Drug and Therapeutics Committee

Minutes from meeting on Friday, 10th August, 2018, 1230

Present: Dr Clare Barlow, Consultant Oncologist, MPH – Chair.
Esther Wixey, Clinical and Medicines Information Pharmacist, MPH – Acting Secretary.
Mark Ashley, Principal Pharmacist, MPH.
Dr Mark Dayer, Consultant Cardiologist, MPH.
Shaun Green, Associate Director, Head of Medicines management, Somerset CCG.
Nigel Ankcorn, Lead Pharmacist Medicines Information, MPH

Apologies: Dr Adrian Fulford, Stephen Sampson

Invitees: None

		Action
1	**Apologies and declaration of interests:** Dr Clare Barlow- Sponsorship from BMS to attend ESMO (European Society Medical Oncology meeting Oct 2018) None relevant to this meeting	
2	**Minutes of previous meeting** The minutes for the meeting: 12th May, 2018 were accepted.	EW
3	**Antimicrobial Prescribing Group** No exceptions reported.	
4	**Matters arising**	
4.1	**Magnesium sulphate injection 50%** - Maternity risk assessment pending Post meeting note: Need to liaise with Alyson Govier	JB
4.2	**Homeopathic and Naturopathic remedies in hospital** – Not medicines therefore should not be prescribed. Patients can self-administer if wishes. These remedies should be documented in medical notes as potential for adverse effects/interactions. Post meeting note: Decision made that nurses should not administer. • Addition to Drugs policy?	JB
4.3	**Ecolab chlorhexidine 2% in 70% alcohol** – Trust board outcome? Roll to next meeting for JB to update.	JB
4.4	**Emergency Department extended and advanced practice medicines policy** – Post meeting note: The policy is now ready. Martin Horton (Consultant/lead ACP Emergency medicine) is submitting this to the GSU (Governance support unit).	
4.5	**SOP Guidelines for the management of Opioid Dependent Individuals in the Acute Hospital Setting** – Approved at May meeting. Now on Trust policy portfolio.	
4.6	**Thromboprophylaxis for patients having hip and knee arthroplasty surgery. Ben Squires** – Draft guidelines circulated and accepted. Post meeting note: On database.	
4.7	**Procedures and guidelines for review:** Drug allergy procedure- no changes. Hypnotics/sleeping tablets guideline- no changes Identification and assessment of patient's own drugs- Post meeting note: Presented at the MDC (Medicines governance committee)	

5 5.1	**Applications completed by virtual D&TC process.** Midostaurin for Advanced systemic mastocytosis. Compassionate use. Sarah Allford. Approved 18/06/2018.2nd patient. Deepak Mannari. Approved: 10/07/2018.	
5.2	Co-enzyme Q10 for mitochondrial myopathy. Stefen Brady, Neurology Consultant. Not approved. Post meeting note: Invited to the November meeting for further discussion.	
5.3	Humulin R Kwikpen U500 insulin. Unlicensed. Rhodri King. Approved: 25/7/2018 (subject to risk assessment). Post meeting note: Risk assessment approved. Nursing home is unable to pick up from MPH- Dr Rhodri King to issue FP10	
5.4	Cinacalcet to treat hypercalcaemia metastatic pancreatic neuroendocrine tumour. Emma Cattell. Approved 09/07/2018.	
5.5	Inotuzumab ozogamicin (Besponsa™) to treat B-ALL. Deepak Mannari. IFR supported 13/07/2018. Post meeting note: Outcome?	
5.6	Abiraterone for salivary duct carcinoma. Petra Jankowska. IFR supported. 01/08/2018. Post meeting note: Outcome?	
6	**Biosimilars –** Adalimumab Arovi (enoxaparin sodium)	
7	**Progress of NICE TAs implementation, report from Lincoln Andrews –** Review next meeting and check for sustained progress.	
8	**Nutritional products (Ursula Green), Lead for Nutrition and Dietetics) –** Nothing to report	
9 9.1	**Early Access to Medicines Scheme (EAMS): -** Post meeting note: Early access to medicines scheme (EAMS) scientific opinion: patisiran-LNP to treat adults with hereditary transthyretin-mediated amyloidosis 3/8/18	
10 10.1	**Regional Medicines Optimisation Committees (RMOC)** **Access to pan-regional antidotes and other rarely used medicines-** Organisations should ensure they are aware of existing publications and NHS England advice on access to antidotes in the emergency department (RCEM/NPIS advice, previous advice from the CPhO and National Clinical Director for Urgent Care, a 2012 audit against the RCEM/NPIS advice and the follow-up audit conducted in 2014. Organisations should be aware that future national audit of compliance against the RCEM/NPIS advice is planned during the autumn of 2018, and that the RMOC will receive the results of this work. In preparation for the above audit, provider organisations should review their stock holdings against the existing RCEM/NPIS advice. With reference to pan-regional antidotes. Can access to these medicines within the required 4-hour time frame be assured? Rarely used medicines database available to on call pharmacists. Checking position? (Review stock holdings against the existing RCEM/NPIS advice). Liaise with A&E	
10.2	**Free of charge (FOC) medicines schemes-**	

	Defined as a licensed or unlicensed medicine provided free of charge by the pharmaceutical company to an individual or cohort of patients. Commissioners and providers must only undertake a free of charge scheme if the principles outlined in this policy are followed. Trusts or commissioners should not sign up to free of charge scheme which is solely offering a licensed medicine free of charge in advance of NICE approval. The committee reviewed the RMOC guidance. It was considered that the existing well-established processes for approval of FOC medicines schemes at the Trust is robust and decisions made are evidence based. Unlikely we will need to make any significant changes to current practice.	
10.3	**Insulin preparations-** Trusts and commissioners should ensure that the principles in guidance and check list are completed for each insulin product to accompany any clinical evaluation and supporting documentation as part of the decision-making process. Highlights errors due to insulin withdrawal from unfamiliar device into standard insulin syringe. This presented a risk of overdose if the strength is not considered when determining volume required. Is the right training & equipment available? Ambulance staff encouraged to bring in needles with pen devices when admitting patients on insulin. Prescriptions should include the brand name, strength and device. Preferable for patients to self-administer their insulin if possible. Are arrangements in place for timely supply of refillable pen device, needles etc.	
11 11.1	**Human Normal Immunoglobulin** No shortage at present. Compliant with framework.	
11.2	Post meeting note: Letter from commissioners re. Normal Human Immunoglobulin availability & supply; NHS England is making arrangements to establish a sub-regional Immunoglobulin Assessment Panel (IAP) hosted by North Bristol NHS Trust to which requests for immunoglobulin should be submitted. Until the NBT hosted IAP is established please ensure	
	1. No new patients are to start on Cuvitru subcutaneous immunoglobulin due to full volume being allocated to current patients. 2. Patients receiving Subcuvia not to switch to alternative product, Shire have made supplies available until the end of 2019. 3. Ensure that current immunoglobulin assessment panel arrangements are in place and continue to manage local demand for immunoglobulin until sub-regional IAPs operating and pay close attention to the following: • Use of immunoglobulin should be prioritised for the treatment of red and blue indications • Use in those grey indications which are presumed to be immune-mediated disorders with little or no evidence of efficacy (right hand side of grey indications table) is not routinely commissioned • Consider plasma exchange wherever clinically appropriate as a viable alternative to immunoglobulin in other grey indications until further notice • Appropriateness, dose and frequency of immunoglobulin in all existing and new patients must be reviewed • Ensure compliance with dosing recommendations in immune thrombocytopenic purpura (1g/kg) • In patients with chronic inflammatory demyelinating polyneuropathy (CIDP) consider a trial of steroids before commencing immunoglobulin	

	• Consider an adequate trial of antibiotic prophylaxis before commencing immunoglobulin replacement in secondary antibody deficiency Letter sent to all registered database users. **DH Immunoglobulin (HNIg) database** – The SSQD Immunoglobulin Management dashboard publication period Q4 2017-18 at the meeting was circulated & reported. **IAP membership** – Previous plan to contact Lisa Lowry (consultant haematologist) and Simon Shields (Consultant Neurologist) inviting them to join IAP is currently on hold until details of the new sub-regional IAP are clarified, as local processes may then be subject to change.	CB
12 12.1	**NICE Technology Appraisals**	

NICE TA	Name	Recommendation
520	Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy	Recommended Accepted
521	Guselkumab for treating moderate to severe plaque psoriasis	Recommended Accepted
522	Pembrolizumab for untreated locally advanced or metastatic urothelial cancer when cisplatin is unsuitable	Recommended Accepted
523	Midostaurin for untreated acute myeloid leukaemia	Recommended Accepted
524	Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma	Recommended Accepted
525	Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy	Recommended Accepted
526	Arsenic trioxide for treating acute promyelocytic leukaemia	Recommended Accepted
527	Beta interferons and glatiramer acetate for treating multiple sclerosis	Recommended (brand restriction) Accepted
528	Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer	Recommended Accepted
529	Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer	Recommended Accepted
530	Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy	Not recommended
531	Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer	Recommended Accepted
532	Cenegermin for treating neurotrophic keratitis	Not recommended
533	Ocrelizumab for treating relapsing–remitting multiple sclerosis	Recommended Accepted
534	Dupilumab for treating moderate to severe atopic dermatitis	Recommended Accepted
535	Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine	Recommended Accepted
536	Alectinib for untreated ALK-positive advanced non-small-cell lung cancer	Recommended Accepted
537	Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs	Recommended Accepted

13 13.1 13.2	**New Drug Requests** Ceftazidime / avibactam (Zavicefta™). Robert Baker. Approved. Ceftolozane / tazobactam (Zerbaxa™). Robert Baker. Approved.	

13.3	Mexiletine for inherited (Primary) Paediatric Erythromelagia. Louise Newbury / Alison Kelly (Bristol). Approved for named patient. Post meeting note: Prescriber informed that all strengths now unlicensed. Funding agreed by directorate. Patient now receiving via outpatient with regular ECG monitoring.	
13.4	Methoxyflurane inhalation vapour (Penthrox™) for emergency pain relief in trauma patients. Post meeting note: Paul Bain (A&E consultant) Invited to next meeting with costings.	
15	**Drug safety updates (DSU)** **MPSA reports monthly circulation to CSLs: 5/2018, 6/2018, 7/2018.** via Jenny Lloyd.	
16	**Formulary review** Calcium and Vit D non-formulary for patients not receiving a bisphosphonate or Denosumab (SG) Post meeting note: No evidence alone as bone protection & not for dietary insufficiency. Guidance needs reviewing. Contact Dr Solanki SG raised Rifaxamin and Degarelix as items on SPF agenda for proposed change in traffic light status	CB
17	**Shared Care Protocols** Nothing to report	

18	**AOB**
	Thank you to NA for 21 years as secretary to the DTC.
	
	Following recent outbreak of measles in geographical proximity SG raised issues around post-exposure prophylaxis
	• Link to Gov.uk guidance on Pharmacy intranet
	  ○ Infants under 6 months of age who have had close contact with a likely or confirmed measles case should be offered Human normal immunoglobulin (HNIG) issued from PHE stockholders on request.
	  ○ Subcutaneous infusions are not considered practical for immunosuppressed individuals and so intravenous immunoglobulin (IVIG) is the recommended product to be used for post-exposure treatment. IVIG is not sourced from PHE but should be available through NHS hospital pharmacies. This would constitute a grey indication in the current National Demand Management plan.
	• Isolation/tracing protocol available via policies on Trust intranet (Measles - Infection Control Information and Guidelines)
	• Waiting for confirmation from PHE as to when and how to request stock. Currently have 6 vials in stock
	
	SG asked CB to discuss Trust position on adjuvant bisphosphonates in the treatment of breast cancer, now that NICE guidance is available.
	Post-meeting note: CB has discussed with Dr Saiqa Spensley, who has confirmed breast oncology team now plan to proceed with adjuvant bisphosphonate therapy.	

19	**Next meeting:** 23rd November 2018 Proposed dates in 2019: 8th February, 10th May, 26th July and 22nd November.	

Drug and Therapeutics Committee

Minutes from meeting on Friday, 23rd November 2018 1230

Present: Dr Clare Barlow, Consultant Oncologist MPH – Chair.
Esther Wixey, Clinical and Medicines Information Pharmacist, MPH – Secretary.
Mark Ashley, Principal Pharmacist, MPH.
Jon Beard, Chief Pharmacist, MPH.
Dr Mark Dayer, Consultant Cardiologist, MPH.
Shaun Green, Associate Director, Head of Medicines Management, Somerset CCG.
Steve DuBois, Chief Pharmacist, SOMPAR.

Apologies: Dr Stephen Haydock, Consultant General Medicine, MPH, Dr Adrian Fulford, General Practitioner, St James Medical Centre.

Invitees: Lincoln Andrews, Compliance Audit Manager, Richard Welbourn, Consultant UGI and Bariatrics and Helen Kohler, Lead Bariatric Nurse Specialist.

		Action
1	**Apologies and declaration of interests:** None relevant to this meeting. Conflicts of interest audit and training link circulated. Aim to complete module 1 prior to meeting in February.	ALL
2	**Minutes of previous meeting** The minutes for the meeting: 10th August 2018 Accepted.	
3	**Antimicrobial Prescribing Group** No exceptions to report. Circulate minutes when available.	EW
4 4.1	**Matters arising** Magnesium sulphate injection 50% - Maternity risk assessment. Need to liaise with Alyson Govier.	CB
4.2	Ecolab chlorhexidine 2% in 70% alcohol. DTC recommended that this is not a licenced medicinal product and therefore should not be used. Trust management have made the decision to maintain current practice.	
4.3	Cannabis-based products for medicinal use. Minimal evidence available. Expectation of low demand after trying all other licenced/off label options. Products are unlicensed therefore would be obtained as 'specials' via the unlicensed drugs policy procedures following application through the DTC on a named patient basis. Post meeting note: NHSE have confirmed that a 'Specialist' is technically any doctor listed on a GMC specialist register. However, being a specialist does not automatically make someone a cannabis specialist. They expect the number of patients using these drugs to be 'in the tens not the hundreds'.	
4.4	Probiotic VSL#3 for ulcerative colitis and Crohn's disease no longer available as reimbursed prescription product therefore request for non-formulary. Agreed. VSL replaced by another product. Would need NDR. Post meeting note: VSL has been replaced in the drug tariff by VivoMixx. CCG is happy if GI wish to use this for pouchitis. Email sent to GI clinical lead Dr Daniel Pearl.	
4.5	Homeopathic and Naturopathic remedies in hospital. Addition to Drugs policy?	JB/EW

5	**Applications completed by virtual D&TC process.**	
5.1	IFR for Airsonette Laminar Flow Device for a patient with difficult to control allergic asthma, on maximal conventional treatment and currently being maintained on daily steroids. Requested by Dr Nerys Beynon Consultant Paediatrician. DTC supported application 24/8/18 Outcome of IFR request. Refused, parents looking into self-funding.	
5.2	Co-enzyme Q10 for mitochondrial myopathy. Dr Stefen Brady, Neurology Consultant. Not approved. For further discussion. Can be prescribed regionally therefore no longer required.	
5.3	Durvalumab for a patient as adjuvant treatment following radical sequential or concurrent chemoradiotherapy for non-small cell cancer with >/=1% PDL1 expression. Requested by Dr Julie Wather Consultant Clinical Oncologist. DTC supported application 8/11/18	
5.4	Tedizolid for a patient who is currently on a course of linezolid for 4 weeks to treat Enterococcus faecalis in bone culture. Linezolid is not licensed for longer than 4 weeks due to adverse effects and there have been recent cases of linezolid related myelosuppression and optic neuropathy within the trust. Requested by Dr Susan Hardman Consultant Microbiologist. Approved 8/11/18	
5.5	Quizartinib for a patient with AML with FLT-3 ITD treated on AML 18. Requested by Dr Deepak Mannari. Consultant haematologist. Company have confirmed that drug will be free of charge; Patients may continue Quizartinib until there is a lack of clinical benefit or the occurrence of unacceptable toxicity. In addition, patient enrollment may continue 18 months post regulatory approval depending on the country regulation or until the marketed medication is available. Approved 21/11/18	
5.6	Somatorelin for a patient who needs this GHRH/arginine test for suspected growth hormone deficiency in which an insulin tolerance test is contraindicated. Requested by Dr Julia Thomas Consultant Endocrinologist. Approved 14/11/18	
5.7	Denosumab to treat symptomatic hypercalcaemia in a patient with relapsed clear cell ovarian cancer. No longer responding to bisphosphonates. Requested by Dr Clare Barlow. Approved 14/11/18	
6	**Progress of NICE TAs implementation, report from Lincoln Andrews** A few recent TAs have gone out and are awaiting response from clinical teams. A number of TAs (mostly from across acute medicine) have now been awaiting response for a significant period of time. LA is chasing these and will raise at the forthcoming CD meeting. Just one TA non-compliant. Staffing within the governance unit is improving, so further progress is expected before the next DTC meeting. CCG keen to monitor progress and understand any delays in the process.	
7	**Biosimilars**	
7.1	Clexane; Clarify brand on discharge	
7.2	Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis for adults off licence.	
8	**Nutritional products (Ursula Green), Lead for Nutrition and Dietetics)** Nothing to report.	
9	**Early Access to Medicines Scheme (EAMS): -** Nothing to report.	

10	**Regional Medicines Optimisation Committees**	
10.1	Guidance - Prescribing of Liothyronine. No change. Hospital only.	
10.2	Homely Remedies. No change. Many care homes have own policies.	
10.3	Best Value Biologicals: Adalimumab. Switched to Biogen.	
11	**Human Normal Immunoglobulin (Sub regional IVIG panel)**	
11.1	Red & some blue indications (TBC) will be retrospectively approved. Some new Blue (TBC), all new grey and black indications will require application to sub regional panel in advance. Only approved requests will be funded.	
11.2	Requesting clinician representation from MPH (to cover Yeovil). This will involve a monthly meeting in Bristol. Contact Medical Director for Haematology or Neurology clinician representation.	CB
11.3	Haematologists confirmed only prescribing 1g/kg for ITP and no 2g/kg cases found on database. Post meeting note. The Sub Regional IVIG panel have been informed. Need to contact all IVIG prescribers to inform them that any requests for prospective review need to be forwarded to sub-regional panel for approval prior to prescribing.	EW
12	**NICE Technology Appraisals**	

NICE TA	Name	Recommendation
538	Dinutuximab beta for treating neuroblastoma	Recommended
539	Lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours	Recommended
540	Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma	Recommended (restrictions apply)
541	Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia	Recommended
542	Cabozantinib for untreated advanced renal cell carcinoma	Recommended
543	Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs	Recommended (restrictions apply)
544	Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma	Recommended

13	**New Drug Requests**	
13.1	Methoxyflurane inhalation vapour (Penthrox™) for emergency pain relief in trauma patients. Requested by Dr Paul Bain (A&E Consultant). Ask Medical director for funding? Refer to next meeting.	
13.2	Adjuvant bisphosphonates in the treatment of breast cancer as per NICE guidance. Requested by Dr Saiqa Spensley; agreed to give adjuvant bisphosphonates. The recommendations are for 2-3 years. Yeovil are giving 3 years and we need to decide whether we give 2 or 3 years. Same policy across the county? Looking at where best to give the treatment as there are capacity issues at present on BDU.	
13.3	Cacicol preservative-free ophthalmic solution containing polycarboxymethylglucose sulfate which mimics the function of the extraCellular matrix. It is intended for the management of	CB

	chronic corneal wound healing, such as persistent epithelial defects, neurotrophic keratitis/ulcers and persistent anterior corneal dystrophies with ulceration and associated pain. Dr Indy Sian Consultant Ophthalmologist. Not approved 23/11/18. No evidence to support use. For review when RCTs complete.	
13.4	Tedizolid for bone and joint or diabetic foot infection caused by multi-resistant bacteria, as follow on after 4 weeks of linezolid, or instead of linezolid if linezolid – induced side effects occur. Requested by Dr Susan Hardman Consultant Microbiologist. Not approved 23/11/18. Cost ~£1000/week. Named patient basis only.	CB
13.5	Lidocaine patch for severe rib fracture patients. Requested by Dr James Sidney ICU Consultant. Refer to next meeting.	
13.6	Somatorelin for GHRH/arginine test for suspected growth hormone deficiency in which an insulin tolerance test is contraindicated. Requested by Dr Julia Thomas (Consultant Endocrinologist). Approved 23/11/18.	CB
13.7	Emend for use pre and post gastric balloon placement requested by Richard Welbourn Consultant UGI and Bariatrics. Change to Akynzeo which is a different 5-HT/NK1 receptor antagonist, this will be off licence but more cost effective. Need to complete new drug request form and feedback after 1 year. Approved 23/11/18.	CB
15	**MHRA Drug Safety Updates** Circulation to CSLs: 8/2018, 09/2018, 10/2018 via Jenny Lloyd. Need to forward future CSLs correspondence to Lisa Brocklehurst.	
16	**Other Formulary issues**	
16.1	Oxeltra is now the preferred long acting Oxycodone Brand in Somerset. This has been circulated to CSLs and memos will be sent to wards with orders.	
16.2	Testavan. Another testosterone gel. Discussed and approved for addition to formulary at SPF 21st Nov. Approx. equivalent price and shortage of some products, so agreed to add to formulary as another option.	
16.3	Request to supply Prazocin high cost (~£3000) for Bristol paediatric patient, GP unable to obtain. Decision made to leave with Bristol to supply or they would need to complete an IFR application if patient were to be supplied from T&S.	
17	**Shared Care Protocols** Nothing to report	
18	**Any other Business**	
18.1	EMA (European Medicines Agency) review Quinolones- can cause long-lasting, disabling and potentially permanent side effects involving tendons, muscles, joints and the nervous system. A/W response re. managing risks/benefits from APG	
18.2	Rifaxamin pathway (amended version) has been circulated to Gastroenterologists for comment.	
18.3	Rectal irrigation systems pathway. Duration of treatment and initial hospital supply being clarified.	
18.4	Patient safety alert; Management of life threatening bleeds from AV fistulae and grafts	
19	**Next meeting:** 8th February 2019 Proposed dates in 2019: 10th May, 26th July and 22nd November.	

Taunton and Somerset NHS NHS Foundation Trust	Protocol
Title: Assessment and investigation of Deep Venous Thrombosis (DVT)	
Author(s): Dr Andrew Thompson, Dr Simon Davies	
Document Lead: Dr Thompson	
Accepted by: VTE Group	**Active date:** 21 March 2016
Accepted date: 21.03.16 (minor amendment 30.04.18)	**Review date:** 21 March 2019
Applies to: Adult patients with suspected Deep Venous Thromboses	**Exclusions:** Paediatrics
Purpose: To improve patients diagnosis and management of Deep Venous Thromboses	
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Key Points:

1. Introduction

- **Deep vein thrombosis** (DVT) is a common disease, often asymptomatic, but presenting with clinical symptoms in about 1 per 1,000 people per year in the general population. The deep veins of the lower limbs are affected most commonly, with leg pain and/or swelling occurring following occlusion of a major leg vein, but thrombosis may affect other sites, including the upper limbs, intracranial and splanchnic veins. It requires specific investigation and treatment.

- Complications include **pulmonary thromboembolism** (PE) and **post-thrombotic syndrome** (PTS). See separate guidelines for the diagnosis and management of pulmonary embolisms. (insert link)

- **Post-thrombotic leg syndrome** (chronic leg pain, swelling, dermatitis, ulcers) is a consequence of damage to leg vein valves by DVT. Approximately 30% of patients/people develop some symptoms of PTS

after lower limb DVT. Leg ulcers are observed in 2-10% of patients approximately 10 years after their first symptomatic DVT.[1-5]

- **Venous thromboembolism** (VTE) is defined as DVT with or without PE. It has a high mortality when untreated but treatment also carries risks, principally haemorrhage. Therefore, accurate confirmation of diagnosis is essential in all cases, usually by imaging. In addition, the duration of treatment with antithrombotics requires individual and careful consideration of the balance of benefits (reduced risk of recurrent thrombosis) and risks (principally haemorrhage).

2. Initial Assessment

- Acute venous thromboembolism should be suspected in patients with a combination of suggestive symptoms and/or signs. Most patients with confirmed PE do not have clinically evident DVT and around 30% of patients with symptomatic DVT have asymptomatic PE.

- Suggestive symptoms and signs:

  DVT: unilateral leg pain, swelling, tenderness, increased temperature, pitting oedema, prominent superficial veins

  PE: breathlessness, chest pain, haemoptysis, collapse, tachycardia, hypotension, tachypnoea, raised jugular venous pressure, focal signs in chest, hypoxia/cyanosis.

- Neither history or examination or blood tests are sufficiently accurate to diagnose DVT's in isolation, and a validated clinical decision rule (the Wells score – see DVT pathway and Appendix below) should be used in the initial assessment of outpatients presenting with suspected deep vein thrombosis – which will stratify patients into likely or unlikely to have a DVT. **Nb** The Wells score is not validated for use in hospitalised

patients, pregnant women or DVT in sites other than the lower limb. These patients should be assumed to be at high risk.

- Patients unlikely to have a DVT should have a D-Dimer measured, and if negative it is extremely unlikely a DVT is present. (In individuals in whom DVT was excluded by a combination of a low Wells score and a negative D-Dimer the rate of symptomatic and fatal PE was found to be 1 in 2,222 and 1 in 10,000 respectively[6])

- Many studies have suggested that the D-dimer normal reference range can be adjusted for age – whereby the upper limit of normal for patients above 50 in whom a DVT is unlikely on the Wells score is age/100 ugFEU/ml (ie for 82 years, upper range of normal is 0.82 ugFEU/ml)[7]

- Patients likely to have a DVT should have imaging to confirm or exclude a diagnosis of VTE.

- Patients with suspected DVT should be treated with therapeutic doses of Low Molecular Weight Heparin (LMWH) until the diagnosis has been deemed very unlikely or oral anticoagulant therapy has been established.

3. Confirmation of DVT

- The preferred initial imaging test for patients with suspected DVT is duplex ultrasound because of its non-invasive nature and high sensitivity (94-99%) and specificity (89-96%) for symptomatic lower limb proximal DVT when compared to the historical gold standard of contrast venography.[6,8] Sensitivity and specificity are considerably lower for asymptomatic above-knee DVT[8] and for below-knee (calf) DVT.[7,9]

- For upper extremity DVT duplex ultrasound is also preferred. [11] However false-negative studies do occur and if clinical suspicion remains high, contrast venography may be required to confirm a diagnosis of upper extremity DVT. [12]

- US is the recommended imaging test for diagnosing DVT in pregnant patients due to the absence of radiation exposure. [13,14]

- If the imaging is positive for a DVT the patient needs to be anti-coagulated. (See below)

- A negative test using a high sensitivity D-dimer assay combined with an initial negative US is associated with a less than 1% risk of missed DVT obviating the need for repeat scanning. The value of the test falls off, however, in patients with prolonged symptoms or who have had heparin for more than 24 hours. [15]

- There is evidence, however, to support the contention that distal DVT may propagate and subsequently become clinically relevant. [16] Therefore patients who have a negative or inadequate initial scan but who have a persisting clinical suspicion of deep vein thrombosis or whose symptoms do not settle should have a repeat ultrasound scan at around 7 days. This should include patients who were 'likely' in the Modified Wells score to have a DVT and had a negative scan, but a positive D-Dimer. Treatment with LMWH is not necessary during this 7 day interval, as they have a very low risk of complications.

- Patients with complete unilateral leg swelling may have a negative US for an above knee DVT if the level of the obstruction is above the limb – ie within the pelvis, and this diagnosis needs to be considered in such patients.

4. For confirmed DVT

- Patients with confirmed proximal DVT should receive anticoagulation for at least 3 months. Longer or shorter durations of anticoagulation may be considered depending on the site of the clot, cause of the DVT and on-going risk factors. For patients with cancer 6 months treatment is recommended, and then the oncologists should be asked to advise whether it can be discontinued.

- Anti-coagulation can be by injection or oral medication. The options include LMWH, warfarin or a directly acting oral anticoagulant (DOAC). If warfarin is chosen then LMWH should be continued until warfarin is established with an INR ≥2.0 for 24 hours. Both LMWH and directly acting oral anti-coagulants (of which there are 2 classes the factor IIa inhibitors (eg dabigatran) or factor Xa inhibitors (eg. Apixaban, edoxaban or rivaroxaban)) start immediately and their timing needs to linked to any anti-coagulation use prior to the DVT being confirmed. The choice of anti-coagulant needs to take into consideration renal or liver failure, the need for anti-coagulation needs to take into consideration platelet and clotting function (eg. If platelets <50 it may still be appropriate to consider anti-coagulation with supporting platelets – this needs careful discussion.)

- Use of LMWH instead of warfarin should be considered in cases of cancer associated DVT's, as there is some evidence that Dalteparin was superior to reducing recurrent VTE[17]. If LWMH is not being used, advice from pharmacy is recommended as there may be drug interactions with anti-cancer agents.

- The SPC for Clexane has recently changed to recommending a twice daily regime of 100 IU/kg (1mg/kg) for symptomatic PE, recurrent VTE or VTE in patients with cancer, obesity, and/ or proximal (vena iliac) thrombosis. The trust has considered this recommendation, alongside the previous experience of using the 1.5mg/kg od dose for

the last 17 years with few complications (both dose regimes have been approved for the treatment of VTE) and decided that for patient comfort a once a day dose regime should continue to be available for our patients.

- Warfarin should be prescribed for the community as per AF ie. 'low and slow' 2mg daily so daily blood tests are not required. (See Warfarin Administration Record), the GP practice informed that warfarin has been commenced, and a plan established as to who is going to administer the LMWH.

- The decision of which DOAC to use remains a clinical decision. Consideration of renal function needs to take place, and the difficulty in reversibility in cases of emergency bleeding (currently only Dabigatran has a licensed reversal agent, although Factor Xa antidotes are in production).

- If anti-coagulation is contra-indicated an IVC filter should be considered and discussed with haematology and radiology.

- All patients presenting with venous thromboembolism should have a full clinical history and examination, a CXR, blood tests (full blood count, calcium and liver function tests) and urinalysis undertaken with the aim of detecting underlying conditions contributing to the development of thrombosis (eg cancer) and assessing suitability for antithrombotic therapy. Patients with unprovoked venous thromboembolisms have a 1 in 10 chance of having an underlying cancer, given the high incidence of cancer in this population the initial screen will detect about half of the cancers.

- Unselective screening for cancer in patients with deep vein thrombosis or pulmonary embolism is not indicated. (SIGN guidance). For patients aged over 40 years, with a first unprovoked VTE, further investigations can be considered if suspicion remains after history, examination and

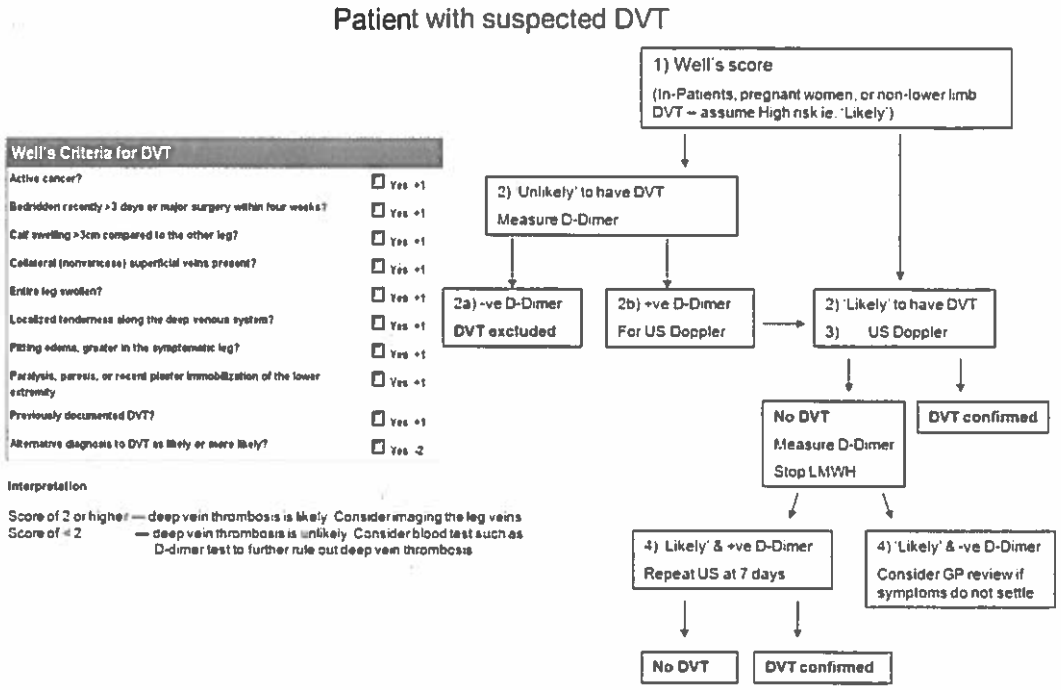
initial tests. Only abdo-pelvis CT, a sputum sample for cytology and mammography are cost effective methods for screening for occult cancer. (NICE guidance)

- Testing for inherited forms of thrombophilia (antithrombin, protein C, protein S deficiency and factor V Leiden and prothrombin G20210A) does not influence initial management of venous thromboembolism and should not be performed routinely. Antiphospholipid antibodies increase the risk of VTE recurrence. Testing for this thrombophilic state should be considered in patients with an unprovoked VTE and in whom no other risk factors have been identified if they are going to end warfarin treatment and would otherwise consider extending anticoagulation. (NICE guidance). GP's should be asked to send blood for antiphospholipid antibodies three weeks after completion of warfarin treatment,

- Patients who have had an unprovoked DVT and have a first degree relative with an unprovoked VTE, who plan to stop anticoagulation but would otherwise continue anticoagulation if an inherited form of thrombophilia was diagnosed should be tested for antithrombin protein C,and protein S deficiency in addition to antiphospholipid antibodies.

- The British Committee for Standards in Haematology guideline advises that DVT patients unlikely to be suitable for outpatient treatment include those with coexistent serious medical pathology, severe acute venous obstruction (phlegmasia cerulea dolens), severe pain, renal impairment, significant communication or mobility problems, poor social circumstances, known heparin allergy and those with active bleeding or at high risk of bleeding. [18]

5. DVT Pathway



6. Audit and Compliance

- Compliance with and recording of risk assessment in all patients admitted to or presenting acutely at hospital with DVT's will be audited.

- The rate of healthcare-associated VTE will be recorded and monitored routinely by the Trust Thrombosis Committee

7. Review

- This guideline will be reviewed in Mar 2019

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http://www.sign.ac.uk/guidelines/fulltext/122/index.html

http://guidance.nice.org.uk/CG/Wave21/5/Consultation/Latest

9. Appendix

Well's Criteria for DVT	
Active cancer?	☐ Yes +1
Bedridden recently >3 days or major surgery within four weeks?	☐ Yes +1
Calf swelling >3cm compared to the other leg?	☐ Yes +1
Collateral (nonvaricose) superficial veins present?	☐ Yes +1
Entire leg swollen?	☐ Yes +1
Localized tenderness along the deep venous system?	☐ Yes +1
Pitting edema, greater in the symptomatic leg?	☐ Yes +1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	☐ Yes +1
Previously documented DVT?	☐ Yes +1
Alternative diagnosis to DVT as likely or more likely?	☐ Yes -2

Interpretation:
Score of 2 or higher — deep vein thrombosis is likely. Consider imaging the leg veins.
Score of < 2 — deep vein thrombosis is unlikely. Consider blood test such as D-dimer test to further rule out deep vein thrombosis

Taunton and Somerset NHS NHS Foundation Trust	Protocol - Respiratory Medicine

Title: Assessment, investigation and treatment of pulmonary embolism

Keywords – venous thromboembolism, CTPA, anticoagulation

Authors: Dr Dinesh Shrikrishna, Dr Justin Pepperell and Dr Andrew Thompson

Document Lead – Dr Dinesh Shrikrishna, Consultant Physician General and Respiratory Medicine

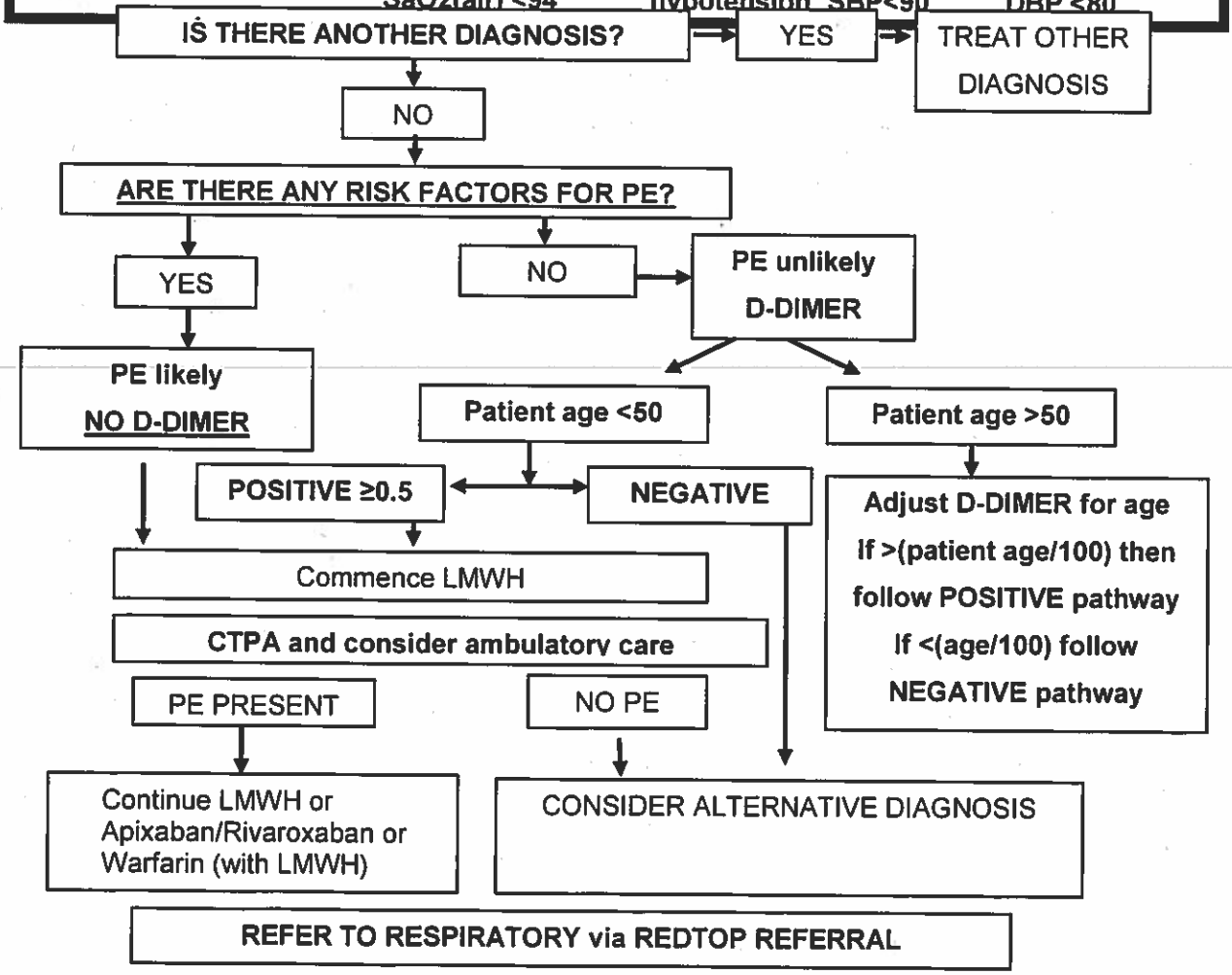
Accepted by: Acute Physicians	**Active date:** 18 December 2017
Accepted date: 18 December 2017	**Review date:** 18 December 2020
Applies to: All medical patients	**Exclusions:** Nil

Purpose: To standardise the care of patients with suspected Pulmonary Embolus

IF YOU SUSPECT A MASSIVE PE AND ARE CONSIDERING THROMBOLYSIS

Please request an emergency CTPA and discuss with your Consultant, a senior Respiratory physician or Cardiologist

Patients with heart rate >100, SaO2(air) <94, ECG changes hypotension, raised JVP, SBP<90, SOB at rest, DBP <80



1 Assessment and investigation

1.1 For all patients:

- History (document risk factors and red flag symptoms for malignancy)
- Full general examination and observations
- CXR (to exclude other conditions)
- ECG
- ABG (on air)
- Pregnant patients, see below and refer to trust guidance on 'Acute management of venous thromboembolic disease in pregnancy and the puerperium'
- Patients with a heart rate of >100, raised JVP, SOB at rest, SaO2(air) <94 or hypotension may have haemodynamically significant/major embolism and may benefit from thrombolysis.. Please request a troponin and immediate senior opinion ideally from a Consultant Respiratory or Cardiology Physician.

1.2 Assessment of clinical probability

Clinical probability should be assessed as likely or unlikely and documented both in the notes and on the request card. Note that CTPA requests without clinical probability / D-Dimer may be refused.

Wells score for likelihood of PE

Clinical signs of DVT	3
An alternative diagnosis is less likely than PE	3
Heart rate >100 bpm	1.5
Immobilisation for > 3 days or surgery <30 days	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy	1

≤ 4 PE unlikely	>4 PE likely

1.3 D-Dimer Test

For patients with a Well's score which suggests a PE is unlikely, a D-Dimer should be measured. A negative d-dimer test (<0.5 mcgs feu/ml) or in those over the age of 50 negative age-adjusted D-dimer <(age/100) mcgs feu/ml excludes a PE (ie for 82 years, upper range of normal is 0.82 ugFEU/ml) and no further imaging is required.

The specificity of a D-Dimer for venous thromboembolic disease is low and can be raised due to a variety of conditions such as malignancy, pregnancy, sepsis and inflammation. Therefore its use is only indicated in patients where thromboembolic disease is suspected and the Well's score is ≤ 4.

1.4 Risk factors for pulmonary embolus

Major risk factors (relative risk 5–20):

1. Surgery
    a. Major abdominal/pelvic surgery
    b. Hip/knee replacement/ fractures
    c. Postoperative intensive care
2. Obstetrics
    a. Late pregnancy
    b. Caesarean section
    c. Puerperium up to 6 weeks
3. Lower limb problems
    a. Varicose veins
4. Malignancy
    a. Abdominal
    b. Pelvic
    c. Metastatic
5. Reduced mobility
    a. Hospitalisation
    b. Institutional
6. Miscellaneous
    a. Previous proven VTE
    b. Congenital heart disease

Minor risk factors (relative risk 2–4):

1. Cardiovascular
    a. Congestive cardiac failure
    b. Hypertension
    c. Superficial venous thrombosis
    d. Indwelling central vein catheter
2. Oestrogens
    a. Oral contraceptive
    b. Hormone replacement therapy
3. Miscellaneous
    a. COPD
    b. Neurological disability
    c. Thrombotic disorders
    d. Long distance sedentary travel
    e. Obesity
    f. Inflammatory bowel disease
    g. Nephrotic syndrome, renal replacement therapy, paroxysmal nocturnal haemoglobinuria
    h. Myeloproliferative disorders

1.5 CTPA

The CTPA is now the investigation of choice for the majority of suspected PE.
A negative CTPA excludes the need for anticoagulation.
Requests for CTPA must include the clinical probability assessed as likely or unlikely based on Well's score, and a D-Dimer if the Well's score is ≤ 4. If this information is not available requests may be declined.

1.6 Investigation in Pregnant Patients

Please refer to the Royal College of Obstetricians and Gynaecologists guidance (April 2015) on this

https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37b.pdf

N.B Musgrove Park Hospital no longer have the facility to perform V/Q scanning but are able to perform a CTPA in these patients.

1.7 Investigation as an Out patient

If unable to get same day imaging (note CTPA service available now until 20.30) or a diagnosis of pulmonary embolism has been confirmed, assess suitability for outpatient management.

Outpatient requirements:

1. No exclusion criteria present.

2. Able to return the next day for imaging (if undiagnosed) and given LMWH injection

3. Able to take oral RIVAROXABAN or APIXABAN or able to self-administer LMWH (or alternative arrangement made) if diagnosis confirmed

Exclusion criteria:

1. Respiratory compromise
    a. SOB at rest
    b. pO2 <10kPa
    c. Sats <94%
2. Cardiovascular instability
    a. P>90bpm
    b. SBP<120mmHg
3. ECG changes esp. RV strain
    a. S1Q3T3
    b. New RBBB
    c. Deep S waves in I/AVL with Q waves III
    d. T wave Inversion V1-V4/III/AVF
4. Elevated Troponin
5. Poor pain control especially if requiring iv medication
6. Altered mental state
7. Concomitant illnesses requiring admission, poor social setup
8. Abnormal liver function

If the patient does not meet outpatient requirements, or has an exclusion criteria than refer to AMU for admission. Otherwise complete next steps.

1) If the scan cannot be done before 20.30 the same day then please book the scan through Ordercomms.
Ask the patient to return to AEC before 09:00 and let the patient know they will need to wait for an emergency slot. Ring the CT radiographer in the morning when the patient arrives so that Radiology are aware that they are available to be scanned. The patient will then be reviewed with the result.

2) If PE confirmed follow the Treatment of PE section, if awaiting scan to confirm PE give the patient a dose of Enoxaparin.

3) Fax discharge letter to GP with diagnosis, or presumed diagnosis, correct dose of anti-coagulant and who will be administering it (unless you are planning patient to attend AMU for injections) and duration of anti-coagulation.

4) All patients diagnosed with a PE need to be considered for follow-up at 3 – 6 months for risk assessment and to exclude persisting pulmonary hypertension. This can be done by respiratoryredtop@tst.nhs.uk. An outpatient echo at 3/12 should be considered if a patient has evidence of right sided strain on the initial CTPA / echo or clinical signs.

1.8 Audit and monitoring of assessment and CTPA requests

This process of patient assessment and CTPA requests should be subject to regular audit as part of the Respiratory Department audit programme.

2.0 Treatment of Pulmonary Embolism

2.1 For all patients –

- Initiate LMWH (Enoxaparin) within 1 hour of suspecting PE
- O_2 (high flow to SaO_2 95)
- Analgesia;

2.2 For patients with PE-

- Patients with confirmed PE should commence Apixaban or Rivaroxaban, or should continue LMWH (Enoxaparin) until warfarin is established with an INR ≥2.0 for 24 hours.
- The SPC for Enoxaparin has recently changed to recommending a twice daily regime of 100 IU/kg (1mg/kg) for symptomatic PE, recurrent VTE or VTE in patients with cancer, obesity, and/ or proximal (vena iliac) thrombosis. The trust has considered this recommendation, alongside the previous experience of using the 1.5mg/kg od dose for the last 17 years with few complications (both dose regimes

have been approved for the treatment of VTE) and decided that for patient comfort a once a day dose regime should continue to be available for our patients.

- Continuation of LMWH instead of warfarin may be considered in cases of cancer associated DVT's. For these patients demonstrate self-injection, or book District Nurse/ local hospital.
- Patients should be counselled about having Apixaban/Rivaroxaban or warfarin for the treatment of PE. Rivaroxaban and Apixaban cannot be reversed in cases of emergency bleeding and this is a concern, caution is also required with CYP3A4 drugs (HIV protease inhibitors and azole-antimycotics).
- Warfarin should be prescribed for the community as per AF ie. 'low and slow' 2mg daily so daily blood tests are not required. (See Warfarin Administration Record).

Dosing: -

- For the initial treatment of acute pulmonary embolism, the recommended dosage of Apixaban is 10mg twice daily for the first 7 days followed by 5mg twice daily for 6 months. After the 6 month period, if long-term apixaban is to be used the dose is 2.5mg twice daily. Do not use if creatinine clearance is less than 15ml/min.
- For the initial treatment of acute pulmonary embolism, the recommended dosage of rivaroxaban is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment and prevention of recurrent venous thromboembolism.
- A reduced dosage of 15 mg twice daily for 21 days followed by 15 mg once daily should be considered in people with moderate (creatinine clearance 30–49 ml/min) or severe (creatinine clearance 15–29 ml/min) renal impairment if their risk of bleeding outweighs the risk of recurrent deep vein thrombosis or pulmonary embolism. Do not use if creatinine clearance is less than 15ml/min.
- Refer to current version of the British National Formulary for information on contraindications and cautions with Rivaroxaban and Apixaban use.
- Duration of oral anticoagulation is:
    - 3 months for PE secondary to temporary risk factors
    - Consider lifelong anticoagulation unless contraindication (20% risk of recurrence) for unprovoked embolism;
    - The risk of bleeding should be balanced with that of further VTE.
- If patient is admitted ensure prompt Consultant Respiratory or Cardiology Physician opinion and triage urgently to Coleridge or Fielding for significant embolism (as defined above)

2.3 Management of Incidental Pulmonary Emboli in Patients known to Oncology undergoing staging or monitoring scans

- Radiology to contact Acute Oncology Bleep holder Bleep 3606 (9-5 Mon-Fri) or Beacon Ward #4202/3 (out of hours)

- For subsequent paragraphs 'Oncology' is used to represent either the Acute Oncology Bleep Holder OR the Beacon ward Staff Nurse receiving the call from radiology

- Patient still in radiology department OR patient at home and PE diagnosed Friday 5pm to Monday 9am
    - Oncology to inform AMU and patient to be advised to attend AMU
    - Oncology to document in Mosaiq electronic patient record and send QCL to patients consultant, ensure oncology OPA arranged, if call received out of hours then staff nurse to document on triage sheet
    - AMU team to ensure re contraindications and counsel re LMWH (including bleeding from tumour, known brain metastases, platelets <75, GFR <50ml/min) If advice required then contact oncology consultant on call to discuss
    - AMU to ensure patient suitable for out-patient management (see exclusion criteria above)
    - Commence treatment dose LMWH 1.5 mg/kg or reduced if renal impairment
    - Fax relevant GP surgery discharge summary including dose of LMWH, CT scan report and date of oncology appointment if known (from Cerner)
    - Contact District Nurses to arrange administration if patient not self administering. Fax prescription if necessary.
    - Patient to <u>continue with LMWH until oncology outpatient review</u>

- Patient at home (and PE diagnosed Monday 9am – Friday 5pm)
    - Oncology to contact patient and inform them they will need to attend GP surgery to commence LMWH 1.5 mg/kg (discuss with oncology consultant on call if any concerns regarding commencing anticoagulation eg bleeding from tumour, known brain metastases, platelets <75,). If after 5pm Mon to Thurs then advise patient to attend GP surgery the next day.

- Oncology to contact GP to request treatment dose LMWH 1.5 mg/kg and to advise admission to AMU if not suitable for out-patient treatment (see above exclusion criteria)
- Oncology to fax CT report to GP and letter of request (proforma available on Beacon Ward)
- Oncology to document in Mosaiq electronic patient record and send QCL to patients consultant, ensure oncology OPA arranged, if call received out of hours then Beacon Ward staff nurse to document on triage sheet

2.4 Audit and monitoring of treatment pathway for pulmonary embolism

The key steps of the PE treatment protocol is audited according to the arrangements set out if the monitoring framework of the Trust Policy: Prevention and treatment of venous thromboembolism (VTE) and use of anticoagulants

2.5 Massive Pulmonary Embolism

- Please refer **urgently** to Consultant Respiratory or Cardiology Physician
- CTPA or echocardiography may confirm massive PE However we would not recommend thrombolysis is routinely given/considered solely on the basis of echocardiographic findings, this is a more complex decision for a Consultant Respiratory or Cardiology Physician
- Thrombolysis is the first line treatment for massive PE with haemodynamic compromise and may be instituted when the patient is shocked as suggested by
  - Systolic blood pressure less than 90mmHg for > 15 minutes,
  - Or systolic blood pressure more than 40mmHg below normal for > 15 minutes
  - Tachycardic
  - Features of RV strain (ECG and or echo or CTPA)
  - Failure to maintain SaO_2 despite high flow oxygen
  - Raised Troponin level
- It is HAZARDOUS, and treatment should be a Consultant decision.
- The risks of thrombolysis should be explained to the patient
- Thrombolysis should be given on CCU ITU or HDU and step down care to Coleridge/Fielding ward
- Heparin should be discontinued prior to thrombolysis
- Avoid invasive procedures during thrombolysis
- tPa Alteplase is recommended
  - 10mg bolus of alteplase IV over 1-2 minutes followed by
  - 90mg alteplase IV over 2 hours

- Use 1.5mg/kg infusion dose if < 65kg
- TPA Thrombolysis should be followed by IV unfractionated heparin for 48 hours
- Check APPT after thrombolysis if > 2x normal repeat APTT after 4 hours
- Heparin should only be started when aPTT returns to less than 2x control.
- Start heparin using the Heparin Anticoagulation Chart.
- aPTT checks at
    - Baseline, 6 hr. & 12 hr.
    - 6 hours after any dose change. •
    - Thereafter once daily aPTT.
- Recheck aPTT immediately if bleeding, recurrent ischaemia or hypotension.
- Target aPTT: 1.5-2.5 times control (adjust as per Oral Anticoagulant Chart).
- For aPTTs obtained < 12 hours post initiation of tPA therapy do not discontinue or decrease the infusion unless significant bleeding occurs or aPTT ratio is > 4.8. Adjust the infusion upward if aPTT ratio is < 1.6.
- Monitor FBC on alternate days; watch out for falling Hb (bleeding) and heparin-induced thrombocytopenia.
- An alternative thrombolysis is Streptokinase 250,000 U in 30 mins followed by 100,000 U/hr for 24 – 48 hours

2.6 Additional points

- Patients diagnosed with a PE need to be considered for follow-up at 3 – 6 months for risk assessment and to exclude persisting pulmonary hypertension. This can be done by respiratoryredtop@tst.nhs.uk. An outpatient echo at 3/12 should be considered if a patient has evidence of right sided strain on the initial CTPA / echo or clinical signs.
- Leg ultrasound is an alternative to lung imaging in those with clinical DVT.
- Many patients with malignant disease develop VTE but few patients with VTE have malignant disease. NICE advocates that if there are no red flags for malignancy in the history no further investigations are warranted if a full clinical examination (including rectal examination), chest imaging and bloods are normal. Targeted investigations should focus on any red flag symptoms. Generalised red flags warrant sputum cytology, CT abdomen and pelvis and mammography (female) as per NICE
- Current organisation for outpatient management of DVT could be extended to include stable patients with PE
- The decision for lifelong anticoagulation is patient specific.

- It is recognised that dabigatran and edoxaban are licensed for VTE however because these medications are felt to be a less practical option (parenteral anticoagulation needed for at least 5 days) they are not considered in this guidance.

References

These guidelines are supported by the NICE guidelines for Venous thromboembolic diseases – last updated November 2015.

https://www.nice.org.uk/guidance/cg144

and by the NICE guidance on the use of Rivaroxaban and Apixaban for PE.

https://www.nice.org.uk/guidance/ta287

https://www.nice.org.uk/guidance/ta341

Taunton and Somerset NHS Foundation Trust	Trust Guideline
Title: Anticoagulation for atrial fibrillation (AF)	
Author(s): Dr Mark Dayer, Consultant Cardiologist	
Document Lead: Dr Mark Dayer	
Accepted by: Acute Medicine Governance Committee	**Active date**: 8th November 2016
Accepted date: 8th November 2016	**Review date**: 8th November 2019
Applies to: Adults patients only	**Exclusions:** None
Purpose: To provide guidance on the anticoagulation management of adult patients with atrial fibrillation	
VERSION CONTROL - This document can only be considered current when viewed via the Policies and Guidance database via the Trust intranet. If this document is printed or saved to another location, you are advised to check that the version you use remains current and valid, with reference to the active date.	

Key points:

- This guideline is based on the European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation published in 2016. It is also in line with the NICE 2014 guidelines.
- Atrial fibrillation is a common condition that increases the risk of stroke and other embolic events.
- Anticoagulation can reduce the risk of stroke by ⅔, but increase the risk of bleeding, and therefore careful weighting of the risks and benefits in individual patients is required.
- When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.
- Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.
- Please note that guidelines are not rigid prescriptions for all patients and are simply there to guide and inform decision-making. By definition, following a guideline is never mandatory (Wikipedia).

Conflicts of Interest:

Dr Dayer has received speaker fees, advisory board fees and educational support from Boehringer-Ingelheim (Dabigatran), Bayer (Rivaroxaban), Pfizer (Apixaban) and Daiichi Sankyo (Edoxaban).

Treatment:

1. In all patients with atrial fibrillation/flutter or paroxysmal atrial fibrillation/flutter (they should be treated the same) consideration should be given to anticoagulation.

2. In patients with non-valvular AF the CHA_2DS_2-VASc score should be used to determine risk (**Table 1**). Probably the best estimate of the annual risk over 10 years of an embolic event according to the score can be found in **Table 2**. Note that heart failure refers to moderate to severe left ventricular systolic dysfunction, or recently decompensated heart failure requiring hospital admission, regardless of ejection fraction. Women who have no other risk factors (i.e. women who are < 65 years with lone AF) should also be regarded as truly low risk and treated as though they have a CHA_2DS_2-VASc score of 0. Patients with valve-related AF should be anticoagulated unless there is a contraindication.

Table1.

	Risk factor	Score
C	Congestive heart failure/LV dysfunction[1]	1
H	Hypertension	1
A_2	Age ≥ 75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/Thromboembolism	2
V	Vascular disease[2]	1
A	Age 65-74	1
Sc	Sex category (i.e. Female)	1
[1] Mod-severe LV impairment or recent admission with decompensated heart failure, irrespective of ejection fraction		
[2] Prior MI, peripheral arterial disease, aortic plaque		

Table 2. **(Olesen et al. BMJ. 2011; 342: d214)**

CHA_2DS_2-VASc Score	Annual risk of event
0	0.66%
1	1.45%
2	2.92%
3	4.28%
4	6.46%
5	9.97%
6	12.52%
7	13.96%
8	14.10%
9	15.89%

3. Patients with a CHA_2DS_2-VASc score of ≥ 1 should be considered for oral anticoagulation (**Table 3**). Some patients may not need anything. Aspirin is **not** recommended to prevent strokes in atrial fibrillation in the latest ESC guidelines, except where OAC cannot be used.

Table 3.

CHA_2DS_2-VASc score	Recommended therapy
≥2	Oral anticoagulation (OAC)
1	Either OAC or aspirin 75mg od; strongly preferred OAC
0	Either no therapy or aspirin 75mg od; preferred no therapy

4. If anticoagulation is recommended then there should be consideration as to whether there are relevant cautions or contra-indications. The HAS-BLED score should be calculated (**Table 4**) and if the score is ≥ 3 caution should be exercised, but a high HAS-BLED score alone is not a reason to deny people anticoagulation. One estimate of the annual risk of bleeding according to the HAS-BLED score can be found in **table 5.** Please remember that bleeding is not usually fatal and does not usually have long-term consequences, unlike stroke. It should also be noted that bleeding-risk calculators are not well validated and are based on relatively small numbers of events, however the HAS-BLED score appears to be the best there is at present. Age is not a contra-indication and neither are falls (Garwood and Corbett. Ann Pharmacother 2008;42:523-32), although the data from this last study are open to criticism, both for the complex statistical modelling and the fact it only considers subdural haematoma; an individualised decision is necessary. This guideline is not designed to list all cautions and contra-indications to anticoagulation. Correctable risk factors for bleeding should be addressed before commencing anticoagulation.

Table 4.

	Characteristic	Score
H	Hypertension[1]	1
A	Abnormal renal[2] / liver function[3] (1 point each)	1 or 2
S	Stroke	1
B	Bleeding[4]	1
L	Labile INRs[5]	2
E	Elderly[6]	1
D	Drugs[7] or alcohol[8] (1 point each)	1 or 2
[1] Systolic BP > 160mmHg		
[2] Chronic dialysis, transplantation, Cr ≥ 200 µmol/l		
[3] Bilirubin > 2x ULN + AST/ALT 3xULN		
[4] Previous bleeding history and/or predisposition to bleeding		
[5] TTR < 60%		
[6] Age > 65 years		
[7] Concomitant use of drugs such as aspirin, NSAIDS		
[8] Alcohol consumption > 8u / week		

Table 5.

HAS-BLED Score	Risk of major bleed
0	1.13%
1	1.02%
2	1.88%
3	3.72%
4	8.70%
≥5	12.5%

5. The new oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban, and Edoxaban) should **not** at present be combined with aspirin or other antiplatelet agents. Warfarin **may** be combined with aspirin or other antiplatelets in particular circumstances. In patients taking aspirin for vascular disease, oral anticoagulants are an acceptable substitute. If a new anticoagulant is to be used in this situation then Rivaroxaban, Apixaban or Edoxaban are preferred, as there are concerns of a marginal increase in the rate of heart attack with Dabigatran.

    a. Discussion should take place with the stroke team for patients taking dual antiplatelet therapy to prevent stroke/TIA.
    b. Discussion should take place with the cardiologists for patients taking dual antiplatelet therapy to treat NSTEMIs and/or stents. **Dual antiplatelet therapy should never be stopped in a patient with a stent without prior discussion with a cardiologist.** In patients on single antiplatelet therapy with a stent in situ the antiplatelet agent should be continued alongside warfarin in all but exceptional cases.

6. Dabigatran, Rivaroxaban, Apixaban and Edoxaban are new oral anticoagulants recommended for use in patients with **non-valvular** atrial fibrillation (i.e. patients without mitral stenosis or mechanical valves. They are NICE approved (hyperlinks: Dabigatran, Rivaroxaban, Apixaban, Edoxaban) and "green drugs" approved for use in Somerset. They do not need monitoring in the same way as warfarin. At baseline U&E and LFTs should be checked. U&Es should be checked every 6 months. Bloods may need to be repeated if the clinical situation changes.

7. They are approved for use if there is one or more of the following risk factors:

    a. Previous stroke, transient ischaemic attack or systemic embolism.
    b. Left ventricular ejection fraction below 40%.
    c. Symptomatic heart failure of New York Heart Association (NYHA) class 2 or above.
    d. Age 75 years or older.
    e. Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

    The guidance for Apixaban and Edoxaban is slightly different: Apixaban or Edoxaban is recommended as an option for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation with 1 or more risk factors such as:

    a. Prior stroke or transient ischaemic attack.
    b. Age 75 years or older.
    c. Hypertension.
    d. Diabetes mellitus.
    e. Symptomatic heart failure.

8. In patients with renal disease, there is specific guidance in NICE CG182 about which anticoagulant to use (Section 1.6.17). It suggests that clinicians should consider apixaban *in preference to* warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m2 and non-valvular atrial fibrillation who have 1 or more of the following risk factors:

    a. Prior stroke or transient ischaemic attack.
    b. Age 75 years or older.
    c. Hypertension.
    d. Diabetes mellitus.
    e. Symptomatic heart failure.

The section makes no reference to the other NOACs. Of note, there is no such specific recommendation in the latest ESC guidance. There is the comment, however, that in those patients with mild or moderate renal impairment, the outcomes are better with NOACs than warfarin.

9. Dabigatran is a twice-daily drug. There are two doses – 150mg bd and 110mg bd. The higher dose is more effective than warfarin at preventing stroke but has a similar risk of serious bleeding; the risk of intracranial bleeding is much lower. The lower dose is as effective as warfarin at preventing stroke but has a lower risk of bleeding. **We will generally cardiovert patients on Dabigatran.** Patients should be aware that there is more clinical experience with warfarin than Dabigatran in this situation. Patients should specifically sign to say that they have taken the drug for 4 consecutive weeks without missing a dose.

10. Complete information on Dabigatran can be found in the Summary of product characteristics (SPC). Patients should generally be given the higher dose. The lower dose should be used in those aged > 80, or taking verapamil. In those aged 75-80, or at a higher risk of bleeding, or who have oesophagitis, gastritis or gastro-oesophageal reflux, or a creatinine clearance of 30-50 ml/min, the lower dose should be considered. Dabigatran should not be used in patients with a creatinine clearance of < 30 ml/min or in those with elevated liver enzymes (> 2x ULN) or in those with pre-existing clotting disorders.

11. Rivaroxaban is a once daily drug. There are two doses – 15mg and 20mg. It is as effective as warfarin at preventing stroke. There is a similar risk of serious bleeding; the risk of intracranial bleeding is much lower. **We will generally cardiovert patients on Rivaroxaban** following the publication of the X-Vert trial. Note we still recommend at least 4 weeks of Rivaroxaban prior to cardioversion and have **not** agreed the 1 week option presented in the paper. Patients should specifically sign to say that they have taken the drug for 4 consecutive weeks without missing a dose.

12. Complete information on Rivaroxaban can be found in the SPC. Patients should generally be given the higher dose. The lower dose should be used in those with a creatinine clearance of between 30-49 ml/min. It may be used with caution in patients with a creatinine clearance of 15-30ml/min. Rivaroxaban is contra-indicated in patients with a creatinine clearance of < 15ml/min or in those with hepatic disease associated with a coagulopathy.

13. Apixaban is a twice-daily drug. There are two doses – 5mg bd and 2.5mg bd. It is more effective than warfarin at preventing stroke. The rates of major bleeding, including intracranial bleeding, are lower than with warfarin and there was a significant

reduction in mortality. **We will generally cardiovert patients on Apixaban.** Patients should be aware that there is more clinical experience with warfarin than Apixaban in this situation. Patients should specifically sign to say that they have taken the drug for 4 consecutive weeks without missing a dose.

14. Complete information on Apixaban can be found in the SPC. Patients should generally be given the higher dose. The lower dose should be used in those with at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133µmol/l. The lower dose should also be used in patients with severe renal impairment (Creatinine Clearance of 15-29ml/min). Apixaban is contra-indicated in patients with a creatinine clearance of < 15ml/min or in those with hepatic disease associated with a coagulopathy.

15. Edoxaban is a once-daily drug. There are two doses – 60mg OD and 30mg OD. Edoxaban was non-inferior to warfarin. The rates of major bleeding, including intra-cranial bleeding were significantly lower than with warfarin. **We will generally cardiovert patients on Edoxaban.** The ENSURE-AF trial has confirmed its safety. Patients should be aware that there is more clinical experience with warfarin than Edoxaban in this situation. Patients should specifically sign to say that they have taken the drug for 4 consecutive weeks without missing a dose.

16. The summary of product characteristics states that the recommended dose is 60 mg once daily. The recommended dose is 30 mg once daily in people with one or more of the following clinical factors: moderate or severe renal impairment (creatinine clearance 15–50 ml/min); body weight of 60 kg or less; concomitant use of the P-glycoprotein inhibitors ciclosporin, dronedarone, erythromycin or ketoconazole. Edoxaban is contra-indicated in patients with a creatinine clearance of < 15ml/min or in those with hepatic disease associated with a coagulopathy

17. This guideline will be reviewed after 3 years, or following changes in treatment recommendations.