National Institute for Health and Care Excellence

Final

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

[C] Evidence review for investigations for cancer in people with unprovoked venous thromboembolism

NICE guideline NG158

Evidence review underpinning recommendations 1.8.1 and 1.8.2 in the guideline

March 2020

Final version

This evidence review was developed by the NICE Guideline Updates Team

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Contents

Cancer investigations for people with an unprovoked venous thromboembolism (VTE)

Review question

Do investigations for cancer in people with unprovoked VTE improve outcomes (morbidity and mortality)?

Introduction

VTE risk is increased in people with cancer and an unprovoked VTE may be the first indication of an underlying malignancy. The presence of cancer has implications for the treatment of VTE as different agents and treatment durations are preferred in cancer-associated VTE as opposed to VTE without cancer. Furthermore, it is important that cancer is identified as early as possible as to maximise the effectiveness of its treatment. Conversely, cancer investigations may be time consuming, costly to perform, and may expose those people undergoing them to, stress, anxiety and, for certain investigations, radiation risk; it is therefore important that people are not unnecessarily subjected to them.

The (2012) NICE guideline for VTE recommends offering basic investigations (physical examination, chest X-ray, blood tests and urinalysis) to patients diagnosed with unprovoked DVT or PE and this has led to a shift in practice towards more extensive investigations (CT of chest ,abdomen and pelvis, PET scanning) being offered for people presenting with an unprovoked VTE. Additionally, it recommended considering an abdomino-pelvic CT scan in people over 40 years with a first unprovoked VTE who do not have signs of cancer. This recommendation has led to an increased use of these CT scans in practice.

A 2017 Cochrane review relating to this issue contained more recent – and better quality - evidence from randomised controlled trials (RCTs). This review found that although the evidence suggests that screening for cancer leads to a greater number of cancers being detected, this did not translate into any significant benefits with regards to mortality outcomes, prompting NICE to revisit this question here.

The aim of this review is to determine whether investigations for cancer in people with unprovoked VTE improve outcomes. It identified studies that fulfilled the conditions listed in Table 1. For full details of the review protocol, see appendix A.

PICO table

Table 1 PICO table for cancer investigations in people with VTE

Population	Adults (aged 18+) with an unprovoked VTE Unprovoked VTE is defined as: DVT or PE in a patient with: • No antecedent major clinical risk factor for VTE who is not having hormone replacement therapy (oral contraceptive or hormone replacement therapy) or

	• Active cancer, thrombophilia or a family history of VTE, because these are underlying risks that remain constant in the patient.
Intervention	Routine investigations for cancer including: • Abdominopelvic CT • Mammography • Chest x-ray • Blood tests • Urinalysis • PET scan • MRI scan • Ultrasound
Comparator	No routine* investigations for cancer/usual care *Investigations for cancer at the discretion of the clinician in the comparator group would not result in exclusion (e.g. in response to presence of other symptoms) but trials in which all participants in a comparator arm were given the investigation would be excluded.
Outcomes	Mortality outcomes: • All-cause mortality • Cancer related mortality Morbidity outcomes: • Characteristics of diagnosed cancer (e.g. primary tumour, stage, localised (curable) versus advanced (palliative) as defined in included studies). • Time to cancer diagnosis Other outcomes: • Length of hospital stay • Quality of life – Generic and disease-specific measures will be reported – Overall score will be reported (data on subscales will not be reported) • Adverse events – Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. – Incidental findings

Methods and process

This evidence review was developed using the methods and process described in developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in Appendix B.

A Cochrane review that matched that review protocol was identified (Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE (review) Robertson, 2017). This review was judged to be of high quality according to the ROBIS systematic review quality checklist and was fully applicable. Consequently, it was used as a direct source of evidence for the review (see Appendix B for details of how published systematic reviews were incorporated).

Results from the Cochrane review were presented as Odds ratios (ORs) however these were converted to Risk ratios (RRs) by the NICE Guideline Updates Team because the committee were more familiar with RRs and found them easier to understand. The data needed for this conversion was already reported in the Cochrane review.

The primary studies included in the Cochrane review were also examined to see whether any additional outcomes or subgroups were reported that matched the review protocol that were not reported in the original Cochrane review. No additional details were reported.

We would like to thank the Cochrane Vascular group for their assistance with the literature searching for the review.

The studies contained within this review used different screening strategies. For the purposes of this review, we have classified these as basic or extensive. Basic strategies refer to investigations that do not include comprehensive imaging (such as a physical examination, blood tests etc) and extensive strategies include imaging tests (such as comprehensive CT scans) in addition to any basic screening .The basic strategies and the type of imaging used in extensive strategies differed between studies. For information on the exact screening strategies used in each study see Table 2 and the evidence tables in Appendix E for more details.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Protocol deviation

Priority screening was not used for this review. All references returned by the search were screened at title and abstract level.

Clinical evidence

Included studies

The Robertson (2017) Cochrane review was judged to be fully applicable and of high quality therefore a search was carried out to identify studies published between the search date for the original review and the date of the date of this review for the VTE guideline (July 2018). Any additional studies identified were combined, where possible, with the evidence contained within the Cochrane review.

The systematic search carried out by the Cochrane vascular group found 3,736 references (see appendix C for literature search strategy). Taken together with the Cochrane review itself and the 4 primary studies included in it this made 3,741 references for the first stage of screening. Based on title and abstract, 3,727 references were excluded, and 14 references were ordered for screening at full text because they met the inclusion criteria specified in the review protocol (appendix A).

Of the 13 references screened as full texts, 8 articles were excluded, leaving 5 articles (the 4 articles included in the Cochrane review and the Robertson 2017 Cochrane review itself). The clinical evidence study selection is presented as a diagram in appendix D.

A second set of searches, using the original search strategies, were conducted at the end of the guideline development process to capture papers published whilst the guideline was being developed. These searches returned 6,272 references in total for all the questions included in the update, and these were screened on title and abstract. No additional relevant references were included for full text screening.

For the full evidence tables and GRADE profiles for included studies, please see appendix E and appendix G respectively. The references of individual included studies are given in appendix K.

Excluded studies

See Appendix J for a list of references for excluded studies, with reasons for exclusion.

Summary of clinical studies included in the evidence review

The Robertson (2017) review included 4 studies. The characteristics of these studies are shown in Table 2.

Table 2 Summary of included RCTs

Author (year)	Design	Sample size	Comparison (see appendix E for full details)	Follow-up	Outcomes
Carrier 2015	RCT	854	Extensive screening (basic screening plus CT) versus basic screening alone	1-year	Cancer-related mortality All-cause mortality Time to cancer diagnosis (mean time only) Characteristics of diagnosed cancer *-Rates of different types of cancers and early-stage (T1-2, N0,M0) cancer detection.*
Piccioli 2004	RCT	201	Extensive testing (including ultrasound and CT) versus tests at physician's discretion.	2-years	Cancer-related mortality Characteristics of diagnosed cancer *-Rates of different types of cancers, early-stage (T1-2,N0,M0) and late-stage (T3) cancer detection.*
Prandoni 2016	RCT	195	Extensive testing (including CT) versus tests at physician's discretion	2-years	Cancer-related mortality
Robin 2016	RCT	394	Extensive screening (basic screening plus 18-fluorodeoxyglucose PET/CT scan) versus basic screening alone	2-years	Cancer-related mortality All-cause mortality Time to cancer diagnosis (mean time only) Characteristics of diagnosed cancer

Author (year)	Design	Sample size	Comparison (see appendix E for full details)	Follow-up	Outcomes
					-Rates of different types of cancers, early-stage (T1-2,N0,M0) and late-stage (T3) cancer detection.

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix E for the evidence tables with risk of bias at the individual study level, appendix F for forest plots and appendix G for GRADE tables. Please refer to the evidence statement section for an overall summary of the evidence.

Risk of bias was assessed using the Cochrane risk of bias tool judgements reported in the original Cochrane review (Robertson, 2017), but the overall decision about applicability and risk of bias was made by the Guideline Updates Team.

Economic evidence

Included studies

A systematic search was carried out for this review question to identify relevant economic analyses. This search returned 346 records. In addition, 1 paper was identified from the economic evidence review for the 2012 update of the guideline. Of these records, 345 were excluded on title and abstract. The remaining 2 papers were screened in full, and 1 was included in the evidence review.

An additional search was conducted at the end of the guideline development process to capture economic evidence published while the guideline was being developed. This was conducted as a single rerun search covering all questions in the guideline. This search returned 2,013 records in total, all of which were excluded on title and abstract for this review question.

Excluded studies

1 study was excluded at the full text review stage.

Summary of economic studies included in the evidence review

Coyle et al. (2017) conducted a cost-utility analysis with a 1-year time horizon comparing a comprehensive abdominal and pelvic CT scan in combination with limited occult cancer screening (“extensive screening”) to a strategy of limited occult cancer screening alone (consisting of basic blood testing, chest radiography, and age- and sex-appropriate screening for breast, cervical and prostate cancer) in patients with an unprovoked VTE, from the perspective of the Canadian healthcare system. This evaluation was a within-trial analysis based on outcomes of the SOME trial (described in Carrier 2015 in the clinical evidence review).

Resource use data were collected during the trial at 4 months, 8 months and 12 months, and included physician visits, emergency room visits, hospitalisations, additional cancer investigations, and adverse events. Unit costs were taken from standard Canadian healthcare system sources. QALYs were calculated from EQ-5D scores measured at baseline and at 12 months.

Base case results showed that the extensive screening strategy produced an additional cost of CAD$551, and a trivially small QALY loss (<0.001) compared to the limited screening strategy. Therefore, the extensive screening strategy was dominated by limited screening. Probabilistic sensitivity analysis (conducted via non-parametric bootstrapping) found that extensive screening was cost effective in 28.3% of iterations at a threshold of CAD$50,000 (~£30,000) per QALY.

This evaluation was classified as being partially applicable, since it was conducted from a non-NHS perspective. It was categorised as having potentially serious limitations, since the analysis used a short time horizon and did not model effects of the strategies on survival.

Evidence statements

Extensive testing versus clinically indicated tests only

Very low quality evidence from up to 2 RCTs reporting data on up to 396 people with unprovoked VTE **found an increase** in early-stage cancer detection and a shorter time to cancer-diagnosis in those participants offered extensive testing for cancer compared to people tested only when clinically indicated.

Very low to low quality evidence from up to 2 RCTs reporting data on up to 396 people with unprovoked VTE **could not differentiate** any-cause mortality, cancer-related mortality or late-stage cancer detection between people offered extensive testing for cancer and people tested only when clinically indicated.

Standard screening plus PET/CT versus standard screening alone

Low to moderate quality evidence from up to 2 RCTs reporting data on up to 1,248 people with unprovoked VTE **could not differentiate** all-cause mortality, cancer-related mortality, early-stage or late-stage cancer detection, or time to cancer diagnosis between people offered standard screening plus PET/CT compared to people offered standard screening alone.

Economic evidence statements

One partially applicable study (Coyle et al., 2017) with potentially serious limitations found that a strategy of extensive cancer screening (comprehensive CT of the abdomen and pelvis as well as limited occult cancer screening) was dominated by a strategy of limited occult cancer screening alone. Probabilistic sensitivity analysis found that the extensive screening strategy was cost effective in only 28.3% of iterations at a threshold of CAD$50,000 (~£30,000) per QALY.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Cancer-related and all-cause mortality were identified as being the most important outcomes for this review question. Additionally, the committee agreed that the characteristics of cancers detected were of importance, particularly early-stage cancers, as these have the greatest potential for treatment. However, the committee noted that this outcome was difficult to interpret, as detection of cancers at an early stage can make curative treatment more likely, but also may result from overdiagnosis of very early-stage cancers that may never have an impact on survival or quality of life.

The quality of the evidence

The quality of the evidence was moderate for some mortality outcomes, but low to very low for all other outcomes and comparisons included in the review. The committee was concerned with the methodological differences between studies and the differences in the screening strategies used by these studies relative to each other.

There was particular concern regarding the degree to which the strategies employed by the different studies reflected those likely to be used in the NHS. The committee noted that the basic screening strategies used in both arms for the two trials comparing standard screening with standard screening and an additional PET or CT scanning (Carrier 2015 and Robin 2016) were very extensive and are not likely to reflect those strategies carried out currently in the NHS.

In addition, the studies comparing screening to screening only at the physician's discretion (Piccioli 2004 and Prandoni 2016) were conducted in Italy and therefore it is unclear whether the extent to which physicians investigate for cancer is comparable to the UK. The committee noted that Piccioli 2004 was terminated early, in part due to physicians in the control arm (investigations only at the physician's discretion) having shown an increased tendency to initiate screening in control participants after noticing a trend towards increased early stage cancer detection in the experimental arm. The committee again had concerns around whether this would reflect UK practice and noted the uncertainty around the extent to which participants in "physician's discretion" arm would have received investigative screening.

The committee were very concerned with the lack of precision in the studies included in this review, meaning that the accuracy of the effect estimates is uncertain and noted that due to this imprecision there is a scarcity of evidence relating to the use of extensive screening versus basic screening, and for the use of screening versus screening only at the physician's discretion.

Benefits and harms

Evidence from randomised controlled trials did not show a clear benefit from extensive screening compared with using diagnostic tests only at the discretion of the clinician in response to signs and symptoms of cancer. There was some evidence that showed extensive screening increased the number of early stage cancers detected and reduced the time to cancer diagnosis, but the committee noted that these outcomes were difficult to interpret. Early stage cancer diagnosis might mean that more cancers are potentially curable

but might also mean that cancers that are unlikely to ever have an impact on mortality or morbidity are unnecessarily identified and treated.

Evidence from randomised controlled trials comparing screening strategies that included PET or CT scanning compared with strategies that did not also showed no benefit of PET or CT scanning for any of the reported outcomes.

The committee also noted that there are negative consequences associated with screening for cancer, including patient anxiety regarding the potential presence of cancer and undergoing invasive, time-consuming tests. Some diagnostic tests for cancer (e.g. PET and CT scans) involve exposure to radiation. It is therefore important that investigations for cancer are not unnecessarily undertaken.

Consequently, the committee decided not to recommend extensive testing for cancer in people with unprovoked VTE. However, the committee acknowledged that unprovoked VTE is associated with an increased cancer risk, and so they agreed that a review of the individual's history (which may include the results of any previous imaging investigations), a physical examination and blood tests should be offered to assess possible symptoms or signs of cancer. They noted that the baseline blood tests should include tests of full blood count, renal and hepatic function, PT and APTT (prothrombin time and activated partial thromboplastin time). The committee agreed that the previous recommendation to routinely offer extensive screening to people with unprovoked VTE is not justified by current evidence, which does not show a benefit associated this level of screening. They therefore recommended that extensive screening is not conducted unless the person has other signs or symptoms that could indicate cancer. In addition, the committee agreed that it is good practice to encourage participation in sex-specific national screening programmes.

Although the committee agreed that the balance of benefits and harms to the individual with unprovoked VTE and cost to the health service was not in favour of extensive testing for cancer in all cases, further investigations should be considered when people have relevant symptoms or signs of cancer. They made a recommendation to reflect these points and cross referred to the NICE guideline on suspected cancer which contains additional relevant information.

Cost effectiveness and resource use

The committee discussed the cost-effectiveness of extensive screening and additional PET/CT scanning for cancer. They concluded that, since clinical evidence does not show that additional testing produces a statistically significant benefit in cancer-related mortality or all-cause mortality, the additional costs of extensive testing are unlikely to be justified by the health benefits produced. In addition, extensive cancer screening may lead to unnecessary patient anxiety, and PET/CT scans subject patients to unnecessary radiation. This conclusion is supported by the results of the analysis included in the economic literature review (Coyle et al., 2017), which found that extensive screening is unlikely to be cost effective at a threshold of CAD$50,000 (~£30,000). The committee noted that results of the meta-analysis conducted for the clinical review indicate that extensive screening does produce a borderline-significant increase in the number of early-stage cancers detected. However, this finding was not supported by evidence that early-stage detection translates into actual health benefits.

The committee indicated that an additional economic analysis (Di Nisio et al., 2005), based on the results of Piccioli 2004 study included in the clinical review, was included in the

evidence review for the 2012 update to this guideline. However, this analysis was excluded from the evidence review for the current update for several reasons. First, the study is a cost-effectiveness rather than a cost-utility analysis (reporting outcomes in terms of cost per life year gained, rather than cost per QALY). Since a relevant cost-utility analysis was identified in the literature (Coyle et al., 2017), this higher-quality evidence was prioritised. Second, it is unclear how the authors of the Di Nisio study calculated life years gained. This shortcoming was acknowledged in the 2012 update of the guideline and, because of this, the previous committee only considered outcomes in terms of cost per cancer diagnosis. Third, the study evaluates a total of 22 different screening strategies for cancer. Considering the Piccioli 2004 study on which the analysis is based has a sample size of 201 patients, it does not seem likely that the cancer detection rate for each of these strategies could be determined with any degree of accuracy. Fourth, the authors of the Di Nisio study do not conduct a probabilistic sensitivity analysis, and therefore do not characterise the uncertainty around their results. Finally, the absolute number of early-stage cancers detected by the extensive screening strategy reported by Piccioli 2004 is something of an outlier compared to the results of the other studies included in the clinical review. The Piccioli study reports an early-stage cancer detection rate of 9.1% (9 out of 99 patients) from extensive screening, compared to a mean of 1.8% in the extensive screening or PET/CT screening arms of the other 3 studies. Therefore, it seems likely that the Di Nisio evaluation overestimates the cost effectiveness of extensive screening.

The committee considered the potential resource impact of their recommendation and determined that it is likely to reduce the amount of extensive cancer screening and will therefore produce a cost saving. Offering a full history and physical examination is already current practice, so this aspect of the recommendation is not expected to produce any additional costs.

Appendices

Appendix A – Review protocol

Field (based on PRISMA-P	Content
Review question	Do investigations for cancer in people with unprovoked VTE improve outcomes (morbidity and mortality)?
Type of review question	Intervention
Objective of the review	The 4-year surveillance review identified new evidence to suggest that CT scans of the abdomen and pelvis in addition to routine or limited screening (as recommended in the 2015 version of the guideline) do not provide a clinically significant benefit in diagnosis or mortality rates for cancer in patients with VTE. Furthermore, the lack of benefit in additional cancer screening and the increased risk of radiation from CT scans was highlighted. This new evidence is inconsistent with the current recommendation to offer further investigations for cancer to all patients with unprovoked DVT or PE, therefore updated guidance is required on this.
Eligibility criteria – population/disease	Adults (18+ years) with a first, unprovoked VTE Unprovoked VTE is defined as: 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) or • Active cancer, thrombophilia or a family history of VTE, because these are underlying risks that remain constant in the patient.
Eligibility criteria – intervention(s)	Routine investigations for cancer including: • Abdominopelvic CT • Mammography • Chest x-ray • Blood tests

	• Urinalysis • PET scan • MRI scan • Ultrasound
Eligibility criteria – comparator(s)/control or reference (gold) standard	No routine* investigations for cancer/usual care *Investigations for cancer at the discretion of the clinician in the comparator group would not result in exclusion (e.g. in response to presence of other symptoms) but trials in which all participants in a comparator arm were given the investigation would be excluded.
Outcomes and prioritisation	• All-cause mortality • Cancer related mortality • Characteristics of diagnosed cancer (e.g. primary tumour, stage, localised (curable) versus advanced (palliative) as defined in included studies). • Time to cancer diagnosis • Length of hospital stay • Quality of life – Generic and disease-specific measures will be reported – Overall score will be reported (data on subscales will not be reported) • Adverse events – Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. – Incidental findings
Eligibility criteria – study design	Randomised controlled trials
Other inclusion exclusion criteria	English language papers only.
Proposed sensitivity/sub-group analysis	• Older people (defined as people over the age of 65) • People who have stage 3 to 5 chronic kidney disease. • People with a family history of cancer • People with a higher baseline cancer risk
Selection process – duplicate	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found

screening/selection/analysis	between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	This is an update of a question in CG144 (2012). Searches to be run from 02/08/2011.
Identify if an update	This is an update of a question in CG144 (2012). Searches to be run from 02/08/2011. <u>Recommendations that may change due to the update:</u> 1.5.1Offer 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. **[2012]** 1.5.2Consider 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 PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 1.5.1). **[2012]**
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual

Search strategy – for one database	For details please see appendix C of the evidence review
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Methods for assessing bias at outcome/study level	See appendix B
Criteria for quantitative synthesis (where suitable)	See appendix B
Methods for analysis – combining studies and exploring (in)consistency	See appendix B
Meta-bias assessment – publication bias, selective reporting bias	See appendix B
Assessment of confidence in cumulative evidence	See appendix B
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.

Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.
- A random 10% sample of the studies remaining in the database when the threshold were additionally screened, to check if a substantial number of relevant studies were not being correctly classified by the algorithm, with the full database being screened if concerns were identified.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.

- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 3. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 3: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not

Quality	Applicability	Use of systematic review
		covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. No MIDs were identified through this process. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. The committee agreed that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. The committee chose not to specify any other MIDs by consensus.

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised mean difference where no other MID was available, an MID of 0.5 was used. For relative

risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

The 'Evidence to Recommendations' section of each review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 4.

Table 4: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Publication bias

Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

Appendix C – Literature search strategies

The Cochrane Vascular group updated the searches used for "Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE (review)", (Robertson, 2017) on July 11th 2018 and 1st April 2019. The sources were the vascular group register, CENTRAL, clinicaltrials.gov, ICTRP search portal, Medline, Embase, CINAHL and AMED.

Strategies for the searching of the register and Medline are presented below.

Vascular Register search

#1 venous thromboembolism or vte AND INREGISTER AND 02/01/2017_TO_11/07/2018:CRSCREATED
#2 cancer or malignan* or tumour or tumor AND INREGISTER AND 02/01/2017_TO_11/07/2018:CRSCREATED
#3 screen* or test* AND INREGISTER AND 02/01/2017_TO_11/07/2018:CRSCREATED
#4 #1 AND #2 AND #3

Medline Strategy

1 THROMBOSIS/
2 THROMBOEMBOLISM/
3 Venous Thromboembolism/
4 exp Venous Thrombosis/
5 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab.
6 exp Pulmonary Embolism/
7 (PE or DVT or VTE).ti,ab.
8 ((vein* or ven*) adj thromb*).ti,ab.
9 (blood adj3 clot*).ti,ab.
10 (pulmonary adj3 clot*).ti,ab.
11 (lung adj3 clot*).ti,ab.
12 or/1-11
13 exp NEOPLASMS/
14 malignan*.ti,ab.
15 neoplas*.ti,ab.
16 cancer*.ti,ab.
17 (carcinoma* or adenocarcinoma*).ti,ab.
18 (tumour* or tumor*).ti,ab.
19 Trousseau.ti,ab.
20 or/13-19
21 exp Mass Screening/
22 exp Early Diagnosis/
23 screen*.ti,ab.
24 diagnos*.ti,ab.
25 assess*.ti,ab.

26 investigat*.ti,ab.
27 test.ti,ab.
28 testing.ti,ab.
29 or/21-28
30 12 and 20 and 29
31 randomized controlled trial.pt.
32 controlled clinical trial.pt.
33 randomized.ab.
34 placebo.ab.
35 drug therapy.fs.
36 randomly.ab.
37 trial.ab.
38 groups.ab.
39 or/31-37
40 exp animals/ not humans.sh.
41 39 not 40
42 30 and 41
43 (2017* or 2018*).ed.
44 42 and 43
45 from 44 keep 1-549

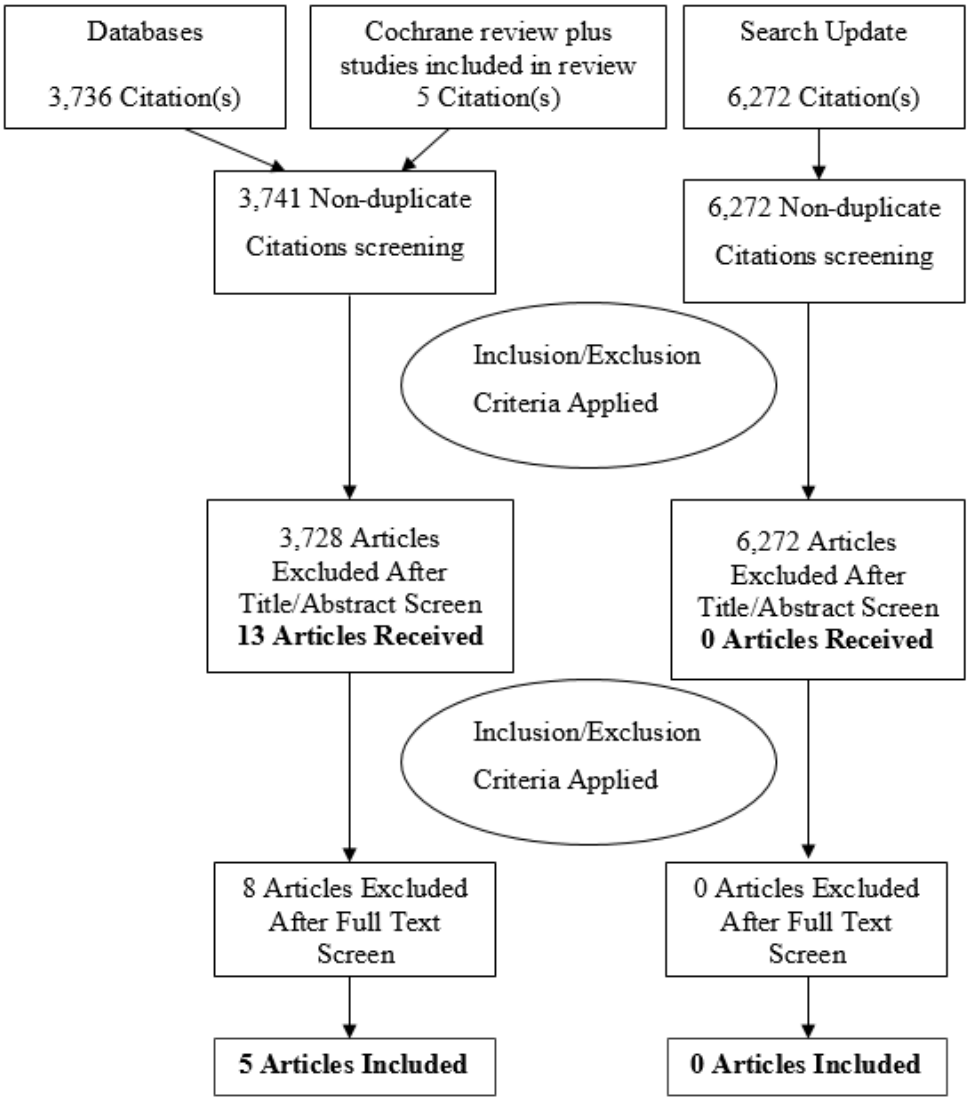
Searches to identify economic evidence published since the previous guidline were run on 17th July 2018 in Medline, Medline in Process, Embase, Econlit , NHS EED and the Health Technology Assessment Database. A single search to identify economic evidence across all questions was re run on 9th April 2019. The Medline trategy is presented below.

1 Venous Thrombosis/
2 (phlegmasia adj2 dolens).tw.
3 (thrombo* adj2 (vein* or venous)).tw.
4 (venous adj stasis).tw.
5 dvt.tw.
6 Venous Thromboembolism/ or Embolism, paradoxical/
7 vte.tw.
8 exp pulmonary embolism/
9 ((pulmonary or lung) adj4 (embol* or thromboembo* or microembol*)).tw.
10 (pulmonary adj infarction).tw.
11 or/1-10
12 exp *neoplasms/di
13 ((cancer$ or neoplasm$ or malignan$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$) adj4 (screen$ or test$ or diagnos$ or detect$ or occult or search$ or assess$ or investigat$ or scan* or exam*)).tw.
14 "Early Detection of Cancer"/
15 or/12-14
16 11 and 15
17 Economics/
18 exp "Costs and Cost Analysis"/
19 Economics, Dental/
20 exp Economics, Hospital/
21 exp Economics, Medical/
22 Economics, Nursing/

23 Economics, Pharmaceutical/
24 Budgets/
25 exp Models, Economic/
26 Markov Chains/
27 Monte Carlo Method/
28 Decision Trees/
29 econom$.tw.
30 cba.tw.
31 cea.tw
32 cua.tw.
33 markov$.tw.
34 (monte adj carlo).tw.
35 (decision adj3 (tree$ or analys$)).tw.
36 (cost or costs or costing$ or costly or costed).tw.
37 (price$ or pricing$).tw.
38 budget$.tw.
39 expenditure$.tw.
40 (value adj3 (money or monetary)).tw.
41 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
42 or/17-41
43 "Quality of Life"/
44 quality of life.tw.
45 "Value of Life"/
46 Quality-Adjusted Life Years/
47 quality adjusted life.tw.
48 (qaly$ or qald$ or qale$ or qtime$).tw.
49 disability adjusted life.tw.
50 daly$.tw.
51 Health Status Indicators/
52 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
53 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
54 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
55 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
56 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
57 (euroqol or euro qol or eq5d or eq 5d).tw.
58 (qol or hql or hqol or hrqol).tw.
59 (hye or hyes).tw.
60 health$ year$ equivalent$.tw.
61 utilit$.tw.
62 (hui or hui1 or hui2 or hui3).tw.
63 disutili$.tw.
64 rosser.tw.
65 quality of wellbeing.tw.
66 quality of well-being.tw.
67 qwb.tw.

68 willingness to pay.tw.
69 standard gamble$.tw.
70 time trade off.tw.
71 time tradeoff.tw.
72 tto.tw.
73 or/43-72
74 42 or 73
75 16 and 74
76 (201108* or 201109* or 20111* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018*).ed.
77 75 and 76
78 limit 77 to english language

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

Systematic review

Cochrane review (Robertson, 2017)

Study type	Systematic review
Databases searched	• CENTRAL *Cochrane register of studies* • WHO international clinical trials registry platform *Searched for details of ongoing and unpublished clinical trials* • Clinicaltrials.gov *Searched for details of ongoing and unpublished clinical trials* • ISRCTN registry *Searched for details of ongoing and unpublished clinical trials* • Cochrane specialised register *Maintained by the CIS and is constructed from weekly electronic searches of MEDLINE, Embase, CINAHL and AMED, and through hand searching relevant journals.*
Study inclusion criteria	• Randomized or quasi-randomized controlled trial *randomized within three months of VTE (other time points acceptable for sub-group analysis)* • Published studies

Study type	Systematic review
	or studies in progress with preliminary results available
Study exclusion criteria	None
Participant inclusion criteria	People with a first episode of unprovoked VTE (DVT of the lower limb or PE)
Participant exclusion criteria	Pre-existing or clinically apparent cancer diagnosis
Interventions	• Extensive tests versus tests at the physician's discretion *See individual study evidence tables (Piccioli 2004, Prandoni 2016) for further details.* • Standard testing plus PET/CT scanning versus standard testing alone *See individual study evidence tables (Carrier 2015, Robin 2016) for further details.*
Outcome measures	• Cancer characteristics *Type, stage (early or advanced) and overall frequency of cancer diagnoses.* • Cancer-related mortality • VTE-related mortality
Risk of bias	• Study eligibility and criteria: Low risk of bias *Review adhered to pre-defined objectives and eligibility criteria. Eligibility criteria were unambiguous, relevant to review question and there without inappropriate restrictions.* • Identification and selection of studies: Low risk of bias

Study type	Systematic review
	Search conducted using the Specialised Register (16 February 2017) and the Cochrane Register of Studies, and additionally searched the reference lists of relevant articles and searched the conference proceeding abstracts of the following societies: 1. International Society for Thrombosis and Haemostasis (ISTH) (2003 to 2016); 2. American Society for Hematology (ASH) (2004 to 2016). Search strategy was appropriate. • Data collection and study appraisal: Low risk of bias *Sufficient study characteristics were provided, all relevant study results were collected, and a formal risk of bias assessment was conducted.* • Synthesis and findings: Low risk of bias *All relevant identified studies were included in the evidence synthesis and all pre-defined analyses were reported. Although there were differences between studies in the types of cancer tests given, these were not deemed to be sufficiently large enough to limit pooling of results (in those instances where studies were combined for meta-analysis). Heterogeneity was minimal and biases were typically minimal or addressed when applicable.* • Overall risk of bias: Low • Applicability: Fully applicable

Studies contained within systematic review

The evidence tables below were based on information provided in the Cochrane review. Risk of bias and directness domains were decided by the Guideline Updates Team.

Carrier 2015

Study type	Randomised controlled trial
Funding	Heart and Stroke Foundation of Canada.
Location	Canada (9 centres)
Sample	854

Study type	Randomised controlled trial
Mean age (SD)	Screening + CT group: 53.4 (14.2) years Screening only group: 53.7 (13.8) years
% female	Screening + CT group: 29.3% Screening only group: 35.7%
Inclusion/exclusion criteria	Inclusion • First, unprovoked VTE (proximal lower-limb DVT, PE, or both). *Unprovoked VTE defined as VTE in absence of known overt active cancer, current pregnancy, thrombophilia (hereditary or acquired), previous unprovoked VTE or a temporary predisposing factor in the previous 3 months, including paralysis, paresis or plaster immobilisation of the legs, confinement to bed for ≥ 3 days or major surgery.* Exclusion: • <18 years old • Refusal or inability to provide informed consent • Allergy to contrast media; creatinine clearance <60 mL per minute • Claustrophobia or agoraphobia • Weight >130 kg; ulcerative colitis • Glaucoma
Intervention (Screening plus CT)	Screening procedure: Complete history and physical examination, measurement of complete blood counts and serum electrolyte and creatinine levels, liver-function testing and chest radiography. Sex-specific screening conducted if it had not been performed in previous year. Breast examination, mammography, or both performed in women > 50 years of age and Pap testing and a pelvic examination performed in women 18-70 years of age who had never been sexually active. Prostate examination, PSA test, or both performed in men aged > 40 years.

Study type	Randomised controlled trial
	CT: Additional, comprehensive CT of abdomen and pelvis (virtual colonoscopy and gastroscopy, biphasic enhanced CT of liver, parenchymal pancreatography, and uniphasic enhanced CT of distended bladder). *Reproduced from the Cochrane review (Robertson, 2017)
Control (screening only)	Underwent screening (same as intervention group) only
Outcome	1 year follow up. • Characteristics of diagnosed cancers *Rates of early-stage cancer detection (T1−2,N0,M0 according to the World Health Organization TNM classification system)* • Cancer-related mortality • All-cause mortality • Time to cancer diagnosis (no SD given)
Risk of bias	Random sequence generation (selection bias) • *Low risk*- randomisation list using random-number tables. Allocation concealment (selection bias) • *Low risk*- used a central Web-based randomisation system Blinding of participants and personnel (performance bias) • *Low risk- p*articipants and study personnel were unblinded but this is unlikely to affect outcomes. Blinding of outcome assessment (detection bias) • *Low risk- blinded* Incomplete outcome data (attrition bias) • *Low risk*

Study type	Randomised controlled trial
	Selective reporting (reporting bias) • *Low risk* Other bias • *Low risk* Overall risk of bias • *Low* Applicability • Directly applicable

Piccioli 2004

Study type	RCT
Funding	Associazone Italiana per le Ricerca sul Cancro
Location	Italy (Undisclosed number of centres)
Sample	201
Mean age (SD)	Screening group: 66.2 (13.1) years No screening group: 66.6 (13.1) years
% female	Screening group: 45.5% No screening group: 54.9%

Study type	RCT
Inclusion/exclusion criteria	Inclusion: • Apparently cancer-free • Documented first, unprovoked symptomatic deep vein thrombosis of the lower extremity or pulmonary embolism *Unprovoked VTE defined as VTE in absence of known overt active cancer, current pregnancy, thrombophilia (hereditary or acquired), previous unprovoked VTE or a temporary predisposing factor in the previous 3 months, including paralysis, paresis or plaster immobilisation of the legs, confinement to bed for ≥ 3 days or major surgery.* Exclusion: • <25 years old • Recognised risk factor for VTE (malignant disease, trauma of the leg, surgical procedures or immobilisation within 6 months, confirmed spontaneous VTE in a first-degree relative, deficiency of antithrombin, protein C or S, presence of circulation lupus anticoagulant, oestrogen use, pregnancy or childbirth) • Previously documented VTE • Malignant disease identified at routine physical examination, history taking, laboratory assessment or chest X-ray at referral • Unable to attend follow-up date due to geographic inaccessibility
Intervention	Screening procedure: combination of ultrasound and CT scan of abdomen and pelvis, gastroscopy or double-contrast barium swallow, flexible sigmoidoscopy or rectoscopy followed by barium enema or colonoscopy, haemoccult, sputum cytology and tumour markers including carcinoembryonic antigen, _-fetoprotein and CA125. In addition, women had gynaecological examination, Pap smear and mammography. Men had a transabdominal ultrasound of prostate and total PSA test *Reproduced from the Cochrane review (Robertson, 2017)
Control	No standardized screening, tests performed at physician's discretion.
Outcome	2-year follow-up. • Cancer-related mortality

Study type	RCT
	Defined as death due to malignant disease itself, or death due to complications of diagnostic or surgical procedures performed to diagnose or treat cancer. • Characteristics of diagnosed cancer *Reported the rates of different types of cancers, early-stage cancer detection (defined as T1-T2, N0,M0) and late-stage cancer detection (T3).*
Risk of bias	Random sequence generation (selection bias) • *Low risk* Allocation concealment (selection bias) • *Low risk-* randomized centrally Blinding of participants and personnel (performance bias) • *Low risk- p*articipants and study personnel were unblinded but this is unlikely to affect outcomes. Blinding of outcome assessment (detection bias) • *Low risk- blinded* Incomplete outcome data (attrition bias) • *Low risk* Selective reporting (reporting bias) • *Low risk* Other bias • *High risk* - study terminated early after inclusion of only 201 participants after 5 years for several reasons. First, only 5 of the more than 40 potential participating centres could contribute participants to the study. Second, some medical ethics committees rejected the protocol because of the absence of screening for occult cancer in the control group, other centres could not start because the proposed extensive screening was judged to be unethical. Finally, identification of cancer at an apparent early stage in the extensive screening group led to an increasing tendency among physicians in participating hospitals to initiate screening for cancer in control participants

Study type	RCT
	Overall risk of bias • *High – Study terminated early and there were instances of cancer screening taking place in control group.* Applicability • Directly applicable

Prandoni 2016

Study type	RCT
Funding	None stated
Location	Italy (5 centres)
Sample	195
Mean age (SD)	Extensive screening group: 69.3 (14) years. Control group: 69.0 (14) years
% female	Extensive screening group: 44.9% Control group: 51.5%
Inclusion/exclusion criteria	Inclusion: • Apparently cancer-free on initial screening • Objectively diagnose, first, unprovoked VTE Exclusion:

Study type	RCT
	• <18 years old • Previously documented VTE • Unable to attend follow-up date due to geographic inaccessibility • Known allergy to contrast medium • Prior CT scan of torso for any reasons within 6 months from presentation.
Intervention (extensive screening)	Screening procedure: extensive screening with mandatory CT scan of thorax, abdomen and pelvis together with haemoccult test or any test at physician's discretion according to good clinical practice *Reproduced from the Cochrane review (Robertson, 2017)
Control	Personalised strategy consisting of additional testing based on physicians' judgements and participants' preferences, including a 'no-further testing' option *Reproduced from the Cochrane review (Robertson, 2017)
Outcome	3, 6, 12 and 24months' follow-up. • Cancer-related mortality *Defined as death due to malignancy or death due to the complications of the diagnostic or surgical procedures performed to diagnose or treat cancer*
Risk of bias	Random sequence generation (selection bias) • *Low risk-* Allocation concealment (selection bias) • *Low risk- Concealed* allocation was ensured by employing serially numbered, opaque, sealed envelopes. Each participating centre was initially assigned a lot of 20 envelopes, while subsequent allocations were in lots of 10, as needed

Study type	RCT
	Blinding of participants and personnel (performance bias) • *Low risk- p*articipants and study personnel were unblinded but this is unlikely to affect outcomes. Blinding of outcome assessment (detection bias) • *Low risk- blinded* Incomplete outcome data (attrition bias) • *Low risk* Selective reporting (reporting bias) • *Low risk* Other bias • *High risk* - interim analysis scheduled after inclusion of approximately half of planned sample size. Based on results of this analysis, study promoters decided to stop study enrolment because of low recruitment rate and of failure to show an appreciable advantage of CT-based strategy over control strategy for detection of occult cancers. Overall risk of bias • *Moderate – Study stopped at interim analysis stage (planned prospectively) due to failure of CT strategy to show advantage.* Applicability • Directly applicable

Robin 2016

Study type	RCT
Funding	Programme Hospitalier de Recherche Clinique (French Department of Health)
Location	France (4 centres)

Study type	RCT
Sample	394
Mean age (SD)	Screening group: 64 (range 48-77) years Limited-screening group: 62 (50-75) years
% female	Screening group: 46.7% Limited-screening group: 48.2%
Inclusion/exclusion criteria	Inclusion: • Apparently cancer-free on initial screening • Diagnosed, unprovoked VTE (proximal DVT or PE) *Unprovoked VTE defined as VTE not provoked by major inherited or acquired risk factor including surgery, trauma or fracture during 3 months before VTE event, known antiphospholipid antibody syndrome or known deficiency in antithrombin, protein C or protein S* Exclusion: • <18 years old • Ongoing pregnancy • Active malignant disease (known malignant disease which was active or treated during previous 5 years) • Not insured under French National Social Security programme • Hypersensitivity to 18F-FDG or any of the excipients according to summary of product characteristics in France • Unable or unwilling to give consent
Intervention (Screening)	Screening strategy consisting of limited strategy + 18F-FDG PET/CT scan of chest, abdomen and pelvis. *Reproduced from the Cochrane review (Robertson, 2017)

Study type	RCT
Control **(limited screening)**	Limited screening strategy (physical examination, usual laboratory tests and basic radiographs) *Reproduced from the Cochrane review (Robertson, 2017)
Outcome	2-years duration • All-cause mortality • Cancer-related mortality • Characteristic of cancer *Reported the rates of different types of cancers, early-stage cancer detection (defined as T1-T2, N0,M0) and late-stage cancer detection (T3).*
Risk of bias	Random sequence generation (selection bias) • *Low risk*- randomisation using computer-generated block sizes of six, stratified by centre. Allocation concealment (selection bias) • *Low risk*- randomised centrally and concealed from investigators. Unique study participant number and study group allocation was given after patients' basic information and eligibility criteria were entered by the study personnel. Blinding of participants and personnel (performance bias) • *Low risk- p*articipants and study personnel were unblinded but this is unlikely to affect outcomes. Blinding of outcome assessment (detection bias) • *High risk- unblinded* Incomplete outcome data (attrition bias) • *Low risk* Selective reporting (reporting bias) • *Low risk*

Study type	RCT
	Other bias • *Low risk* Overall risk of bias • *Low – participants, investigators and outcome assessors were unblinded however this was not deemed as potentially having a significant impact on the outcomes.* Applicability • Directly applicable

Appendix F – Forest plots

The following plots used data taken from the Cochrane review. However, for the outcome of all-cause mortality, data were taken from the individual studies as the Cochrane review excluded certain types of mortality from their analysis. For this review, the outcomes of all-cause mortality includes all deaths occurring during the study period.

Extensive testing versus clinically indicated tests only

Figure 1: Cancer-related mortality

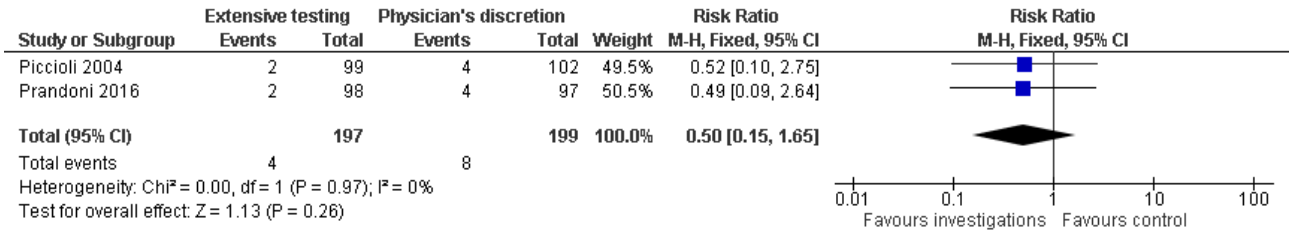


Figure 2: Early-stage cancer detection

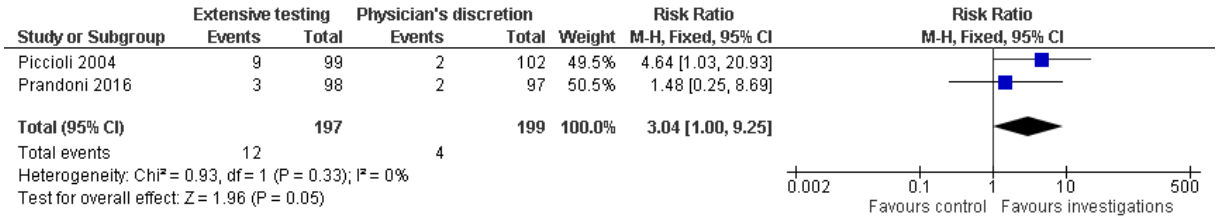
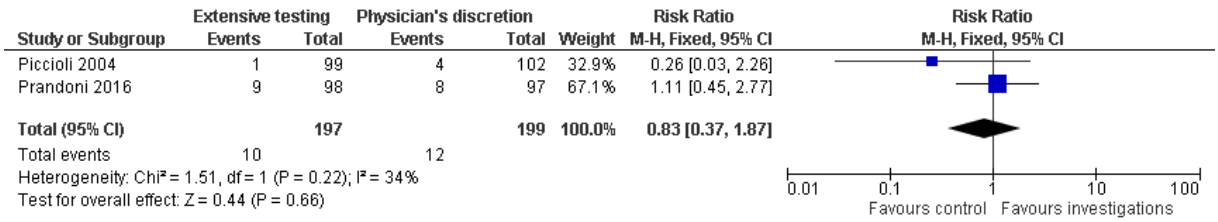


Figure 3: Late-stage cancer detection



Standard screening plus PET/CT versus standard screening alone

Figure 4: All-cause mortality (including cancer- related mortality)

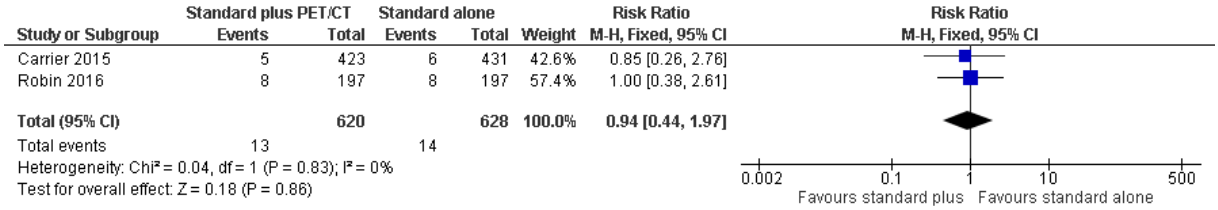


Figure 5: Cancer-related mortality

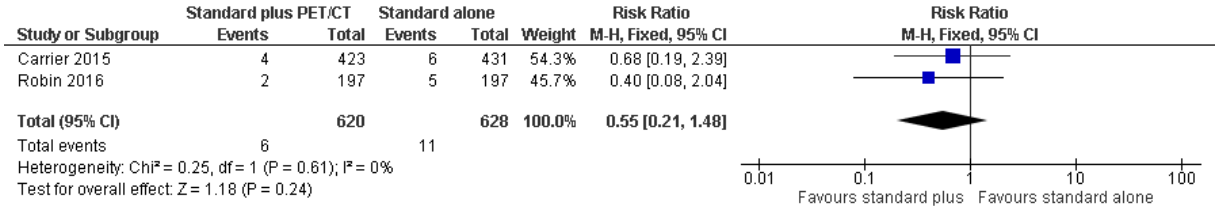
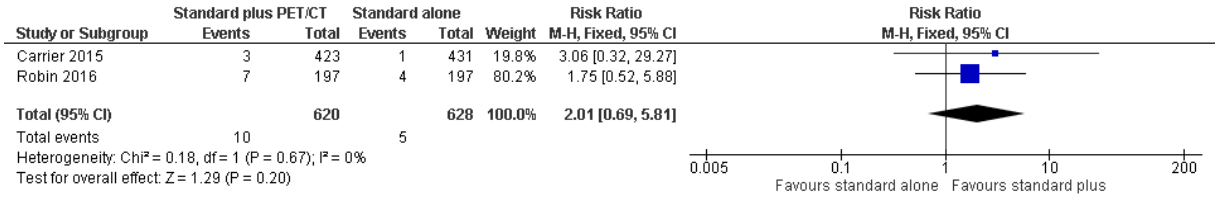


Figure 6: Early-stage cancer detection



Appendix G – GRADE profiles

The following GRADE tables were completed by the NICE Guideline Updates Team tables are based on evidence on effect sizes from the Cochrane review (Robertson et al. 2017). However, the dichotomous data has been altered to show RR, not OR, and the choice of fixed effect or random effects model is made according to the methods in appendix B.

Extensive testing versus clinically indicated tests only

Quality assessment						No of patients		Effect			Quality
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Screening**	**Control**	**Relative (95% CI)**	**Absolute: control**	Absolute: intervention (Screening)	
Any-cause mortality (2-years) (follow-up 2 years): RR <1 favours screening											
1 (Prandoni 2016)	RCT	Serious[6]	N/A	Not serious	Serious[7]	7/98	11/89	RR 0.58 (0.23, 1.43)	12.36 per 100	7.17 per 100 (2.84 to 17.67)	Low
Cancer-related mortality (2-years) (follow-up 2 years): RR <1 favours screening (Figure 1)											
2	RCT	Very serious[1]	Not serious	Not serious	Serious[7]	4/197	8/199	RR 0.50 (0.15, 1.65)	4.02 per 100	2.01 per 100 (0.60 to 6.63)	Low
Early-stage cancer detection: RR<1 favours control (Figure 2)											
2	RCT	Very serious[1]	Not serious	Not serious	Serious[4]	12/197	4/199	RR 3.04 (1.00, 9.25)	2.01 per 100	6.11 per 100 (2.01 to 18.59)	Very low
Late-stage cancer detectioup to 2 yearn: RR<1 favours control (Figure 3)											
2	RCT	Very serious[1]	Serious[5]	Not serious	Very serious[2]	10/197	12/199	RR 0.83 (0.37, 1.87)	6.03 per 100	5.01 per 100 (2.23 to 11.28)	Very Low
Time to cancer diagnosis: Mean difference <0 favours screening											
1 (Piccioli 2004)	RCT	Very serious[3]	N/A	Not serious	Serious[8]	Mean: 1.0 months	Mean: 11.6 months	-	-	-	Very low

1. Both studies were terminated early with other risks of bias present
2. 95% confidence interval crosses 2 MIDs (0.8,1.25)
3. Study was terminated early and identification of early-stage cancer lead to increasing tendency to screen control group
4. 95% confidence interval crosses 1 MID (1.25).
5. I^2>33.3%

Quality assessment						No of patients		Effect			Quality
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Screening**	**Control**	**Relative (95% CI)**	**Absolute: control**	Absolute: intervention (Screening)	

6. Study was at moderate risk of bias
7. 95% confidence interval crosses the line of no effect.
8. Standard deviations not given but the difference between groups was reported as significant (P<0.001).

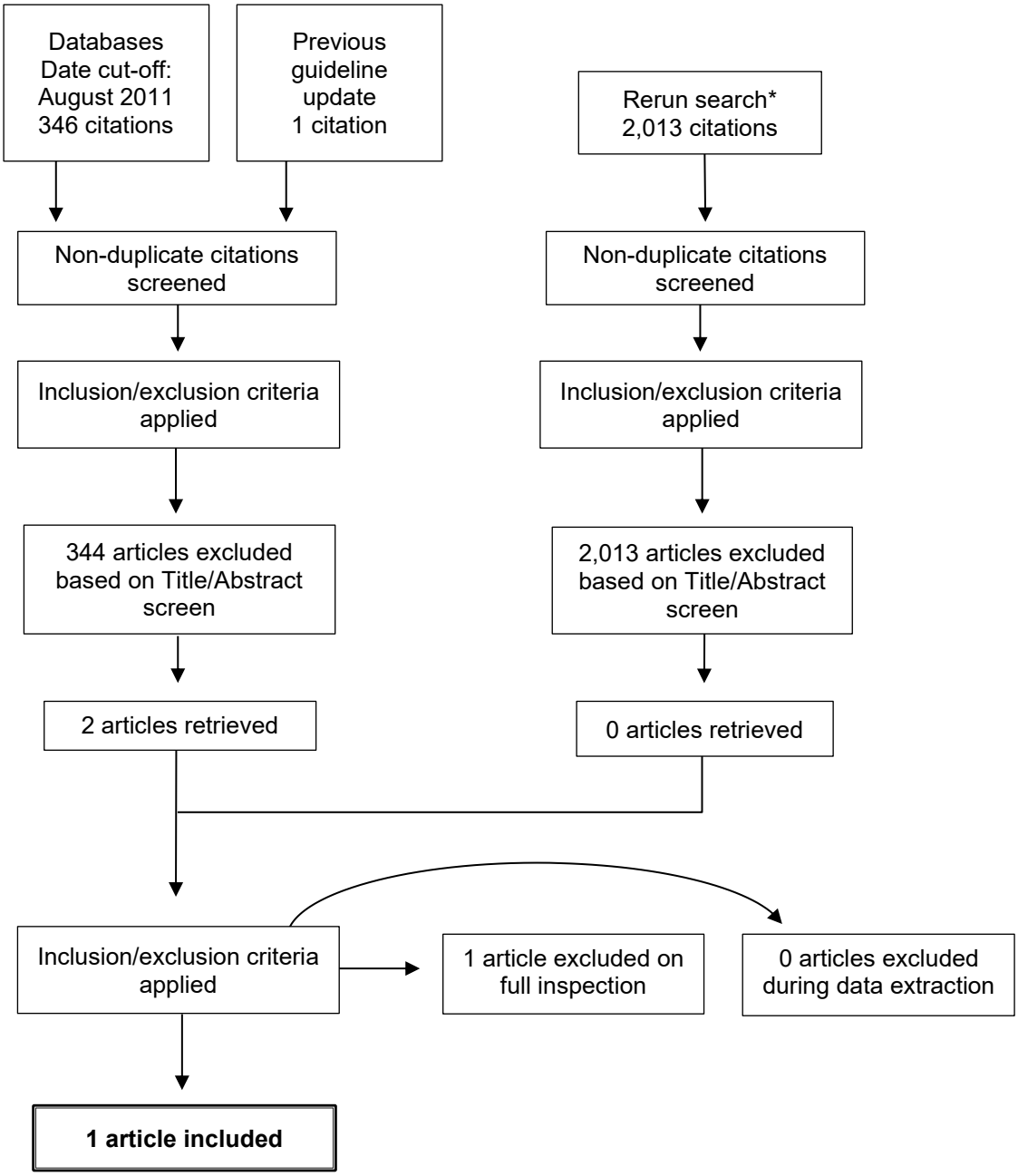
1 **Standard screening plus PET/CT versus standard screening alone**

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Screening plus	Control	Relative (95% CI)	Absolute: Control	Absolute: intervention (Screening plus)	
All-cause mortality (1- to 2-years): RR <1 favours screening plus (Figure 4)											
2	RCT	Not serious	Not serious	Not serious	Serious[1]	13/620	14/628	RR 0.94 (0.44, 1.97)	2.23 per 100	2.10 per 100 (0.98, 4.39)	Moderate
Cancer-related mortality (1- to 2-years): RR <1 favours screening plus (Figure 5)											
2	RCT	Not serious	Not serious	Not serious	Serious[1]	6/620	11/628	RR 0.55 (0.21, 1.48)	1.75 per 100	0.96 per 100 (0.37, 2.59)	Moderate
Early-stage cancer detection: RR<1 favours control (Figure 6)											
2	RCT	Not serious	Not serious	Not serious	Very serious[2]	10/620	5/628	RR 2.01 (0.69, 5.81)	0.80 per 100	1.60 (0.55, 4.63)	Low
Late-stage cancer detection: RR<1 favours control											
1 (Robin 2016)	RCT	Not serious	N/A	Not serious	Very serious[2]	2/197	2/197	RR 1.00 (0.14, 7.03)	1.02 per 100	1.02 per 100 (0.14, 7.14)	Low
Time to cancer diagnosis: Mean difference <0 favours screening											
1 (Carrier 2015)	RCT	Not serious	N/A	Not serious	Very serious[3]	Mean: 4.0 months	Mean: 4.2 months	-	-	-	Low

1. 95% confidence interval crosses the line of no effect.
2. 95% confidence interval crosses 2 MIDs (0.8, 1.25).
3. Standard deviations not given and the difference between groups was reported as non-significant (P=0.88)

2

Appendix H – Economic evidence study selection



**Combined for all questions in the guideline*

Appendix I – Economic evidence profiles

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Coyle (2017)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Extensive cancer screening (comprehensive abdominal and pelvic CT scan plus limited occult cancer screening) versus limited occult screening alone	Canada	1 year N/A (time horizon only 1 year)	Extensive cancer screening produces an incremental cost of CAD$551 and a trivially small QALY loss (<0.001) compared to limited screening. Extensive cancer screening is therefore dominated by limited screening in the base case.	Probabilistic sensitivity analysis found that extensive cancer screening is cost effective in 28.3% of iterations at a threshold of CAD$50,000 (~£30,000) per QALY.

(a) Conducted from a non-NHS perspective
(b) Short time horizon, no modelling of effects of strategies on survival

Appendix J – Excluded studies

Clinical studies

Study	Reason for exclusion
Klein, A.; Shepshelovich, D.; Spectre, G.; Goldvaser, H.; Raanani, P.; Gafter-Gvili, A., Screening for occult cancer in idiopathic venous thromboembolism - Systemic review and meta-analysis, European Journal of Internal Medicine, 42, 74-80, 2017	More recent systematic review included that covers the same topic
Robin, P.; Le Roux, P. Y.; Lacut, K.; Planquette, B.; Prevot-Bitot, N.; Lavigne, C.; Pastre, J.; Merah, A.; Le Gal, G.; Salaun, P. Y., Performance of fluorodesoxyglucose positron-emission tomography combined with low-dose computed tomography for cancer screening in patients with unprovoked venous thromboembolism, PLoS ONE, 12 , 6, 2017	Secondary publication of an included study that does not provide any additional relevant information
Ebell, Mark H., Routine CT Scans for Occult Malignancy Not Useful in Patients with Unprovoked VTE, American Family Physician, 93, 1, 59-60, 2016	Review article but not a systematic review
Robin, P.; Le Roux, P. Y.; Le Moigne, E.; Planquette, B.; Prevot-Bitot, N.; Roy, P. M.; Pastre, J.; Merah, A.; Couturaud, F.; Le Gal, G.; Salaun, P. Y., Additional testing following screening strategies for occult malignancy diagnosis in patients with unprovoked venous thromboembolism, Thrombosis Research, 155, 6-9, 2017	Secondary publication of an included study that does not provide any additional relevant information
Robin, P.; Le Roux, P. Y.; Tromeur, C.; Planquette, B.; Prevot-Bitot, N.; Lavigne, C.; Pastre, J.; Merah, A.; Couturaud, F.; Le Gal, G.; Salaun, P. Y., Risk factors of occult malignancy in patients with unprovoked venous thromboembolism, Thrombosis Research, 159, 48-51, 2017	Secondary publication of an included study that does not provide any additional relevant information
Coyle, K.; Carrier, M.; Lazo-Langner, A.; Shivakumar, S.; Zarychanski, R.; Tagalakis, V.; Solymoss, S.; Routhier, N.; Douketis, J.; Coyle, D., Cost effectiveness of the addition of a comprehensive CT scan to the abdomen and pelvis for the detection of cancer after unprovoked venous thromboembolism, Thrombosis Research, 151, 67-71, 2017	Secondary publication of an included study that does not provide any additional relevant information
van Es, Nick; Ga, Grégoire Le; Otten, Hans-Martin; Robin, Philippe; Piccioli, Andrea; Lecumberri, Ramón; Jara-Palomares, Luis; Religa, Piotr; Rieu, Virginie; Rondina, Matthew; Beckers, Mariëlle M.; Prandoni, Paolo; Salaun, Pierre-Yves; Di Nisio, Marcello; Bossuyt, Patrick M.; Büller, Harry R.; Carrier, Marc; Le Gal, Grégoire, Screening for Occult Cancer in Patients	Systematic review used as source of primary studies

Study	Reason for exclusion
With Unprovoked Venous Thromboembolism: A Systematic Review and Meta-analysis of Individual Patient Data, Annals of Internal Medicine, 167, 6, 410-417, 2017	
Gallus, Alexander, 2017 - Review: In patients with a first VTE, extended testing for undiagnosed cancer does not reduce mortality, ACP Journal Club, 167, 12, 3-3, 2017	Systematic review used as source of primary studies

Economic studies

Study	Reason for exclusion
Di Nisio, M., Otten, H.M., Piccioli, A., Lensing, A.W.A., Prandoni, P., Büller, H.R. and Prins, M.H., 2005. Decision analysis for cancer screening in idiopathic venous thromboembolism. Journal of Thrombosis and Haemostasis, 3(11), pp.2391-2396.	Health outcomes not reported in terms of QALYs

Appendix K – References

Included clinical studies

Robertson, L.; Yeoh, S. E.; Stansby, G.; Agarwal, R.; Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE; Cochrane Database of Systematic Reviews; 2017; vol. 2017 (no. 8)

Containing:

Piccioli, A., Lensing, A. W. A., Prins, M. H., Falanga, A., Scannapieco, G. L., Ieran, M., ... & Prandoni, P. (2004). Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial. *Journal of Thrombosis and Haemostasis*, *2*(6), 884-889.

Carrier, M., Lazo-Langner, A., Shivakumar, S., Tagalakis, V., Zarychanski, R., Solymoss, S., ... & Le Gal, G. (2015). Screening for occult cancer in unprovoked venous thromboembolism. *New England Journal of Medicine*, *373*(8), 697-704.

Prandoni, P., Bernardi, E., Dalla Valle, F., Visonà, A., Tropeano, P. F., Bova, C., ... & Piccioli, A. (2016). Extensive computed tomography versus limited screening for detection of occult cancer in unprovoked venous thromboembolism: a multicenter, controlled, randomized clinical trial. In *Seminars in thrombosis and hemostasis* (Vol. 42, No. 08, pp. 884-890). Thieme Medical Publishers.

Robin, P., Le Roux, P. Y., Planquette, B., Accassat, S., Roy, P. M., Couturaud, F., ... & Sanchez, O. (2016). Limited screening with versus without 18F-fluorodeoxyglucose PET/CT for occult malignancy in unprovoked venous thromboembolism: an open-label randomised controlled trial. *The Lancet Oncology*, *17*(2), 193-199.

Included economic studies

Coyle, K., Carrier, M., Lazo-Langner, A., Shivakumar, S., Zarychanski, R., Tagalakis, V., Solymoss, S., Routhier, N., Douketis, J. and Coyle, D., 2017. Cost effectiveness of the addition of a comprehensive CT scan to the abdomen and pelvis for the detection of cancer after unprovoked venous thromboembolism. Thrombosis research, 151, pp.67-71.