National Institute for Health and Care Excellence

Suspected cancer: recognition and referral

[C] Diagnostic review for endometrial cancer: unscheduled bleeding, HRT and cancer referral

NICE guideline NG12

Evidence underpinning recommendations 1.5.12 to 1.5.15 and research recommendations

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Draft for consultation

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Endometrial cancer: unscheduled bleeding, HRT and cancer referral

1.1 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?

1.1.1 Summary of the protocol

Table 1: PIRDS inclusion criteria

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.

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	Endometrial Cancer diagnosis within 12 months following an episode of unscheduled bleeding.
Study type	• Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies

Abbreviations: HRT: hormone replacement therapy.

For the full protocol see appendix A in the technical appendices document.

1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol and appendix J in the technical appendices document.

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

1.1.2.1 Search methods

The searches for the effectiveness evidence were run on 21 October 2025. The following databases were searched: Cochrane CDSR (Wiley), Embase (Ovid) and Medline ALL (Ovid). Limits were applied to remove animal papers, non-English language papers, and conference abstracts. Filters were used to limit to OECD countries, diagnostic, and cohort studies. A date limit was applied from January 2015 to October 2025.

The searches for the cost effectiveness evidence were run on 21 October 2025. The following databases were searched Embase (Ovid), International Health Technology Assessment Database (INAHTA), Medline ALL (Ovid). Limits were applied to remove animal papers, non-English language papers, and conference abstracts. Filters were used to limit to cost effectiveness studies. A date limit was applied from January 2015 to October 2025.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in appendix B.

1.1.3 Diagnostic evidence

1.1.3.1 Included studies

Study selection

A systematic search was carried out to identify potentially relevant studies as detailed in appendix J in the technical appendices document. See appendix B in the technical appendices document for the literature search strategy. The study selection process is presented as a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram in appendix C in the technical appendices document.

A systematic search of the literature was conducted, and a total of 9 papers were identified for full paper review but none of these studies were applicable, and 0 studies were included for this review question

1.1.3.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion, are given in appendix I.

1.1.4 Summary of studies included in the diagnostic evidence

No studies of diagnostic evidence were included following full text review.

1.1.5 Summary of diagnostic evidence

No studies of diagnostic evidence were included following full text review.

1.1.6 Economic evidence

1.1.6.1 Included studies

A search was performed to identify published economic evaluations of relevance to this review question. See the literature search strategy in **appendix B** in the technical appendices document.

No/ economic studies were identified which were applicable to this review question. (see economic study selection flow chart in **appendix G** in the technical appendices document).

1.1.6.2 Excluded studies

No economic studies were reviewed at full text stage.

1.1.7 Summary of economic evidence used in decision-making

No economic evidence was identified which was relevant to this review question.

1.1.8 Economic model

No original economic modelling was completed for this review question.

1.1.9 Committee discussion and interpretation of the evidence

1.1.9.1 Is the problem a priority

Identifying the appropriate patients for urgent suspected endometrial cancer referral in primary care is key to ensuring appropriate referral. There are not currently recommendations within this guideline for those taking hormone replacement therapy (HRT) who may be having bleeding that is potentially not what is expected with the type of HRT that they are taking.

The NHS Business Services Authority (NHSBSA) published data (Hormone Replacement Therapy - England - April 2015 to June 2023) that shows that in 2022/23, HRT prescriptions in England rose by 47%, with a 29% increase in patients receiving treatment. With the increasing rates of HRT prescriptions, it is key that those who need onwards referral for potential endometrial cancer are referred while those who may not don't have the unnecessary stress and anxiety associated with unnecessary cancer referrals. The absence of guidance on how to manage unscheduled bleeding in HRT users may lead to unnecessary referrals, with avoidable referrals of low-risk individuals.

1.1.9.2 Test accuracy and certainty in the test accuracy

There was no evidence identified in the systematic review search.

1.1.9.3 Balance of effects

The committee noted the lack of evidence identified for this review question. They agreed that this is a key decision making question in practice and have developed a research recommendation. They further agreed that this

research recommendation should be sent to the NIHR for connsideration for their commissioning programmes.

With the rising HRT presccription rates the committee agreed that some guidance from NICE is needed in this area. This may help to suport the appropriate onward referral for those who need it and reduce the unneccessary referral of those who are at much low risk of endometrial cancer.

The committee noted that there is a related guideline from the British Menopause Society (BMS) on the management of unscheduled bleeding in women using HRT, published in April 2024. This was developed in partnership with key stakeholders and Royal Colleges. This guideline includes initial evaluation of unscheduled bleeding in HRT users, with a detailed clinical assessment, considering factors such as bleeding patterns, HRT preparations, regimen (sequential or continuous), duration of use, and individual risk factors for cancer.

The committee noted that the BMS guideline recommendations were largely informal consensus and expert opinion based, as although focused evidence searches had been undertaken there is a lack of evidence in this area.

The committee outlined that the BMS guidance is useful resource and is referred to in practice. But they also wanted to note the pauity of evidence and the consenus expert opinion basis underpinning BMS guideline. In consideration of this they developed the research recommendation and agreed to raise awareness of the BMS guideline.

The committee also added further definitions for unexplained post-menopausal bleeding and unschedualed bleeding with HRT to ensure clarity around the recommendations.

1.1.9.4 Feasibility

As the guidline will raise awarenness of the BMS guidleine and promote clinical consideration in this area, this may reduce unnecessary referals in

women with unscheduled bleeding on HRT. This may lead to reduced stress and anxiety related to uncessary referrals to urgent suspected cancer service.

The research recommendation may lead to further evidence to suppport future guideline development in this area.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.12 to 1.5.15 and the research recommendation on unscheduled vaginal bleeding for the detection of endometrial cancer in those taking HRT.

1.1.11 References

1.1.11.1 Diagnostic evidence

No studies of diagnostic evidence were included for this review question.

1.1.11.2 Economic evidence

None