The specialist authority for menopause & post reproductive health

Management of unscheduled bleeding on hormone replacement therapy (HRT) Frequently Asked Questions

To support healthcare professionals with the implementation of the BMS, BSGE, BGCS, FSRH, GIRFT, RCGP and RCOG joint guideline on the management of unscheduled bleeding on HRT, the Lead Authors, together with colleagues in the NHS Faster Diagnosis Programme Team, have collated a list of the frequently asked questions that have been submitted since the guideline was published.

Some of the questions relate to areas where there is a paucity of evidence. If research groups have high-quality evidence which provides clarity to any of these areas, it is hoped that these data will be published. The guideline is a dynamic document that will be updated as soon as more evidence is published, as its ultimate aim is to improve quality of life for women by reducing investigations for those who are at low-risk of endometrial cancer.

Unscheduled bleeding

1. Where it states in the algorithm 'Bleeding ongoing or increasing?', is there a minimal time period for this at all? Is there a time frame for referral if abnormal bleeding patterns persist?

The following information is contained on pages 20-21 of the guideline:

- Refer for ultrasound within any time-frame of starting ccHRT / sHRT if presenting with:
  - — Prolonged withdrawal bleeds (more than 7 days), and/or
  - — Heavy bleeding (flooding and / or clots), and/or
  - — Persistent bleeding, even light, which occurs most days for 4 weeks or more, and/or
  - — One major or two minor risk factors for endometrial cancer
- Refer for ultrasound if more than six months after starting HRT and:
  - — Reports bleeding with ccHRT after an interval of amenorrhoea
  - — Develops unscheduled bleeding on sHRT having had prior, light regular withdrawal bleeds
- If a woman has unscheduled bleeding and you are providing adjustments to her HRT, assessing her at 4 week intervals would be appropriate. A referral should be considered if a) the bleeding has improved but is still ongoing after 6 months of adjustments or b) prior to the six months if there is no improvement in the intensity/frequency at follow-up. We have updated the flowchart with this information and it is included in this FAQ document.

2. Can specific guidance be given about bleeding where an IUD is in place? Can evidence be shared around current thresholds?

The same advice would apply to women who use the 52 mg LNG IUD as for other preparations - heavy/prolonged bleeding or irregular bleeding where previously there has been amenorrhoea - should trigger assessment as per the flowchart in the guideline. Women who are established on HRT (> 6 months after initiation) should have a thin endometrium with an IUD and the same thresholds for ccHRT should apply. As per the guideline, if the endometrium is obscured, and an endometrial thickness cannot be measured, then these women should be referred for endometrial assessment - as hyperplasia and polyps can still occur in women who have risk factors for cancer and have a 52 mg LNG IUD in situ.

3. Will the women who continue to bleed after 4 weeks off HRT be added to the flow diagram as they are referenced in the guide but not in the diagram and could inadvertently be missed?

An updated version of the flowchart which includes this area has been developed and is included in this FAQ document.

Hormone Replacement Therapy (HRT)

1. What is the consensus on an incidental finding of a thickened endometrium in women taking continuous combined or sequential preparations?

This information is contained in Appendix 3 and page 24 of the guideline:

TVS: Asymptomatic (no unscheduled bleeding) with incidental ET≥ 10mm and *no* riskfactors for endomentrial cancer	Urgent	Hysteroscopy + biopsy (preferable) or blind biopsy alone – resources dependent
TVS: Asymptomatic (no unscheduled bleeding) with incidental ET≥ 10mm with risk factors for endomentrial cancer (x1 major or x2 minor)	USCP	Hysteroscopy + biopsy (preferable) or blind biopsy alone – resources dependent

In women who are asymptomatic, with one major or 2 minor risk factors for cancer, and have an endometrial thickness > 4mm (ccHRT) or > 7mm (sHRT), but less than 10 mm, a pragmatic consensus panel decision, in the absence of safety data for this cohort, recommended endometrial assessment until these data are available.

2. Why has the guideline not emphasized that undertreating women is also associated with harm? (Ongoing symptoms, poor QOL, increased risk of osteoporosis and CVD)

If unscheduled bleeding is occurring and it is a woman's choice to decline endometrial cancer exclusion tests (after informed counselling and explorations of barriers to this), then stopping HRT should be offered as cessation of bleeding within 4 weeks of this would provide reassurance that an underlying cancer is unlikely. If these women stop bleeding and wish to restart HRT, this was covered in the guideline and has been updated on the flowchart included in this FAQ document.

If women proceed with investigations, continuing or stopping HRT is the choice of the woman (as also discussed in the guideline). This should be considered woman-centred advice, as many units were declining to review women on the fast-track pathway unless all women referred had stopped HRT and were still bleeding; these recommendations were therefore made following discussions with cancer unit leads and the British Gynaecological Cancer Society to maintain quality of life but also safety.

Stopping HRT for a short period of time whilst awaiting cancer exclusion tests, if this is what occurs (as with either of the scenarios outlined above), will not lead to significant harm to long-term fracture risk or cardiovascular risk. Any potential downside of stopping HRT for a short while needs to be balanced against the potential risk of aggravating an, as yet undiagnosed, endometrial cancer. This is particularly pertinent in those with established risk factors.

Evidence base

1. Where is the evidence that shows an increased risk of endometrial cancer in women who take estradiol, as many of the studies reporting a causal relationship between unopposed estrogen therapy and the development of endometrial hyperplasia and carcinoma are not using transdermal estradiol?

Pharmacokinetic studies have consistently reported that all forms of estrogen (including estradiol given by whatever route) and conjugated equine estrogens exert stimulatory effects on the endometrium comparable to the premenopausal proliferation-phase. Progestogen use, either sequentially or continuously, opposes this stimulation by inducing a secretory state. Given the extensive supportive literature over the past 50 years assessing the impact of estrogen on the endometrium such as Whitehead et al, NEJM 1981; Kuhl et al, Climacteric 2002; Pickar et al, Climacteric 2020, it was not felt necessary to specifically include this in the guideline to avoid increasing the overall length.

Whilst there is evidence that CEE has a more potent effect on liver enzymes, there is no evidence from basic science that this difference is seen in the endometrium; in relation to clinical application, 0.3-0.45 mg CEE is comparable to 25-37.5 mg transdermal estradiol. Other physiological examples which illustrate this are women with PCOS where estradiol production is maintained but progestogen is infrequent (in line with ovulation effects) and in women with a raised BMI. Data over the past 50 years have consistently reported unopposed estrogen to be a risk for endometrial cancer.

With regards to estradiol specific effects (oral and transdermal) on the endometrium, multiple studies have demonstrated the same proliferative effect. For example: PEPI 1995, Korson 1999, Kurman 2000, Archer 2005, Furness et al 2012 (Cochrane review), Sriprasert 2021 (Elite). There are no data, either pharmacokinetic or clinical, to indicate that transdermal estradiol, at equivalent doses, has any lesser effect on the endometrium than other forms of estradiol.

2. Where is the evidence that higher progestogen doses are beneficial for women using high estrogen doses?

The recommendations in relation to the dose and duration protective effect of progestogens on the endometrium are supported by multiple studies going back to the 1970s. Some of these are referenced in the guideline, including a Cochrane review (CD000402 Furness et al, 2012) which mostly assessed the association with progestins and included tables on the minimum recommended progestogen dose with low- to moderate-dose estrogen. In a systematic review, Stute et al (2016), addressed endometrial proliferation and cancer risk with various progestins including micronised progesterone, and recommended incremental increases in progestin dosages, including micronised progesterone.

In comparison to more established progestins, the evidence base for micronised progesterone dose and duration of use when combined with higher-dose estrogen, is suboptimal. However, an absence of evidence cannot be taken to mean safety and there are currently no data to suggest that micronised progesterone has any more potent effect on the endometrium than other widely available progestins. Multiple high-quality studies are currently in progress, which will add to this evidence base and the guideline will be updated when these data are published.

3. There has been confusion about progesterone dosing since the publication of the guideline. Many doctors seem to have interpreted the guideline differently, stating that progesterone only needs to be increased in those who are experiencing unscheduled bleeding whilst others are increasing in women who are using high dose estrogen - even in the absence of bleeding.

Could you please a) clarify if progestogens should be increased in women taking high dose estrogen even if not bleeding, b) what action should they take for these women if they are not presenting with bleeding and c) audits may identify women on higher than licensed doses of estrogen, started by specialist clinics but without unscheduled bleeding – what specific action should they take in this scenario?

a) There is good evidence that use of 200 mg micronised progesterone used sequentially and 100mg used continuously in women taking low to moderate dose transdermal estradiol provides endometrial protection for up to 5 years of use (PEPI trial, KEEPs and E3N). There is more limited safety data for women using high dose estrogen – particularly in those who have additional risk factors for endometrial cancer such as a raised BMI. Given the low rates of inactive endometrium reported with 200 mg of sequential MP and 100 mg of continuous MP with low to moderate dose estrogen, and high rates achieved with 300mg and 200 mg respectively, Stute et al (2016) recommended this higher starting dose when initiating HRT and to consider reducing to the lower dose of micronised progesterone if amenorrhoea was reported three months later AND low dose estrogen was prescribed. Based on the limited evidence available the guideline consensus group continued this recommendation of offering the increased dose of progesterone if high-dose estrogen was prescribed (even in the absence of bleeding). Retrospective studies are being completed in this area; these data may enable stratification of dose by the presence of additional risk factors or bleeding pattern, rather than high-dose estrogen alone. When these data are available the guideline will be updated.

b) The patient and the prescriber should be aware that they are potentially on a sub-optimal dose of progestogen and in the event of any unscheduled bleeding the dose should be immediately increased. In the absence of bleeding we would advise that the patient should be made aware of the guideline recommendation and at the next consultation the increase in dose discussed with them.

c) The patient and prescriber should be aware that they are using off-label dosages of estrogen and there is a lack of safety data relating to the appropriate dose of progestogen in these scenarios. If prescribing of higher dose estrogen is considered necessary to manage symptom control (when preparation changes, holistic management and other causes of ongoing symptoms have been excluded) then the onus is on the recommending clinician to discuss this with the patient to enable joint, informed, and documented, decision-making (see question 5 below).

4. a) Where is the evidence that lower dose HRT achieves greater rates of amenorrhoea and b) that lower dose estrogen should be prescribed to women with a BMI >30?

a) The guideline states: 'Lower dose HRT achieves greater rates of amenorrhoea and if women have mild symptoms, this should be considered when initiating sHRT or ccHRT.' The use of the words 'consider' and 'when initiating' does not suggest this should apply to all women, nor that we are advocating low dose HRT should only be offered without adjustment to symptoms. Clinical studies that demonstrate greater rates of amenorrhoea with lower dose HRT include DF Archer Fertil Steril 2001, JC Stevenson Maturitas 2010, Tsiligiannis et al Maturitas 2020. Pharmacological principles advise that the lowest effective dose of any medication should be prescribed and then increased dependent upon clinical need and the side effect profile.

b) This was not stated in the guideline. Table 6 provides recommendations for reducing and managing unscheduled bleeding on HRT in general and for specific conditions, including women with a BMI over 30. Reducing the dose of estrogen, and supplementing with non-hormonal options (if required), is suggested as one potential adjustment (along with several other alternatives) and was not targeted to women with a raised BMI alone.

5. Where is the evidence that higher off-label doses of estrogen are harmful?

As stated in the guideline, there is limited evidence in relation to some of the recommendations, but it is important to emphasise that lack of evidence is not evidence of absence of harm and does not imply safety. By definition, off label dosages have not been subjected to the rigorous evaluation normally associated with regulated doses.

In some areas, pragmatic and precautionary principles were applied and agreed on as consensus by the expert panel and the endorsing agencies i.e. practical compromise to reduce referrals whilst at the same time maintaining patient safety. If prescribing of higher dose estrogen is considered necessary to manage symptom control (when preparation changes, holistic management and other causes of ongoing symptoms have been excluded) then the onus is on the recommending clinician to provide evidence (short and long-term follow-up) that in their population, low- and high-risk women, it is not affecting cancer risk.

The aim, as stated in the guideline, is to update the recommendations when data from high-quality evidence become available - appropriately designed (and powered) studies, with long-term follow-up and risk stratification (see Appendix 5 of the guideline for research recommendations).

6. a) In your admirable attempt to improve the management of these women, do you think that you had to make compromises, without an evidence base, to keep everyone in your group happy?

Where the evidence base was weak, pragmatic and precautionary principles were applied to ensure safety – decisions in these areas were made on consensus of an expert panel which included representatives from primary and secondary care. When data subsequently become available, these recommendations will be adjusted if suggested by the study outcomes.

b) Should you not be leading the collection of evidence, so that sanity can return to USC clinics, and to prevent women from being inappropriately worried and put through painful invasive testing?

Retrospective data collection is already in progress nationally and prospective data will be collected once the guideline is implemented. This guideline has helped to highlight the evidence gaps that should be urgently prioritised and we hope that these areas of uncertainty will be supported by NIHR bids.

Endometrial thickness

1. Can you describe the rationale for the endometrial thickness used for sHRT and cHRT and how this will be reviewed given the limited evidence?

The rationale for the endometrial thickness thresholds can be found on page 23 of the guideline. The main points to consider when reflecting on these cut offs are i) only high-risk women with individual risk factors for cancer will now be referred (higher pre-test probabilities of endometrial disease) and ii) in the research priorities at the back of the guideline we have highlighted this area given the limited evidence which reports on the accuracy of TVS endometrial thickness thresholds in predicting endometrial hyperplasia or cancer on subsequent histology when women present with unscheduled bleeding on HRT.

Implementation

1. What do you foresee are the challenges to implementing this guidance? Successes and barriers to implementation will be presented at 'share and learn' sessions which will be facilitated by the National Faster Diagnosis Programme Team who are also working in collaboration with the BMS Lead Authors and other key stakeholders to produce Implementation Guidance to support organisations. Some areas which may lead to challenges in implementation are:

- Education relating to initiation of HRT preparations which are least likely to be associated with abnormal bleeding, whilst providing symptom control;
- Education relating to adjustment of HRT preparations in women who present with unscheduled bleeding;
- Changes in the fast-track referral forms/criteria;
- Direct access ultrasound - changes will need to be made to ultrasound referral pathways, order forms and reporting criteria with auditing of any changes to sonography department workloads and how this can be streamlined/supported;
- Direct access from ultrasound to the fast-track service whilst ensuring clinical governance principles are upheld e.g. responsibility for DNAs, etc;
- Lack of national standards/targets for urgent pathways in gynaecology (as opposed to USCP);
- Perceived increase in workload for primary care; education sessions relating to unnecessary tests/patient anxiety, risk of cancer with unscheduled bleeding and total reduction in referrals by providing adjustments in HRT need to be implemented.

2. Could you clarify how Cancer Waiting Times (CWT) rules apply for the pathways within the algorithm please?

For patients who have been referred for a direct access diagnostic ultrasound, processes and protocols should be clearly defined and agreed across stakeholders and articulate how patients are referred to the appropriate pathways. Two scenarios are outlined briefly below:

a. Direct access ultrasound performed in the community:

i. Abnormal result: Where community providers are utilised for urgent TVUS, they should have the ability to refer directly to a USC pathway. Cancer Waiting Times Guidance v12, section 2.2.9 should be applied in these cases. Patients should not be referred back to the Primary Care Clinician for referral on a USC as this will potentially delay the time to diagnosis/exclusion of cancer. Further details on data recording can be found within section 2.2.9 of the CWT guidance.

ii. **Normal result**: Patients with a normal result where no further investigation is required and where there is confidence in the exclusion of cancer, should be managed by primary or community care. Patients should receive appropriate follow-up in these settings.

b. Direct access ultrasound performed in secondary care:

i. **Abnormal result**: The patient should be directly triaged and referred on to a cancer pathway from an abnormal direct access diagnostic scan with a suspicion of cancer. As per Cancer Waiting Times Guidance v12, section 2.2.9, these patients should be counted as a USC referral, and not an upgrade, with the cancer referral to treatment period start date recorded as the date of triage in to secondary care management for the purpose of patient tracking and management. The source of referral for outpatients should be recorded as a referral from a general medical practitioner. This will support reduction in time to diagnosis/exclusion of cancer. Further details on data recording can be found within section 2.2.9 of the CWT guidance.

ii. **Normal result**: Patients with a normal result where no further investigation is required and where there is confidence in the exclusion of cancer, should be managed by primary or community care. Patients should receive appropriate follow-up in these settings.

Stratification of urgent vs 2WW

1. The pathway suggests a TVUSS on an urgent pathway and for this to be completed within 6 weeks. Can you describe the rationale for a) the urgent referral and b) the 6-week time period?

The patients these recommendations pertain to are below the NICE 3% risk threshold for cancer i.e. they do not meet the USC pathway and therefore should not be prioritised over those who are at higher risk. Given the limited evidence pertaining to risk of developing cancer, over time, in these lower risk women, the consensus opinion of the expert group, which was supported by the reviewing societies, was to take a precautionary approach until data could guide whether these women could be moved to a routine pathway. As the risk is below the 3% threshold, but potentially not negligible risk, the urgent (within 6 week) recommendation was agreed upon.

A 6-week target for an urgent pathway will still be a significant challenge for many gynaecology/radiology services, but we hope this target will be a driver for change.

2. Are you anticipating that this guidance will result in an increase or decrease in direct access TVS requests (where this is available to primary care)? If you are anticipating an increase, what provisions and discussions have been had with Radiology services?

We are working with the NHSE Cancer Diagnostic pathway team and hope that this guideline will enable equitable access to ultrasound in primary care which will facilitate the pathway.

Pilot data from centres with access to ultrasound in primary care suggest a reduction in ultrasound referrals of around 40% based on the stratification of risk factors discussed in the guideline. Ongoing audits to evaluate the impact on service provision after implementation of this guideline will provide evidence that can inform the allocation/ reallocation of health service resources.

3. Everyone who works in this field receives dozens of referrals per month where the ET is 4-8mm in women on ccHRT. The likelihood of cancer is well below 3% and they should not be seen in USC clinics. One of the effects of this guideline will be to reduce the number of women attending Urgent Suspected Cancer clinics, and this will be welcomed by many. However, the guidance does not go far enough. NICE sets a threshold for an USC referral of a 3% likelihood of cancer, when the risk of cancer in women who bleed on HRT is less than 2%, even with long-term use. You have tried to stratify risk according to risk factors and endometrial thickness, which would be reasonable if there was robust evidence to support the decisions you have made.

The majority of the women currently referred to the USCP with unscheduled bleeding on HRT are at low-risk of cancer, below the 3% threshold. The aim of the guideline is to stratify the few who are at higher risk. In these women, the ultrasound thresholds are in place to ensure accuracy of cancer detection is not reduced. The aim is to collect data over the next 12 to 24 months to assess rates of hyperplasia and cancer in these women and whether higher thresholds, and changes to the risk stratification, can be advised. It is worth noting that NG12 NICE guidance for suspected cancers, although including postmenopausal bleeding, does not provide a narrative on stratification of risk with unscheduled bleeding on HRT. In the absence of its acknowledgement, there has been no clear guidance to date, which is what the British Menopause Society and supporting societies, are trying to address.

4. I am interested to see the evidence for safety of the change in practice and risk stratifying to urgent and 2WW groups, bearing in mind the medicolegal aspect of delayed diagnosis and associated anxiety and mental health.

Where there is evidence to guide the recommendations, this has been clearly stated in the guideline. Where there are limited data to support a strong recommendation, pragmatic and precautionary principles were applied and agreed on by the expert panel and the endorsing agencies, i.e. practical compromise to reduce referrals whilst at the same time maintaining patient safety, e.g. referral to the USCP of women with an incidental finding of a thickened endometrium with risk factors for cancer. The aim is to collect data across the country over the next 12-24 months to identify if some of the recommendations have been over-cautious, or justified, in their approach.

It is worth noting this guideline was commenced in response to an overwhelming increase in demand for USCP services for women with unscheduled bleeding on HRT. In a resource-limited setting, this adversely affected many units' ability to review women with PMB who are at higher risk of cancer (10%), within recommended time-frames. This led to a significant deterioration in gynaecological cancer waiting times nationally. Removing the low-risk women from the USCP is therefore beneficial to improving CWT for those women who are at high-risk of endometrial cancer.

Authors: Dr Kristyn Manley, Mr Tim Hillard, Professor Justin Clark, Dr Jo Morrison, Mr Haitham Hamoda, Dr Heather Currie, Kathy Abernethy, Mrs Anna Murray in collaboration with the medical advisory council of the British Menopause Society

PUBLICATION DATE: DECEMBER 2024
REVIEW DATE: APRIL 2027

www.womens-health-concern.org
Reg Charity No: 279651
Company Reg No: 1432023

www.thebms.org.uk
Reg Charity No: 1015144
Company Reg No: 02759439

Management of unscheduled bleeding on hormone replacement therapy (HRT)
Frequently asked questions

Primary Care

Primary or secondary care responsibility

Urgent suspicion of cancer pathway (USCP)

UNSCHEDULED BLEEDING ON HRT
1. Assess cancer risk factors and bleeding pattern
2. Identify HRT regimen, duration, compliance
3. Offer examination (e.g. eligible/due cervical screening)
4. Offer investigations if indicated e.g. cervical screening/genital swabs

1 major or 3 minor risk factors for endometrial cancer?

NO

YES → USCP for endometrial assessment (28-day Faster Diagnosis Standard (FDS))

- Any heavy / persistent bleeding, or
- 2 minor cancer risk factors, or
- More than 6 months since starting HRT, or
- More than 3 months after a change in dose or preparation

NO

OPTIMISE HRT for 6 months

Bleeding improved but ongoing after 6 months OR no improvement in intensity/frequency during the 6 months

Discuss all options including stop HRT vs non-hormonal alternatives

Patient decision to stop HRT?

NO → **Urgent TVS** (within 6 weeks)

YES

Bleeding ongoing after 4 weeks off HRT?

YES

USCP for endometrial assessment (28-day FDS)

If the patient declines investigations, explore barriers, recommend weaning off HRT and offer non-hormonal alternatives

NO

Continued cessation of HRT acceptable

No further investigation required

Restart HRT

Offer adjustments in HRT, for 6 months in total

Bleeding improved but ongoing after 6 months OR no improvement in intensity/frequency during the 6 months → **Urgent TVS** (within 6 weeks)

Bleeding increasing/ persistent → **Urgent TVS** (within 6 weeks)

YES

ULTRASOUND
- sHRT ET >7 mm
- ccHRT ET >4 mm
- Endometrium incompletely visualised

NO

OPTIMISE HRT for 6 months

Bleeding improved but ongoing after 6 months OR no improvement in intensity/frequency during the 6 months

Endometrial assessment on urgent referral/ pathway

YES

USCP for endometrial assessment (28-day FDS)*

If the patient declines investigations, explore barriers, recommend weaning off HRT and offer non-hormonal alternatives

Please note: If an USC referral is recommended, and investigations are declined, recommend weaning off HRT and offer non-hormonal alternatives. Offer follow-up at 4 weeks; recommend USC referral if bleeding continues on stopping HRT. If bleeding ceases and there is a preference to restart HRT, offer adjustments for three months before recommending a TVUS on an urgent pathway if bleeding is continuing after this interval. This is a group with higher risk of endometrial cancer.

MAJOR risk factors for endometrial cancer
- BMI ≥ 40
- Genetic predisposition (Lynch / Cowden syndrome)
- Estrogen-only HRT for > 6 months in women with a uterus
- Tricycling HRT (quarterly progestogen) for > 12 months
- Prolonged sHRT regimen: use for more than 5 years when started in women aged ≥ 45
- 12 months or more of using norethisterone or medroxyprogesterone acetate for < 10 days / month or, micronised progesterone for < 12 days / month, as part of a sequential regimen

MINOR risk factors for endometrial cancer
- BMI 30-39
- Unopposed estrogen > 3 months but < 6 months
- Tricycling HRT (quarterly progestogen) for > 6 but < 12 months
- > 6 months but < 12 months of using norethisterone or medroxyprogesteorne acetate for < 10 days / month or, micronised progesterone for < 12 days / month, as part of a sequential regimen
- Where the progestogen dose is not in proportion to the estrogen dose for > 12 months (including expired 52 mg LNG-IUD)
- Anovulatory cycles, such as in Polycystic ovarian syndrome
- Diabetes

*** Cancer Waiting Times Guidance v12:** Where a pathway has been implemented and agreed locally where a patient is directly triaged from an abnormal direct access diagnostic scan with a suspicion of cancer then the decision to triage directly would act as the start of the pathway and counted as an urgent suspected cancer referral, and not an upgrade. Please refer to section 2.2.9 of the guidance for further information.

Q1P2425