University Hospital Southampton
NHS Foundation Trust

Treatment of Adult Cancer Associated Thrombosis Guideline v1.0

Trust reference		Version number	1.0
Description	Provides recommendations for safe and effective prescription of anticoagulant therapy (including direct oral anticoagulants) for adults with venous thromboembolism and active cancer.		
Level and type of document	Level 1: applicable across the Trust Clinical guideline – controlled document		
Target audience	Clinical staff working with adult patients diagnosed with cancer and venous thromboembolism		
List related documents / policies (do not include those listed as appendices)	▪ Pulmonary Embolism – Diagnosis and Management in Adults Guideline ▪ Diagnosis and management of suspected or confirmed deep vein thrombosis (DVT) in adults ▪ GU-087 Adult Oral Anticoagulation Guidelines ▪ UHS Venous thromboembolism in pregnancy diagnosis and management guideline ▪ GU-084 Thromboprophylaxis and Risk Assessment Guideline for Adults		
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Document sponsor	Dr Michelle Oakford DCD, division D		

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1 Version control

Date	Author(s)	Version created	Approval committee	Date of approval	Date next review due	Key changes made to document
Jan 24	Sara Boyce	1.0	Drugs Committee	28/11/23	January 2025	New document

2 Index

3 Introduction

Patients with cancer have a 4 to 7 fold increased risk of venous thromboembolism (VTE).[1] This is a common cause of morbidity and mortality in this patient group. Managing VTE in the context of cancer often involves additional challenges: variable bleeding risk, thrombocytopenia and multiple drug-interactions. Historically there was a preference for treating cancer-associated thrombosis with low molecular weight heparin (LMWH), based on the CLOT trial (2003).[2] Since then, evidence has been accumulating in support of the safe and effective use of direct oral anticoagulants (DOACs). This guideline has been produced to take account of recently published data and international guidance on the use of direct oral anticoagulants in patients with cancer.

4 Scope

This guideline applies to adult patients (≥18 years old) admitted to University Hospital Southampton NHS Foundation Trust with diagnoses of venous thromboembolism and cancer (present or treated within the last 6 months).

Exclusions:

- Primary VTE prophylaxis for patients with cancer.
- Suspected high risk/massive pulmonary embolism, please see: “Pulmonary Embolism – Diagnosis and Management in Adults Guideline”.
- Pregnancy, please see: “Venous thromboembolism in pregnancy diagnosis and management Guideline”.
- Superficial vein thrombosis.
- Atypical site thrombosis (any site other than upper or lower limb deep/pelvic vein thrombosis or pulmonary embolism).
- Basal cell carcinoma (in the absence of another cancer diagnosis).

5 Aim/purpose

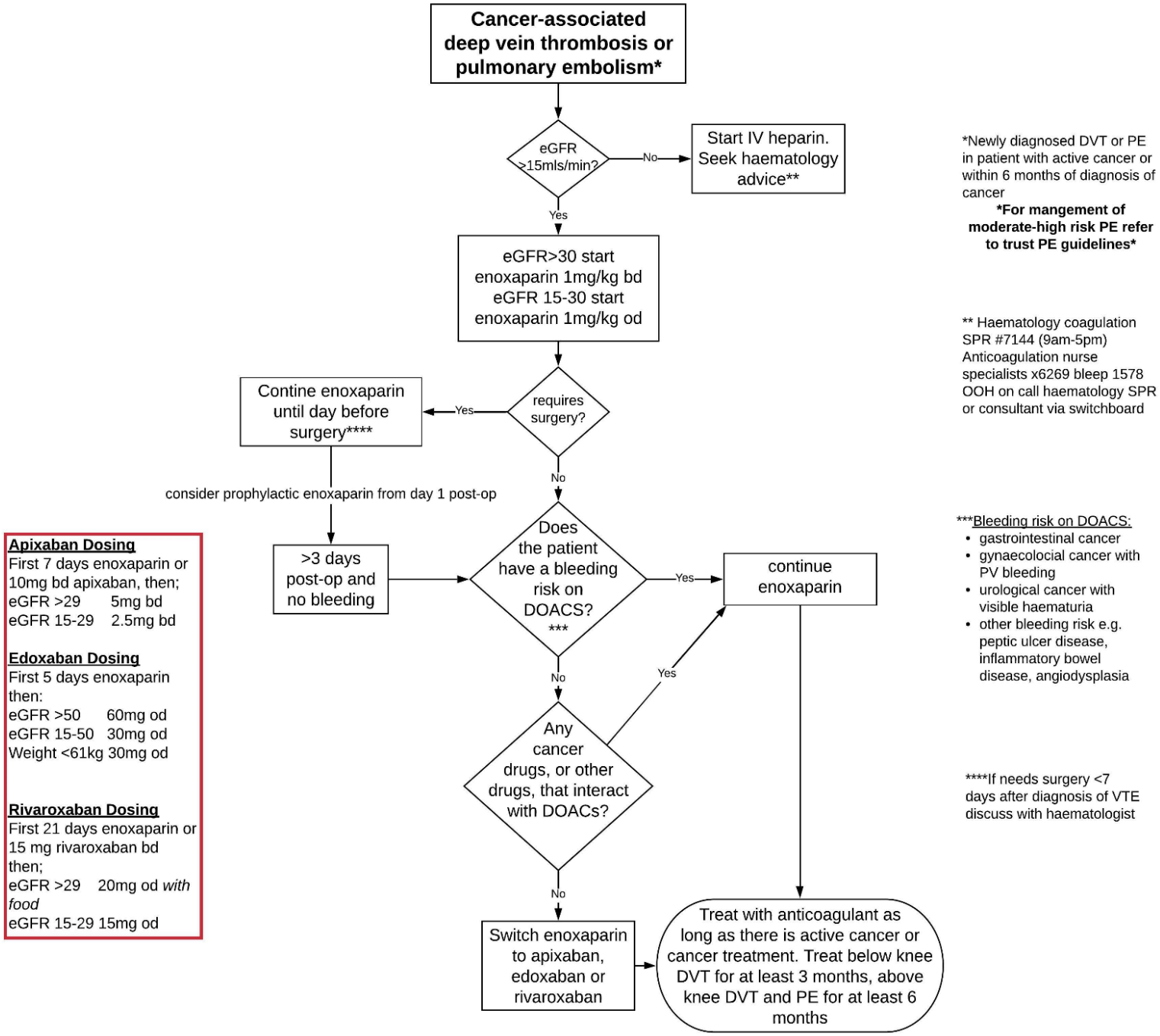
To update local guidance on treatment of venous thromboembolism in patients with cancer, specifically introducing the use of direct oral anticoagulants in line with current published evidence and international guidance.

6 Definitions

DOAC	Direct oral anticoagulant – a class of oral anticoagulant medication that includes factor Xa inhibitors (Apixaban, Edoxaban and Rivaroxaban) and a factor IIa inhibitor (Dabigatran)
DVT	Deep vein thrombosis – when a thrombus (blood clot) forms in a deep vein, usually in the leg
LMWH	Low molecular weight heparin – an anticoagulant that is administered as a subcutaneous injection (e.g. enoxaparin)
PE	Pulmonary embolism – when a thrombus (blood clot) travels to and lodges in an artery of the lung
UFH	Unfractionated heparin – an anticoagulant that can be administered subcutaneously or as an intravenous infusion
VKA	Vitamin K antagonist – a class of oral anticoagulant that includes warfarin
VTE	Venous thromboembolism – a term incorporating DVT and PE

7 Anticoagulation for Cancer Associated VTE

Treatment Pathway



7.1 Safety and Efficacy of Anticoagulants

The standard of care for cancer associated VTE has been LMWH based on the results of the CLOT trial in 2003, which demonstrated lower rates of recurrent VTE in patients treated with LMWH compared to warfarin.[2]

There are four major randomised controlled trials supporting the non-inferiority of DOACs in terms of efficacy and safety in treating cancer associated VTE.

Clinical Trial	Patients (n)	Intervention	Major Bleeding (%)	Recurrent VTE (%)
ADAM-VTE[3]	150 150	Apixaban Dalteparin	0 1.4	0.7 6.3
CARAVAGGIO[4]	584 584	Apixaban Dalteparin	3.8 4.0	5.6 7.9
SELECT-D[5]	203 203	Rivaroxaban Dalteparin	6 4	4 11
HOKUSAI VTE Cancer[6]	522 524	Edoxaban* Dalteparin	6.9 4.0	7.9 11.3

* Edoxaban was preceded by at least 5 days of LMWH (standard management for treatment of VTE)

Meta-analysis pooling results from these trials indicates a significantly reduced risk of recurrent VTE with DOACs compared to LMWH, similar rates of major bleeding but an increased risk of minor bleeding with DOACs.[7]

- **Enoxaparin (LMWH), apixaban, edoxaban or rivaroxaban can be used for the treatment of cancer associated VTE.**
- **Dabigatran should not be used to treat cancer-associated VTE due to a lack of evidence in this patient group.**

7.2 Bleeding Risk

Two of the trials reported a higher risk of major bleeding with DOACs compared to LMWH. Upper gastrointestinal tract bleeding was the commonest major bleeding event and this was overrepresented in patients with gastrointestinal cancers. Subgroup analysis of the HOKUSAI VTE Cancer population indicated that a combination of 3 risk factors was associated ($p<0.05$) with a higher rate of major bleeding with edoxaban compared to dalteparin.[8] These risk factors included: gastrointestinal or urothelial cancer diagnosed within the preceding six months, primary or metastatic brain tumour, regionally advanced or metastatic cancer, surgery within the preceding two weeks and bevacizumab treatment within the preceding two weeks.

Assessment of the bleeding risk is nuanced and requires assimilation of multiple factors which we cannot comprehensively cover within the guideline. Individual assessment of a patient's bleeding risk is essential before prescribing any anticoagulant.

LMWH should be used as an anticoagulant in the following scenarios:

- **Pre- and Perioperatively (for non-neurosurgical procedures, consider switching to a DOAC if >2 days post-operative and no evidence of bleeding).**
- **Gastrointestinal cancer.**
- **Gynaecological cancer with active or recent, non-menstrual PV bleeding.**
- **Urothelial cancer with active or recent haematuria.**

7.3 Drug Interactions

Cancer patients are frequently prescribed multiple anticancer therapies alongside supportive medications. Polypharmacy increases the risk of drug-to-drug interactions, which can result in an increased risk of bleeding or undertreatment of the VTE. A significant advantage of LMWH over DOACs is the reduced risk of such interactions.

It is important to consider direct toxicity with concurrent anticoagulants, antiplatelet agents, non-steroidal anti-inflammatory drugs and potential pharmacokinetic interactions. Indirect toxicity can also occur through gastrointestinal adverse effects increasing the bleeding risk i.e., mucositis and colitis.

All DOACs are substrates of P-glycoprotein whilst apixaban and rivaroxaban are also substrates of the cytochrome P450 system (particularly CYP3A4.) Enzyme inhibitors may increase anticoagulant effect and inducers reduce anticoagulant effect.

Resources for reviewing DOAC interactions include:

- UHS Medicines Advice Service: medicinesadvice@uhs.nhs.uk
- Cancer Drug Interactions from Radboud UMC and University of Liverpool cancer-druginteractions.org
- European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation (2021)

Given the complexity of the therapeutic regimes involved, we recommend that <u>all</u> patients are referred for Pharmacist led drug interaction evaluation before starting a DOAC for cancer associated VTE and that this should be repeated if the cancer management changes.

7.4 Prescribing Guidance (Including in Renal Impairment)

Creatinine clearance is an important determinant of anticoagulant safety and restricts the strategies available to us.

I) Creatinine Clearance ≥30ml/min

Initial treatment: enoxaparin 1mg/kg BD, apixaban 10mg BD or rivaroxaban 15mg BD

Ongoing anticoagulation:

- Apixaban 10mg BD for 7 days, then 5mg BD
- Edoxaban 60mg* OD after 5 days initial treatment with enoxaparin
- Rivaroxaban 15mg BD for 21 days, then 20mg OD with food
- Enoxaparin 1mg/kg BD or 1.5mg/kg OD (if twice daily injections not tolerated)
- Warfarin (if other options contraindicated)

* Edoxaban is also dose reduced to 30mg OD if the patient weighs ≤60kg.

The summary of product characteristics (SPC) dose of enoxaparin for treating VTE in patients with cancer is 1mg/kg BD. Theoretically there is less peak effect and therefore a lower associated bleeding risk with BD as opposed to OD dosing regimens. In patients with a low bleeding risk, we believe it is appropriate to convert to 1.5mg/kg OD dosing for outpatients in order to improve their quality of life.

DOACs and warfarin are both contraindicated in pregnancy; please refer to the trust: “Venous thromboembolism in pregnancy diagnosis and management guideline”.

Breastfeeding patients must not be prescribed DOACs; enoxaparin is preferred with warfarin as an alternative if other options are contraindicated.

II) Creatinine Clearance 15-29ml/min

Initial treatment: enoxaparin 1mg/kg OD

Ongoing anticoagulation:

- Apixaban 2.5mg BD after 7 days initial treatment with enoxaparin (avoids high dose lead in)

- Edoxaban 30mg OD after 5 days initial treatment with enoxaparin (dose reduced)
- Rivaroxaban 15mg OD (with food) after 21 days initial treatment with enoxaparin
- Enoxaparin 1mg/kg OD
- Warfarin (if other options contraindicated)

Of the DOACs, apixaban has the greatest evidence base for safety and efficacy in this patient group. It also has the advantage of an evidence-based dose reduction to 2.5mg BD after 6 months of treatment, reducing the bleeding risk if longer term anticoagulation is warranted.

III) **Dialysis-Dependent or Creatinine Clearance <15ml/min**

Initial treatment: unfractionated heparin

Ongoing anticoagulation:

- Cases should be discussed on an individual basis with a Haematologist specialising in haemostasis and thrombosis

DOACs are unlicensed and warfarin is typically the recommended long-term anticoagulant for patients with this degree of renal impairment. There has been increasing, cautious use of LMWH in this circumstance but this should be initiated after discussion with Haematology, who will coordinate monitoring anti-Xa levels and appropriate dose titration.

7.5 Duration of Anticoagulation

A minimum of six months anticoagulation should be given to treat proximal DVT and PE in patients with cancer.

Distal DVTs (below the knee) are at significant risk of extension/recurrence in cancer patients. We recommend a minimum of three months' anticoagulation.

After the initial period of anticoagulation, a decision on whether to continue anticoagulation should be based on individual evaluation of the risk-benefit ratio, incorporating: cancer activity, tolerability and patient preference.

There is an evidence-based dose reduction for apixaban to 2.5mg BD after six months of initial treatment (although this was validated in patients without active cancer) The lower dose is attractive for long term prevention as one would anticipate a lower bleeding risk.

7.6 Incidental Cancer Associated VTE

Incidental diagnoses of VTE are common in patients with cancer. Multiple retrospective trials have suggested a similar rate of recurrence between asymptomatic and symptomatic VTEs.[9] (Dan Exeter Blood 2013) There is also evidence of an equivalent increase in mortality for asymptomatic and symptomatic VTE (Dentali et al Thromb Res 2010) and reduction in mortality if an incidental PE is treated (Sun et al Lung Cancer 2010).[10,11]

Subsegmental PE remains an area of controversy, with limited data to support rational decision making. More often than with other forms of VTE, there is a need to confirm the diagnosis before committing a patient to anticoagulation (for example with a dedicated CT pulmonary angiogram following on from an incidental diagnosis on a cancer staging CT scan).

All cancer associated VTE should be treated, including incidental VTE and subsegmental PEs with the same approach. Treatment of subsegmental PEs needs to be considered on a case-by-case basis in patients with concerning bleeding risk.

8 Management of Cancer Associated VTE in Specific Scenarios

8.1 Extremes of Body Weight

There is a growing body of clinical and pharmacokinetic data supporting the safe use of rivaroxaban and to a lesser extent apixaban in patients with a BMI >40 kg/m^2 or weight >120kg. After reviewing these, the International Society of Thrombosis and Haemostasis (ISTH) published the following recommendation in July 2021:

"For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight based LMWH (per manufacturers' recommendations), and fondaparinux are also options."[12]

Cancer patients who weigh >120kg can be offered standard dose rivaroxaban. Please contact Haematology to discuss this before initiating treatment. A peak rivaroxaban specific anti-Xa level should be arranged once the patient has transitioned to the 20mg OD dose and taken this for at least seven days. The blood sample must be taken within the hospital, between 2-4 hours after taking their rivaroxaban. The result should be discussed with Haematology in order to determine the ongoing safety.

The only weight-based dose adjustment for DOACs being used to treat VTE is a dose reduction in edoxaban from 60mg to 30mg OD for patients weighing ≤60kg.

8.2 Thrombocytopenia (Low Platelet Count)

In this scenario a heightened risk of bleeding must be balanced against undertreatment of thrombosis.

DOACs should be avoided in patients with a platelet count <50x10^9/L.

A haematologist should be contacted for advice before initiating anticoagulation for patients with a platelet count of <50x10^9/L, or a rapidly falling platelet count

In most instances we will recommend cautious use of enoxaparin adjusted to match the patient's current platelet count (table 1), which is based on current British Society of Haematology guidelines.[13]

Platelets (x10^9/L)	Recommended Treatment
≥50	Treatment dose enoxaparin
25-49	Prophylactic dose enoxaparin (discuss with haematology)
≤24	No anticoagulation

Within the first month of treatment for a symptomatic VTE, we recommended prescribing platelet transfusions (for non-immune causes of thrombocytopenia) to facilitate treatment dose anticoagulation to be safely given. Please be aware that the duration of response to a platelet transfusion is short (days), so a full blood count should be checked prior to administering anticoagulation. For example, if the current platelet count is below 50x10^9/L, a platelet transfusion should be administered the same day and a repeat full blood count taken ~1 hour post-transfusion. If the new platelet count is >50x10^9/L and there are no current bleeding symptoms, treatment dose enoxaparin should be given that day.

In patients diagnosed with new VTE (within the last 4 weeks) and active bleeding or prolonged, severe thrombocytopenia that does not sufficiently respond to platelet transfusions, a retrievable inferior vena cava filter should be considered.

Patients with autoimmune thrombocytopenia will not respond to platelet transfusions and an anticoagulant strategy should be discussed with their Haematology consultant on a case-by-case basis.

8.3 Cancer Involving the Central Nervous System

Patients with cancer involving the central nervous system (CNS) are at increased risk of both intracranial haemorrhage and VTE. Anticoagulation carries greater risks, meaning the threshold for initiating treatment should be higher.

Unfortunately, the four major randomised controlled trials supporting the use of DOACs in cancer associated thrombosis either excluded patients with brain metastases/primary CNS disease or the numbers recruited were low (n=77 cumulatively). Whilst historically LMWH has been favoured, a meta-analysis of retrospective studies has shown a lower risk of intracranial haemorrhage with DOACs compared to LMWH.[14]

With the gradual accumulation of data supporting a lower risk of ICH with DOACs compared to LMWH, there has been a shift towards parity in the international community. The American Society of Clinical Oncology 2020 and International Initiative on Thrombosis and Cancer 2019 now both recommend the use of either LMWH or DOAC for the treatment of VTE in patients with primary or metastatic brain tumours.[15,16]

Whilst reversibility of anticoagulation is a consideration, protamine sulphate is underwhelming in terms of altering outcomes for patients who develop an ICH on LMWH. Andexanet alfa (the reversal agent for apixaban and rivaroxaban) is only licensed for life-threatening gastrointestinal haemorrhage in England and edoxaban has no licensed reversal agent at the time of writing.

LMWH or a DOAC (apixaban, edoxaban or rivaroxaban) can be prescribed for the treatment of VTE in patients with cancer involving the CNS after consideration of their individual bleeding risk, drug interactions and patient preference.

8.4 Impaired Drug Absorption

Altered oral drug absorption may be influenced by the site of cancer, bowel resections, significant emesis, altered gastric pH and gut motility.

There is limited evidence for the safe use of DOACs under these circumstances. In general, LMWH is preferred. If this is not acceptable, warfarin can be used with caution as its effectiveness can be measured through INR monitoring.

Rivaroxaban is primarily absorbed in the stomach so it may be safe to use if gastrointestinal abnormalities are distal to this. Please discuss the case with Haematology prior to using rivaroxaban in this scenario. Anti-Xa levels can support adequate drug absorption but there is less experience in correlating the result with adequate anticoagulant effect than for LMWH (anti-Xa) or warfarin (INR).

8.5 Enteral Feeding Guidance

There is evidence to support safe administration of apixaban and rivaroxaban by enteral feeding tubes so long as they terminate in the stomach. Edoxaban should only be taken orally as an intact tablet.[17]

8.6 Treatment Failure

The risk of recurrent/breakthrough VTE whilst receiving anticoagulation is 3-4 times higher in patients with cancer than those without.[18] High quality data is lacking; our recommendations for this scenario are based on a combination of registry data and expert opinion.[15, 19, 20]

First confirm the diagnosis of recurrent VTE by comparing current to previous imaging. Check the dose of anticoagulant is correct and sensitively inquire about concordance with treatment. If unable to address the underlying issues for non-concordance, switching to a more tolerable but less clinically favourable anticoagulant regime could be justified.

If there are no obvious factors preventing adequate anticoagulation with their existing regime, we initially recommend the following:

Previous Anticoagulation	Recommendation
LMWH	Check peak anti-Xa level and consider increasing dose by 20-25% after discussion with Haematology
DOAC	Switch to LMWH
Warfarin	Switch to LMWH

Discussion with Haematology to determine a suitable ongoing anticoagulation strategy is reasonable.

9 Implementation

The policy will be displayed on Staffnet and sent to the Care Group Management Teams. The Care Group Management Teams will be expected to cascade to all relevant staff groups.

The guideline will be highlighted to Oncologists and Haematologists during their induction process (anticipated high users).

10 Roles and responsibilities

Medical Director

- Accountable for ensuring the policy is in place and that divisions implement and monitor it.

Divisional Management Teams

- To ensure these guidelines are disseminated and implemented within the division, monitoring performance and ensuring action is taken where necessary.
- Divisional governance managers to support DMT in implementing the Policy.

Medical Staff

- The UHS clinical team will provide the patient with suitable information regarding VTE and the anticoagulant prescribed. If a DOAC is prescribed a counselling checklist will be discussed with the patient. This includes drug interactions, side effects, pregnancy and monitoring. A blood screen will be undertaken to exclude specific contraindications to the anticoagulant. This will include a full blood count, clotting screen, renal function and liver function tests.

Nursing Staff

- It is the admitting nurse's responsibility to weigh the patient to enable accurate calculation of the enoxaparin dose and creatinine clearance.
- It is the responsibility of the discharging nurse to ensure that patients are offered information on the correct use and duration of treatment at home.
- If the patient is discharged on a direct oral anticoagulant, it is the responsibility of the discharging nurse to ensure that the counselling checklist has been completed and filed in the medical notes. A patient information booklet and alert card must be provided.

- If the patient is discharged on enoxaparin, it is the responsibility of the discharging nurse to ensure that the patient/carer is taught how to administer this or to arrange administration and appropriate arrangements have been made for disposal of sharps.
- If the patient is discharged on warfarin, it is the responsibility of the discharging nurse to ensure that follow up has been arranged for INR testing.
- It is the responsibility of the discharging nurse to ensure that patients/carers are offered verbal and written information on the signs and symptoms of VTE.

11 Document review

The “Treatment of Cancer Associated Thrombosis Guideline” will be reviewed in one year after publication.

12 Process for monitoring compliance

Compliance with these guidelines will not be routinely reviewed unless a concern is identified. This may be through incidents, complaints, claims or performance issues.

Element to be monitored	Incidents and referrals for recurrent VTE in cancer patients
Lead (name/job title)	Dr Sara Boyce
Tool	audit
Frequency	Every 2 years
Reporting arrangements	Thrombosis committee/Cancer care group board

If monitoring identifies deficiencies actions plans will be developed to address them.

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