVT	
17. Need for leg care, wearing compression stockings, rest and moderate exercise.	
18. What to do if experiencing worsening pain, leg swelling or discolouration or dyspnoea.	

APPENDIX 3 CHECKLIST FOR INITIATION OF RIVAROXABAN/APIXABAN

ANTICOAGULATION THERAPY CHECK LIST FOR NEW POSITIVE PATIENTS UHL

Diagnosis:

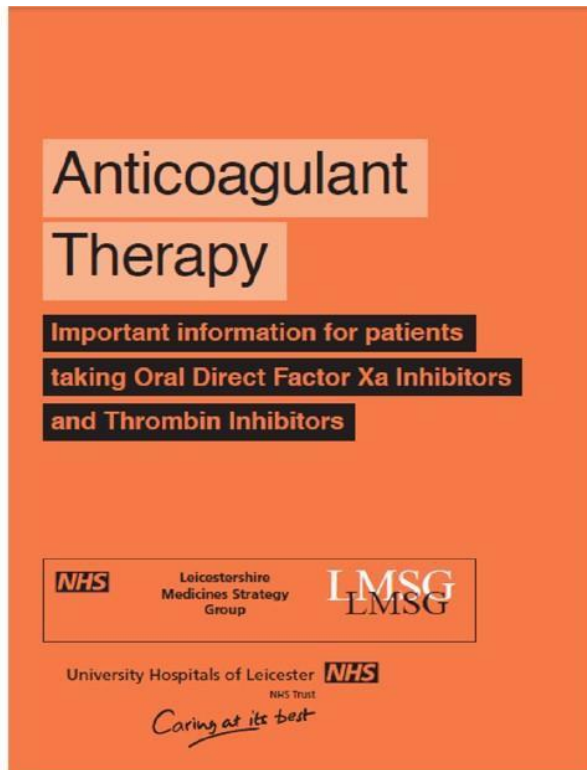
Seen by:

Date:

Please tick each point once the patient has been informed of the following:

1. Ensure patient meets criteria and has no contraindications	
2. Explain clinical need for anticoagulation	
3. How Rivaroxaban/Apixaban works. Take Rivaroxaban with food	
4. Risks/benefits of anticoagulants	
5. Importance of compliance - using a calendar/mobile phone to remember doses / appointments	
6. Obtaining supply of medication from: <ul style="list-style-type: none"> • Hospital initially • Repeat prescriptions from GP 	
7. Discuss current drug therapy and the need to inform clinic of change of medication	
8. Check interactions with current drug therapy	
9. To ask their local pharmacist for advice on medications and possible interactions	
10. Aware of possible side effects of therapy eg bleeding, bruising	
11. For women only, contraception, periods, pregnancy and HRT	
12. Lifestyle issues discussed, smoking, exercise, weight control and work	
13. Orange anticoagulant booklet/ alert card given	
14. UHL Rivaroxaban/Apixaban Medicine Leaflet given	
15. Contact numbers given	
FOR PATIENTS WITH DVT	
17. Need for leg care, wearing compression stockings, rest and moderate exercise.	
18. What to do if experiencing worsening pain, leg swelling or discolouration or dyspnoea.	

APPENDIX 4 PATIENT INFORMATION RIVAROXABAN/APIXABAN



The Anticoagulant Therapy Booklet provides the patient with important information about anticoagulant treatment. The booklet should be used by the prescriber to record contact details and patient specific information upon initiation and whenever renal and hepatic function tests have been undertaken. Patients should keep the book at home for easy reference but take it to show the pharmacist when they collect their prescription.

Order supplies from LRI.print@interservefm.com
Order Code LLR0053
Minimum order 50 booklets
A cost code will be required

Anticoagulant Alert Card

This patient is taking anticoagulant therapy
This card should be carried at all times and shown to healthcare professionals

Name of patient: _____

Address: _____

Postcode: _____ Telephone: _____

Name of next of kin: _____

Hospital number: _____ NHS Number: _____

An Anticoagulant Alert Card should be given to the patient at initiation. The card should be filled in and carried with the patient at all times in the event of an emergency.

Contact marie.harvey@uhl-tr.nhs.uk for supplies
A cost code will be required



UHL Medicine Leaflets describe in simple terms what the medicine is for, how to take it and side effects to look out for. Give one to each patient at initiation.

To print, click [here](#) and search on the A-Z browser for the correct leaflet.
Alternatively A5 colour copies can be ordered from medicines.info@uhl-tr.nhs.uk. See [here](#) for further information.

APPENDIX 5 TAIT AND SEFCICK 1998

Pre Treatment INR <1.3 and not on Amiodarone

Warfarin 5mg days 1-4


Check INR day 5, 8 & 12

INR Day 5	Warfarin Dose From Day 5	INR Day 8	Warfarin Dose From Day 8
<1.7	5mg	<1.7 1.8-2.4 2.5-3.0 >3.0	6mg for 7 days 5mg for 7 days 4mg for 7 days 3mg for 4 days
1.8-2.2	4mg	<1.7 1.8-2.4 2.5-3.0 3.1-3.5 >3.5	5mg for 7 days 4mg for 7 days 3.5mg for 7 days 3mg for 4 days 2.5mg for 4 days
2.3-2.7	3mg	<1.7 1.8-2.4 2.5-3.0 3.1-3.5 >3.5	4mg for 7 days 2.5mg for 7 days 2mg for 7 days 1.5mg for 4 days 1mg for 4 days
2.8-3.2	2.8-3.2	2mg <1.7 1.8-2.4 2.5-3.0 3.1-3.5 >3.5	3mg for 7 days 2.5mg for 7 days 2mg for 7 days 1.5mg for 4 days 1mg for 4 days
3.3-3.7	1mg	<1.7 1.8-2.4 2.5-3.0 3.1-3.5 >3.5	2mg for 7 days 1.5mg for 7 days 1mg for 7 days 0.5mg for 4 days omit for 4 days
>3.7	0mg	<2.0mg 2.0-2.9 3.0-3.5	1.5mg for 4 days 1mg for 4 days 0.5 for 4 days

Tait RO, Sefcick A 1998

A warfarin induction regime for outpatient anticoagulation in patients with atrial fibrillation.

Appendix 6

University Hospitals of Leicester  NHS Trust	Treatment of Deep Vein Thrombosis & Pulmonary Embolism ADMINISTRATION GUIDE Enoxaparin (Inhixa®)
Record patient's weight to prescribe correct dose of Enoxaparin.	
Adjustments for patients with severe renal impairment	
<p>Some of the doses below are off label and differ from the SPC. As this is the recommendation from UHL, prescribers will be protected by UHL vicarious liability</p>	

		Renal Function	
Bodyweight		CrCl ≥30ml/min	CrCl <30ml/min
Up to 100kg		1.5mg/kg OD or 1mg/kg BD ¹	1mg/kg OD ²
>100kg		1mg/kg BD	1mg/kg OD ²

¹Dose of 1.5mg/kg is recommended in uncomplicated patients with low risk of VTE reoccurrence. Dose of 1mg/kg BD is recommended in patients with risk factors such as: obesity, cancer, recurrent VTE, proximal thrombosis, symptomatic pulmonary embolism or any other circumstances that are deemed clinically appropriate.

²Monitor heparin assay after 4th dose and every 4 days thereafter.

CrCl <15 and/or impossible to monitor heparin levels: An alternative anticoagulant would be preferred: consider Tinzaparin in the first instance or seek Haematology advice.

Enoxaparin (Inhixa®) is supplied as prefilled syringes, please see below for Enoxaparin dose-banding guidance. Prescribe by brand name INHIXA® as different brands have different injection techniques.

UHL dosing table for the treatment of Pulmonary Embolism and Deep Vein Thrombosis.
 Agreed between the Pharmacy and Haematology departments. January 2024

Enoxaparin (Inhixa®) Dose-Banding Guidance

Enoxaparin sodium (Inhixa) 1.5mg/kg OD dosing		
Patient Weight (kg)	<u>1.5mg/kg OD</u>	Suggested pre-filled syringe(s) to be used
40 – 46.9	60mg	60mg
47 – 59.9	80mg	80mg
60 – 73.9	100mg	100mg
74 – 89.9	120mg	120mg
90 – 99.9	150mg	150mg

Enoxaparin sodium (Inhixa) 1mg/kg BD dosing for >100kg		
Weight > 100kg	<u>1mg/kg BD</u>	Suggested pre-filled syringe(s) to be used
100 – 109.9	100mg BD	100mg
110 – 134.9	120mg BD	120mg
135 – 150	150mg BD	150mg

Enoxaparin sodium (Inhixa) 1mg/kg OD in CrCl <30ml/min (or BD if using 1mg/kg BD dosing in CrCl >30ml/min)		
Patient Weight (kg)	<u>1mg/kg</u>	Suggested pre-filled syringe(s) to be used
40 – 46.9	40mg	40mg
47 – 54.9	50mg*	50mg* (NOTE: Use 60mg PFS and expel 0.1ml)
55 – 69.9	60mg	60mg
70 – 89.9	80mg	80mg
90 – 109.9	100mg	100mg
110 – 134.9	120mg	120mg
135 – 150	150mg	150mg

When using pre-filled syringes, the air bubble should not be expelled from the syringe before the injection in order to avoid the loss of the medicinal product.

* To administer a 50mg dose, use the 60mg in 0.6ml graduated pre-filled syringes, discard the excess (0.1mls) to administer the correct dose (0.5mls).

APPENDIX 7 Ambulatory record of results for Low molecular Weight Heparin and Warfarin Initiation

Day 1 **Date** **Day**

LMWH dose	Time	Sig	Print
Warfarin	INR	Dose	Sig

Comments

Day 5 **Date** **Day**

LMWH dose	Time	Sig	Print
Warfarin	INR	Dose	Sig

Check platelets: Y/N

Comments

Check platelets: Y/N

Referral made to anticoagulation **Date**.....

Referral made by **Print Name**.....

Signature

APPENDIX 8: SCREENING FOR UNDERLYING MALIGNANCY IN PATIENTS WITH A POSITIVE DIAGNOSIS OF PE

Pretest Probability of Malignancy following Positive PE

Patient Ref No:	CTPA or V/Q scan Date
Name:	Prev Thrombotic History: Yes No
Address:	Active Malignancy: Yes No
Tel No:	

Weight loss > 7lbs in 6 months	Yes	No	Yes = consider imaging with abdominal-pelvic CT scan/USS/endoscopy/colonoscopy
Recent abdominal pain	Yes	No	
Recent dysphagia	Yes	No	
Recent alteration in bowel habit/melena	Yes	No	
Haematuria (perform urinalysis)	Yes	No	
Bilateral DVT	Yes	No	
Unexplained PV bleeding	Yes	No	Yes = gynaecological screen
Smoker or smoked within last 5 years	Yes	No	Yes = Review CTPA for malignancy
Male > 60 years	Yes	No	Yes = PSA
Male < 60 years with urinary problems	Yes	No	Yes = PSA
Female aged 25 to 64: ?attended cervical screening	Yes	No	No = refer to GP
Female aged 50-70: ?attended breast cancer screening within last 3 years	Yes	No	No = GP to refer
Abnormal screening bloods (FBC/Calcium/LFTs)	Yes	No	Yes = Repeat and consider targeted further investigation
Focused clinical examination complete (including breast and/or testicular exam where indicated)	Yes	No	

History taken by:

Date:

APPENDIX 9 DECISION AID FOR ORAL ANTICOAGULANT TREATMENT IN PULMONARY EMBOLISM

	WARFARIN	Direct Oral Anticoagulant (DOAC)
Does this medicine reduce the risk of DVT/PE?	Once diagnosed with a DVT/PE, warfarin reduces your risk of having another one. Without treatment, about 25 out of 100 people will have another DVT/PE. On warfarin, about 3 out of every 100 people will have another DVT/PE.	In clinical trials DOACs are as effective as warfarin at reducing the risk of having another DVT or PE
Risk of bleeding	The most common side effect of all anticoagulants is bleeding which can occur inside or outside of the body. Bleeding into the brain (haemorrhagic stroke), stomach or bowels are the most serious side effects. The risk of serious bleeding is very small occurring in about 1 in 500 people in clinical trials	The risk of bleeding with DOACs is approximately the same or less than warfarin in clinical trials
Can the effects of the medicine be reversed?	An antidote (vitamin K) can be given to reverse the blood thinning effects of warfarin.	The majority of DOACs do not yet have a licenced antidote (exception dabigatran). If you need urgent treatment for bleeding or an emergency operation blood products can be given. The time taken for the blood thinning effect of DOACs to wear off is much quicker than warfarin.
How much is known about his medicine?	Warfarin has been used for a long time in a lot of people and a great deal is known about its benefits and long term side effects.	DOACs have only been licenced to treat DVT/PE since 2016 so less is known about their benefits and side effects. We do not know what the long term side effects are.
Do I need regular blood tests to monitor the dose?	Warfarin is taken once a day. At the beginning of therapy a heparin injection is given into the skin (subcutaneously) for a minimum of 5 days and until your warfarin becomes effective at the right level. You will require regular blood tests to monitor the blood thinning effect of warfarin (INR) both at the start and throughout your treatment. The dose will be adjusted according to results.	DOACs are taken once or twice a day. There is no need to have heparin injections as the onset of these medications in thinning the blood is very quick. They have a predictable effect on the body and no blood tests are needed to monitor the blood thinning effect. However, you will need to have a blood test at the start, and after 6 to 12 months, to monitor your kidneys and liver function if you are still taking the medication.
What are the risks if I forget to take the medication?	If you regularly forget to take warfarin, you could lose the anticoagulant effect putting yourself at increased risk of recurrent DVT/PE	Taking DOACs as they have been prescribed is very important. If you regularly forget to take your medication, you could lose the anticoagulant effect more quickly than if taking warfarin.
Food, alcohol and other medicines	Warfarin is affected by some foods, alcohol and other medications. You may need to alter your diet.	DOACs are not affected by food/alcohol. There are limited interactions with other drugs.

Agreed Anticoagulant choice:

Patient name:

Signature:.....

Health care professional name:.....

Signature:.....

