National Institute for Health and Care Excellence

Suspected cancer: recognition and referral

[C] Technical appendices for endometrial cancer: unscheduled bleeding, HRT and cancer referral

NICE guideline NG12

Technical data underpinning diagnostic review [C]

January 2026

Draft for consultation

ISBN: [XXX]

Contents

Appendix A Review protocols

Review protocol for endometrial cancer: unscheduled bleeding, HRT and cancer referral

Review protocol for diagnostic review of unscheduled vaginal bleeding for suspected endometrial cancer referral

Review title	Endometrial cancer: Unscheduled bleeding, HRT and cancer referral.
Review question	What is the diagnostic accuracy of unscheduled vaginal bleeding for the detection of endometrial cancer in adults taking HRT to inform decision making for referral via a suspected cancer pathway?
Objective	Develop recommendations on unscheduled bleeding that applies to people taking HRT and includes guidance on when referral onwards via a suspected cancer referral should be considered.
Searches	The following bibliographic databases will be searched: • Medline ALL (Ovid platform) • Embase (Ovid platform) • Cochrane Database of Systematic Reviews (Wiley platform) • Epistemonikos (for systematic reviews-only) Searching for systematic reviews will be limited to Epistemonikos and the Cochrane Database of Systematic Reviews-only. The full search strategies for all databases will be published as an appendix to the final evidence review.
Condition or domain being studied	Endometrial Cancer diagnosis within 12 months following an episode of unscheduled bleeding.

Population	Inclusion:
	Adults taking HRT (peri or post-menopausal):
	• Combined oestrogen and progestogen HRT
	  ○ Sequential combined HRT
	  ○ Continuous combined HRT
	  ○ Any combined
	• Oestrogen-only HRT
	
	Unscheduled bleeding is irregular bleeding after changing or initiating HRT that should be bleed free. Unscheduled bleeding within first 6 months of initiating HRT (occurs in up to 40% of women) or within 3 months of a change of dose or preparation is common).
	
	*When a paper includes populations from primary and secondary care and the data cannot be disaggregated if at least 80% of the population are from primary care the

	paper will be considered and not excluded based on 'population'. Exclusion: • Adults previously diagnosed with any type of cancer.
Intervention/Exposure/Test	Unscheduled bleeding single episode in adults taking HRT Unscheduled bleeding multiple episodes in adults taking HRT Where the evidence provides data consideration will be given to: • Duration of bleeding • Heaviness of bleeding
Reference standard	Endometrial Cancer diagnosis within 12 months following an episode of unscheduled bleeding.
Types of study to be included	Include published full-text papers: • Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies
Other exclusion criteria	• All other study types • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/ study quality • Studies using qualitative methods only • Studies where multivariate regression analysis was not conducted, or where important confounders were not adjusted for in the analysis, will be excluded. Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Theses and dissertations • Papers not published in the English language. • Preprints • Papers published before 2015 • non-OECD studies
Context	In November 2024, an exceptional surveillance review of the suspected cancer: recognition and referral guideline (NG12) and Menopause: diagnosis and management guideline (NG23) was undertaken. It highlighted the need for section 1.5 (gynaecological cancers) regarding endometrial cancer and referral to cancer pathway in NG12 (recommendations 1.5.10 to 1.15.12) and section 1.4 (Discussing management options with people aged 40 or over) on starting and stopping HRT, including initial management of unscheduled bleeding on HRT in NG23 (recommendations 1.4.1 to 1.4.4) to be updated to clarify the definition of "unexplained" bleeding and how it relates to bleeding caused by hormone

	replacement therapy (HRT). HRT can cause 'unscheduled' bleeding, which often occurs within the first 6 months when starting treatment as the body adjusts to hormone changes. Unexplained irregular bleeding may be part of unscheduled bleeding, but in some cases, could require further investigation if it persists or is severe. Currently there is a lack of guidance in NG23 on how to manage unscheduled bleeding on HRT which impacts potential referral to suspected cancer pathway outlined in NG12. This guidance update of NG12 will update recommendations in section 1.5 to clarify the definition of unexplained bleeding and address bleeding caused by HRT.
Primary outcomes	Accuracy of unscheduled bleeding as a referral criteria: • Sensitivity • Specificity • Positive predictive value • False negative rate The suggested thresholds for sensitivity and specificity are: • Sensitivity – upper 90, lower 10 • Specificity – upper 80, lower 50 The threshold for PPV that would trigger a referral to the suspected cancer pathway is 3% as established by the Committee responsible for the 2015 update of NG12 (Suspected cancer: recognition and referral) and retained by the 2024 update of NG23 (Menopause) and this will be retained
Secondary outcomes	Not applicable
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion

	and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • QUADAS-2 for diagnostic accuracy studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. The 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted when possible. The results will be meta-analysed, if feasible, to provide a summary estimate indicating the likelihood of cancer diagnosis in the 12 months following. The positive predictive value will form the basis of the risk estimate. A positive predictive value (PPV) threshold of 3% or more for cancer investigation will be used and indicates that further investigations are required as there is seen to be a 3% risk of cancer. Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metaDTA app (https://crsu.shinyapps.io/MetaDTA/). Cochrane Review Manager software may be used to help with visually displaying information. Sensitivity, specificity, positive predictive value and false negative rates with 95% CIs will be used as outcomes for diagnostic test accuracy. These diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/
Analysis of sub-groups	Evidence will be stratified where possible by: • peri or post-menopausal? • Length of unscheduled bleed? • Heaviness of bleed? • Single vs multiple unscheduled bleeding

<table>
<tr><td></td><td>Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:
Groups identified in the equality and health inequalities assessment (EHIA) as outlined in the scope including:
socioeconomic and geographical factors
age
ethnicity
disabilities
people for whom English is not their first language or who have other communication needs.
trans people
non-binary people
Where evidence is stratified or sub-grouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups.
Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.</td></tr>
<tr><td>Type and method of review</td><td>☐ Intervention
☒ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☐ Other (please specify)</td></tr>
<tr><td>Language</td><td>English</td></tr>
<tr><td>Country</td><td>England</td></tr>
<tr><td>Anticipated or actual start date</td><td>October 2025</td></tr>
<tr><td>Anticipated completion date</td><td>November 2025</td></tr>
<tr><td>Stage of review at time of this submission</td><td><table><tr><th>Review stage</th><th>Started</th><th>Completed</th></tr><tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr><tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr><tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr><tr><td>Data extraction</td><td>☐</td><td>☐</td></tr><tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr><tr><td>Data analysis</td><td>☐</td><td>☐</td></tr></table></td></tr>
<tr><td>Named contact</td><td>5a. Named contact
NICE</td></tr>
</table>

	5b Named contact e-mail SuspectedCancer@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
Review team members	• Robby Richey – Topic lead • Steven Barnes – Technical advisor • James Jagroo – Senior technical analysts • Armina Paule - Technical analyst • James Hawkins - Health economist • Amy Finnegan - Information specialist • Jon Littler – Project manager
Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Unscheduled bleeding, HRT, endometrial cancer, suspected cancer.
Details of existing review of same topic by same authors	This is a new review question.
Current review status	☐ Ongoing

	☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
Additional information	N/A
Details of final publication	www.nice.org.uk

Abbreviations: CI: confidence interval; EHIA: Equality and Health Inequalities Impact Assessment; Embase: Excerpta Medica dataBASE; EPPI: Evidence for Policy & Practice Information; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HRT: hormone replacement therapy; Medline: Medical Literature Analysis and Retrieval System; MetaDTA:meta-analysis of diagnostic test accuracy studies; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; ROBIS: Risk of Bias in Systematic Reviews.

Economic review protocol

ID	Field	Content
1.	Review title	Endometrial cancer: Unscheduled bleeding, HRT and cancer referral.
2.	Objective	To identify economic studies that compare different criteria for referral to cancer pathways for suspected endometrial cancer in people with unscheduled bleeding and taking HRT.
3.	Inclusion criteria	• Populations, interventions and comparators must be as specified in the effectiveness review protocol. • Relevant comparative economic study design: cost–utility analysis, cost–effectiveness analysis, cost–consequences analysis, comparative cost analysis • Decision analytic model-based or within-trial economic analyses • OECD countries (except USA) • Healthcare and personal social services cost perspective • Studies published from 2015 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs. High-quality studies in line with the NICE reference case (recent UK NHS/PSS cost-utility analyses using the QALY as the measure of outcome) are the most applicable to NICE decision making. Not all studies meeting the inclusion criteria will therefore necessarily be used in decision-making - see Review strategy below for details.
4.	Exclusion criteria	• Conference posters or abstract only studies – these do not provide sufficient information for quality assessment. • Studies published before 2015 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs. • Studies from non-OECD countries or the USA – these are considered unlikely to be applicable to the UK NHS setting due to substantial differences in healthcare delivery and unit costs.

		• Non-comparative economic analyses including cost-of-illness studies. • Letters, editorials or commentaries, study protocols or reviews of economic evaluations (recent reviews will be ordered and the bibliographies will be checked for relevant individual economic studies, which will then be ordered and checked for eligibility). • Non-English language papers. • Studies considering exclusively intervention costs, e.g. medicine acquisition costs, without considering wider healthcare costs associated with unexplained weight loss for suspected cancer. • Studies comparing costs of branded vs generic forms of the same medicine. • Studies only focussing on productivity losses or gains.
5.	Search strategy	An economic study search will be undertaken using question-specific terms. For search details see appendix B below.

6.	Review strategy	• Studies meeting the inclusion and exclusion criteria will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist in appendix H of Developing NICE guidelines: the manual.
		• The NICE economic evaluation checklist assesses:
		  ○ Applicability to the NICE guideline decision making context with consideration of the NICE reference case relevant to the guideline. Recent UK studies that use the NICE reference case methods are the most applicable when considering cost effectiveness.
		  ○ Methodological limitations.
		• The aim is to present the best available economic evidence to inform committee decision-making in the context of the guideline, the current UK NHS setting and NICE methods. Therefore, the health economist may not present all studies that meet inclusion criteria. If recent high quality, UK cost-utility analyses are available for a question, it is often not deemed informative to present studies that are less applicable or lower quality such as older UK analyses or analyses from other countries. A similar principle is deemed to apply more generally when considering applicability and methodological limitations. Some specific examples are given below:
		  ○ If multiple versions of a model are available for the UK and other countries it is usually reasonable to only present the UK version.
		  ○ If multiple versions of the same UK model are available, it is usually reasonable to present only the most recent.
		  ○ If there has been a NICE MTA or guideline model that informs current NHS practice it is usually reasonable not to present older studies, unless they address a different subpopulation or other specific issue.
		  ○ If a UK model that includes all interventions in the decision space is available it may be reasonable not to present studies that only include individual or fewer interventions, if the analysis is sufficiently applicable and of good methodological quality.

		• Quality and relevance of effectiveness data used in the economic analysis: the more closely the clinical effectiveness data used in the economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.
		• Hierarchy of economic evaluation evidence based on quality assessment
		  ○ 'Directly applicable' and 'Minor limitations' (only recent UK CUAs can get this rating). Usually presented and used in decision-making.
		  ○ Directly or partially applicable combined with minor or potentially serious limitations (other than 1). Discretion over whether these are presented and used in decision-making, depending on the availability of more relevant evidence.
		  ○ 'Not applicable' or 'Very serious limitations'. Typically not presented and not used in decision-making.
		
		The health economist will make a decision based on the relative applicability and quality of the available evidence for each question, in discussion with the guideline committee if required. All decisions will be transparently reported in the evidence report. Studies that are presented to the committee and used in decision-making when formulating recommendations will be included in the summary tables and will have an evidence extraction. Other studies may not be presented to the committee in detail but will be listed, with the reason for not being presented to the committee and thus not used in decision-making being provided. Committee members can review and query the decision not to present studies with the health economist and will be provided with full details of these studies where requested.

Appendix B Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches. The MEDLINE strategies below were quality assured (QA) by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309 (6964), 1286.

Date limits

A date limit of 1 January 2015 to 21 October 2025 was applied, as stated in the review protocol as the last update for this topic was undertaken in 2015.

Search filters and classifiers

Effectiveness searches

Cohort filter:

The terms used for cohort studies are standard NICE practice that have been developed in house.

Diagnosis filter:

The Medline and Embase searches were limited to diagnosis evidence using the optimal filter. Additional terms were added to the filter.

Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from MEDLINE: analytical survey. *BMJ*. 2004;328:1040-2.

OECD countries filter:

The MEDLINE and Embase searches were limited to evidence from Organisation for Economic Co-operation and Development (OECD) member states using the validated NICE filter.

The OECD countries filters were used without modification:

Ayiku, L., Hudson, T., Williams, C., Levay, P., & Jacob, C. (2021). The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. *Journal of the Medical Library Association*, 109(4), 583–589.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

> Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

> Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

- No reruns were performed for this search.

Effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	21/10/2025	Wiley	Issue 10 of 12, October 2025	7
Embase	21/10/2025	Ovid	1974 to 2025 October 17	252
Epistemonikos	21/10/2025	https://www.epistemonikos.org/	n/a	113
MEDLINE ALL	21/10/2025	Ovid	1946 to October 20, 2025	78

Search strategy history

Database name: Cochrane CDSR

Searches
#1 MeSH descriptor: [Uterine Neoplasms] explode all trees 5635
#2 ((endometr* or uter* or womb or adnexa* or serous* or ovar*) NEAR/4 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or rhabdomyosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or lesion* or hyperplasi* or adenoma*)):ti,ab 14188
#3 Choriocarcinoma*:ti,ab,kw 48
#4 {or #1-#3} 18253
#5 MeSH descriptor: [Hemorrhage] this term only 6249
#6 MeSH descriptor: [Uterine Hemorrhage] this term only 815
#7 MeSH descriptor: [Menorrhagia] this term only 507
#8 MeSH descriptor: [Metrorrhagia] this term only 172
#9 ((bleed* or blood* or discharge*) NEAR/3 (unusual* or abnormal* or unexplain* or unschedule* or unexpect* or atypical* or irregular* or suspicio* or suspect* or vagin* or uterin* or endometr* or duration* or prolong* or heavy or heaviness* or spotting)):ti,ab,kw 16247
#10 MeSH descriptor: [Menopause] explode all trees 9114

Searches
#11 (((menopaus* or perimenopaus* or postmenopaus*) NEAR/3 (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) or PMB):ti,ab,kw 2728
#12 #10 AND #11 1267
#13 {or #5-#9} 22673
#14 #12 or #13 23838
#15 MeSH descriptor: [Hormone Replacement Therapy] explode all trees 3762
#16 ((hormon* or oestrogen* or estrogen* or oestradiol* or estradiol* or progesterone* or progestin*) NEAR/2 (therap* or treatment* or replace* or tablet* or patch* or gel* or spray* or implant*)):ti,ab,kw 24258
#17 (HRT or HT):ti,ab,kw 7301
#18 {or #15-#17} 29306
#19 #4 and #14 and #18 with Cochrane Library publication date Between Jan 2015 and Oct 2025, in Cochrane Reviews 7

Database name: Embase

Searches
1 exp uterus tumor/ or exp uterus cancer/ or choriocarcinoma/ (293297)
2 ((endometr* or uter* or womb or adnexa* or serous* or ovar*) adj4 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or rhabdomyosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or lesion* or hyperplasi* or adenoma*)).ti,ab. (315489)
3 Choriocarcinoma*.ti,ab. (8790)
4 or/1-3 (508862)
5 exp bleeding/ (1316270)
6 ((bleed* or blood* or discharge*) adj3 (unusual* or abnormal* or unexplain* or unschedule* or unexpect* or atypical* or irregular* or suspicio* or suspect* or vagin* or uterin* or endometr* or duration* or prolong* or heavy or heaviness* or spotting)).ti,ab,kf. (97789)
7 exp postmenopause bleeding/ (847)
8 exp menopause/ and (((menopaus* or perimenopaus* or postmenopaus*) adj3 (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) or PMB).ti,ab,kf. (3152)
9 or/5-8 (1374509)
10 exp hormone substitution/ (78177)
11 ((hormon* or oestrogen* or estrogen* or oestradiol* or estradiol* or progesterone* or progestin*) adj2 (therap* or treatment* or replace* or tablet* or patch* or gel* or spray* or implant*)).ti,ab,kf. (140846)
12 (HRT or HT).ti,ab,kf. (129006)
13 or/10-12 (295911)
14 4 and 9 and 13 (2827)
15 Longitudinal study/ or Retrospective study/ or Prospective study/ or Cohort analysis/ (3783808)
16 (cohort adj (study or studies or analys* or data)).ti,ab. (636438)
17 ((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab. (3112208)
18 exp case control study/ (262570)

Searches
19 case control*.ti,ab. (241908)
20 Cross-sectional studies/ (773642)
21 (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. (822182)
22 or/15-21 (5751523)
23 sensitiv*.tw. (2384978)
24 diagnostic accuracy.sh. (355771)
25 diagnostic.tw. (1474158)
26 ((likelihood adj ratio*) or lr or plr or nlr).ti,ab. (98311)
27 or/23-26 (3789970)
28 14 and (22 or 27) (926)
29 limit 28 to english language (884)
30 29 not conference*.db,pt,su. (609)
31 letter.pt. or letter/ (1403535)
32 (note or editorial).pt. (1872817)
33 (letter or comment*).ti. (265627)
34 or/31-33 (3340660)
35 randomized controlled trial/ or random*.ti,ab. (2657798)
36 34 not 35 (3302554)
37 30 not 36 (599)
38 37 not clinical trial.pt. (545)
39 38 and (2015* or 2016* or 2017* or 2018* or 2019* or 202*).dc,dd. (272)
40 animal/ (1735323)
41 nonhuman/ (8347975)
42 exp Animal Experiment/ (3441825)
43 exp Experimental Animal/ (917004)
44 animal model/ (1978856)
45 exp Rodent/ (4402397)
46 (rat or rats or mouse or mice or rodent*).ti. (1739236)
47 or/40-46 (10977333)
48 47 not human/ (7739960)
49 39 not 48 (270)
50 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or

Searches
philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1957186)
51 exp "organisation for economic co-operation and development"/ (3714)
52 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (4100416)
53 european union/ (34206)
54 developed country/ (37327)
55 or/51-54 (4137350)
56 50 not 55 (1784216)
57 49 not 56 (252)

Database name: Epistemonikos

Searches
(title:(((endometr* OR uter* OR womb OR adnexa* OR serous* OR ovar*) AND (cancer* OR carcinoma* OR malignan* OR neoplas* OR tumour* OR tumor* OR mass OR masses OR cyst* OR adenocarcin* OR sarcoma* OR teratoma* OR teratocarcinoma* OR cystadenocarcin* OR rhabdomyosarcoma* OR leiomyosarcoma* OR carcinosarcoma* OR granulosa* OR metasta* OR meta-sta* OR (meta AND sta*) OR lesion* OR hyperplasi* OR adenoma*)) OR Choriocarcinoma*) OR abstract:(((endometr* OR uter* OR womb OR adnexa* OR serous* OR ovar*) AND (cancer* OR carcinoma* OR malignan* OR neoplas* OR tumour* OR tumor* OR mass OR masses OR cyst* OR adenocarcin* OR sarcoma* OR teratoma* OR teratocarcinoma* OR cystadenocarcin* OR rhabdomyosarcoma* OR leiomyosarcoma* OR carcinosarcoma* OR granulosa* OR metasta* OR meta-sta* OR (meta AND sta*) OR lesion* OR hyperplasi* OR adenoma*)) OR Choriocarcinoma*)) AND (title:(((bleed* OR blood* OR discharge*) AND (unusual* OR abnormal* OR unexplain* OR unschedule* OR unexpect* OR atypical* OR irregular* OR suspicio* OR suspect* OR vagin* OR uterin* OR endometr* OR duration* OR prolong* OR heavy OR heaviness* OR spotting)) OR ((menopaus* OR perimenopaus* OR postmenopaus*) AND (bleed* OR blood* OR discharg* OR menstru* OR menses OR period* OR haemorrhag* OR hemorrhag* OR menorrhagi* OR metrorrhagi* OR hypermenorrh* OR menometrorrhag*)) OR PMB) OR abstract:(((bleed* OR blood* OR discharge*) AND (unusual* OR abnormal* OR unexplain* OR unschedule* OR unexpect* OR atypical* OR irregular* OR suspicio* OR suspect* OR vagin* OR uterin* OR endometr* OR duration* OR prolong* OR heavy OR heaviness* OR spotting)) OR ((menopaus* OR perimenopaus* OR postmenopaus*) AND (bleed* OR blood* OR discharg* OR menstru* OR menses OR period* OR haemorrhag* OR hemorrhag* OR menorrhagi* OR metrorrhagi* OR hypermenorrh* OR menometrorrhag*)) OR PMB)) AND (title:(((hormon* OR oestrogen* OR estrogen* OR oestradiol* OR estradiol* OR progesterone* OR progestin*) AND (therap* OR treatment* OR replace* OR tablet* OR patch* OR gel* OR spray* OR implant*)) OR (HRT OR HT)) OR abstract:(((hormon* OR oestrogen* OR estrogen* OR oestradiol* OR estradiol* OR

Searches
progesterone* OR progestin*) AND (therap* OR treatment* OR replace* OR tablet* OR patch* OR gel* OR spray* OR implant*)) OR (HRT OR HT)))
Limits applied:
Year: 2015-2025
Publication type: Systematic Review

Database name: Medline ALL

Searches
1 exp uterine neoplasms/ (158497)
2 ((endometr* or uter* or womb or adnexa* or serous* or ovar*) adj4 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or rhabdomyosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or lesion* or hyperplasi* or adenoma*)).ti,ab. (221420)
3 Choriocarcinoma*.ti,ab. (7142)
4 or/1-3 (328920)
5 hemorrhage/ or uterine hemorrhage/ or menorrhagia/ or metrorrhagia/ (102511)
6 ((bleed* or blood* or discharge*) adj3 (unusual* or abnormal* or unexplain* or unschedule* or unexpect* or atypical* or irregular* or suspicio* or suspect* or vagin* or uterin* or endometr* or duration* or prolong* or heavy or heaviness* or spotting)).ti,ab,kf. (62943)
7 exp Menopause/ and (((menopaus* or perimenopaus* or postmenopaus*) adj3 (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) or PMB).ti,ab,kf. (3393)
8 or/5-7 (159624)
9 exp Hormone Replacement Therapy/ (27370)
10 ((hormon* or oestrogen* or estrogen* or oestradiol* or estradiol* or progesterone* or progestin*) adj2 (therap* or treatment* or replace* or tablet* or patch* or gel* or spray* or implant*)).ti,ab,kf. (99312)
11 (HRT or HT).ti,ab,kf. (94674)
12 or/9-11 (194875)
13 4 and 8 and 12 (821)
14 exp Case-Control Studies/ (1645566)
15 exp Cohort Studies/ (2805395)
16 Cross-Sectional Studies/ (562296)
17 Comparative Study.pt. (1963571)
18 (case adj (control or series)).tw. (299486)
19 (cohort adj (study or studies)).tw. (418802)
20 cohort analy$.tw. (15929)
21 longitudinal.tw. (390611)
22 prospective.tw. (833870)
23 retrospective.tw. (944816)
24 cross sectional.tw. (657416)
25 or/14-24 (6069152)
26 (sensitiv: or predictive value:).mp. or accurac:.tw. (2961030)
27 ((likelihood adj ratio*) or lr or plr or nlr).ti,ab. (67051)

Searches
28 diagnos*.ti. (765607)
29 or/26-28 (3599303)
30 25 or 29 (8844004)
31 13 and 30 (327)
32 animals/ (7758911)
33 exp Animals, Laboratory/ (1013182)
34 exp Animal Experimentation/ (10784)
35 exp Models, Animal/ (695297)
36 exp Rodentia/ (3755721)
37 (rat or rats or mouse or mice or rodent*).ti. (1543544)
38 or/32-37 (7895220)
39 38 not humans/ (5478924)
40 31 not 39 (324)
41 limit 40 to english language (298)
42 limit 41 to overall (0)
43 41 not 42 (298)
44 letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ (2968475)
45 (letter or comment*).ti. (220707)
46 44 or 45 (3050496)
47 randomized controlled trial/ or random*.ti,ab. (1812731)
48 46 not 47 (3022416)
49 43 not 48 (297)
50 49 and (2015* or 2016* or 2017* or 2018* or 2019* or 202*).ed,dt. (84)
51 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1460854)
52 "organisation for economic co-operation and development"/ (710)

Searches
53 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3713040)
54 european union/ (18688)
55 developed countries/ (21906)
56 or/52-55 (3730117)
57 51 not 56 (1366681)
58 50 not 57 (78)

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	21/10/2025	Ovid	1974 to 2025 October 17	17
International HTA Database	21/10/2025	https://database.inahta.org/	n/a	3
MEDLINE ALL	21/10/2025	Ovid	1946 to October 20, 2025	8

Search strategy history

Database name: Embase

Searches
1 exp uterus tumor/ or exp uterus cancer/ or choriocarcinoma/ (293297)
2 ((endometr* or uter* or womb or adnexa* or serous* or ovar*) adj4 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or rhabdomyosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or lesion* or hyperplasi* or adenoma*)).ti,ab. (315489)
3 Choriocarcinoma*.ti,ab. (8790)
4 or/1-3 (508862)
5 exp bleeding/ (1316270)
6 ((bleed* or blood* or discharge*) adj3 (unusual* or abnormal* or unexplain* or unschedule* or unexpect* or atypical* or irregular* or suspicio* or suspect* or vagin* or uterin* or endometr* or duration* or prolong* or heavy or heaviness* or spotting)).ti,ab,kf. (97789)

Searches
7 exp postmenopause bleeding/ (847)
8 exp menopause/ and (((menopaus* or perimenopaus* or postmenopaus*) adj3 (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) or PMB).ti,ab,kf. (3152)
9 or/5-8 (1374509)
10 exp hormone substitution/ (78177)
11 ((hormon* or oestrogen* or estrogen* or oestradiol* or estradiol* or progesterone* or progestin*) adj2 (therap* or treatment* or replace* or tablet* or patch* or gel* or spray* or implant*)).ti,ab,kf. (140846)
12 (HRT or HT).ti,ab,kf. (129006)
13 or/10-12 (295911)
14 4 and 9 and 13 (2827)
15 limit 14 to english language (2642)
16 15 not conference*.db,pt,su. (2014)
17 letter.pt. or letter/ (1403535)
18 (note or editorial).pt. (1872817)
19 (letter or comment*).ti. (265627)
20 or/17-19 (3340660)
21 randomized controlled trial/ or random*.ti,ab. (2657798)
22 20 not 21 (3302554)
23 16 not 22 (1922)
24 23 not clinical trial.pt. (1825)
25 24 and (2015* or 2016* or 2017* or 2018* or 2019* or 202*).dc,dd. (691)
26 animal/ (1735323)
27 nonhuman/ (8347975)
28 exp Animal Experiment/ (3441825)
29 exp Experimental Animal/ (917004)
30 animal model/ (1978856)
31 exp Rodent/ (4402397)
32 (rat or rats or mouse or mice or rodent*).ti. (1739236)
33 or/26-32 (10977333)
34 33 not human/ (7739960)
35 25 not 34 (678)
36 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/

Searches
or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1957186)
37 exp "organisation for economic co-operation and development"/ (3714)
38 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (4100416)
39 european union/ (34206)
40 developed country/ (37327)
41 or/37-40 (4137350)
42 36 not 41 (1784216)
43 35 not 42 (651)
44 Health economics/ (37723)
45 exp health care cost/ (379402)
46 exp Fee/ (47306)
47 exp Budget/ (37516)
48 Funding/ (83609)
49 budget*.ti,ab. (54293)
50 cost*.ti. (217028)
51 (economic* or pharmaco?economic*).ti. (86976)
52 (price* or pricing*).ti,ab. (84504)
53 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (355135)
54 (financ* or fee or fees).ti,ab. (281491)
55 (value adj2 (money or monetary)).ti,ab. (4719)
56 or/44-55 (1235908)
57 43 and 56 (17)

Database name: International HTA Database

Searches

Line	Search query	Hits
#1	"Uterine Neoplasms"[mhe]	238
#2	(endometr* or uter* or womb or adnexa* or serous* or ovar*) AND (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor*	312

Searches		
	or mass or masses or cyst* or adenocarcin* or sarcoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or rhabdomyosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or lesion* or hyperplasi* or adenoma*)	
#3	Choriocarcinoma*	0
#4	(Choriocarcinoma*) OR ((endometr* or uter* or womb or adnexa* or serous* or ovar*) AND (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or rhabdomyosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or lesion* or hyperplasi* or adenoma*)) OR ("Uterine Neoplasms"[mhe])	476
#5	"Hemorrhage"[mh]	137
#6	"Uterine Hemorrhage"[mh]	20
#7	"Menorrhagia"[mh]	28
#8	"Metrorrhagia"[mh]	1
#9	((bleed* or blood* or discharge*) and (unusual* or abnormal* or unexplain* or unschedule* or unexpect* or atypical* or irregular* or suspicio* or suspect* or vagin* or uterin* or endometr* or duration* or prolong* or heavy or heaviness* or spotting))	405
#10	"Menopause"[mhe]	71
#11	((menopaus* or perimenopaus* or postmenopaus*) AND (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) OR (PMB)	44
#12	(((menopaus* or perimenopaus* or postmenopaus*) AND (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) OR (PMB)) AND ("Menopause"[mhe])	14
#13	((((menopaus* or perimenopaus* or postmenopaus*) AND (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) OR (PMB)) AND ("Menopause"[mhe])) OR (((bleed* or blood* or discharge*) and (unusual* or abnormal* or unexplain* or unschedule* or unexpect* or atypical* or irregular* or suspicio* or suspect* or vagin* or uterin* or endometr* or duration* or prolong* or heavy or heaviness* or spotting))) OR ("Metrorrhagia"[mh]) OR ("Menorrhagia"[mh]) OR ("Uterine Hemorrhage"[mh]) OR ("Hemorrhage"[mh])	526
#14	"Hormone Replacement Therapy"[mhe]	35

Searches		
#15	((hormon* or oestrogen* or estrogen* or oestradiol* or estradiol* or progesterone* or progestin*) AND (therap* or treatment* or replace* or tablet* or patch* or gel* or spray* or implant*))	285
#16	HRT or HT	25
#17	(HRT or HT) OR (((hormon* or oestrogen* or estrogen* or oestradiol* or estradiol* or progesterone* or progestin*) AND (therap* or treatment* or replace* or tablet* or patch* or gel* or spray* or implant*))) OR ("Hormone Replacement Therapy"[mhe])	299
#18	((HRT or HT) OR (((hormon* or oestrogen* or estrogen* or oestradiol* or estradiol* or progesterone* or progestin*) AND (therap* or treatment* or replace* or tablet* or patch* or gel* or spray* or implant*))) OR ("Hormone Replacement Therapy"[mhe])) AND (((((menopaus* or perimenopaus* or postmenopaus*) AND (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) OR (PMB)) AND ("Menopause"[mhe])) OR (((bleed* or blood* or discharge*) and (unusual* or abnormal* or unexplain* or unschedule* or unexpect* or atypical* or irregular* or suspicio* or suspect* or vagin* or uterin* or endometr* or duration* or prolong* or heavy or heaviness* or spotting))) OR ("Metrorrhagia"[mh]) OR ("Menorrhagia"[mh]) OR ("Uterine Hemorrhage"[mh]) OR ("Hemorrhage"[mh])) AND ((Choriocarcinoma*) OR ((endometr* or uter* or womb or adnexa* or serous* or ovar*) AND (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or rhabdomyosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or lesion* or hyperplasi* or adenoma*)) OR ("Uterine Neoplasms"[mhe]))	8

Database name: MEDLINE ALL

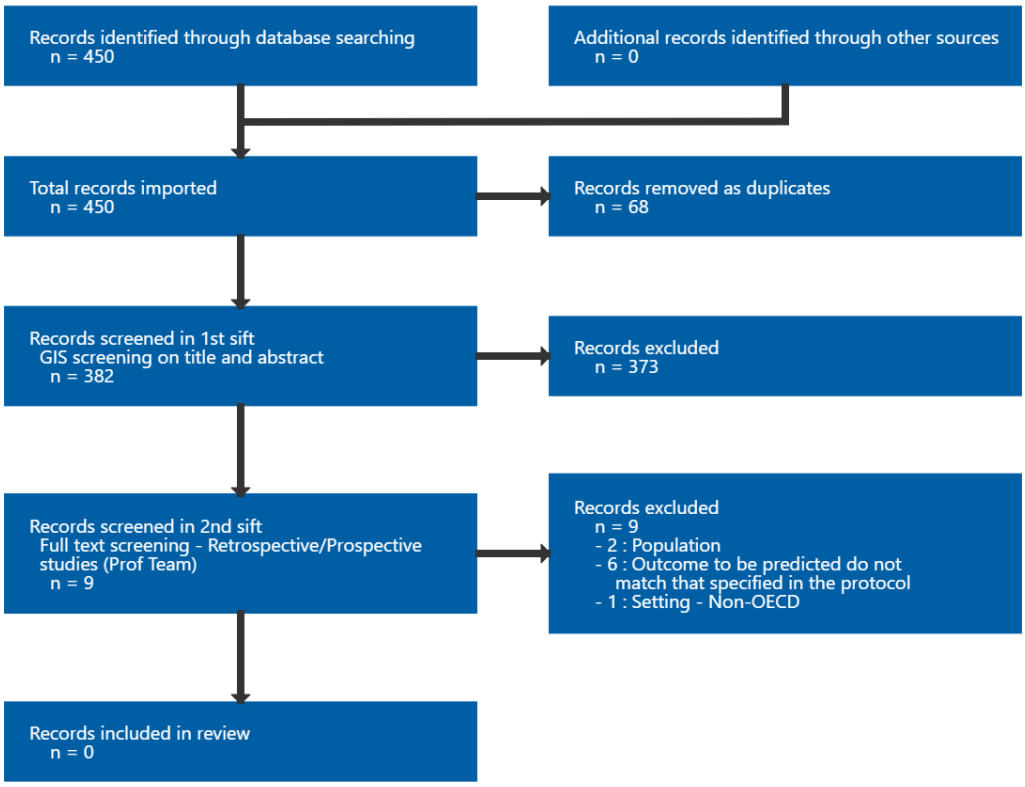
Searches
1 exp uterine neoplasms/ (158497)
2 ((endometr* or uter* or womb or adnexa* or serous* or ovar*) adj4 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or rhabdomyosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or lesion* or hyperplasi* or adenoma*)).ti,ab. (221420)
3 Choriocarcinoma*.ti,ab. (7142)
4 or/1-3 (328920)
5 hemorrhage/ or uterine hemorrhage/ or menorrhagia/ or metrorrhagia/ (102511)
6 ((bleed* or blood* or discharge*) adj3 (unusual* or abnormal* or unexplain* or unschedule* or unexpect* or atypical* or irregular* or suspicio* or suspect* or vagin* or uterin* or endometr* or duration* or prolong* or heavy or heaviness* or spotting)).ti,ab,kf. (62943)
7 exp Menopause/ and (((menopaus* or perimenopaus* or postmenopaus*) adj3 (bleed* or blood* or discharg* or menstru* or menses or period* or haemorrhag* or hemorrhag* or

Searches
menorrhagi* or metrorrhagi* or hypermenorrh* or menometrorrhag*)) or PMB).ti,ab,kf. (3393)
8 or/5-7 (159624)
9 exp Hormone Replacement Therapy/ (27370)
10 ((hormon* or oestrogen* or estrogen* or oestradiol* or estradiol* or progesterone* or progestin*) adj2 (therap* or treatment* or replace* or tablet* or patch* or gel* or spray* or implant*)).ti,ab,kf. (99312)
11 (HRT or HT).ti,ab,kf. (94674)
12 or/9-11 (194875)
13 4 and 8 and 12 (821)
14 animals/ (7758911)
15 exp Animals, Laboratory/ (1013182)
16 exp Animal Experimentation/ (10784)
17 exp Models, Animal/ (695297)
18 exp Rodentia/ (3755721)
19 (rat or rats or mouse or mice or rodent*).ti. (1543544)
20 or/14-19 (7895220)
21 20 not humans/ (5478924)
22 13 not 21 (808)
23 limit 22 to english language (736)
24 limit 23 to overall (0)
25 23 not 24 (736)
26 letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ (2968475)
27 (letter or comment*).ti. (220707)
28 26 or 27 (3050496)
29 randomized controlled trial/ or random*.ti,ab. (1812731)
30 28 not 29 (3022416)
31 25 not 30 (726)
32 31 and (2015* or 2016* or 2017* or 2018* or 2019* or 202*).ed,dt. (228)
33 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or

Searches
seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1460854)
34 "organisation for economic co-operation and development"/ (710)
35 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3713040)
36 european union/ (18688)
37 developed countries/ (21906)
38 or/34-37 (3730117)
39 33 not 38 (1366681)
40 32 not 39 (222)
41 Economics/ (27554)
42 Value of life/ (5850)
43 exp "Costs and Cost Analysis"/ (282760)
44 exp Economics, Hospital/ (26322)
45 exp Economics, Medical/ (14472)
46 Economics, Nursing/ (4014)
47 Economics, Pharmaceutical/ (3170)
48 exp "Fees and Charges"/ (31761)
49 exp Budgets/ (14419)
50 budget*.ti,ab. (40694)
51 cost*.ti. (160934)
52 (economic* or pharmaco?economic*).ti. (69449)
53 (price* or pricing*).ti,ab. (61833)
54 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (255967)
55 (financ* or fee or fees).ti,ab. (191757)
56 (value adj2 (money or monetary)).ti,ab. (3511)
57 or/41-56 (840835)
58 40 and 57 (8)

Appendix C Study selection

Figure 1 Diagnostic evidence study selection



Appendix D Diagnostic evidence

No evidence was identified which was applicable to this review question.

Appendix E Forest plots

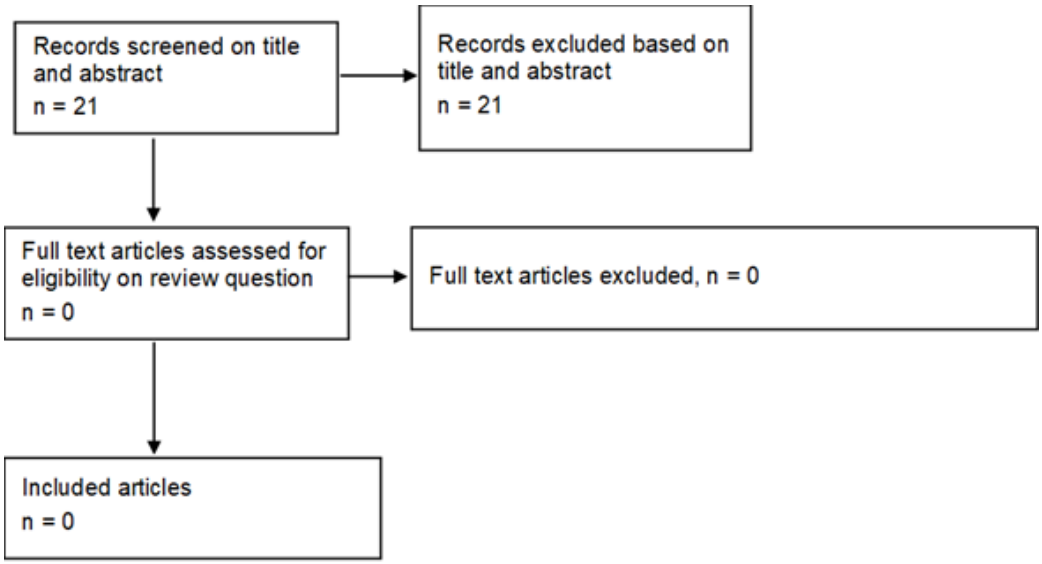
No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE summary

No evidence was identified which was applicable to this review question.

Appendix G Economic evidence study selection

Figure 2: Economic evidence study selection flow chart



Appendix H Economic evidence tables

No economic evidence was identified for this review question

Appendix I Excluded studies

Diagnostic

Table 1 Studies excluded from the diagnostic review

Study	Code [Reason]
Buchanan, Charlotte; Robinson, Megan; Macdonald, Madeleine C (2022) Endometrial cancer rate in Hormone replacement therapy users with postmenopausal bleeding: Retrospective cohort study. Post reproductive health 28(3): 143-148	- Outcome to be predicted do not match that specified in the protocol *No relevant outcomes reported. Reports measures of detection rate, but the numbers reported are for prevalence. Diagnostic test accuracy data on the unscheduled vaginal bleeding are not reported.*
Clarke, Megan A, Long, Beverly J, Del Mar Morillo, Arena et al. (2018) Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA internal medicine 178(9): 1210-1222	- Population *Systematic review including participants in protocol (51/92 people who take HRT), and out of protocol (41/92 people who do not take HRT). Studies including participants who take HRT ere checked against protocol criteria and were not relevant (49/51 studies were published before 2015, 1/51 was conducted in Hong Kong and 1/52 reported DTA data on ultrasounds and not on unscheduled vaginal bleeding).*
Clarke, Megan A, Long, Beverly J, Sherman, Mark E et al. (2020) A prospective clinical cohort study of women at increased risk for endometrial cancer. Gynecologic oncology 156(1): 169-177	- Outcome to be predicted do not match that specified in the protocol *No relevant outcomes reported. Reports measures of association using one-way ANOVA tests. Diagnostic test accuracy data on the unscheduled vaginal bleeding are not reported.*
Mainar, L.B., Sierra, J.N., Sarrado, L.A. et al. (2021) Clinical and demographic factors in endometrial and ovary carcinoma: Synchronous carcinoma vs stage IIIA endometrial carcinoma. European Journal of Gynaecological Oncology 42(4): 643	- Outcome to be predicted do not match that specified in the protocol *No relevant outcomes reported. Reports comparison of the characteristics between the patients with endometrial and ovarian synchronous carcinoma with patients diagnosed with endometrial carcinoma with metastatic ovarian involvement. Diagnostic test accuracy data on the unscheduled vaginal bleeding are not reported.*
Musonda, P., Burbos, N., Duncan, T.J. et al. (2011) Comparing the performance of two clinical models in estimating the risk of endometrial cancer in symptomatic postmenopausal women. European Journal of Obstetrics and Gynecology and Reproductive Biology 159(2): 433	- Outcome to be predicted do not match that specified in the protocol *No relevant outcomes reported. Reports accuracy measures for predictive models, based on combining multiple variables: diabetes, endometrial thickness, frequency of bleeding, age and BMI. Diagnostic test*

Study	Code [Reason]
	accuracy data on the unscheduled vaginal bleeding are not reported.
Perveen, S., Azhar, M.S., Shah, F. et al. (2022) Association of Postmenopausal Bleeding with Endometrial Carcinoma. Pakistan Journal of Medical and Health Sciences 16(3): 103	- Setting - Non-OECD *Study conducted in Pakistan.*
Sladkevicius, Povilas and Valentin, Lil (2016) Prospective validation of two mathematical models to calculate the risk of endometrial malignancy in patients with postmenopausal bleeding and sonographic endometrial thickness >=4.5 mm. European journal of cancer (Oxford, England : 1990) 59: 179-188	- Outcome to be predicted do not match that specified in the protocol *No relevant outcomes reported. Reports measures of DTA of two models. Included variables in the models: patient's age in years, use of hormone replacement therapy, endometrial thickness, and colour content of the endometrial scan or vascularity index). Diagnostic test accuracy data on the unscheduled vaginal bleeding are not reported.*
van Maldegem, Laura D P R, van der Zande, Johanna A, van Werkhoven, Lucy A et al. (2024) Recurrent postmenopausal bleeding: Pathological findings and predictive factors. A multicenter, prospective, observational study. Acta obstetricia et gynecologica Scandinavica 103(7): 1283-1291	- Outcome to be predicted do not match that specified in the protocol *No relevant outcomes reported. Reports measures of association (in odds ratio) between HRT use and risk of endometrial malignancy among women with one or more episodes of postmenopausal bleeding. HRT includes in protocol (Oestrogen and Progestogen) and out of protocol (Mirena IUD, Tamoxifen and Aromatase inhibitor) types of hormones. Diagnostic test accuracy data on the unscheduled vaginal bleeding are not reported.*
Verbakel, Jan Yvan, Heremans, Ruben, Wynants, Laure et al. (2022) Risk assessment for endometrial cancer in women with abnormal vaginal bleeding: Results from the prospective IETA-1 cohort study. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 159(1): 103-110	- Population *Population includes women in secondary and tertiary care with abnormal vaginal bleeding (such as, postmenopausal bleeding, heavy menstrual bleeding, intermenstrual bleeding, bleeding during continuous combined estrogen-gestagen therapy, or abnormal bleeding during sequential estrogen-gestagen therapy). Results are reported in aggregate. The paper does not report when the bleeding started and how long participants were on HRT.*

Abbreviations: ANOVA: Analysis of Variance; DTA: diagnostic test accuracy; HRT: hormone replacement therapy; IUD: Intrauterine Device; OECD: Organisation for Economic Co-operation and Development.

Economic

No economic evidence was identified for this review question.

Appendix J Methods

Development of the guideline

Guideline covers

The methods outlined here relate to the update of recommendations on:

- Endometrial cancer in the NICE guideline on suspected cancer: recognition and referral guideline (NG12) (Recommendations 1.5.10 and 1.5.11) which outline when to refer patients with unexplained post-menopausal bleeding via the suspected cancer pathway or when to consider a direct access ultrasound scan.

- To address the changes listed above consideration will be given to cross referring to the BMS guideline on the management of unscheduled bleeding on HRT.

Guideline does not cover

The methods outlined here do not apply to any other recommendations in NICE guidelines on suspected cancer: recognition and referral guideline (NG12).

Methods – diagnostic

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.

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

Developing the review questions and outcomes

The review question developed for this guideline was based on the key areas identified in the guideline scope. They were drafted by the NICE guideline development team and refined and validated by the guideline committee.

The review question was based on the following frameworks:

Population, index test(s), reference standard and outcome for reviews of diagnostic and predictive accuracy.

Full literature search, critical appraisal and evidence reviews were completed for the review question.

Reviewing research evidence

Review protocol

The review protocol was developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review.

Searching for evidence

Evidence was searched for each review question using the methods specified in Developing NICE guidelines: the manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. At least 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Data synthesis for diagnostic accuracy data

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in

some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The ‘raw’ 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline were as follows:

Sensitivity is the probability that the feature will be positive in a person with the condition.

- sensitivity = TP/(TP+FN)

Specificity is the probability that the feature will be negative in a person without the condition.

- specificity = TN/(FP+TN)

False negative rate (FNR) describes the proportion of actual positives that are incorrectly classified as negatives and describes how often a test fails to detect something. A high FNR means the test is missing a lot of actual cases.

- FNR = 1 - sensitivity

Positive predictive values describe the probability that a person with a positive feature has the disease.

- PPV = TP/ (TP+FP)

Meta-analysis of the findings will be undertaken where more than 2 studies were included for this review. Meta-analysis should not be performed on 2 studies as a minimum of 3 studies is needed to estimate the 5 parameters needed for a bivariate meta-analysis (mean and variance of logit sensitivity, mean and variance of logit specificity, and the correlation between logit sensitivity and logit specificity).

Appraising the quality of evidence

Diagnostic accuracy studies

Individual diagnostic accuracy studies will be quality assessed using the QUADAS-2 tool. Each individual study will be classified into one of the following three groups:

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

Each individual study will also be classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies will be rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

GRADE for diagnostic accuracy evidence

Evidence from diagnostic accuracy studies will initially be rated as high quality and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 2 below.

The choice of primary outcome for decision making will be determined by the committee and GRADE assessments will be undertaken based on these outcomes.

In all cases, the downstream effects of diagnostic accuracy on patient-important outcomes will be considered. This will be done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences will be incorporated here in addition.

GRADE assessments will only be undertaken for sensitivity and specificity where available but results for positive predictive values and false negative rates are also presented alongside those data.

The committee will be consulted to set 2 clinical decision thresholds for each measure: the value above which a test would be recommended, and a second below which a test would be considered of no clinical use. These values will be used to judge imprecision (see below).

If studies could not be pooled in a meta-analysis, GRADE assessments will be undertaken for each study individually and reported as separate lines in the GRADE profile.

These criteria will be used to apply preliminary ratings, but will be overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 2 Rationale for downgrading quality of evidence for diagnostic accuracy data

GRADE criteria	Reasons for downgrading quality
Risk of bias	• Not serious (don't downgrade): less than 50% overall weighting some concerns/high risk of bias

GRADE criteria	Reasons for downgrading quality
	• Serious (downgrade 1 level): more than 50% some concerns/high risk of bias • Very serious (downgrade 2 levels): more than 50% high risk of bias.
Indirectness	• Not serious (don't downgrade): less than 50% of overall weighting partially direct or indirect. • Serious (downgrade 1 level): more than 50% of overall weighting partially direct or indirect. • Very serious (downgrade 2 levels): more than 50% of overall weighting indirect.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses will be conducted. Where data was pooled it will be checked visually to identify inconsistency. Where there are apparent differences in effect size due consideration will be given to the appropriateness of pooling studies.
Imprecision	The most appropriate primary pair of measures (for example: sensitivity/specificity, likelihood ratio) will be used as described this in the review protocol. And appropriate thresholds with will be discussed with the guideline committee.
Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome will be downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain will be excluded from GRADE profiles to improve readability.

Appendix K Research recommendations

Research recommendation

What is the diagnostic accuracy of unscheduled vaginal bleeding for the detection of endometrial cancer in adults taking HRT to inform decision making for referral via a suspected cancer pathway?

Why this is important

There is a lack of research on the diagnostic impact and cost-effectiveness of unscheduled vaginal bleeding for the detection of endometrial cancer in adults taking HRT. The committee highlighted that the recent systematic review undertaken by NICE to inform its recent update of the endometrial cancer recommendations in NG12 identified no studies. The committee also flagged that the recently published BMS guideline (British Menopause Society, 2024) also highlighted a paucity of evidence in the area. A diagnostic test accuracy study would provide data to support recommendation development on what approach should be adopted in primary care when making clinical decisions regarding suspected endometrial cancer risk in this population.

Rationale for research recommendation

Importance to the population

The committee highlighted that in practice those taking HRT may be referred to suspected cancer pathway irrespective of the timing of HRT initiation or changes in HRT dose or preparation. These referrals can be unnecessary and potentially cause unnecessary stress and anxiety, for those referred and may increase the burden on system resources. The committee reviewed the equality and health inequalities assessment (EHIA) and discussed overall issues regarding access to services and delayed diagnosis that may impact those with protected and other characteristics and highlighted the need for consideration of these groups when undertaking research.

Relevance to NICE guidance

No evidence was identified for this review question in this recent update, so the committee could not make a recommendation that addresses referrals to the suspected cancer pathway for those taking HRT. Evidence would enable future recommendations to guide clinical practice in this area.

Relevance to the NHS

More evidence would support optimal decision making ensuring appropriate referrals for those at higher risk and reducing unnecessary referrals, reducing stress on existing system resources and unnecessary stress and anxiety on individuals.

Current evidence base

The evidence review that sought to answer the question “What is the diagnostic accuracy of unscheduled vaginal bleeding for the detection of endometrial cancer in adults taking HRT to inform decision making for referral via a suspected cancer pathway?” identified no studies.

Table 3 Research recommendation protocol outline

Population	Adults taking HRT (peri or post-menopausal):
	• Combined oestrogen and progestogen HRT
	  ○ Sequential combined HRT
	  ○ Continuous combined HRT
	  ○ Any combined
	• Oestrogen-only HRT

Index test	Unscheduled bleeding single episode in adults taking HRT Unscheduled bleeding multiple episodes in adults taking HRT Where the evidence provides data consideration will be given to: • Duration of bleeding • Heaviness of bleeding
Reference standard	Endometrial Cancer diagnosis within 12 months following an episode of unscheduled bleeding.
Diagnosis of interest	Accuracy of unscheduled bleeding as a referral criterion for Endometrial cancer assessed via: • Sensitivity (upper 90, lower 10) • Specificity (upper 80, lower 50) • Positive predictive value (PPV that would trigger a referral to the suspected cancer pathway is 3%)

	• False negative rate (Sub-group analysis of groups with protected or other characteristics where data is available)
Study type	• Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies

Other information	Stratify evidence by:
	• peri or post-menopausal
	• length of unscheduled bleed
	• heaviness of bleed
	• single vs multiple unscheduled bleeding
	• EHIA:
	  ○ socioeconomic and geographical factors
	  ○ age
	  ○ ethnicity
	  ○ disabilities
	  ○ people for whom English is not their first language or who have other communication needs
	  ○ trans people
	  ○ non-binary people

Abbreviations: EHIA: Equality and Health Inequalities Impact Assessment; HRT: hormone replacement therapy; PPV: positive predictive value.