NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

QUALITY STANDARDS PROGRAMME

Quality standard topic: Management of VTE diseases

Output: Full briefing paper

Introduction

This briefing paper presents a structured evidence review to help determine the suitability of recommendations from the key development sources listed below, to be developed into a NICE quality standard. The draft quality statements and measures presented in this paper are based on published recommendations from these key development sources:

Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.

NICE clinical guideline 144 (2012). Available from www.nice.org.uk/guidance/CG144

Structure of the briefing paper

The body of the paper presents supporting evidence for the draft quality standard reviewed against the three dimensions of quality: clinical effectiveness, patient experience and safety. Information is also provided on available cost-effectiveness evidence and current clinical practice for the proposed standard.

Evidence from the clinical guideline is presented and should be read alongside the full recommendations and link to evidence sections in the full clinical guideline.

1. Timing of investigations

1.1 NICE CG 144 recommendation paragraph 1.1.1(KPI), 1.1.2, 1.1.3 (KPI), 1.1.4 (KPI) 1.1.7, 1.1.8, 1.1.9 (KPI), 1.1.10 (KPI) and 1.1.14

1.1.1 Relevant NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.1.1 (KPI) If a patient presents with signs or symptoms of deep vein thrombosis (DVT), carry out an assessment of their general medical history and a physical examination to exclude other causes. 1.1.2 If DVT is suspected, use the two-level DVT Wells score (see table 1) to estimate the clinical probability of DVT. 1.1.3 (KPI) Offer patients in whom DVT is suspected and with a likely two-level DVT Wells score (see table 1) either: • a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test or • a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested. Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan. 1.1.4 (KPI) Offer patients in whom DVT is suspected and with an unlikely two-level DVT Wells score (see table 1) a D-dimer test and if the result is positive offer either: • a proximal leg vein ultrasound scan carried out within 4 hours of being requested or • an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested. 1.1.7 If a patient presents with signs or symptoms of pulmonary embolism (PE), carry out an assessment of their general medical history, a physical examination and a chest X-ray to exclude other causes. 1.1.8 If PE is suspected, use the two-level PE Wells score (see table 2) to estimate the clinical probability of PE. 1.1.9 (KPI) Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score (see table 2) **either**: • an immediate computed tomography pulmonary angiogram (CTPA) **or** • immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out

	immediately. Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected. 1.1.10 (KPI) Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score (see table 2) a D-dimer test and if the result is positive offer **either**: • an immediate CTPA **or** • immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. 1.1.14 If a patient presents with signs or symptoms of both DVT (for example a swollen and/or painful leg) and PE (for example chest pain, shortness of breath or haemoptysis), carry out initial diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations on clinical judgement.
Proposed quality statement	People with suspected VTE have diagnostic investigations completed within 24 hours of presentation.
Draft quality measure	**Structure:** Evidence of local arrangements to ensure people with suspected VTE complete diagnostic investigations within 24 hours. **Process:** The proportion of people who receive complete diagnostic investigations within 24 hours of presentation. Numerator – The number of people in the denominator receiving full diagnostic investigations within 24 hours of presentation. Denominator – The number of people with VTE.
Definitions	The complete diagnostic investigations are as outlined in the PE and DVT algorithms in the NICE clinical guideline 144. Suspected VTE is where the diagnostic investigations have not yet confirmed VTE
Discussion points for TEG	As written, this statement is broad as it covers both populations within the pathway (DVT and PE) while using a single timeframe (24 hours) as the sentinel quality marker. The 24 hour requirement refers only for patients in whom DVT is suspected. The PE recommendations are based on 'immediate'.

1.1.2 Clinical and cost-effectiveness evidence

For the recommendations identified above, the GDG considered the avoidance of undiagnosed and untreated DVT and PE to be the most important outcomes, followed by concerns about the number of additional diagnostic tests (which are non-invasive, with few side effects) that patients

receive. The DVT Wells scores are the most widely validated pre-test probability scores and have been widely used in the NHS.

Recommendations 1.1.1, 1.1.2, 1.1.3 and 1.1.4 describe the investigations that should be carried out if DVT is suspected, relating to DVT diagnostic algorithm (see appendix B).

Recommendations 1.1.7, 1.1.8, 1.1.9 and 1.1.10 describe the investigations that should be carried out if PE is suspected PE, relating to the PE diagnostic algorithm (See appendix C). Recommendation 1.1.14 covers diagnostic investigations if a patient presents with signs or symptoms of both DVT and PE.

In making the recommendations for diagnostic investigations, the GDG discussed how delays in accessing ultrasound scans are currently a potential problem. In situations where delay in access is unavoidable, strategies are required to ensure patients receive treatment in the interim. The conclusions from the evidence reviews and GDG considerations are reflected in the set of recommendations above identified for this draft statement.

1.1.3 Patient experience

None identified.

1.1.4 Patient safety

A patient safety incident is any unintended or unexpected incident which could have or did lead to harm for one or more patients receiving NHS care (see Appendix A). A comprehensive analysis of recent reported incidents (please see full accompanying report from the NPSA) identifies the delay in diagnostic investigations as a priority area relating to patient safety.

1.1.5 Current practice

The NICE costing report for CG144 noted that current practice in respect to the recommendations to carry out a proximal leg vein ultrasound scan within 4 or 24 hours of being requested, appear to be variable. Expert opinion suggests that at present, ultrasound scan is a limited resource, and access can be a problem, especially at weekends or in more rural areas.

1.1.6 Current indicators

None identified.

2. Interim therapeutic dose anticoagulation therapy-DVT

2.1 *NICE CG 144 recommendation paragraph 1.1.3 (KPI) and 1.1.4 (KPI)*

2.1.1 Relevant NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.1.3 (KPI) Offer patients in whom DVT is suspected and with a likely two-level DVT Wells score (see table 1) either: • a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test or • a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested. Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan. 1.1.4 (KPI) Offer patients in whom DVT is suspected and with an unlikely two-level DVT Wells score (see table 1) a D-dimer test and if the result is positive offer either: • a proximal leg vein ultrasound scan carried out within 4 hours of being requested or • an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.
Proposed quality statement	People with suspected DVT, where diagnostic investigations take longer than 4 hours, are offered interim therapeutic dose anticoagulation therapy.
Draft quality measure	**Structure:** Evidence of local arrangements to ensure people with suspected DVT where diagnostic investigations take longer than 4 hours are offered interim therapeutic dose anticoagulation therapy. **Process:** The proportion of people with suspected DVT where diagnostic investigations take longer than 4 hours who receive interim therapeutic dose anticoagulation therapy. Numerator – The number of people in the denominator receiving interim therapeutic dose anticoagulation therapy. Denominator – The number of people with suspected DVT whose diagnostic investigations take longer than 4 hours.
Definitions	Suspected DVT is where the diagnostic investigations have not yet confirmed DVT

2.1.2 Clinical and cost-effectiveness evidence

Recommendations 1.1.3 and 1.1.4 are intended to follow up patients with the appropriate tests after the pre-probability testing with a DVT Wells score.

The evidence is primarily drawn from (i) a large meta-analysis of diagnostic studies assessing the sensitivity and specificity of D-dimer tests for ruling out DVT and (ii) a large meta-analysis of ultrasound strategies. D-dimer tests have relatively high sensitivity but low specificity (false positive results common). Overall, the evidence showed that that ultrasound scans are effective as confirmatory tests (confirming the presence of DVT).

The four-hour limit to the ultrasound scan was based on safety considerations

Evidence shows that people can be at risk of deterioration or at risk of a PE if a confirmation scan is not available. That is why anticoagulants are recommended if there is a delay in getting access to a scan.

2.1.3 Patient experience

None identified

2.1.4 Patient safety

A comprehensive analysis of recent reported incidents (please see full accompanying report from the NPSA) identifies omission and delay in treatment as a priority area relating to patient safety.

2.1.5 Current practice

The NICE costing report for CG144 noted that current practice in respect to the recommendations to carry out a proximal leg vein ultrasound scan within 4 or 24 hours of being requested, appear to be variable. Expert opinion suggests that at present, ultrasound scan is a limited resource, and access can be a problem, especially at weekends or in more rural areas.

2.1.6 Current indicators

None identified

3. Interim therapeutic dose anticoagulation therapy-PE

3.1 NICE CG 144 recommendation paragraph 1.1.9 and 1.1.10 (KPI)

3.1.1 NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.1.9 (KPI) Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score (see table 2) **either**: • an immediate computed tomography pulmonary angiogram (CTPA) **or** • immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected. 1.1.10 (KPI) Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score (see table 2) a D-dimer test and if the result is positive offer **either**: • an immediate CTPA or • immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.
Proposed quality statement	People with suspected PE where diagnostic investigations take longer than 1 hour are offered interim therapeutic dose anticoagulation therapy.
Draft quality measure	**Structure:** Evidence of local arrangements to ensure people with suspected PE where diagnostic investigations take longer than 1 hour are offered interim therapeutic dose anticoagulation therapy. **Process:** The proportion of people with suspected PE where diagnostic investigations take longer than 1 hour who receive interim therapeutic dose anticoagulation therapy. Numerator – The number of people in the denominator receiving interim therapeutic dose anticoagulation therapy. Denominator – The number of people with suspected PE where diagnostic investigations take longer than 1 hour.
Definitions	Diagnostic investigations – these will be based on the algorithm.

3.1.2 Clinical and cost-effectiveness evidence

The most important outcome considered for recommendations 1.1.9 and 1.1.10 is the number of PE missed. This is balanced against minimising the

number of patients receiving unnecessary imaging or anticoagulation treatments.

For recommendation 1.1.9, the GDG concluded that CTPA is a sensitive test and patients with PE are unlikely to be missed. However, if CTPA is negative in a patient with suspected DVT, a proximal leg vein ultrasound scan should be offered so that the patient can get treated. Given that PE is potentially life threatening, the potential harms from a dose of a parenteral anticoagulant is less than the potential harms from delay of treatment. Based on the economic considerations, the GDG concluded that offering a CT scan to people with suspected PE and a 'likely' two level PE Wells score is part of the most cost-effective strategy.

In respect to timing, it was highlighted that untreated PE has an important risk of mortality. That is why anticoagulants are recommended if there is a delay in getting access to a CTPA, and stopped if the scan result is negative. A single dose of parenteral anticoagulant is likely to have an overall benefit to patients who are waiting for diagnostic imaging to exclude a PE.

For recommendation 1.1.10, the GDG concluded that offering a CT scan to people with suspected PE, an 'unlikely' PE Wells score **and** positive D-dimer test is part of the most cost-effective strategy.

The GDG decided to recommend anticoagulation if diagnosis of PE cannot be confirmed immediately based on safety reasons; no economic evidence was considered to inform this recommendation. The GDG recognised the importance of finding a safe and cost-effective strategy to identify which patients can be sent home safely (through the use of a PE Wells score and D-dimer), and reduce the number of people who get referred for a CTPA.

3.1.3 Patient experience

The guideline developers noted that people with claustrophobia may find the process of CTPA difficult.

3.1.4 Patient safety

A comprehensive analysis of recent reported incidents (please see full accompanying report from the NPSA) identifies the timeliness of drug therapy as a priority area relating to patient safety.

3.1.5 Current practice

No national data identified for access and timing of CTPA. The GDG noted that access to CTPA is usually unproblematic.

3.1.6 Current indicators

None identified

4. Mechanical interventions

4.1 NICE CG 144 recommendation paragraph 1.2.9 (KPI), 1.3.4

4.1.1 Relevant NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.2.9 (KPI) Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications, and: • advise patients to continue wearing the stockings for at least 2 years • ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions • advise patients that the stockings need to be worn only on the affected leg or legs. 1.3.4 Advise patients about the correct application and use of below-knee graduated compression stockings, how long they should be worn and when they should be replaced.
Proposed quality statement	People with proximal DVT are offered below-knee graduated compression stockings a week after diagnosis.
Draft quality measure	**Structure:** Evidence of local arrangements to ensure people with proximal DVT are offered below-knee graduated compression stockings within a week of diagnosis or when swelling is reduced **Process:** The proportion of people with proximal DVT who receive below-knee graduated compression stockings within a week of diagnosis or when swelling is reduced Numerator – The proportion of people in the denominator receiving below-knee graduated compression stockings within a week of diagnosis Denominator – The number of people with proximal DVT.
Definitions	NICE clinical guideline 144 states that below–knee graduated stockings graduated stockings should have an ankle pressure of 23mmHg Proximal DVT is defined as a DVT in the popliteal vein or above. Proximal DVT is sometimes referred to as 'above-knee DVT'. Contraindications – The GDG noted contraindications Note: these will be used within the draft quality standard.
Discussion points for TEG	As written, the draft statement does not include the term **'when swelling is reduced'** from the source recommendation. This is potentially an undefined term and would be very difficult to measure in the context of a quality statement. However, additional detail would be given in the definitions section so

	that this information is not lost. A full list of contraindications would be set out in the definitions section of the quality standard. Is incidence of post-thrombotic syndrome an appropriate outcome for this statement?

4.1.2 Clinical and cost-effectiveness evidence

The GDG discussed the safety and efficacy of graduated compression stockings (GCS) in the management of DVT and the prevention of Post-thrombotic Syndrome (PTS).

Recommendation 1.2.9 is drawn from evidence reviewed from two randomised controlled trials using knee length graduated compression hosiery in patients with proximal DVT. In the effectiveness review, no trials of thigh length graduated compression stockings were found. Overall, there was evidence to show a clinically important reduction in the incidence of PTS.

A simple cost analysis was conducted which concluded that the cost of two year treatment was deemed to be offset by the reduction in incidence of PTS showed by the clinical review.

The GDG discussed what ankle pressure should be recommended. It was noted that the stockings indicated for prevention of PTS were either class III stockings, or class II stockings if poorly tolerated. Either British Class III stockings (25-35 mm Hg) or and European Class II (23-32 mm Hg) would be appropriate. The terminology ‘over 23 mm Hg’ was chosen so that any stocking above this pressure could be considered. The GDG agreed that it was better for a patient to wear stockings even if the pressure was lower than that used in the clinical trials.

Based on consensus, recommendation 1.2.9 advises people to continue wearing the stockings for at least 2 years and this was based on the advice given to participants in the trials reviewed. The GDG concluded that patients should be encouraged to continue using stockings for 2 years, until further trial information is available.

The need for appropriate advice in respect to application, use and how long they should be worn is further supported in recommendation 1.3.4 which is an advice recommendation.

4.1.3 Patient experience

Skin problems or inconvenience to patients was widely discussed and the GDG agreed that patients need to be aware of the reason the stockings were prescribed and how to use them correctly.

The GDG discussed what ankle pressure should be recommended. It was noted that adherence may be lower if the compression pressure is higher because they are more difficult to apply and remove and less comfortable to wear on a day to day basis.

People who use graduated compression stockings to prevent PTS are expected to wear the stockings over a long period of time. The GDG noted that some of the contraindications mentioned can develop over time in certain people. However, information on adherence is not consistently reported in the full clinical guideline.

4.1.4 Patient safety

No issues identified relating specifically to mechanical interventions (see full accompanying report from the NPSA for broader themes).

4.1.5 Current practice

Comments received during consultation on the guideline suggested that the use of below-knee stockings is currently very low in the NHS.

4.1.6 Current indicators

None identified

5 Assessing risk factors

5.1 NICE CG 144 recommendation paragraph 1.2.1 (KPI)

5.1.1 Relevant NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.2.1 (KPI) Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions: • For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay. • For patients with an increased risk of bleeding consider UFH. • For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 1.2.7 and 1.2.8 on pharmacological systemic thrombolytic therapy in pulmonary embolism). Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3 on VKA for patients with confirmed proximal DVT or PE) is 2 or above for at least 24 hours, whichever is longer.
Proposed quality statement	People with VTE continuing anticoagulation therapy beyond/after/following an initial dose are offered an assessment of renal function and weight.
Draft quality measure	**Structure:** Evidence of local arrangements to ensure people with VTE continuing anticoagulation therapy beyond an initial dose are offered an assessment of renal function and weight **Process:** The proportion of people with VTE continuing anticoagulation therapy beyond an initial dose who receive an assessment of renal function and weight Numerator – The number of people in the denominator receiving an assessment of renal function and weight Denominator – The number of people with VTE continuing anticoagulation therapy beyond an initial dose.

5.1.2 Clinical and cost-effectiveness evidence

Recommendation 1.2.1 is based on evidence review of direct comparisons for all three groups of pharmacological agents available for the initial anticoagulation of VTE.

In reaching their conclusions, the GDG noted the importance of individual patient circumstances, such as comorbidities and contraindications in order to offer the most suitable agent. As set out in the GDG conclusions, important considerations include: renal status, Risk of bleeding or need for surgery or thrombolysis, risk of HIT, appropriate dose, patient preferences, route of administration for UFH.

In respect to renal status and appropriate dose, the GDG noted that dose adjustment and monitoring may be required as patients with renal impairment may accumulate excessive amounts of these drugs in the body. It was noted that dosing errors in administering LMWH to patients have been the subject of a National Patient Safety Agency alert (NPSA Rapid Response Report 14); doses were frequently not adjusted to the appropriate clinical indication, weight or renal function.

An important consideration for this recommendation is that patients should be weighed prior to receiving LMWH to ensure that they are prescribed the correct dose, especially in obese patients. Renal function should also be considered in all patients, although renal function testing should not delay the first dose it should be taken into account for subsequent doses.

5.1.3 Patient experience

The GDG noted the importance of patient preference and that both UFH and LMWH are of porcine origin which may be a concern to some patients.

5.1.4 Patient safety

A comprehensive analysis of recent reported incidents (please see full accompanying report from the NPSA) identifies the lack of risk assessment as a priority area relating to patient safety.

Dosing errors in administering LMWH to patients have been the subject of a National Patient Safety Agency alert (NPSA Rapid Response Report 14[1]); doses were frequently not adjusted to the appropriate clinical indication, weight or renal function. Patients should be weighed prior to receiving LMWH to ensure that they are prescribed the correct dose, especially in obese patients.

5.1.5 Current Practice

None identified.

[1] NPSA. http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=66780&type=full&

6. Thrombolytic therapy for PE

6.1 NICE CG 144 recommendation paragraph 1.2.7

6.1.1 Relevant NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.2.7 Consider pharmacological systemic thrombolytic therapy for patients with PE and haemodynamic instability (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE).
Proposed quality statement	People with PE and haemodynamic instability are offered pharmacological systemic thrombolytic therapy.
Draft quality measure	Structure: Evidence of local arrangements to ensure people with PE and haemodynamic instability are offered pharmacological systemic thrombolytic therapy Process: The proportion of people with PE and haemodynamic instability who receive pharmacological systemic thrombolytic therapy Numerator – The number of people in the denominator receiving pharmacological systemic thrombolytic therapy Denominator – The number of people with PE and haemodynamic instability
Definition	Haemodynamically unstable PE is when a patient with PE also has a low blood pressure defined by a systolic blood pressure < 90mmHg or a pressure drop of ≥40 mmHg for >15 minutes if not caused by an arrhythmia, hypovolaemia or sepsis. The haemodynamically unstable patient subgroup will include groups previously referred to as massive PE.
Discussion points for TEG	The basis of this draft statement is a consider recommendation.

6.1.2 Clinical and cost-effectiveness evidence, noting

The GDG reviewed the clinical and cost-effectiveness of thrombolytic therapy compared to anticoagulation for people with haemodynamically unstable PE and for people with haemodynamically stable PE. Clinical trials identified were classified as either of haemodynamically unstable PE or haemodynamically stable PE according to the majority of patients in each group.

The evidence suggests that treatment with pharmacological thrombolytic therapy may have advantages over anticoagulation in the relative reduction of overall mortality and VTE related mortality. However, pharmacological thrombolytic therapy is associated with the increased risk of harm from major bleeding.

In the evidence reviewed, the baseline risk of mortality was higher in the haemodynamically unstable subgroup (14%) than in the haemodynamically stable subgroup (4%). Therefore, overall clinical benefit was taken into account.

The GDG considered pharmacological thrombolytic therapy to have an overall benefit in the haemodynamically unstable subgroup but not the stable subgroup. However, limitations were identified in the quality of evidence. In addition, various definitions of severity were used for the studies reviewed, and there were no clear differentiation between patients with haemodynamically stable and unstable PE.

The potential of bias and uncertainty in the clinical evidence led the GDG to make recommendations where treatments should be considered for haemodynamically unstable patients rather than offered. An important consideration for this 'consider' recommendation is that treatment should be considered by the clinician and patient preference should be taken into account when feasible.

Recommendation 1.2.7 is therefore based on the clinical evidence reviewed and supported by GDG opinion, and therefore it is a "consider" recommendation.

6.1.3 Patient experience

An important consideration for this 'consider' recommendation is that treatment should be considered by the clinician and patient preference should be taken into account when feasible.

6.1.4 Patient safety

A comprehensive analysis of recent reported incidents (please see full accompanying report from the NPSA) identifies delay in treatment as a priority area relating to patient safety.

6.1.5 Current practice

None identified.

6.1.6 Current indicators

None identified.

7 Investigations for cancer

7.1 NICE CG 144 recommendation paragraph 1.5.1, 1.5.2 (KPI)

7.1.1 Relevant NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.5.1 Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer: • a physical examination (guided by the patient's full history) and • a chest X-ray and • blood tests (full blood count, serum calcium and liver function tests) and • urinalysis. 1.5.2 (KPI) Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or who do not have signs or symptoms of cancer based on initial investigation(see recommendation 1.5.1).(see recommendation 1.5.1).
Proposed quality statement	People with unprovoked VTE, aged 40 years and over, are offered further screening investigations for cancer.
Draft quality measure	**Structure:** Evidence of local arrangements to ensure people with unprovoked VTE over 40 are offered screening investigations for cancer. **Process:** The proportion of people with unprovoked VTE over 40 who receive screening investigations for cancer. Numerator – The number of people in the denominator receiving screening investigations for cancer. Denominator – The number of people with unprovoked VTE over 40.
Definition	Unprovoked VTE is defined as a DVT or PE in a patient with no antecedent major clinical risk factor for VTE who is not having hormonal therapy (oral contraceptive or hormone replacement therapy). Patients with active cancer, thrombophilia or a family history of VTE should also be considered as having an unprovoked episode because these underlying risks will remain unchanged in the patient. In this context, investigations for cancer refer to the investigation of patients who present symptomatically with a DVT and/or PE to determine whether the VTE could be related to a previously undetected cancer.
Discussion points for TEG	Recommendation 1.5.2 is a consider recommendation. Quality statements are, in general, based on the use of ‘offer’.

7.1.2 Clinical and cost-effectiveness evidence

The evidence review set out to establish whether investigations for cancer in patients with spontaneous VTE (DVT or PE) improve patient outcomes (morbidity and mortality).

Recommendation 1.5.1

The potential benefit of detecting cancer early and initiating treatment (reducing potential mortality and morbidity), and of instituting the optimal form and duration of anticoagulation (reducing potential morbidity for complication of anticoagulation treatment or recurrence) was considered against the potential harm from using these tests.

One randomised controlled trial was found which assessed the value of intensive investigations for cancer, in addition to routine history, examination, blood tests and chest x-rays in patients with a first episode of an unprovoked VTE. This showed that showed that the combination of tests as set out in recommendation 1.5.1 detect cancer in about 10% of patients with first episode unprovoked VTE with no prior cancer diagnosis.

Recommendation 1.5.1 is an 'offer' recommendation. In making this recommendation, the GDG concluded that there are few disadvantages in offering routine tests to all patients with unprovoked VTE.

Recommendation 1.5.2.

Recommendation 1.5.2 relating to further investigations is a 'consider' recommendation, drawn from data from the single RCT included in the study. The evidence was assessed to be of low quality, and uncertainty about the estimates obtained because of the small sample size and study limitations are noted. The economic evidence suggested that further assessment for cancer in patients with an idiopathic VTE is cost-effective.

The GDG decided the potential harms and additional costs that may be associated with further testing may be outweighed by the number of cancers detected and its impact on the management of the VTE. In making this recommendation, the GDG considered that the patient might want to undergo **further investigation** knowing that the risk of cancer is 1 in 10 patients.

The recommendation was chosen by the GDG to be a Key Priority for Implementation (KPI) as they considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes patient choice and means patients reach critical points in the care pathway more quickly.

In respect to the age range, the GDG concluded that people with an apparently unprovoked VTE over the age of 40 years are most likely to benefit.

7.1.3 Patient experience

Cancer patients are at particular risk of VTE. The GDG considered that the patient might want to undergo **further investigation** knowing that the risk of cancer is 1 in 10 patients.

7.1.4 Patient safety

No issues identified relating specifically to investigations for cancer (see full accompanying report from the NPSA for broader themes).

7.1.5 Current practice

The full clinical guideline notes that current clinical practice, in regards to the extent of investigations to determine the underlying cause of VTE, is variable.

7.1.6 Current indicators

None identified.

8 Thrombophilia testing

8.1 NICE CG 144 recommendation paragraph 1.6.1 and 1.6.4

8.1.1 Relevant NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.6.1 Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment. 1.6.4 Do not offer thrombophilia testing to patients who have had provoked DVT or PE.
Proposed quality statement	People with provoked VTE or people who are continuing anti-coagulation therapy do not have testing for thrombophilia.
Draft quality measure	**Structure:** Evidence of local arrangements to ensure people with provoked VTE or those continuing anti-coagulation therapy do not have testing for thrombophilia **Process:** The proportion of people with provoked VTE or those continuing anti-coagulation therapy who have testing for thrombophilia Numerator – The number of people in the denominator who have testing for thrombophilia Denominator – The number of people with provoked VTE or those continuing anti-coagulation therapy **Outcome:** Rates of thrombophilia testing
Definitions	Provoked VTE is defined as VTE which occurred in the presence of an antecedent (within 3 months) and transient major clinical risk factor for VTE (for example surgery, trauma, significant immobility and pregnancy or puerperium). The GDG also considered VTE that occurred in association with hormonal therapy (oral contraceptive or hormone replacement therapy) to be provoked as it has been shown that these patients are at a lower risk of recurrence. Continuing anticoagulation therapy is defined as the phase of anticoagulation treatment after the initial phase. This is usually with VKA treatment, though LMWH may be used particularly in cancer patients. See also ‘initial phase of treatment’ and ‘long-term treatment’.

8.1.2 Clinical and cost-effectiveness evidence

The evidence review set out to establish the effectiveness of thrombophilia testing in preventing recurrence of a venous thromboembolic event.

<u>Recommendation 1.6.1</u>

No clinical evidence was identified.

A UK health economic model showed that thrombophilia testing is cost-effective in patients with PE in men younger than 70 years and women younger than 50 years who had a DVT. However, the testing strategy was deemed to be cost-effective because of its implications on the management of the patient (therefore the patient would be prescribed anticoagulation). It was concluded that if the patient is already receiving long-term anticoagulation, thrombophilia testing becomes unnecessary and increases costs with no additional benefits.

Recommendation 1.6.4

No clinical or economic evidence was found. As part of other considerations, the GDG considered that people who have a provoked VTE are at less risk of recurrence and will be given short-term anticoagulation as standard treatment whether they have thrombophilia or not. Testing therefore has no utility as it does not change patient management.

8.1.3 Patient experience

The GDG commented there may be a psychological impact associated with thrombophilia testing that could lead to stress and anxiety in patients.

8.1.4 Patient safety

No issues identified relating specifically to thrombophilia testing (see full accompanying report from the NPSA for broader themes).

8.1.5 Current practice

The GDG discussed current practice in relation to how patients who currently have a provoked VTE are at less risk of recurrence and will be given short-term anticoagulation as standard treatment whether they have thrombophilia or not.

8.1.6 Current indicators

None identified.

9 Treatment and review in active cancer patients

9.1 NICE CG 144 recommendation paragraph 1.2.2 (KPI)

9.1.1 Relevant NICE clinical guideline recommendations and proposed quality statement

Guideline recommendations	1.2.2 (KPI) Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months. At 6 months, assess the risks and benefits of continuing anticoagulation.
Proposed quality statement	People with active cancer and confirmed proximal DVT or PE, are offered 6 months treatment with LMWH [and then reviewed].
Draft quality measure	**Structure:** Evidence of local arrangements to ensure people with active cancer and confirmed proximal DVT or PE, are offered 6 months treatment with LMWH. **Process:** The proportion of people with active cancer and confirmed proximal DVT or PE who receive 6 months treatment with LMWH. Numerator – The number of people in the denominator receiving 6 months treatment with LMWH. Denominator – The number of people with active cancer and confirmed proximal DVT or PE.
Definitions	For the purpose of this recommendation, the GDG considered the evidence available and defined active cancer as: receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma (BCC).

9.1.2 Clinical and cost-effectiveness evidence

The GDG considered for recommendation 1.2.2 that recurrent VTE, mortality and major bleeding were the most important outcomes. The other important outcome was quality of life.

In patients with cancer, the evidence considered for the recommendation suggests that anticoagulation for 6 months with LMWH leads to better outcomes compared to switching to a VKA after initial LMWH treatment. There was an important reduction of recurrent VTE in patients who had used LMWH compared to VKA when these were given over 6 months in patients with cancer. The treatment has an overall benefit compared to VKA. It is uncertain whether there are any important differences in the quality of life of patients as no studies included this as an outcome. Data were only available up to 6 months and only for patients with proximal DVT or PE.

Data from economic analyses suggest that use of LMWH instead of VKA is cost-effective. As there is stronger evidence from economical studies of additional benefits of LMWH in patients with cancer than patients without cancer, the GDG reported this intervention is likely to be more cost-effective in this group of patients.

In making this recommendation, the GDG agreed that at 6 months, the need to continue anticoagulation should be reassessed and discussed with the patient.

9.1.3 Patient experience

Using LMWH instead of VKA requires patients to have daily subcutaneous injections instead of taking oral tablets. The GDG considered patient preference and practicalities such as whether patients can reliably self-inject or have a carer (such as a relative or district nurse) to help to administer the injection and which should be taken into consideration. The ability of people who are offered treatment to adhere to the treatment plan is also important.

9.1.4 Patient safety

No issues identified relating specifically to treatment and review in active cancer patients (see full accompanying report from the NPSA for broader themes).

9.1.5 Current practice

No current practice data identified.

9.1.6 Current indicators

None identified.

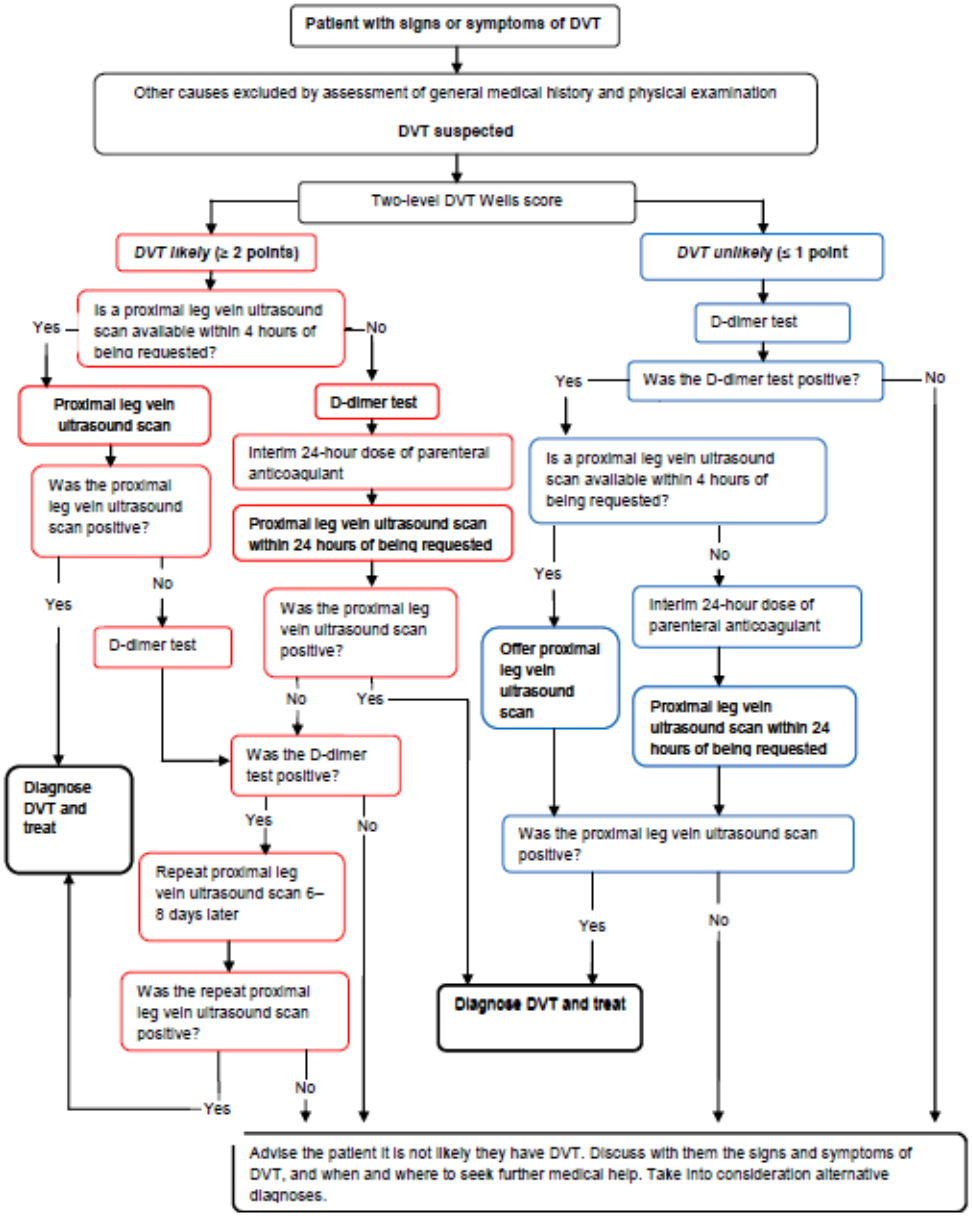
Appendix A: Definition of patient safety

The National Patient Safety Agency (NPSA) defines patient safety in the following terms:

Every day more than a million people are treated safely and successfully in the NHS, but the evidence tells us that in complex healthcare systems things will and do go wrong, no matter how dedicated and professional the staff. When things go wrong, patients are at risk of harm, and the effects are widespread and often devastating for patients, their families and the staff involved. Safety incidents also incur costs through litigation and extra treatment, and in 2009/10 the NHSLA paid out approximately £827, 000,000 in litigation costs and damages. These incidents are often caused by poor system design rather than the error of individuals i.e. ‘they are an accident waiting to happen’.

In short patient safety could be summarised as ‘The identification and reduction of risk and harm associated with the care provided to patients ‘or ‘Preventing patients from being harmed by their treatment’. Examples of this might be ‘operating on or removing the wrong organ, ten times the dose of an opioid, giving a colonoscopy to the wrong patient with the same name as someone else in the waiting room etc.’ These risks are unlikely to be identified through clinical trials or traditional evidence bases and so other evidence sources, such as the National Reporting and Learning System, need to be analysed to highlight the risks and improve system development. This does not however give an accurate picture of prevalence in that way that methods such as casenote review may do.

Appendix B: DVT diagnostic algorithm



Appendix C: PE diagnostic algorithm