Suspected cancer: recognition and referral guideline

ID	Field	Content
1.	Review title	Endometrial cancer: Unscheduled bleeding, HRT and cancer referral
2.	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?
3.	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.
4.	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.
5.	Condition or domain being studied	Unscheduled bleeding in adults taking HRT

6.	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.
7.	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
8.	Reference standard	Endometrial Cancer diagnosis within 12 months following an episode of unscheduled bleeding
9.	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 • Papers published between 2015-2025
10.	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
11.	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.
12.	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
13.	Secondary outcomes	Not applicable
14.	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.

15.	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.
16.	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 and positive predictive value 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/"

17.	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
		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.

18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	October 2025		
22.	Anticipated completion date	November 2025		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE **5b Named contact e-mail** SuspectedCancer@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	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
26.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.
27.	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.
28.	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].
29.	Other registration details	[Give the citation and link for the published protocol, if there is one.]
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
31.	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.

32.	Keywords	Unscheduled bleeding, HRT, endometrial cancer, suspected cancer.
33.	Details of existing review of same topic by same authors	This is a new review question.
34.	Current review status	☐ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk