Suspected Cancer:

recognition and management of suspected cancer in children, young people and adults

Update of clinical guideline 27

Appendix H: Review protocols for Suspected Cancer update 2015

Developed for NICE by the National Collaborating Centre for Cancer

© 2014 National Collaborating Centre for Cancer

This document is an update of the review protocols which accompanied NICE clinical guideline 27 (published June 2005) and will replace them.

Evidence has been reviewed on the recognition and management of suspected cancer in children, young people and adults. New review protocols developed as part of this update are highlighted in peach. You are invited to comment on the highlighted text only. Appendix J contains content from the 2005 Evidence Review which is being deleted as it has been updated.

The original NICE guideline and supporting documents are available from http://www.nice.org.uk/guidance/CG27

PATIENT INFORMATION
GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Patient information

Guideline subgroup members: Sue B, David, Susan H, Euan and Joan

Review question: What are the information needs of:
- Patients who are referred for suspected cancer and their carers/families, and
- Patients who are being monitored (for suspected cancer) in primary care and their carers/families?

Economic priority: Low

Question in PICO format

Population	Situation	Timing	Outcomes	Study types
- Patients who are referred for suspected cancer and their carers/families - Patients who are being monitored (for suspected cancer) in primary care and their carers/families	Information needs associated with: - referral for suspected cancer - monitoring (for suspected cancer) in primary care.	At the time of being referred for suspected cancer and during monitoring for suspected cancer in primary care.	Information reported by patients/carers to be useful/not useful or wanted/not wanted when being referred for suspected cancer and when being monitoring for suspected cancer in primary care.	Primarily Qualitative Also screen for quantitative studies and if enough time, include relevant quantitative studies

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library; Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED, google and charities for charity reports.
Can we apply date limits to the search	A date limit of 1980 was applied to the core databases. For additional searches on google and charities' websites no date limit was applied, as those databases are not structured in a way that allows date limits to be applied.
Are there any study design filters to be used (RCT, systematic review, diagnostic test)?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will be included in our evidence table) and how will we analyse the results? Which quality checklist will we use for	Demographic data describing the included patients/participants (age, gender, suspected cancer/referral type or reason for monitoring, relationship to referred/monitored patient, and setting along with any other relevant patients/participant

appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	details reported in the studies) will be extracted along with recruitment strategy including the inclusion and exclusion criteria. The included studies will be appraised using the NICE checklist for qualitative studies (http://publications.nice.org.uk/the-guidelines-manual-appendices-bi-pmg6b/appendix-h-methodology-checklist-qualitative-studies). All the information reported by the study participants to have been needed/not needed and wanted/not wanted will be extracted for each study and the results will be summarised narratively, split by population (patient/carer/family) if the data allow it.

Note any changes to the protocol or other considerations below

SAFETY NETTING

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Safety-netting

Guideline subgroup members: Yoryos, Lindsay, Susan, Joan

Review question: What safety-netting strategies are effective in primary care for patients being monitored for suspected cancer?

Economic priority: Low

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
• Patients with symptoms that might indicate cancer presenting in primary care who have been investigated in primary care but the test is negative/borderline • Patient with symptoms that might indicate cancer presenting in primary care who have not been investigated • Patients who have been investigated in secondary care but with a negative	Safety netting	No safety-netting Other safety-netting	Cohort studies Proportion of patients with cancer in the safety netted population Comparative studies Proportion of patients with cancer Emergency presentation Stage at diagnosis Survival Delayed diagnosis Psychological morbidity

investigation and persistent symptoms			

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library; Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	Safety netting, Ongoing-care, Surveillance Watchful waiting, Watch and wait, Wait and see High risk patient, Diagnostic error, Monitoring Deferred referral, Unexplained persistent symptoms Timely re-appraisal, False negative, Diagnostic error High risk patient, False negative, Deferred referral, Unexplained persistent symptoms Timely re-appraisal

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, safety-netting strategy, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (II) tool for cohort studies and the Cochrane tool for intervention studies. The proportion of patients with cancer will be extracted for all the study types and, if feasible, the results will be meta-analysed, to provide a summary estimate indicating the risk of cancer associated with safety-netting. For comparative studies, the number of patients presenting as emergencies, the stage at diagnosis, survival, delayed diagnosis and psychological morbidity will also be extracted for each of the groups.

Note any changes to the protocol or other considerations below

LUNG

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Euan, Karen, Stuart

Review question: What is the risk of lung cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Occupational history Asbestos Radon Cannabis	Including: Cough (new cough / changed cough) Dyspnoea (shortness of breath) Wheezing Haemoptysis Fatigue Loss of weight Loss of appetite Shoulder pain (Pancoast tumour) Chest/rib pain Pleuritic pain Hoarseness (recurrent laryngeal nerve palsy) Stridor Facial swelling Facial flushing Swelling of upper limb Distended veins upper limb Neck swelling Distended veins neck Light headedness Finger clubbing Persistent or recurrent chest infection Pleural effusion Radicular pain Referred pain Lower limb weakness Impaired walking Sensory impairment Bladder or bowel incontinence Spinal tenderness Muscle weakness / swallowing problems / coordination problems / hyponatraemia --- Abnormal spirometry Abnormal chest x-ray Fever <u>Generic list</u> fatigue appetite loss weight loss	Cancer diagnosis	Positive predictive value

	thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

LUNG

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for lung cancer

Guideline subgroup members: Euan, Karen, Stuart

Review question: Which investigations of symptoms of suspected lung cancer should be done with clinical responsibility retained by primary care?

Economic priority: Medium

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected lung cancer	Chest x-ray CT Sputum cytology Bronchoscopy	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the	1980

search	
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

MESOTHELIOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Euan, **Karen**, Stuart

Review question: What is the risk of mesothelioma in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation	Including: Generic list fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis	Cancer diagnosis	Positive predictive value

Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Asbestos exposure Occupational history	hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target

	cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

MESOTHELIOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for mesothelioma

Guideline subgroup members: Euan, **Karen**, Stuart

Review question: Which investigations of symptoms of suspected mesothelioma should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected mesothelioma	Chest x-ray CT Abdominal x-ray Ultrasound	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review,	Primary care data only

diagnostic test). Primary care data only?	
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

OESOPHAGEAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Sue B, Yoryos, **Lindsay**

Review question: What is the risk of oesophagael cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of	Including: Epigastric pain Chest pain Pain or discomfort in the throat or back Pain in the form of a burning sensation when swallowing food Pain or soreness behind the breastbone, or between the shoulder blades Reflux (acid regurgitation) heartburn Indigestion	Cancer diagnosis	Positive predictive value

cancer Ethnicity Alcohol exposure Immuno-suppression Chronic iron deficiency anaemia History of Barretts oesophagus Dietary history Betel HPV	Acid indigestion Dyspepsia persistent acid reflux persistent hiccups or regurgitation of food, Dysphagia Feeling that your food is sticking in your throat Hoarseness, or chronic cough Coughing up blood Nausea vomiting Regurgitation Constipation Low cholesterol Hypercalcemia Generic list fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass Symptoms of metastases **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance		

	lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>OESOPHAGEAL</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for oesophageal cancer

Guideline subgroup members: Sue B, Yoryos, **Lindsay**

Review question: Which investigations of symptoms of suspected oesophageal cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected oesophageal cancer	Upper GI endoscopy Ba swalLow Chest X-Ray	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations beLow

PANCREAS

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Sue B, Stuart, Lindsay, Euan

Review question: What is the risk of pancreatic cancer in patients presenting in primary care with symptom(s)?

Economic priority: Medium

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression BRCA1/BRCA2 Chronic pancreatitis Diabetes High intake of processed meat Ulcerative colitis Gastric ulcer Lack of physical activity Cystic fibrosis	Including: Abdominal mass Epigastric mass Lumps Abdominal distension Unusual and sustained bloating Back pain Abdominal pain Abdominal discomfort Colic Epigastric pain Pain when eating early satiety Appetite loss Weight loss Anorexia Muscle weakness Cachexia Change in bowel habit Constipation Diarrhoea Pale coloured stools floating stools, steatorrhoea, foul smelling, difficult to flush Dark urine Jaundice Yellow skin itching Unusual belching Delayed gastric emptying hiccups, flatulence, and regurgitation dyspepsia indigestion heartburn Diabetes Dyspnoea Breathlessness Altered sleep patterns Fatigue Nausea Vomiting malaise Thromboembolism Unprovoked VTE	Cancer diagnosis	Positive predictive value

	migratory thrombophlebitis Trousseau's Syndrome DVT Dysgeusia Asthenia Pancreatitis Rectal bleeding Depression/low mood Fever Shivering (rigor) Night sweats Unusual naevi or moles (indicative of any familial cancer syndrome) <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance		

	seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>PANCREAS</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for pancreatic cancer

Guideline subgroup members: Sue Ballard, Lindsay, Stuart, Euan

Review question: Which investigations of symptoms of suspected pancreatic cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected pancreatic cancer	Ultrasound CT MRI? CEA CA19-9 Beta hCG CA72-4	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

STOMACH

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Lindsay, Sue B, Liliana

Review question: What is the risk of cancer of the stomach in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Salt intake Dietary history H pylori Pernicious anaemia HIV/AIDS Reflux Occupational history	Including: Persistent (every day) heartburn (acid reflux) 'Silent reflux' Sleep apnoea, Sleep disorders, Chronic cough Hoarseness Chest pain (non-heartburn) Dyspepsia Persistent hiccups or regurgitation of food Difficulty or pain in swallowing food Food sticking in the throat Dysphagia Short of breath Vomiting, Nausea, Sickness Anorexia Feeling full very early when eating meals Persistent indigestion, acidity, burping and vomiting trapped wind and frequent burping Water brash Bloating Pain/discomfort in the upper abdomen Pain just under your breastbone (sternum) or slightly lower down. Metallic taste Bleeding Feeling breathless Blood clots Fluid in the abdomen Blood in your stool Black stools Vomit streaked with blood <u>Generic list</u> fatigue appetite loss weight loss thromboembolism	Cancer diagnosis	Positive predictive value

	raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

STOMACH

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for stomach cancer

Guideline subgroup members: Lindsay, Sue B, Liliana

Review question: Which investigations of symptoms of suspected stomach cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected stomach cancer	Upper GI endoscopy Barium meal Abdo USS	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library.

	Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>SMALL INTESTINE</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Lindsay, **Joan**, Sue B

Review question: What is the risk of small intestine cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer <u>Subgroups:</u> Age Sex Smoking Familial syndromes	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression			

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>SMALL INTESTINE</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for small intestine cancer

Guideline subgroup members: Lindsay, **Joan**, Sue B

Review question: Which investigations of symptoms of suspected **small intestine/gall bladder cancer** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	**Test**	**Comparison**	**Outcomes**
Patients presenting to primary care with symptoms of suspected small intestine cancer	Capsule endoscopy Barium folLow through CT	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

GALL BLADDER

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Sue B, **Stuart**, David

Review question: What is the risk of gall bladder cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient

	groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

GALL BLADDER

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for gall bladder cancer

Guideline subgroup members: Sue B, **Stuart**, David

Review question: Which investigations of symptoms of suspected **gall bladder cancer** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected cancer of the gall bladder	Ultrasound LFT CT CA19-9	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review,	Primary care data only

diagnostic test). Primary care data only?	
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>LIVER</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Sue B, **Stuart**, David

Review question: What is the risk of liver cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer	Including: Abdominal mass Enlarged tender liver Distinct sound in the liver (hepatic bruit) Abdominal distension Swollen abdomen Ascites – excess fluid/swelling in abdomen and/or legs Abdominal pain/tenderness Discomfort or pain in abdomen Epigastric/hypochondrial	Cancer diagnosis	Positive predictive value

Ethnicity Alcohol exposure Immuno-suppression Chronic hepatitis Cirrhosis Aflatoxin exposure Occupation Diabetes HIV Betel quid Anabolic steroids Liver infection	pain Right shoulder tip pain Pain in right shoulder – referred pain Gastrointestinal bleeding Abnormal bleeding (gastrointestinal) dilated (widened) veins called esophageal varices Fine blood vessels visible on the skin in a radial pattern resembling the legs of a spider (known as spider naevi) Vomiting blood Dark black tarry stools Feeling full or bloated after eating, even after a small meal Confusion Diarrhoea Jaundice Dark coloured urine and pale coloured stools Jaundice Itching Cachexia Muscle wasting Hypercalcaemia (Erythrocytosis) Fever Sweats A high temperature and sweating fever with high temperatures and shivers Being sick Nausea/feeling sick Vomiting A sudden worsening of health in somebody with known chronic hepatitis or cirrhosis Weakness and tiredness Lethargy Loss of libido Erectile dysfunction Swollen testicles Blood in urine Breast development in men Gynaecomastia Stomach pain and cramps mistaken for period pains Flushing <u>Generic list</u> fatigue appetite loss weight loss		

	thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for liver cancer

Guideline subgroup members: Sue B, **Stuart**, David

Review question: Which investigations of symptoms of suspected liver cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected liver cancer	Ultrasound CT MRI Alpha Feta Protein	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate:

	CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>COLORECTAL</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Liliana, Jeanne, Joan

Review question: What is the risk of colorectal cancer in patients presenting in primary care with symptom(s)?

Economic priority: High

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial	Including: Rectal bleeding Abdominal mass Rectal mass Tenesmus Abdominal distension Abdominal pain Appetite loss Constipation Diarrhoea	Cancer diagnosis	Positive predictive value

syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression IBD Sexual practices Polyps Occupational history	Epigastric pain Dyspepsia Colic Dyspnoea Fatigue Jaundice Lower urinary tract symptoms Lumps Pelvic mass Pelvic pain Thromboembolism Vomiting Weight loss Change in bowel habit Anaemia Raised levels of inflammatory markers Thrombocytosis Hepatomegaly Night sweats Abnormal lft <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain**		

	confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for colorectal cancer

Guideline subgroup members: Liliana, Jeanne, Joan

Review question: Which investigations of symptoms of suspected colorectal cancer should be done with clinical responsibility retained by primary care?

Economic priority: High

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected colorectal cancer	Colonoscopy Sigmoidoscopy CT colonoscopy/ colonography CT CEA FOB Barium enema	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

ANAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Liliana, Jeanne, **Joan**

Review question: What is the risk of anal cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the

approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

ANAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for anal cancer

Guideline subgroup members: Lilliana, Jeanne, **Joan**

Review question: Which investigations of symptoms of suspected **anal** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected anal cancer	Proctoscopy Sigmoidoscopy	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies.

the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

BREAST

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Joan, Nicki, Jeanne

Review question: What is the risk of breast cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression BRCA1/BRCA2 HRT Combined hormonal contraceptive (CHC) use Lack of physical activity Reproductive history Lack of breast	Including: Breast lump Breast pain Nipple bleeding Nipple inversion Skin change (on breast) Unilateral 'eczema' around nipple (Paget's disease) [searching on 'nipple may be simplest for the three nipple symptoms] Skin changes – dimpling, peau d'orange, ulceration Nipple discharge Generic list fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass Symptoms of metastases	Cancer diagnosis	Positive predictive value

feeding	**Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

BREAST

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for breast cancer

Guideline subgroup members: Joan, Nicki, Jeanne

Review question: Which investigations of symptoms of suspected breast cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected breast cancer	Ultrasound Mammography FNA	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

ENDOMETRIAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Joan, Nicki, Richard

Review question: What is the risk of endometrial cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Diabetes Lack of physical activity Reproductive	Including: Post menopausal vaginal bleeding Abnormal/change in pre-menopausal vaginal bleeding (heavy/heavier periods,menorrhagia, long periods, inter-menstrual bleeding, more frequent periods, irregular bleeding) Vaginal discharge Lower abdominal pain Lower abdominal pressure Pelvic pain Pelvic pressure Pain on sexual intercourse Abdominal swelling Lump in abdomen Increased Urinary frequency Polyuria Dysuria Constipation	Cancer diagnosis	Positive predictive value

history HRT use Previous complex atypical hyperplasia of endometrium	Leg swelling Abdominal mass Abdominal tenderness Enlarged/or irregular uterus on PV examination Dysmenorrhoea Polymenorrhoea Dyspareunia <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate:

	CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>ENDOMETRIAL</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for endometrial cancer

Guideline subgroup members: Joan, Nicki, Richard

Review question: Which investigations of symptoms of suspected endometrial cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to	Ultrasound Pipelle sampling CA125	Histology/folLow up	Sensitivity Specificity Positive predictive value

primary care with symptoms of suspected endometrial cancer	Hysteroscopy NB ultrasound may be trans-abdominal or trans-vaginal		False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

CERVICAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Joan, Nicki, Richard

Review question: What is the risk of cervical cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

1 **Question in PICO format**

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression HPV HIV COC pill use Sexual history	Including: Unusual vaginal bleeding (Intermenstrual bleeding, postcoital bleeding,irregular vaginal bleeding, any vaginal bleeding in woman past the menopause- better to use PMB post menopausal bleeding) Pain when having sex-dyspareunia Unpleasant smelling vaginal discharge- blood stained vaginal discharge Pain when passing urinedysuria Increased frequency passing urine Constipation Haematuria Urinary Incontinence should this be in the secondaries category Swelling in leg Pelvic pain Abnormal looking cervix Abnormal smear- various grades CIN Enlarged/craggy/firm cervix on vaginal examination Contact bleeding when smear taken <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis	Cancer diagnosis	Positive predictive value

	hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies.

statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

CERVICAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for cervical cancer

Guideline subgroup members: Joan, Nicki, Richard

Review question: Which investigations of symptoms of suspected cervical cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected cervical cancer	Cervical smear	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies.

the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

VULVA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Karen, **Jeanne**, Sue B

Review question: What is the risk of cancer of the vulva in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer Subgroups: Age Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

VULVA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for vulval cancer

Guideline subgroup members: Karen, **Jeanne**, Sue B

Review question: Which investigations of symptoms of suspected **cancer of the vulva** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	**Test**	**Comparison**	**Outcomes**
Patients presenting to primary care with symptoms of suspected cancer of the vulva	Biopsy	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

VAGINAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Joan, Richard, **Nicki**

Review question: What is the risk of vaginal cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer Subgroups:	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

Age Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression			

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

VAGINAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for vaginal cancer

Guideline subgroup members: Joan, Richard, **Nicki**

Review question: Which investigations of symptoms of suspected **vaginal cancer** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected vaginal cancer		Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

PROSTATE

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: David, **Euan**, Yoryos

Review question: What is the risk of prostate cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Occupational history	Including: Nocturia Urinary frequency Urinary urgency poor flow Hesitation Incontinence Urinary retention Feeling of incomplete bladder emptying Dysuria Impotence Erectile dysfunction Loss of libido Pain on ejaculation Haematospermia Haematuria Pelvic discomfort / pain Abnormal rectal examination (prostate enlargement, nodule, hard craggy prostate) Abnormal renal function (raised urea or creatinine) Raised PSA Back pain Swelling in legs Radicular pain Referred pain Lower limb weakness Impaired walking Sensory impairment Bladder or bowel incontinence Spinal tenderness Generic list fatigue appetite loss	Cancer diagnosis	Positive predictive value

	weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

PROSTATE

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for prostate cancer

Guideline subgroup members: David, **Euan**, Yoryos

Review question: Which investigations of symptoms of suspected prostate cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected prostate cancer	PSA MRI for detection	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library.

	Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>BLADDER</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: David, Yoryos**, Karen**

Review question: What is the risk of bladder cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex	Including: Abdominal pain Haematuria Vaginal bleeding Appetite loss Bone or skeletal pain Confusion Recurring urinary infection Fatigue	Cancer diagnosis	Positive predictive value

Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Occupation Alcohol consumption Schistosomiasis Reccurent bladder Infection	Lower urinary tract symptoms: frequency, urgency, pain, dysuria, cystitis, loin pain Pelvic mass Pelvic pain Erectile dysfunction Thromboembolism Weight loss. Anaemia Abnormal liver function tests Hypercalcaemia Raised levels of inflammatory markers Thrombocytosis. <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance		

	seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>BLADDER</u>

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for bladder cancer

Guideline subgroup members: David, Yoryos, **Karen**

Review question: Which investigations of symptoms of suspected bladder cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected bladder cancer	Urine cytology Ultrasound Cystoscopy Blood HCG Urine marker NMP22 Urine marker MCM5	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

RENAL (8)

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: David, **Richard**, Yoryos, Karen

Review question: What is the risk of renal cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Occupation Personal history of hypertension	Including: Abdominal mass abdominal distension, abdominal pain, haematuria, appetite loss, constipation, lower urinary tract symptoms including UTI, vomiting, weight loss, fever including night sweats pelvic mass flank / loin pain scrotal / groin pain varicocoele <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting	Cancer diagnosis	Positive predictive value

	bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

RENAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for renal cancer

Guideline subgroup members: David, **Richard**, Yoryos, Karen

Review question: Which investigations of symptoms of suspected renal cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected renal cancer	Abdominal ultrasound Urine cytology X-ray IVP CT scan of abdomen and pelvis	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

TESTICULAR

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Yoryos, **Karen**, David

Review question: What is the risk of testicular cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer Subgroups: Age Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic

	case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

TESTICULAR

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for testicular cancer

Guideline subgroup members: Yoryos, **Karen**, David

Review question: Which investigations of symptoms of suspected **testicular cancer** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected testicular cancer	Ultrasound	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980

Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

PENIS

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: David, **Yoryos**, Karen

Review question: What is the risk of penile cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer Subgroups: Age Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

Immuno-suppression			

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

PENIS

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for penile cancer

Guideline subgroup members: David, **Yoryos**, Karen

Review question: Which investigations of symptoms of suspected **cancer of the penis** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected penile cancer		Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

MELANOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Richard, Euan, Nicki

Review question: What is the risk of melanoma in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Sun exposure Sunbed exposure Occupation	Including: Change in appearance of skin lesion (see classic complex): • **A**symmetry • **B**orders (irregular) • **C**olor (variegated), and • **D**iameter > 6mm • **E**volving over time • **E**levated above the skin surface • **F**irm to the touch • **G**rowing New pigmented skin lesion Bleeding or ulcerated skin lesion Itching Painful Redness Tingling Burning Friability (pieces that break off Change in size Irregular shape Inflammation Change in sensation) Abnormality under finger or toe nail Decreased visual acuity Visual field loss Flashing lights Floaters Ocular pain Choroidal melanoma on ophthalmoscopy <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia	Cancer diagnosis	Positive predictive value

	unexplained lymphadenopathy or other mass Symptoms of metastases **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient

	groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

MELANOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for melanoma

Guideline subgroup members: Richard, Euan, Nicki

Review question: Which investigations of symptoms of suspected melanoma cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected melanoma	Mole mate dermatoscopy Biopsy Ophthalmoscopy	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review,	Primary care data only

diagnostic test). Primary care data only?	
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>SQUAMOUS CELL CARCINOMA OF THE SKIN</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Richard, Euan, Nicki

Review question: What is the risk of SCC in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity	Including: Rough patch on skin Raised lump on skin Reddish, enlarging flat patch of skin Scaly patch Irritated patch of skin Crusted patch Non-healing patch of skin Ulcerated patch of skin Bleeding from skin lesion Growing bump Changed mole Changed wart Changed skin lesion	Cancer diagnosis	Positive predictive value

Alcohol exposure Immuno-suppression Sun exposure Solar keratosis Sunbed exposure Occupation Immunosuppression	<u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>SQUAMOUS CELL CARCINOMA OF THE SKIN</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for squamous cell carcinoma of the skin

Guideline subgroup members: Richard, Euan, Nicki

Review question: Which investigations of symptoms of suspected SCC should be done with clinical responsibility retained by primary care?

Economic priority: low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected SCC	Dermatoscopy Excision / Biopsy	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>BASAL CELL CARCINOMA OF THE SKIN</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Richard, **Euan**, Nicki

Review question: What is the risk of BCC in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* <u>Subgroups:</u>	Including: Ulcer with raised rolled edge Prominent fine blood vessels around lesion Nodule on skin	Cancer diagnosis	Positive predictive value

Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Sun exposure Solar keratosis Sunbed exposure Occupation Immunosuppression	Pearly / waxy nodule on skin Red patch of skin Patch of skin that looks like a scar Bleeding skin lesion Non-healing skin lesion Ulcerated patch of skin Bleeding from skin lesion Growing bump Changed mole Changed wart Changed skin lesion Generic list fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

BASAL CELL CARCINOMA OF THE SKIN

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for basal cell carcinoma of the skin

Guideline subgroup members: Richard, **Euan**, Nicki

Review question: Which investigations of symptoms of suspected **BCC** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected BCC	Dermatoscopy excision biopsy of lesion	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>LARYNX</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Euan, **Karen**, Stuart

Review question: What is the risk of cancer of the larynx in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>LARYNX</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for laryngeal cancer

Guideline subgroup members: Euan, **Karen**, Stuart

Review question: Which investigations of symptoms of suspected **cancer of the larynx** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected cancer of the larynx	Chest x-ray	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

ORAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Jeanne, Stuart, Richard

Review question: What is the risk of oral cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

•

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer* <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Chewing betel HPV Dietary history Syphilis Cannabis	Including: Ulcers on tongue Ulcers on lip Ulcers in mouth Plaques Bleeding gums Lichen planus Sore throat Dysphagia Pain Pain on chewing Pain on swallowing Earache Toothache Loose teeth Speech impediment Halitosis Swollen lymph glands (under chin, in neck) Bony lumps (on palpate) Pain wearing dentures <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice	Cancer diagnosis	Positive predictive value

	abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The

Collaboration handbook).	positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

ORAL

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for oral cancer

Guideline subgroup members: Jeanne, Stuart, Richard

Review question: Which investigations of symptoms of suspected oral cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected oral cancer	Biopsy	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies

could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

THYROID

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Lindsay, Joan, Karen

Review question: What is the risk of thyroid cancer in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>THYROID</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for thyroid cancer

Guideline subgroup members: Lindsay, Joan, Karen

Review question: Which investigations of symptoms of suspected **thyroid cancer** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected thyroid cancer	Ultrasound Thyroid function tests FNA	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

BRAIN & CNS

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Lindsay, **Jeanne**, Susan H

Review question: What is the risk of brain-central nervous system cancer in patients presenting in primary care with symptom(s)?

Economic priority: Medium

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer*	Including: Headache Nausea and vomiting Abnormal gait Squint	Cancer diagnosis	Positive predictive value

Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression HIV/AIDS Children and young people	Visual disturbance Seizures Growth failure (failure to thrive) Precocious puberty Personality change Imbalance Polyuria Delayed puberty Fatigue Impaired higher functioning: (concentration, memory loss, distraction, behavioural change, co-ordination, speech difficulty) Parental concern Sleep disturbance Hearing loss pallor Confusion Pupil irregularity Bulging fontanelle No red reflex Weakness Abnormal neurological examination Generic list fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass Symptoms of metastases **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction		

	Bone bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

BRAIN & CNS

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for brain & CNS cancer

Guideline subgroup members: Lindsay, **Jeanne**, Susan H

Review question: Which investigations of symptoms of suspected brain and CNS should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected brain and CNS	CT MRI	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Collaboration handbook).	

Note any changes to the protocol or other considerations below

LEUKAEMIA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Liliana, Jeanne, Susan H

Review question: What is the risk of leukaemia in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Occupation Genetic conditions (Down's syndrome) Autoimmune conditions such as rheumatoid arthritis, autoimmune haemolytic anaemia and ulcerative colitis, HIV/AIDS may be	Including: Fever, tiredness, weight loss, dizzy, non-specific aches, bone tenderness, joint pain, muscle pain, lymphadenopathy, bruising, bleeding, nausea, vomiting, diffuse abdominal pain, hepatosplenomegaly, headache, isolated cranial nerve palsies, skin rash, non-blanching erythematous papules, stridor, wheezing, pericardial effusions, superior vena cava syndrome, anaemia, fatigue, dyspnoea (exertional), palpitations, angina, claudication	Cancer diagnosis	Positive predictive value

due to actual condition or the medicines taken for the condition that increases risk Children and young people	thrombocytopenia, epistaxis, gingival haemorrhage, menorrhagia, cutaneous petechiae, haemorrhage (gastrointestinal ,urinary, intracranial retinal), hyperviscosity, hypoxia, respiratory failure, seizures, confusion, coma, visual disturbances, priapism, hyperleukocytosis, convulsion, fits, focal neurology gum hypertrophy, stomatitis, soft tissue masses, testicular involvement (include painless, asymmetric enlargement) neutropaenia, infections (bacterial or fungal of teeth and oropharynx, sinuses, lung, skin, perineum and bowel) <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly		

	jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The

Collaboration handbook).	positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

LEUKAEMIA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for leukaemia

Guideline subgroup members: Liliana, Jeanne, Susan H

Review question: Which investigations of symptoms of suspected leukaemia should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected leukaemia	White blood cell count	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any

appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations beLow

LIVER

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for liver cancer

Guideline subgroup members: Sue B, **Stuart**, David

Review question: Which investigations of symptoms of suspected liver cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	**Test**	**Comparison**	**Outcomes**
Patients presenting to primary care with symptoms of suspected liver cancer	Ultrasound CT MRI Alpha Feta Protein	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

MYELOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Liliana, Yoryos, Lindsay

Review question: What is the risk of myeloma in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Race Radiation exposure	Including: Abnormal bleeding (including, haemoptysis, haematuria, gastrointestinal and vaginal bleeding) Appetite loss Bruising Ankle swelling Malaise Polyuria Thirst Bone or skeletal pain Chest wall or rib pain Confusion Constipation Dyspnoea Epigastric pain (including dyspepsia) Fatigue Focal neurological signs Spinal cord compression Infections suggesting	Cancer diagnosis	Positive predictive value

	Immunocompromise Lower urinary tract symptoms Lumps (including breast, neck, abdominal, bony and soft-tissue masses, unexplained lymphadenopathy) Pain at multiple sites Pathological fracture Shortness of breath Thromboembolism Vomiting Weight loss Anaemia Abnormal liver function tests Hypercalcaemia Raised levels of inflammatory markers Thrombocytosis. Back pain <u>Generic list</u> fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass <u>Symptoms of metastases</u> **Chest** chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain**		

	confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

MYELOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for myeloma

Guideline subgroup members: Liliana, Yoryos, Lindsay

Review question: Which investigations of symptoms of suspected myeloma should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected myeloma	Paraprotein/serum Electrophoresis / Bence-Jones protein (urine test) ESR Viscosity Calcium X-ray	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

NON-HODGKIN LYMPHOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Stuart, Liliana, **Lindsay**

Review question: What is the risk of lymphoma in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression Treatment, Race HIV/AIDS Rheumatoid arthritis Children and young people	Including: Lumps Swollen glands Sweats Breathlessness Cough Weight loss Itch Fatigue Skin rash Alcohol induced pain Feeling of weakness Abnormal bruising Anaemia Fever Abdominal pain Appetite loss Infection suggesting immunocompromise Pathological fracture Abnormal lft Raised levels of inflammatory markers Pallor Generic list fatigue appetite loss weight loss thromboembolism raised levels of inflammatory markers anemia thrombocytosis hypercalcemia unexplained lymphadenopathy or other mass Symptoms of metastases **Chest**	Cancer diagnosis	Positive predictive value

	chest wall or rib pain cough dyspnoea/shortness of breath haemoptysis hoarseness **Liver** abdominal distension abdominal pain Hepatomegaly jaundice abnormal liver function tests vomiting bowel obstruction **Bone** bone or skeletal pain pathological fracture pain at multiple sites **Brain** confusion focal neurological signs headache imbalance personality disturbance lethargy/hyper-somnolence visual disturbance seizures		

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

NON-HODGKINS LYMPHOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for non-Hodgkin's lymphoma

Guideline subgroup members: Stuart, Liliana, **Lindsay**

Review question: Which investigations of symptoms of suspected Non Hodgkins lymphoma cancer should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected non-hodgkins lymphoma	Chest X-Ray CT scan ultrasound LDH	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

HODGKIN'S LYMPHOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Stuart, **Liliana**, Lindsay

Review question: What is the risk of Hodgkin's lymphoma in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

Children and young people			

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>HODGKIN'S LYMPHOMA</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for Hodgkin's lymphoma

Guideline subgroup members: Stuart, **Liliana**, Lindsay

Review question: Which investigations of symptoms of suspected **Hodgkins lymphoma** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected hodgkins lymphoa	Chest X-Ray CT scan ultrasound LDH	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>BONE SARCOMA</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Susan H, **Euan**, Nicki

Review question: What is the risk of bone sarcoma in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer* Subgroups: Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression	Signs and symptoms	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

BONE SARCOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for bone sarcoma

Guideline subgroup members: Susan Hay, **Euan**, Nicki

Review question: Which investigations of symptoms of suspected **bone sarcoma** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected bone sarcoma	X-ray Calcium Alkaline phosphatase	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>SOFT TISSUE SARCOMA</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Susan H, Euan, **Nicki**

Review question: What is the risk of soft tissue sarcoma in patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Patients with symptoms of suspected cancer <u>Subgroups:</u> Age Sex Smoking Familial syndromes Deprivation Obesity Past history of cancer Ethnicity Alcohol exposure Immuno-suppression	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

<u>SOFT TISSUE SARCOMA</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for soft tissue sarcoma

Guideline subgroup members: Susan H, Euan, **Nicki**

Review question: Which investigations of symptoms of suspected **soft tissue sarcoma** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected soft tissue sarcoma	Ultrasound	Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

<u>NEUROBLASTOMA</u>

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Susan H, **Jeanne**

Review question: What is the risk of neuroblastoma in child patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Child patients with symptoms of suspected cancer Any subgroups reported	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

NEUROBLASTOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for neuroblastoma

Guideline subgroup members: Susan H, **Jeanne**

Review question: Which investigations of symptoms of suspected **neuroblastoma** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected neuroblastoma		Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Collaboration handbook).	

Note any changes to the protocol or other considerations below

RETINOBLASTOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Susan H, **Jeanne**

Review question: What is the risk of retinoblastoma in child patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	**Sign/symptom***	**Comparison**	**Outcomes**
Child patients with symptoms of suspected cancer Any subgroups reported	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

RETINOBLASTOMA

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for retinoblastoma

Guideline subgroup members: Susan H, **Jeanne**

Review question: Which investigations of symptoms of suspected **retinoblastoma** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	Test	Comparison	Outcomes
Patients presenting to primary care with symptoms of suspected retinoblastoma		Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below

WILM'S TUMOUR

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: What is the risk of cancer in patients presenting in primary care with symptom(s)?

Guideline subgroup members: Susan H, **Liliana**

Review question: What is the risk of neuroblastoma in child patients presenting in primary care with symptom(s)?

Economic priority: LOW

Question in PICO format

Patients/population	Sign/symptom*	Comparison	Outcomes
Child patients with symptoms of suspected cancer Any subgroups reported	Signs and symptoms of suspected cancer	Cancer diagnosis	Positive predictive value

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980 onwards
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

Criteria for considering studies (e.g., study design)	Diagnostic accuracy studies treating a symptom as a positive test. These studies will either be of a series of patients presenting to primary care with symptom X for whom follow up data is available detailing whether the symptom was of benign or malignant origin (prospective or retrospective), or diagnostic case-control studies where cases are patients with the target cancer and controls are (matched) patients without the target cancer that report the prevalence of symptom X in both patient groups. That is, in both these study types the patients will have symptom X.
What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the following characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each reported symptom the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report a given symptom, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the risk of cancer associated with each symptom. The positive predictive value will form the basis of the risk estimate.

Note any changes to the protocol or other considerations below

WILM'S TUMOUR

GDG subgroup lead fills in highlighted areas, NCCC staff all other area.

Guideline Title GP referral for suspected cancer

Review Protocol for: Primary care tests for Wilm's tumour

Guideline subgroup members: Susan H, **Liliana**

Review question: Which investigations of symptoms of suspected **Wilm's tumour** should be done with clinical responsibility retained by primary care?

Economic priority: Low

Question in PICO format

Patients/population	**Test**	**Comparison**	**Outcomes**
Patients presenting to primary care with symptoms of suspected Wilms		Histology/folLow up	Sensitivity Specificity Positive predictive value False negative rate

tumour			

How the information will be searched

Sources to be searched	Core databases to be searched: EMBASE, medline, pre-medline, web of science, Cochrane library. Specialist databases to be searched if appropriate: CINAHL, BNI, psychinfo, AMED.
Can we apply date limits to the search	1980
Are there any study design filters to be used (RCT, systematic review, diagnostic test). Primary care data only?	Primary care data only
List useful search terms.	

If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate? No

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted). List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	For each included study the folLowing characteristics will be extracted: Study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country, any other relevant characteristics reported such as relevant history or comorbidities), index and reference test characteristics and any other relevant details reported in the studies. The risk of different biases associated with the included studies will be assessed using the QUADAS (I or II) tool for each of the included studies. For each included study the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study report on the index test, the results will be meta-analysed, if feasible, to provide a summary estimate of the sensitivity and specificity of the index test.

Note any changes to the protocol or other considerations below