The specialist authority for menopause & post reproductive health

British Menopause Society

Management of unscheduled bleeding on hormone replacement therapy (HRT)

The British Menopause Society (BMS) is the specialist authority for menopause and post reproductive health in the UK. The BMS educates, informs and guides healthcare professionals, working in both primary and secondary care, on menopause and all aspects of post reproductive health.

BMS guidelines, prepared by the BMS medical advisory council in partnership with other specialist organisations and Royal Colleges, address key disorders and controversial topics relating to menopause and post reproductive health. They reflect new studies and recent medical and scientific information from articles published in professional journals, together with informal consensus.

The guidelines are evidence-based, comprehensively referenced and peer reviewed and they are updated when guidance changes and/or new data becomes available.

This joint guideline has been prepared on behalf of the British Menopause Society, in partnership with the British Society of Gynaecological Endoscopy, British Gynaecological Cancer Society, College of Sexual & Reproductive Healthcare, Getting It Right First Time (GIRFT), Royal College of General Practitioners and the Royal College of Obstetricians & Gynaecologists.

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Key Messages

Assessment of women presenting with unscheduled bleeding on HRT

- **When women present with unscheduled bleeding on HRT, clinical assessment should start with a comprehensive review detailing bleeding patterns, HRT preparations and individual risk factors for cancer. Offer an examination (abdominal, pelvic) and, where relevant, initial investigations such as cervical screening, lower genital tract swabs and body-mass index (BMI).**

Endometrial cancer risk factors in women taking HRT

- **Risk factors for endometrial hyperplasia and cancer, independent of HRT, should be identified. Major risk factors are BMI ≥ 40 and hereditary conditions such as Lynch or Cowden syndrome. Minor risk factors include BMI 30-39, diabetes and polyendocrine metabolic ovarian syndrome (PMOS). Optimisation of modifiable factors can, in themselves, reduce episodes of unscheduled bleeding on HRT and endometrial cancer risk.**
- **A monthly progestogen dose, in proportion to the estrogen dose, is recommended in women with a uterus.**
- **In women using sequential HRT (sHRT), offer a minimum of 10 days norethisterone (NET) or medroxyprogesterone acetate (MPA), or 12 days of micronised progesterone, per month.**
- **Women taking a sequential preparation (sHRT) over the age of 45 should be offered, after five years of use or by age 54 (whichever comes first), a change to continuous combined (ccHRT).**

When to investigate unscheduled bleeding on HRT

- **In the absence of risk factors for endometrial cancer, offer adjustments in the progestogen or HRT preparation, for 6 months in total, if unscheduled bleeding a) occurs within six months of starting HRT or b) is persisting three months after a change in HRT dose or preparation.**
- **If unscheduled bleeding continues in low-risk women, after six months of adjustments, discuss the options of an urgent ultrasound (within six weeks) versus weaning off HRT and consideration of non-hormonal alternatives (to avoid invasive investigations).**
- **For those women who elect to stop HRT, if the bleeding has settled at a 4-week follow-up, and continued cessation of HRT is acceptable, no further investigations are required. If the bleeding has settled at a 4-week follow-up and there is a preference to restart HRT, offer adjustments in HRT for six months and then an urgent ultrasound if bleeding is heavy / persistent during the 6 months or, is continuing after this interval.**
- **Offer an urgent TVS (within 6 weeks) if the first presentation with bleeding occurs more than six months after initiating, or three months after changing, the HRT preparation.**
- **Offer an urgent TVS (within 6 weeks), irrespective of interval since starting, or changing, HRT preparations if a) bleeding is prolonged / heavy or, b) there are 2 minor risk factors for endometrial cancer.**
- **Offer an urgent suspicion of cancer pathway (USCP) referral to women with one major or three minor risk factors for endometrial cancer – irrespective of bleeding type or interval since starting or changing HRT preparations. Adjustments to the progestogen, or stopping HRT, should be offered whilst awaiting assessment.**

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How should unscheduled bleeding on HRT be investigated

- **Women with unscheduled bleeding, in the presence of a uniform endometrium which is fully visualised, and measures ≤ 4 mm with ccHRT or ≤ 7 mm with sHRT, can be reassured that the risk of endometrial cancer is low. Offer HRT adjustments for 6 months and then offer endometrial assessment, on an urgent pathway, if bleeding increases during the 6 months or, is continuing after this interval.**
- **Women with a thickened endometrium on TVS (> 4 mm for ccHRT or > 7 mm for sHRT) should be offered referral to the urgent suspicion of cancer pathway (USCP) for endometrial assessment (biopsy and / or hysteroscopy).**
- **In the presence of a normal endometrial biopsy, discuss adjustments in the progestogen and provide reassurance for three months. If hysteroscopy *and* biopsy are normal, reassurance can be provided for six months.**

Adjusting HRT to reduce unscheduled bleeding episodes

- **Assess adherence and understanding of how to use the prescribed preparation including dose and duration of progestogen – for example, would a combined patch or pill reduce administration errors when compared to a separate estrogen and progestogen component.**
- **Offer all women a 52 mg LNG-IUD; this preparation reduces episodes of unscheduled bleeding when compared to all other preparations.**
- **Oral preparations provide higher rates of amenorrhoea when compared to transdermal preparations and could be offered, if there are no risk factors for thrombosis, as a) a first-line therapy or b) to women who have recurrent unscheduled bleeding with transdermal preparations.**
- **Offer vaginal estrogens if there are atrophic findings on examination.**

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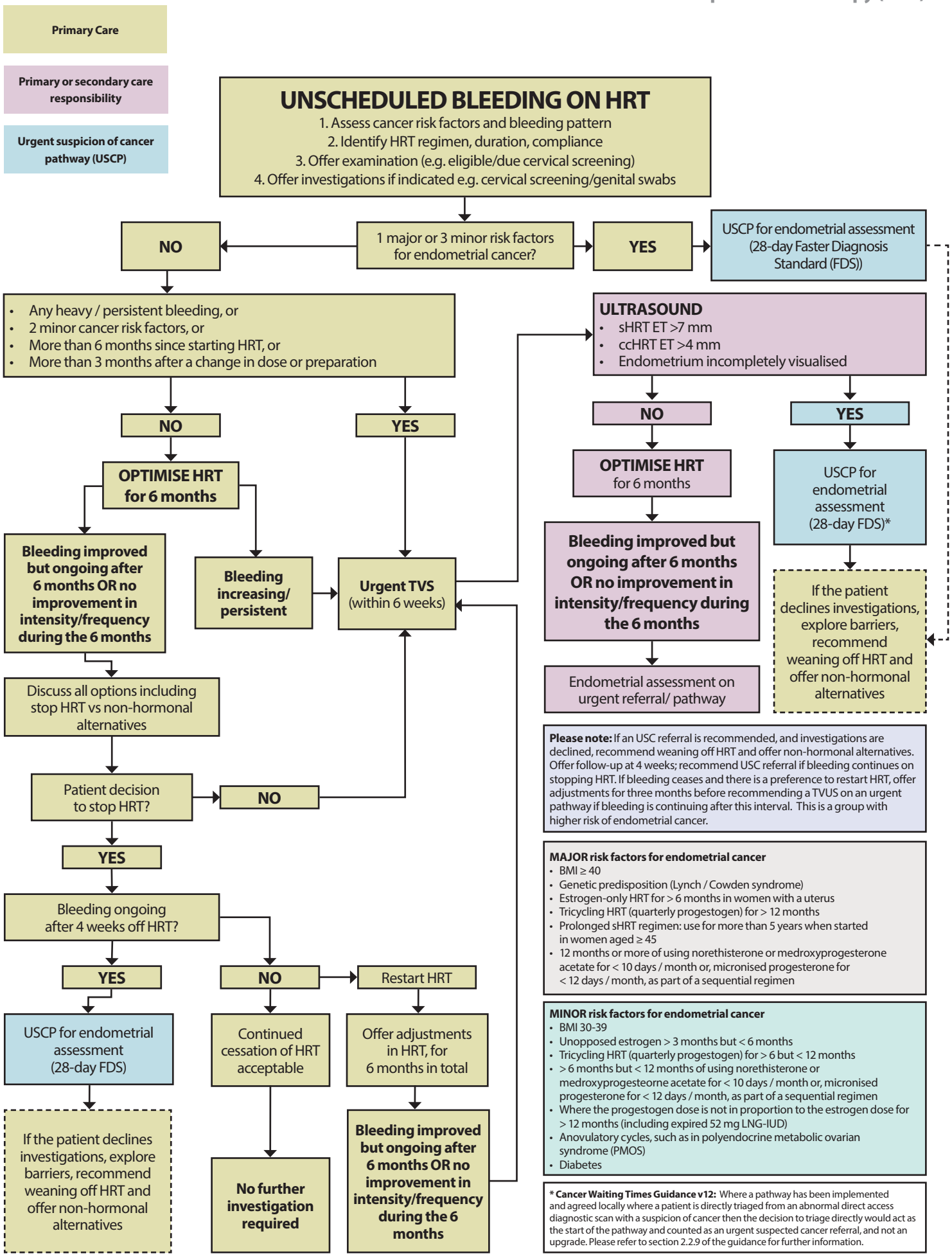

Please note: If an USC referral is recommended, and investigations are declined, recommend weaning off HRT and offer non-hormonal alternatives. Offer follow-up at 4 weeks; recommend USC referral if bleeding continues on stopping HRT. If bleeding ceases and there is a preference to restart HRT, offer 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 polyendocrine metabolic ovarian syndrome (PMOS)
- 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.

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Introduction

Unscheduled bleeding on hormone replacement therapy (HRT) is defined as irregular bleeding which occurs after initiating, or changing, a HRT preparation which should be 'bleed free' – continuous combined hormone replacement therapy (ccHRT) or, which occurs, in addition to the scheduled monthly withdrawal bleed in persons taking sequential preparations (sHRT).[1] Unscheduled bleeding within the first six months of initiating HRT or, within three months of a change in dose or preparation in those already established on HRT, is common. It can affect up to 38% of people using sHRT and 41% using ccHRT.[2] It is a major factor leading to repeat consultations and cessation of HRT.[3]

HRT was prescribed to 1.9 million women in the UK in 2021/2022 – a 35% increase from the preceding year. Over the past decade, prescriptions have increased annually, by 13.6%, in women aged 50 years or older.[4] In England, estradiol gel and micronised progesterone were the top two prescribed HRT items in 2022 with total number of identified persons prescribed micronised progesterone increasing by 125%.[5] In parallel with this increase in prescribing there has been a rapid rise in unscheduled bleeding on HRT and a 43% increase, over the past 3 years, in referrals to the Urgent Suspicion of Cancer Pathway (USCP). Overall this change in referral pattern does not appear to have resulted in more cancers being diagnosed, which rose by 2% over the same interval.[1, 6, 7] An increase in referrals, for those who appear to be at lower risk of endometrial cancer, may impact on the ability of organisational structures to attain the national '28-day faster cancer diagnosis recommendations' and increase anxiety in women awaiting assessment.

The reasons behind this increase are multiple. As well as the steady increase in the use of HRT since the NICE guidance in 2015[8], there has been an increase in use of HRT amongst peri-menopausal women who, by definition, often have irregular bleeding. The wider availability of transdermal preparations has enabled women with complex comorbidities, which may be independent risk factors for endometrial cancer, to access HRT. In addition, there is an increasing tendency for off-label prescribing of higher dose estrogen with sub-optimal dosages of progestogen. Whilst all irregular bleeding is distressing, there is a need to prioritise investigations for those with a potential increased risk of endometrial cancer, over those in whom endometrial cancer is unlikely.

The purpose of this guideline is to provide recommendations which stratify management for unscheduled bleeding according to risk of endometrial cancer, ensuring best outcomes for all women whilst using NHS resources appropriately.

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Methodology

On behalf of the British Menopause Society (BMS) an expert review panel was established, including primary and secondary care clinicians with expertise in the management of menopause, with representatives from key related organisations, including the Royal College of Obstetricians & Gynaecologists (RCOG), the British Gynaecological Cancer Society (BGCS) and the British Society for Gynaecological Endoscopy (BSGE), and service development partners from NHS England and GIRFT (Getting it Right First Time). For each topic, a focused literature review was completed to develop evidence led recommendations which were ratified by consensus review within the panel and by guideline groups. In many areas there is a paucity of evidence and the recommendations are based on expert opinion. This is a live document and as new evidence becomes available, the guidance in these areas will be updated.

No modelling or cost analyses have been performed in drawing up this guideline. This is a clinical guideline designed to facilitate and standardise the management of women presenting with unscheduled bleeding on HRT. Our focus is on utilising resources efficiently to ensure women are not over investigated whilst at the same time not missing those in whom endometrial cancer is a possibility. It is recognised that many organisations have already drawn up their own guidelines based on their own resources and it is hoped this document will serve as a guide to support and inform the further development of these guidelines. Suggested topics for audit are included.

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health. Gynaecological services and delivery of care must be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

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Section 1: Assessment of women presenting with unscheduled bleeding on HRT

When women present with unscheduled bleeding on HRT, clinical assessment should start with a comprehensive review detailing bleeding patterns, HRT preparations and individual risk factors for cancer. Offer an examination (abdominal, pelvic) and, where relevant, initial investigations such as cervical screening, lower genital tract swabs and body-mass index (BMI).

History

- Last menstrual period or withdrawal bleed (before and during HRT)
- Bleeding pattern before starting HRT
- Pelvic pain and / or deep dyspareunia
- Discharge
- Vulvovaginal and / or urinary symptoms
- Bleeding pattern:
  - Number of episodes per month
  - Type; spotting, period-like, flooding
  - Duration of bleeding; if prolonged, is it days or weeks
  - Regularity; such as mid-cycle or before a withdrawal bleed
  - Precipitating factors; such as wiping after urinating or post-coital
- HRT use:
  - Duration since initiation or change in HRT preparation
  - Current preparation, including dose of estrogen and progestogen
  - Type of progestogen, total days in the month it is taken and route (oral / vaginal)
  - Levonorgestrel intrauterine device (52 mg LNG IUD) – type, dose, insertion date, thread checks and whether correctly sited
  - Adherence to estrogen and progestogen regimen
  - Prior preparations and interval of use (including adverse effects that led to cessation)
- Application:
  - Where is it applied
  - If a patch is used, is it sticking well and is there any irritation
  - Awareness of taking the correct order of patches or pills if a sequential preparation
  - Other sources of estrogen (such as herbal/bioidentical)
  - Contraceptive usage, if any[9]
  - Pregnancy risk; compliance with progestogen-only pill (POP), date of last medroxyprogesterone injection, insertion date of implant
  - Cervical screening history: do not delay ongoing assessment if the bleeding pattern prevents smear taking
  - Sexual history
  - Drug interactions; such as anti-epileptics, anti-fungals, COVID vaccinations, St John's Wort
- Malabsorption syndromes
- Endometrial cancer risk factors; such as genetic predisposition to endometrial cancer (Lynch / Cowden Syndrome), BMI ≥ 30, polyendocrine metabolic ovarian syndrome (PMOS) and diabetes.

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Examination and initial investigations

To enable informed consent, discuss what the examination is likely to involve, the intended benefits of completing these and the benefits and risks of any alternate options, including no examination or investigations. Offer, where appropriate and acceptable, the following assessments:

- Abdominal; assess for fibroids, ovarian mass, pain
- Vulvo-vaginal; assess for atrophy, dermatoses, mass, ulceration, prolapse
- Cervical appearance; assess for mass, polyp, ectropion with contact bleeding, visible IUD threads
- Genital tract swabs; vulvovaginal including chlamydia / gonorrhoea (CT/GC) screen – if indicated by sexual history i.e. new partner(s) in the past two years, no exclusive relationship or current sexually transmitted infection symptoms
- Cervical screening if overdue
- Pregnancy test (if appropriate)
- BMI

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Section 2: Endometrial cancer risk factors in women taking HRT

The incidence of endometrial cancer in relation to a woman's individual risk factors and specific HRT preparation are outlined in this section. Table 1 summarises this evidence and categorises these risk factors into major or minor, to enable triage of women who present with unscheduled bleeding onto the correct assessment pathway (non-urgent, urgent and urgent suspicion of cancer pathway (USCP)) as outlined in Sections 3 and 4.

Tables 2 and 3 (combined in Appendix 1) outline prescribed estrogen dosages, in relation to specific transdermal and oral preparations, and the recommended progestogen dose, for low to high dose estrogen.

Table 1: Major and minor factors affecting risk of endometrial cancer in women taking HRT

Major risk factors	• BMI ≥ 40 • Genetic predisposition to endometrial cancer (Lynch / Cowden syndrome) • Estrogen-only HRT for more than 6 months in women with a uterus • Tricycling HRT (quarterly progestogen course) for more than 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	• BMI 30-39 • Unopposed estrogen for more than 3 months but less than 6 months • Tricycling HRT (quarterly progestogen course) for more than 6 months but less than 12 months • More than 6 months, but less than 12 months, of using norethisterone or medroxyprogesterone 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 PMOS • Diabetes

* There is limited evidence relating to the impact on endometrial cancer risk; this should be a research priority to enable improved stratification of risk/pathways (see Table 3).

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Endometrial cancer risk factors independent of HRT use

- **Risk factors for endometrial hyperplasia, independent of HRT, should be identified. Major risk factors include BMI ≥ 40 and hereditary conditions such as Lynch or Cowden syndrome. Minor risk factors include BMI 30-39, diabetes and polyendocrine metabolic ovarian syndrome. Optimisation of modifiable factors can, in themselves, reduce episodes of unscheduled bleeding on HRT and endometrial cancer risk.**

Endometrial cancer is the fourth most common cancer in the UK; the reported incidence in women who present with postmenopausal bleeding (PMB), i.e. those who are not taking HRT, is 3-10%.[10, 11] The incidence increases with age; rates (per 100,000 women) rise sharply from the age of 55 and reach a peak at age 70 to 74. The age-related incidence in the UK is 0.7% for women aged 50-54, 1.2% aged 55-59, 1.3% aged 60-64, and 1.5% aged 65-74.[12]

Genetic factors can increase risk by 30-50%, with conditions such as Lynch and Cowden syndrome considered major factors.[13] Obesity is the strongest risk factor for endometrial cancer with 40% of cases associated with this; BMI ≥ 40 confers a tenfold higher risk when compared to a BMI within the normal range.[14] Consideration of weight loss strategies, and support for this, is associated with a reduction in endometrial hyperplasia and cancer risk.[15, 16] Other factors that affect the bioavailability of estrogen and insulin-like growth factor-1 (IGF-1), such as diabetes, PMOS and unstable liver disease, can increase endometrial cancer risk.[11]

Risk of endometrial cancer in HRT users who DO NOT report unscheduled bleeding

Effect of HRT preparation on endometrial cancer risk

- **Inform amenorrhoeic postmenopausal women taking a continuous combined preparation (ccHRT), which contains licenced doses of estrogen and a proportionate progestogen dose, that endometrial cancer risk appears to be lower than in non-HRT users.**
- **Women taking a sequential preparation (sHRT) over the age of 45 should be offered, after five years of use or by age 54 (whichever comes first), a change to ccHRT.**
- **In women using sHRT, offer a minimum of 10 days norethisterone (NET) or medroxyprogesterone acetate (MPA), or 12 days of micronised progesterone, per month; recommending two weeks per 28 day cycle with progestogen and two weeks without may help to reduce administration and prescribing errors.**
- **A monthly progestogen dose, in proportion to the estrogen dose, is recommended in women with a uterus. It should be noted that more than six months of unopposed estrogen or 12 months of tricycling (estrogen daily with a progestogen course every 3 months), are major risk factors for endometrial cancer.**
- **Counsel women there are limited data relating to the optimal progestogen dose needed to provide endometrial protection in women taking high dose estrogen (particularly in perimenopausal women taking sHRT).**

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Continuous combined HRT (ccHRT):

Administration of daily (continuous) progestogen suppresses endometrial growth leading to amenorrhoea and atrophy.[17] This appears to reduce the risk of endometrial cancer, compared with non-users, with the greatest effect seen in women with a BMI ≥ 30.[18-20] In women who do not report unscheduled bleeding, the risk of endometrial cancer with low to medium dose estrogen, and a progestogen dose which is in proportion, is < 1%.[21] There are limited data assessing risk with high dose estradiol use. Table 2 outlines prescribed estrogen, in relation to specific transdermal and oral preparations for low, medium and high dosages.

Table 2: Prescribed estrogen dose for low, medium and high dose regimens
Approximate equivalent doses of estradiol products for those of average menopause age with symptoms (45-55 yrs)

Product	Low	Medium	High†
Oestrogel (gel pump)	1 pump	2-3 pumps	4 pumps
Sandrena (gel sachet)	0.5 mg	1 mg 2 mg* *See note 2*	2.5-3 mg* *See note 2*
Lenzetto (spray)	1-2 sprays	3 sprays 4 sprays* *See note 3*	5-6 sprays* *See note 3*
Patch	25/30/37.5 mcg	40/50/75 mcg	100 mcg
Oral estradiol	0.5 mg	1-2 mg	3 mg* *See note 4*

** Outside of Summary of Product Characteristic licensing.*

† High doses and doses outside of product license should only be considered in exceptional individualised cases and after full discussion about the relative lack of evidence of additional benefit and risks with these doses. If response has not been assessed with other options, consider offering a change of estrogen preparation before increasing the dose above license.

Notes

1. The table has been drawn up as a practical guide based on a combination of pharmacokinetics, clinical trials and clinical experience. The dose equivalents are subject to significant individual variations in absorption and metabolism, so cannot be precise.
2. Sandrena: high doses have been extrapolated from other gel preparations.
3. Lenzetto has a unique mode of action so data cannot be extrapolated: the excipient pushes estradiol through the skin into a reservoir from which it slowly releases. If going above 3 sprays, advise applying these additional sprays to the contralateral side.
4. Oral estradiol: high doses are rarely used in this age group.
5. Doses for those with premature ovarian insufficiency (POI) are not included in this table.

Sequential/cyclical HRT (sHRT):

In women over 50, who have no unscheduled bleeding and use medroxyprogesterone acetate (MPA) or norethisterone (NET) for 10-12 days of the month, the relative risk of endometrial cancer is similar to non-users. If these progestogens are used for less than 10 days, this risk is three-fold higher after six months use (RR 3.1, 95% CI 1.7-5.7).[21-23] Micronised progesterone (MP), in conjunction with low to medium dose estrogen, provides endometrial protection if given at a dose of 200mg for 12-14 days of the month for up to five years use.[24]

When compared to non-users, if sHRT (progestogen for 10-12 days) is used for more than five years, the risk of endometrial cancer is almost three times higher (RR 2.9 (95% CI 1.8-4.6)).[21-23] In women who are perimenopausal at the natural age (≥ age 45), switching to ccHRT

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should be offered after five years of sHRT or by age 54 (whichever comes first). It can also be considered after 12-18 months of sequential use, if women want to try ccHRT to see if they can achieve a bleed-free regimen at an earlier point.[25]

Tricycling (Long-cycle) Progestogen use and shortened progestogen regimens

This is where estrogen is given daily but a reduced progestogen course (7-10 days) is given every three months. When compared to use of a monthly progestogen course – NET or MPA for 10-12 days – the incidence of endometrial hyperplasia and cancer is higher; 7.5% vs 0% at 12 months (p=0.005) and 11% vs 1.4% by 36 months (p=0.01).[26, 27] The risk of endometrial cancer when tricycling incorporates high dose estrogen, or micronised progesterone, is unknown.

If a shortened duration of progestogen is considered in women with an intolerance to all progestogen types (including 52 mg LNG-IUD and off-license use of licenced doses of estrogen with 150 micrograms of daily desogestrel, 4 mg drospirenone (Slynd) or x3 noriday tablets i.e. 1.05 mg NET), and in whom hysterectomy is not suitable or acceptable, informed counselling about endometrial risk, and the lack of evidence to support surveillance accuracy (six monthly ultrasound), should be discussed and documented.

Unopposed estrogen

There is strong evidence to support an increased risk of endometrial cancer with unopposed estrogen (i.e no progestogen use) in people with a uterus. A Cochrane review[27] reported high rates of endometrial hyperplasia, compared with placebo, after 12 and 24 months of standard dose unopposed estrogen use; OR 8.4 (95% CI 5.5-12.9) and OR 11.9 (95% CI 7.8-18.1) respectively. At one, two and three years, the proportion of women diagnosed with endometrial hyperplasia was 14.7%, 35.5% and 62% (respectively) – compared with 0.3% in the placebo group. There are limited data on risk with high dose unopposed estrogen use.

Progestogen type and endometrial protection

- **Counsel peri- and postmenopausal women considering use of a 52 mg LNG-IUD that it can be used for endometrial protection with low to high estrogen dosages for up to five years.**
- **Counsel women that a) tibolone and b) progestogens (norethisterone, medroxyprogesterone acetate, levonorgestrel, dydrogesterone, micronised progesterone), when combined with licenced doses of estrogen, provide equivalent protection against endometrial cancer.**
- **Women taking high dose estrogen should be informed that the adequacy of endometrial protection provided by micronised progesterone is uncertain. The use of 200 mg as a continuous preparation, and 300 mg as a sequential preparation, should be offered if using high dose estrogen or if unscheduled bleeding occurs with low to medium dose estrogen.**

Levonorgestrel 52 mg intra-uterine device (LNG-IUD)

Mirena® (52 mg LNG IUD) has a four-year license in the UK for progestogenic opposition of estrogen within HRT. The Food and Drug administration recommends use with a uterine depth less than or equal to 10 cm and NICE[28] advises against use if submucosal fibroids are more than 3 cm.

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Studies have shown all 52 mg LNG IUD offer sufficient endometrial protection against low to high dose estrogen for up to five years of use in both peri- and postmenopausal women.[29-33] As a result, it is common and safe practice to use the 52 mg LNG IUD for five years within HRT regimens (outside manufacturer's license). There are a paucity of data relating to endometrial protection when estrogen above high dose is used and whether additional progestogen is required. Women should be counselled about this and the limitations of ultrasound in assessing the endometrium if unscheduled bleeding occurs (with the higher likelihood that hysteroscopy may be required). If at 4 years of use, new unscheduled bleeding develops, a change of 52 mg LNG IUD should be offered (if cancer exclusion tests are normal), particularly in women using over licensed estrogen dosages and in those with a BMI ≥ 40.

There are insufficient data to guide whether a malpositioned 52 mg LNG IUD provides adequate endometrial protection when used as part of HRT. Discuss with the woman a 52 mg LNG IUD may need to be correctly positioned at the fundus for maximum effectiveness. In relation to contraceptive use, the FSRH suggest '*as a general guide any of the following findings would usually be an indication to suggest that the IUC is removed and replaced: IUC > 2 cm from the fundus; IUC within the cervical canal (fully or partially); or IUC user experiencing symptoms that may be related to malpositioned IUC (e.g. pain or bleeding)*'.[29] One study[34] reported an association with irregular endometrial suppression and breakthrough bleeding when a specially designed intracervical LNG-IUD was compared to fundal placement; until high-quality studies assess efficacy for endometrial protection in HRT users, women who present with unscheduled bleeding and a malpositioned 52 mg LNG IUD should be offered alternate progestogens until IUD replacement.

Synthetic Progestogens

Synthetic progestogens such as NET, MPA, levonorgestrel and dydrogesterone, provide equivalent endometrial protection when the dose is in proportion to low and medium dose estrogen (see Table 3).[27, 35, 36] There are limited data assessing optimal dose for endometrial protection when high dose estrogen is prescribed.

Micronised progesterone (MP); dose and duration of use

MP can be used as an oral or vaginal (off-license) preparation. The Kronos Early Estrogen Prevention Study (KEEPs) and Postmenopausal Estrogen/Progestin Interventions trials (PEPI) [37, 38] compared sHRT (200 mg MP with standard dose estrogen) to placebo, over four years, and both reported equivalent endometrial cancer rates. The E3N cohort study[39] assessed endometrial cancer rates in 65,630 HRT users over ten years of whom 40% were taking oral MP; use for less than five years did not appear to increase risk (hazard ratio (HR) 1.39, 95% CI 0.99-1.97).

There is limited evidence assessing the long-term endometrial protective effect (> 5 years) when micronised progesterone is used as a continuous preparation and this should be considered a research priority. Although the European Prospective Investigation into Cancer and Nutrition (EPIC) study reported a two-fold association between micronised progesterone use and endometrial cancer, when compared with non-users (HR 2.42, 95% CI 1.53–3.83), the majority of participants used sequential, rather than continuous preparations, and duration of HRT was not adjusted for.[35]

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There are insufficient data to advise on endometrial cancer risk when micronised progesterone, at a dose used for low or medium dose estrogen, is used in combination with high dose estrogen. Until evidence relating to safety with high dose estrogen is available, a pragmatic approach needs to be considered, as the risk to breast tissue from increasing the progesterone dose is also unknown; the use of 200 mg as a continuous preparation and 300 mg as a sequential preparation should be offered if using high dose estrogen[24, 39-42] or, if unscheduled bleeding occurs with low to medium dose estrogen (Table 3). This should be considered a research priority as high-quality outcomes may enable lower dosage use in women taking high dose estrogen or, conversely, may stratify if women with risk factors for endometrial cancer (diabetes, raised BMI) should be offered increased dose micronised progesterone with lower estrogen dosages.

Unbalanced estrogen to progestogen dose

British Menopause Society (BMS) guidance[25] recommends a progestogen dose in proportion to the estrogen dose in people who have a uterus, to reduce unscheduled bleeding and endometrial cancer risk.[20, 24, 25, 41] Table 3 summarises this section and outlines the progestogen dose that appears to provide adequate endometrial protection for different strengths of licensed estrogen dosages (low, medium and high).

Table 3: Stand-alone progestogen dose per licensed estrogen dose in the baseline population

Estrogen dose	Micronised progesterone *Continuous*	Micronised progesterone *Sequential*	Medoxyprogesterone *Continuous*	Medoxyprogesterone *Sequential*	Norethisterone *Continuous*	Norethisterone *Sequential*	Dydrogesterone *Continuous*	Dydrogesterone *Sequential*	LNG-IUD, 52 mg
Low	100 mg	200 mg	2.5-5 mg	10 mg	5 mg*	5 mg*	10 mg‡	10 mg	for up to 5 years of use
Medium	100 mg	200 mg	5 mg	10 mg	5 mg	5 mg	10 mg‡	10 mg	
High	200 mg	300 mg	10 mg†	20 mg†	5 mg	5 mg	10 mg	20 mg	

* *1 mg provides endometrial protection for low to medium dose estrogen but the lowest stand-alone dose currently available in the UK is 5 mg (off license use of three Noriday POP, i.e. 1.05 mg, could be considered if 5 mg is not tolerated).*

† *There is limited evidence in relation to optimal MPA dose with high dose estrogen; the advised dose is based on studies reporting 10 mg providing protection with up to medium dose estrogen.*

‡ *2.5 mg provides endometrial protection for low dose estrogen and 5 mg for medium dose estrogen but the lowest stand-alone dose currently available in the UK is 10 mg.*

Notes

Drospirenone (DRSP): RCT data suggests 0.5 mg daily DRSP provides endometrial protection with 1 mg oral estradiol over 12 months of use. Extrapolation suggests 4 mg of DRSP should provide protection for up to high dose estrogen (but no dose specific studies have been completed). Dosages of 2 mg DRSP per 1 mg estradiol have been shown to provide better bleed control. Whilst no direct evidence, efficacy has been demonstrated with a dose of 3 mg DRSP when combined with 30 mcg of ethinyl estradiol which is equivalent to high dose estradiol. DRSP 4 mg (Slynd) is licensed in the UK as a progestogen only contraceptive. It can be used off license as the progestogen component of HRT by taking one active hormone tablet 4 mg daily on a continuous basis (omitting the 4 hormone free pills in the pack).

Desogestrel: earlier studies have reported that desogestrel 150 mcg is effective as the progestogen component of HRT with no increase in the risk of endometrial hyperplasia. There is lack of evidence on the use of desogestrel 75 mcg as the progestogen component of HRT. If desogestrel 75 mcg is used as contraception in women receiving HRT, it would be recommended to add further progestogen (e.g. micronised progesterone 100 mg daily or 200 mg for 12 days a month) to provide adequate endometrial protection.

Dienogest: 2 mg can be considered as an option (off license) if other measures have been ineffective.

*(*see the BMS Tool for Clinicians *on Progestogens and endometrial protection).*

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Oral versus vaginal (off-label) micronised progesterone(MP)

A systematic review of 14 studies[24] assessed the impact, on endometrial histology, of using vaginal micronised progesterone. Of the five randomised controlled trials (RCTs) included, the comparator groups were 52 mg LNG-IUD, transdermal NET and oral MPA. Using vaginal micronised progesterone as either a sequential (200 mg for 12 days) or continuous preparation (100 mg / day), for three years, were sufficient to provide endometrial protection with low or medium dose estrogen. There are insufficient data to advise on endometrial protection when vaginal MP is used 100 mg alternate days, 100 mg as a sequential preparation,[24, 25, 41] or for more than three years.

A double-blind placebo-controlled trial with a follow-up of 4.8 years[43], reported that 45 mg of vaginal MP used for 10 days of the month, in combination with low dose estradiol, resulted in higher rates of endometrial hyperplasia (12.7% vs 3.1%, p<0.001).

Histological outcomes in women presenting with unscheduled bleeding on HRT and a thickened endometrium on transvaginal ultrasound

- **In the absence of individual risk factors for endometrial cancer, perimenopausal women taking sHRT, containing low to medium dose estrogen, who have unscheduled bleeding and a thickened endometrium should be counselled that endometrial hyperplasia and cancer risk appears lower than in women with postmenopausal bleeding. The continuing need for sHRT should be regularly assessed as risk increases with duration of use (more than 5 years).**
- **In the absence of individual risk factors for endometrial cancer, postmenopausal women taking ccHRT, containing low or medium dose estrogen, who have unscheduled bleeding and a thickened endometrium should be counselled that endometrial hyperplasia and cancer risk appears lower than women with postmenopausal bleeding. However, the continuing need for long-term ccHRT should be regularly assessed as risk appears to increase with duration of use (more than 5 years).**
- **Women should be counselled that risk of endometrial cancer with high dose estrogen plus micronised progesterone is unknown in the presence of unscheduled bleeding.**

There are limited data on the rates of endometrial cancer in women who present with unscheduled bleeding on HRT. Endometrial outcomes in women with a thickened endometrium and unscheduled bleeding are summarised in Table 4 [1, 44-49] – the studies relating to HRT users, although adjusting for confounders such as BMI / diabetes, included women using standard dose estrogen, for less than 5 years, often in combination with a daily synthetic progestogen and were not adequately powered precluding a more robust evaluation of the relative risks of endometrial cancer. Where reported, an endometrial thickness of 5 mm or more was used for both ccHRT and sHRT. There are limited data assessing outcomes with high dose estrogen (particularly in perimenopausal women who may have intermittent endogenous ovarian activity), micronised progesterone or use of ccHRT for more than five years – these areas should be considered research priorities.

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Table 4: Histological outcomes in women taking standard dose estrogen who have unscheduled bleeding and a thickened endometrium on ultrasound scan

	ccHRT	sHRT	PMB
Atrophy / Inactive	38-66%*	58%^	52%
Polyp	6.8-31%	22%	9%
Hyperplasia	1-2%	2.5-16%	11%
Endometrial Cancer	1.3-2%	5%	9%

* The majority of endometrial biopsies in women taking ccHRT are reported as inactive endometrium.
^ The majority of endometrial biopsies in women taking sHRT are reported as weakly proliferative.

These data suggest that over half the women who present with unscheduled bleeding and a thickened endometrium will have a normal biopsy and up to 30% will have a polyp.[50]

Endometrial hyperplasia and cancer risk in users of ccHRT containing low to medium dose estrogen appears lower than non-users with PMB. However, risk of diagnosing endometrial cancer in women with unscheduled bleeding on ccHRT may increase with duration of use; 4:1000 with up to three years use, 9:1000 with 4-6 years use and 19:1000 with more than six years use.[1] Endometrial cancer risk in women using sHRT appears lower than non-users with PMB, but higher than users of ccHRT; risk may relate to total duration of sHRT use, progestogen dose and / or total number of days in the month of progestogen use – it is important to ascertain these factors when discussing and stratifying risk.

Section 3: When to investigate unscheduled bleeding on HRT

- **In the absence of risk factors for endometrial cancer, offer adjustments in the progestogen or HRT preparation for 6 months in total, if unscheduled bleeding a) occurs within six months of starting HRT or b) is persisting three months after a change in HRT dose or preparation.**
- **If unscheduled bleeding continues in low-risk women, after six months of adjustments, discuss an urgent ultrasound (within six weeks) versus weaning off HRT and consideration of non-hormonal alternatives (to avoid invasive investigations) – according to the woman's preference.**
- **Offer an urgent TVS (within 6 weeks) if the first presentation with bleeding occurs more than six months after initiating, or three months after changing, the HRT preparation.**
- **Offer an urgent TVS (within 6 weeks), irrespective of interval since starting, or changing, HRT preparations if a) bleeding is prolonged / heavy or, b) there are 2 minor risk factors for endometrial cancer.**
- **Offer an urgent suspicion of cancer pathway (USCP) referral to women with one major or three minor risk factors for endometrial cancer – irrespective of bleeding type or interval since starting or changing HRT preparations. Adjustments to the progestogen, or stopping HRT, should be offered whilst awaiting assessment.**

Which bleeding patterns are considered normal for HRT

It is important when assessing and counselling women who present with bleeding on HRT, to understand what is normal for the preparation they are taking. Unscheduled bleeding within the first six months of starting any type of HRT occurs in up to 40% of women.[51]

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Sequential or cyclical HRT (sHRT)
This preparation is prescribed for women who are still having periods in the 12 months preceding the start of HRT (peri-menopausal). Estrogen is used every day and a progestogen is given for 10-14 days of the month (dependent upon the type prescribed). 90% of women on this preparation will have a cyclical bleed (usually at the end of the progestogen phase), lasting 3-7 days which is generally lighter than premenopausal menstruation. Prolonged or heavy withdrawal bleeding is not normal, nor is persistent (almost daily) bleeding.

Continuous combined HRT (ccHRT)
This preparation is recommended for women who have had amenorrhoea for 12 months before starting HRT (including women on contraception or post-ablation). Women are expected to be amenorrhoeic on this preparation six months after initiation.[25, 51] ccHRT is associated with less unscheduled bleeding than sHRT in postmenopausal women.[21, 52-54] If given to perimenopausal women who still have menstrual cycles, endogenous follicular activity can lead to irregular bleeding.

Triaging unscheduled bleeding episodes

Once the initial assessment, as outlined in Section 1, has been completed, the bleeding pattern and underlying individual risk factors for endometrial cancer need to be considered to enable a rational basis for triaging women to either a) conservative management (continue with HRT +/- adjust the current preparation) or b) refer for investigations (primary care direct access or gynaecological services).

Table 5 defines the clinical pathways for assessment of women with unscheduled bleeding, detailing the intervals in which investigations should be offered and by which health care provider. These definitions and time-frames are adapted from the criteria recommended in the NICE guideline 'Suspected cancer: recognition and referral (NG12)'.[55] While the time-frames for referral should remain standardised, the model of care in terms of referral pathway, to reduce the burden on the USCP, will vary according to local infrastructure. For example, if resources within primary care services cannot provide direct access urgent ultrasound then development of an urgent unscheduled bleeding clinic within the gynaecological services could be considered. Or, if there is a paucity of experience at adjusting HRT regimens, consider gynaecological advice and guidance platforms.

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Table 5: Clinical pathways and time-frames for investigating unscheduled bleeding on HRT

	Interval in which a review or investigation should be completed		
PATHWAY	**Non-urgent**	**Urgent**	**USCP**
Direct Access: The assessment and investigation requests are completed through primary care who retain clinical responsibility throughout, including acting on the result.	**Within 12 weeks** No risk factors for endometrial cancer	**Within 6 weeks** < 3% risk of endometrial cancer	
Gynaecological service: Seen within a gynaecological service e.g one-stop, unscheduled bleeding or hysteroscopy clinic. The service takes the responsibility for clinical management.		**Within 6 weeks** < 3% risk of endometrial cancer	
Urgent Suspicion of Cancer (USCP): Seen within a fast-track gynaecological service (e.g. oncology, rapid-access one stop or hysteroscopy clinic), within the national targets in England, Wales or Scotland for suspected cancer referrals. The service takes the responsibility for clinical management.			**Within 2 weeks** > 3% risk of endometrial cancer

When to manage conservatively and offer adjustments to the HRT

The following conservative management strategies can be offered through primary care (or an unscheduled bleeding service) for women with ***no risk factors for endometrial cancer***, who have had a thorough assessment as outlined in Section 1 and who do not report heavy, prolonged or daily bleeding.

- **Unscheduled bleeding which occurs within 6 months of initiating either ccHRT or sHRT:**
  Offer an adjustment in the progestogen or preparation (such as vaginal estrogen if vulvovaginal atrophy is present (see Section 5)), totalling six months of adjustments after the initial presentation. Ensure that the progestogen is in balance with the estrogen dose (see Appendix 1).
- **Unscheduled bleeding continuing 3 months after a change in HRT dose or preparation:**
  If the HRT preparation is changed (such as from a pill to a patch), or the dose is increased, ensure the progestogen is in proportion. If unscheduled bleeding is occurring three months after this change, offer adjustments to the preparation (see Section 5) for six months in total.

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If unscheduled bleeding continues after six months of adjustments, offer an urgent (within 6 weeks) direct access transvaginal ultrasound (TVS) with continued changes to the progestogen component or, weaning off HRT and consideration of non-hormonal alternatives (if there is a preference to avoid invasive investigations).

When to refer for an ultrasound

Urgent pathway (within 6 weeks):

For women who meet the following criteria, offer a *direct access urgent TVS* (or urgent gynaecological service review – dependent upon local resources) versus weaning off HRT and consideration of non-hormonal alternatives (to avoid invasive investigations). If continuing HRT and attending for ultrasound is the woman's preference, continue to make changes to the progestogen component whilst awaiting investigation.

- Within any time-frame of starting ccHRT / sHRT 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
  - — Two minor risk factors for endometrial cancer
- 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 the endometrial thickness is above the recommended range (> 4 mm if ccHRT and > 7 mm if sHRT – see Section 4), refer to the USCP. If the endometrium is within recommended ultrasound limits, offer HRT adjustments (see section 5) and if unscheduled bleeding persists six months after these changes, or the bleeding increases in intensity or frequency during the six months of adjustments, recommend referral to the USCP.

Urgent Suspicion of Cancer Pathway:

Refer women with unscheduled bleeding and one major, or three minor, risk factors (Table 1) to the USCP irrespective of bleeding pattern or interval since starting, or changing, the HRT preparation.

Can HRT be continued if referring for urgent or USCP assessment

- If women are referred for histological assessment of the endometrium following ultrasound, and HRT is continued, it will not affect the accuracy of the pathological assessment, but interpretation would be aided by providing information to the histopathologist on the type of HRT regimen (such as sHRT, ccHRT, 52 mg LNG-IUD) and additional contraceptives such as the copper IUD or progestogen-only pill.
- In women with no risk factors for cancer who are offered TVS on an urgent pathway, discuss ongoing adjustments to the progestogen whilst awaiting investigation.
- If there is a strong preference to avoid ultrasound, and there are no risk factors for endometrial cancer, discuss weaning off HRT (i.e. reduction in dose over weeks until cessation, rather than an abrupt stop) and offer non-hormonal options to manage symptoms.
  - — If bleeding ceases at a 4 week follow-up, and continuing without HRT is acceptable, then no further investigations are required.
  - — If the bleeding ceases at a 4-week follow-up and there is a preference to restart HRT, offer adjustments in HRT for six months. If the bleeding becomes heavy / prolonged

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/ persistent, or continues after the six months of adjustments, recommend urgent ultrasound.
— If bleeding continues despite stopping HRT, recommend an USCP referral.

- If an USCP referral is recommended and acceptable, discuss the advantage of continuing HRT (ongoing menopausal symptom control) versus the potential disadvantage of exacerbating an estrogen driven endometrial cancer.
- If an USCP referral is recommended, and investigations are declined, recommend weaning off HRT and offer non-hormonal alternatives. Offer follow-up at 4 weeks; recommend USCP 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 TVS on an urgent pathway if bleeding is continuing after this interval.

Section 4: How should unscheduled bleeding be investigated

This chapter outlines evidence relating to initial investigations for unscheduled bleeding in women who meet the referral criteria in Section 3. Recommendations for method of endometrial assessment in women who have a thickened endometrium on TVS, and management options relating to subsequent histological outcomes, are discussed. Appendix 2 contains suggested ultrasound reporting criteria and Appendix 3 summarises the ultrasound and histological outcome recommendations made in this section.

Ultrasound

Ultrasound provides high diagnostic accuracy as a first line investigation for women who present with postmenopausal bleeding (PMB)[56-60] and is more acceptable to women than hysteroscopy or biopsy.[61, 62] Transvaginal ultrasound (TVS) is more accurate than transabdominal (TAS) with double-layer endometrial thickness (ET) measured at the point of maximal width.[57] Evidence in relation to the sensitivity of TVS in predicting cancer risk in women with unscheduled bleeding on HRT is scarce, as large studies assessing this in women with PMB often exclude HRT users or do not provide subgroup analyses of HRT preparation or dose.

Endometrial measurements which should determine further investigations

- **Women with unscheduled bleeding, in the presence of a uniform endometrium which is fully visualised, and measures ≤ 4 mm with ccHRT or ≤ 7 mm with sHRT, can be reassured that the risk of endometrial cancer is low. Offer HRT adjustments for 6 months and then offer endometrial assessment, on an urgent pathway, if bleeding becomes persistent or heavy during the 6 months or, is continuing after this interval of adjustments.**
- **Women with a thickened endometrium on TVS (> 4 mm for ccHRT or > 7 mm for sHRT) should be offered referral to the urgent suspicion of cancer pathway (USCP) for endometrial assessment (biopsy and / or hysteroscopy).**
- **When the entire endometrium cannot be visualised on TVS, but the area measured is within normal ultrasound limits, offer urgent endometrial assessment (within 6 weeks).**
- **In the absence of unscheduled bleeding, women with an endometrium ≥ 10 mm should be offered endometrial assessment – consider endometrial blind biopsy if direct access hysteroscopy is not acceptable or feasible (within unit resources). If major risk factors for endometrial cancer are present, refer on an USCP and, in their absence, refer on an urgent pathway (within six weeks).**
- **In the absence of unscheduled bleeding, women who have one major or two minor risk factors for endometrial cancer, and an incidental ET > 4 mm on ccHRT or > 7 mm on sHRT, should be offered endometrial assessment on a USCP.**

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Continuous combined preparations

In studies of women with PMB, TVS ET cut offs of 3 mm, 4 mm and 5 mm are reported to have a sensitivity of 98%, 95% and 90% respectively for predicting endometrial cancer.[56-60] Based on a 26% (95% CI 25-27%) prevalence (pre-test) probability of endometrial disease (carcinoma and hyperplasia) in women with PMB, the post-test probability after a negative scan is reduced to 2.4% (95% CI 1.3–3.9%) when an ET of ≤ 4 mm is used and 5.0% (95% CI 2.9–9.1%) when ≤ 5 mm is used.[58] TVS ET is less accurate at predicting endometrial cancer in Black women because of the higher prevalence of fibroids and non-endometrioid histologic subtypes, when compared with Caucasian women; sensitivity 47.5% vs 97.9% for an ET > 4 mm and of 43.7% vs 86% for an ET > 5 mm.[63] A cut-off of > 5 mm would reduce the number of women who are referred for further invasive investigations but, when compared to > 4 mm, it would reduce the sensitivity and negative predictive value (NPV) of TVS ET for endometrial cancer detection in all women.[63-65]

Women taking ccHRT who have unscheduled bleeding and a ET > 4 mm, should currently be managed in a similar way to non-users who present with PMB[66]; referral to the USCP for endometrial assessment. Blind endometrial biopsy is not recommended if the ET is within normal limits as more than two-thirds will have an insufficient sample.[67] High quality data, in cHRT users, which assesses endometrial pathology in relation to ET should be a research priority as higher ET cut-offs, and stratification to an urgent pathway, or prolonged conservative management, may be enabled dependent upon estrogen dose, duration of HRT use and progestogen type.

Sequential (cyclical) preparations

Studies using licenced doses of estrogen with 12 days of 200 mg micronised progesterone or 10 days of 10 mg MPA report a high NPV (99%) for endometrial cancer when an ET of 7 mm or less is visualised.[68, 69] Until high quality evidence assesses ultrasonographic variation at different intervals in the cycle (such as mid-cycle and immediately after the withdrawal bleed), and correlates this with histological outcomes, women taking sHRT who have unscheduled bleeding and an ET of > 7mm should be offered referral to the USCP for endometrial assessment.

Incomplete visualisation of the entire endometrium

Unsatisfactory ultrasound examinations, where the view of the endometrium is limited (IUD, fibroids, prior ablation, TAS as TVS declined or not appropriate e.g. transgender women who are not sexually active or those with a prior history of assault), have been associated with higher rates of endometrial hyperplasia (27% vs 7%).[63, 69] Offer an urgent (within 6 weeks) endometrial assessment – discuss hysteroscopy (unit resources dependent) over blind biopsy if the endometrium is distorted by fibroids – versus weaning off HRT and consideration of non-hormonal alternatives (to avoid invasive investigations).

Recurrent unscheduled bleeding with a normal endometrial profile

Women who have a normal ET on TVS (≤ 4 mm with ccHRT or ≤ 7 mm with sHRT) but recurrent bleeding that is ongoing six months after adjustments in the progestogen should be offered endometrial assessment on an urgent pathway. If the bleeding increases in intensity or frequency – persistent, almost daily bleeding, prolonged withdrawal bleeds or flooding – referral should be recommended prior to the six months. Discuss hysteroscopy, over blind biopsy (dependent upon unit resources), as it facilitates a 'see and treat' approach, as more than one third of women with recurrent unscheduled bleeding will have polyps on assessment.[1, 44-46, 50]

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Fluid in the endometrial cavity but a normal endometrial thickness

The risk of cancer in postmenopausal women with intracavity fluid appears to be increased in the presence of genital symptoms (vaginal discharge, abnormal vaginal bleeding), a history of colorectal cancer or an abnormal TVS finding (focal cavity lesions e.g. polyps).[70] The decision for endometrial evaluation, in the presence of endometrial fluid and a normal ET, should be based upon symptoms and cancer risk factors (Table 1) – as is the case in women without intracavity fluid.

Asymptomatic (no unscheduled bleeding) with an incidental thickened endometrium

The diagnostic value of TVS ET in asymptomatic postmenopausal women for endometrial cancer is contentious; the diagnostic yield (and prevalence) of premalignant and malignant endometrial cells is lower than in women who report bleeding (< 1% vs 5%).[71-73] A systematic review concluded that the use of TVS ET as a screening test for endometrial cancer could not be justified because of its relatively poor predictive ability and the low prevalence; the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCs)[72] advise a TVS ET threshold value > 10 mm to minimise unnecessary biopsies (high specificity) whilst facilitating the diagnosis of endometrial cancer (moderate sensitivity). In the absence of robust accuracy data, the UKCTOCs and British Gynaecological Cancer Society (BGCS) 10 mm threshold is recommended in women taking HRT.[72, 74] Discuss hysteroscopy as a first line investigation, on an urgent pathway, due to the high prevalence of endometrial polyps with a substantially thickened endometrium[50, 75] or offer endometrial biopsy if hysteroscopy is not acceptable or feasible (within unit resources).

Asymptomatic women with an ET of < 10 mm, who have no major risk factors for endometrial cancer, can be offered adjustments in their progestogen. Only offer endometrial sampling, on an urgent pathway, if unscheduled bleeding occurs.[66] Asymptomatic women who have one major or two minor risk factors for endometrial cancer, and an ET > 4 mm on ccHRT or > 7 mm on sHRT, should be offered endometrial assessment on an USCP[14, 15] – adjustments to the progestogen should be offered at the time of referral.

Endometrial assessment options if a thickened endometrium on TVS

- **Offer endometrial assessment if unscheduled bleeding and a thickened endometrium on ultrasound. A blind outpatient endometrial biopsy can be performed or, hysteroscopy with endometrial sampling, if acceptable to the woman and within unit resources**

Blind outpatient endometrial biopsy, in comparison to hysteroscopy, is cost-effective and quicker to achieve.[64] A systematic review reported that in postmenopausal women who had an adequate pipelle biopsy, the post-test probability of cancer being present with a positive result was 81.7% (95% CI 59.7 – 92.9%) and 0.9% (95% CI 0.4 – 2.4%) with a negative result.[10] The failure rate of blind 'pipelle' endometrial biopsy, in postmenopausal women, is 12% and inadequate rates are 22%. In women taking HRT these proportions may be lower owing to reduced rates of atrophic changes. They concluded that 'a positive test result is more accurate for ruling in disease than a negative test result is for ruling it out', indicating that if hysteroscopy is not possible as a first line investigation, it should be offered, if within unit resources and dependent upon acceptability to the woman, when outpatient biopsy is inadequate or if recurrent episodes occur after a normal blind biopsy and appropriate adjustments in the progestogen.[50, 76]

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Hysteroscopy has a lower failure rate (3.4%) compared to blind endometrial sampling in postmenopausal women. The post-test cancer probability is 71.8% after a positive result and 0.6% with a negative result; sensitivity 86.4% and specificity 99.2%.[10] Removing focal lesions like polyps, as part of a 'see-and-treat' procedure, may improve patient experience by reducing the total number of appointments and procedures but has to be tempered with available resources and patient choice. A randomised control trial reported that half of the women who present with PMB, a TVS ET ≥ 4 mm and a subsequent negative blind endometrial biopsy will have an endometrial polyp and of these polyps, 6% contain endometrial cancer or atypical endometrial hyperplasia.[50] However, removal of polyps in the PMB population does not appear to reduce bleeding episodes[50] and there is a lack of evidence relating to efficacy with recurrent unscheduled bleeding episodes.

Recommendations for management according to endometrial histology

- **If blind endometrial biopsy is reported as normal, offer reassurance and adjustments in the progestogen for 3 months. If unscheduled bleeding persists after this interval, or becomes heavy / prolonged, offer hysteroscopic assessment on an urgent pathway (within six weeks).**
- **In the presence of a normal biopsy and hysteroscopy, discuss adjustments in the progestogen and provide reassurance for six months. If unscheduled bleeding persists after this interval, or becomes heavy / prolonged, offer a repeat TVS on an urgent pathway.**
- **A hysteroscopy should be offered, on an urgent pathway (within six weeks), in the presence of a thickened ET on TVS and a blind biopsy which is reported as an 'insufficient sample'.**
- **If proliferative endometrium is reported on blind biopsy and there are risk factors for endometrial cancer (1 major or 2 minor) and the preparation used is ccHRT, offer hysteroscopy.**
- **If hyperplasia with atypia or endometrial cancer is reported, advise weaning off HRT, discuss non-hormonal alternatives and refer to gynaecology oncology on an USCP.**

In the presence of an insufficient sample on blind biopsy, hysteroscopy (outpatient or daycase) should be discussed. Biopsies with insufficient tissue for diagnosis can be categorised as 'atrophic' (inactive), and the woman reassured, if the result is consistent with the hysteroscopic appearance of the endometrium.[77] If an insufficient sample is obtained, and is inconsistent with the hysteroscopic endometrial appearance, a repeat hysteroscopy should be offered, considering different pain control options (regional or general anaesthetic) to potentially facilitate an increased endometrial tissue yield.

If recommendations for endometrial assessment are offered, based on criteria in sections 3 and 4, and there is a preference to avoid biopsy and / or hysteroscopy, recommend weaning off HRT and offer non-hormonal alternatives; offer follow-up at 4 weeks and if bleeding continues after stopping HRT rediscuss the available options. If bleeding ceases, and continuing without HRT is acceptable, then no further investigations are required. If the bleeding ceases at a 4-week follow-up and there is a preference to restart HRT, offer adjustments in HRT for three months. If the bleeding becomes heavy / prolonged / persistent, or continues after the three months of adjustments, recommend urgent endometrial assessment and cessation of HRT if cancer exclusion tests cannot be completed.

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In the absence of evidence relating to women with unscheduled bleeding but, in line with the recommendations in the (archived) SIGN PMB Guideline[78], women who have a normal hysteroscopy and biopsy can be reassured for six months after this outcome even if unscheduled bleeding continues. Adjustments to the progestogen, and management strategies to reduce cancer risk factors such as diabetes and BMI (if > 30) should be offered to reduce the likelihood of recurrent episodes. Reassessment (TVS within 6 weeks) should be offered before six months if the nature of the bleeding changes e.g. heavier or more persistent. In the absence of evidence relating to women with unscheduled bleeding but, in line with expert opinion, if a blind endometrial biopsy without concomitant hysteroscopic assessment is reported as normal, reassurance can be provided for three months; studies assessing whether this interval can be increased should be a research priority. If bleeding is ongoing, despite adjustments in the progestogen, hysteroscopic assessment should be offered on an urgent pathway. Reassessment before three months should be offered if the nature of the bleeding changes e.g. heavier or more persistent.

If there is proliferative endometrium reported on blind biopsy, there are risk factors for endometrial cancer (one major or two minor) and the preparation used is ccHRT, offer hysteroscopy to enable targeted assessment of the whole endometrium. If the hysteroscopy is normal but unscheduled bleeding continues despite six months of adjustment in progestogen dose or type, offer repeat endometrial assessment. If proliferation is reported on blind endometrial biopsy in women using sHRT or, there are no risk factors for endometrial cancer and using ccHRT, offer adjustments in the progestogen for six months; if bleeding persists after this interval, or the nature of the bleeding changes e.g. heavier or more persistent prior to the six months, offer hysteroscopic assessment.

If the endometrial biopsy reports hyperplasia ***without*** atypia, manage in line with the RCOG/ BSGE Green-top Guideline No. 67 Management of Endometrial Hyperplasia:[79]

- Women taking a sequential preparation who wish to continue HRT (having been offered, and declined, non-hormonal alternatives), should be advised to change to ccHRT – a daily progestogen – offering the 52 mg LNG-IUD first-line or oral high dose NET / MPA (if the LNG-IUD is not acceptable). Discuss a reduction to medium dose estrogen, if using high dose, whilst awaiting follow-up biopsy results.
- Women taking ccHRT should have their need to continue HRT reviewed. Discuss weaning off HRT and starting non-hormonal alternatives versus use of a 52 mg LNG-IUD as a source of progestogen replacement. If a 52 mg LNG-IUD is already in-situ, and within the recommended interval of use, explain the limitations of the available evidence in optimising progestogens to lead to reversal of hyperplasia if HRT is continued; if weaning off HRT and starting non-hormonal options is not acceptable, consider the pros and cons of a hysterectomy.

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Section 5: Adjusting HRT to reduce unscheduled bleeding episodes

Does progestogen type affect rates of unscheduled bleeding?

Levonorgestrel 52 mg intra-uterine device (LNG-IUD)

The 52 mg LNG-IUD reduces systemic progestogenic adverse effects, is a licensed contraceptive, can reduce polyp formation and induce atrophic changes. Non-proliferative endometrium is reported on histology in 89.5% at 12 months, increasing to 94.8% at two years and 97.5% at five years.[80-83]

Cumulative amenorrhoea with high dose estrogen has not been assessed in any of the pivotal studies. In postmenopausal women taking medium dose estrogen, amenorrhoea rates at 12 months with either a 52 mg LNG-IUD, 100 mg daily oral micronised progesterone (MP) or 100 mg vaginal MP are reported as 80%, 67% and 53% respectively.[84, 85]

In perimenopausal women taking medium dose estrogen with either the 52 mg LNG-IUD or NET, irregular spotting is higher in the 52 mg LNG-IUD group at 3 months (33 vs 10%) but at 12 months there is no reported difference (80% amenorrhoea).[83] When sequential oral MPA (5 mg) was compared to the 52 mg LNG-IUD, proliferation and irregular spotting, after 12 months use was higher in the MPA users (38% vs 0%).[86]

Tibolone

This oral preparation has estrogenic, progestogenic and androgenic effects; it should be considered ccHRT. A RCT of 3240 women reported, at 12 months, higher rates of amenorrhoea (78.7%) in those using tibolone when compared to use of medium dose estrogen with 2.5 mg/day MPA (44.9%).[87] This finding, and its equivocal endometrial safety profile, has been corroborated in other large RCTs.[36] Use of tibolone, however, should be cautioned in women over 60 due to the increased risk of cerebrovascular events.

Synthetic progestogens

Higher rates of cumulative amenorrhoea, when compared to micronised progesterone (MP), have been reported in preparations which contain synthetic progestogens (NET, MPA, levonorgestrel) as they are less rapidly metabolised and provide high oral bioavailability.[53, 88] Although breast cancer risk may be marginally higher with these preparations, in comparison to MP, the pros and cons of use should be discussed in women with recurrent unscheduled bleeding.

Micronised progesterone (MP)

Cohort studies have assessed rates of atrophy and proliferation in women taking oral MP. In women using ccHRT (medium dose estrogen), atrophic/inactive endometrial changes were reported in 100% of women using 200 mg/day[89] and 56.4% if using 100 mg for 25 of 28 days.[90] In women using sHRT, 12 days of 200 mg MP with low to medium dose estrogen, atrophy rates were 20.8% – 56%[91, 92] and proliferation 31%.[92] Cumulative amenorrhoea rates with high dose estrogen have not been reported.

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Oral bioavailability can be improved if given with food, but this also affects the adverse effect profile (such as sedation and progestogenic tolerance). Whether this improves episodes of unscheduled bleeding is unclear. In comparison to dydrogesterone, there are some data to suggest MP may have a more favourable bleeding profile.[88]

Does route of HRT (oral, transdermal, vaginal) affect bleeding profile?

Transdermal versus oral preparations

A systematic review of 45 studies compared bleeding profiles over one year in women taking ccHRT as an oral versus transdermal preparation. By three months, amenorrhoea was noted in 65-91% of those taking oral preparations and in 40-65% of those taking transdermal preparations. Cumulative amenorrhoea over 12 months was lower in the transdermal preparations (9-27%), when compared to oral preparations (18-61%), irrespective of the constituents.[93]

As perimenopausal women have higher rates of unscheduled bleeding and proliferation on biopsy, than postmenopausal women,[94, 95] an oral preparation (if no risk factors for thrombosis), could be offered as either, a first-line therapy or, to women whose initial preference was for transdermal but have unscheduled bleeding episodes despite adjustments.

Vaginal versus oral micronised progesterone (MP)

There is no evidence to provide recommendations on whether vaginal MP reduces unscheduled bleeding episodes compared to oral use or when compared to other progestogens. It would, however, be reasonable to trial this (off-license) over three months to assess the impact in women who cannot tolerate other progestogens.

Reducing recurrent episodes of unscheduled bleeding

Although unscheduled bleeding on HRT is common, there are few studies reporting on interventions that reduce recurrent episodes. The suggestions outlined in this section are based on the available evidence and clinical experience; see summary in Table 6.

These changes can be instituted in primary care settings (GP practices or community women's health 'hubs'), following queries to gynaecology advice and guidance platforms or through secondary care unscheduled bleeding, hysteroscopy or USCP clinics.

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Table 6: Recommendations for reducing and managing unscheduled bleeding on HRT

Problem	Potential adjustments
General Principles	• Assess compliance + / – order of pills or patches if using sHRT • At initiation of HRT, consider starting with a low dose preparation • At initiation of HRT, offer a sequential preparation if women are still menstruating and < 55 • Time the start of sHRT to their natural cycle • Offer ccHRT if a) initiating HRT and are postmenopausal or b) have been using sHRT for 5 years and are aged more than 50. • Offer the 52 mg LNG-IUD, if appropriate, to women initiating HRT, particularly if contraception is also required. • Offer change of 52 mg LNG-IUD if new onset unscheduled bleeding at 4 years of use and investigations are normal (particularly if BMI ≥ 40) • Offer vaginal estrogen if atrophic findings on examination.
Poor compliance of non-combined preparations	• Change to a combined patch • Change to a combined oral preparation – consider one containing micronised progesterone (MP) if synthetic progestogens not acceptable • Take MP at the same time as applying the daily gel • Offer the 52 mg LNG-IUD.
Submucosal / intramural fibroids	• Offer the 52 mg LNG-IUD (if submucosal < 3cm and cavity < 10 cm) • Trial an increase in the MP dose • Switch to a synthetic progestogen or give additional progestogens • Consider resection if submucosal and progestogen adjustments are not acceptable or prevents LNG-IUD insertion • Reduce to a lower dose estrogen preparation and supplement with non-hormonal options if required.
BMI ≥ 30	• Offer weight management strategies • Offer the 52 mg LNG-IUD • Increase MP to 200 mg continuous or 300 mg sequential • Reduce to a lower dose estrogen preparation and supplement with non-hormonal options if required.
Perimenopausal and unscheduled bleeding with sHRT	• Desogestrel can suppress endogenous ovarian activity • If < 50 and low thrombotic (VTE) risk consider switching HRT to a COC • Change to an oral preparation (if BMI < 30 and low risk of VTE) • Offer the 52 mg LNG-IUD • Increase the MP dose or change to a synthetic progestogen • 3-month trial of an additional progestogen on top of the current preparation • Reduce the estrogen dose and offer non-hormonal alternatives.
Unscheduled bleeding with ccHRT	• Change to an oral preparation (if BMI < 30 and low risk of VTE) • Offer the 52 mg LNG-IUD • Increase the MP dose or change to a synthetic progestogen • 3-month trial of an additional progestogen on top of the current preparation (including women already using a 52 mg LNG-IUD) • Consider a 6-month trial of sHRT if recently postmenopausal • Reduce the estrogen dose and offer non-hormonal alternatives.

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Basic principles

- Ensure compliance; would a combined patch, changed twice weekly, or a daily pill be easier than a separate estrogen and progestogen component. Consider calendar or phone reminders to enable progestogen component adherence in a sequential preparation.
- Assess understanding of how to use products, i.e. taking correct order of pills or patches if a sequential preparation and how / where they are applying topical products.
- Ensure the progestogen dose is proportionate to the estrogen dose (See Appendix 1).
- Ensure the correct preparation: sHRT if perimenopausal and ccHRT if menopausal/prior ablation/amenorrhoea with contraceptive.
- Lower dose HRT achieves greater rates of amenorrhoea and if women have mild symptoms, this should be considered when initiating sHRT or ccHRT.
- Assess lifestyle factors – offer weight loss strategies and support if a raised BMI (≥ 30) and optimise medical comorbidities.
- Offer vaginal estrogens and/or moisturisers if evidence of localised atrophic changes on the vulva and/or vagina.
- Offer all women with a uterus the 52 mg LNG-IUD at the initial HRT consultation if appropriate (may not be suitable if uterine malformation, submucosal fibroids > 3 cm, history of trauma, endometrial ablation). In particular, counsel women who have existing endometrial cancer risk factors (Table 1) about use as the progestogenic component.
- Assess contraceptive requirements to reduce unplanned pregnancies.

Managing unscheduled bleeding with sequential preparations (sHRT)

- Irregular bleeding is more common in perimenopausal than pre-menopausal women. Unlike contraceptives, HRT will not suppress endogenous ovarian activity. Ways to manage this include:
  - Timing the start of a sequential preparation to their natural cycle, i.e. starting the estrogen component on day 1 of their period and the progestogen on day 15 for a 28-day cycle or day 21 for a 35-day cycle. This facilitates the withdrawal bleed and their natural cycle bleed occuring at the same time.
  - Offer desogestrel in addition to HRT. There are a lack of safety data relating to endometrial safety with 75 microgram desogestrel in conjunction with estrogen replacement; although some studies have reported safety with desogestrel 150 micrograms, it is not currently licensed for this use.
  - Consider a combined oral contraceptive (COC) in women < 50 who are at low risk of thrombosis[9] and require contraceptive. Options which contain estradiol can provide good symptom control in perimenopausal women.
- In women using a progestogen separate to the estrogen i.e. non-combined preparations, discuss using the progestogen 'two weeks on and two weeks off' (rather than 10-12 days of the month) to reduce prescribing and administration errors.
- Oral preparations may achieve greater cumulative rates of amenorrhoea than transdermal; women using sHRT should be < 55 and if low risk for thrombosis this change, in itself, may reduce irregular bleeding.
- Increasing the progestogen dose or changing the progestogen type can be beneficial:
  - Increase oral micronised progesterone (MP) to 300 mg for 14 days of the month[24, 25]
  - Consider using 200 mg MP vaginally for 14 days of the month (off-license use)
  - Change to transdermal estrogen and either oral MPA or NET (if they do not absorb estrogen through an oral route, have ongoing bleeding despite adjustments in MP dose / route, would not accept a 52 mg LNG-IUD and are low risk for thrombosis).

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  - If taking a combined preparation, give an additional progestogen (100 mg MP, 10 mg MPA or 5 mg NET) for three months. If unscheduled bleeding settles with use, but recurs with cessation, discuss long-term use (with the potential increased effect on breast tissue and clot risk) if other options are not acceptable or efficacious.
  - If separate oral norethisterone leads to cessation of bleeding but the 5 mg dose causes adverse progestogenic side effects, consider off-license use of x3 noriday tablets (1.05 mg norethisterone in total) for 10-14 days in combination with low or medium dose estrogen.
  - Re-offer the 52 mg LNG-IUD.
- If a woman reports spotting before the withdrawal bleed, this may represent inadequate stromal formation and increasing the estrogen can, in women taking low dose preparations, be of benefit.[96] Ensure the progestogen dose is in proportion to the estrogen dose.
- Reduce the estrogen dose and offer non-hormonal alternatives (lifestyle, complementary, pharmacological).

Managing unscheduled bleeding with continuous combined preparations (ccHRT)

- Starting ccHRT in women who are perimenopausal can lead to irregular bleeding patterns. Switching to sHRT would be appropriate in women who had menstrual cycles in the 12 months preceding HRT initiation.
- If switching to ccHRT from sHRT, amenorrhoea may be achieved more quickly if a washout period (1 month) is offered to women who have recurrent unscheduled bleeding on sHRT[97, 98] – but this advice needs to be balanced with a transient deterioration in menopausal symptoms.
- Lower dose HRT achieves greater rates of amenorrhoea and if women have mild symptoms, this could be considered (particularly in women > 60 years).
- If using micronised progesterone (MP), prescribe daily use, rather than days 1-25 to reduce administration errors.
- Increasing the progestogen dose or changing the progestogen type can be beneficial:
  - Increase MP to 200 mg per day.[24, 25]
  - Increase MP to 200 mg on days 1-25 of a 28-day cycle (ensure understanding to reduce adherence errors)
  - Consider using 200 mg MP vaginally (off-license use)
  - Change to transdermal estrogen and either oral MPA or NET (if they do not absorb estrogen through an oral route, find a 52 mg LNG-IUD unacceptable, have recurrent bleeding despite adjustments in MP and are low-risk for thrombosis).
  - If taking a combined preparation, an additional progestogen dose can be given (100 mg MP, 5 mg MPA or 5 mg NET). Trial for three months to reduce endometrial proliferation and if this leads to amenorrhoea during use, but bleeding recurrence on cessation, then discuss long-term use (with the potential increased effect on breast tissue and clot risk) if other options are not acceptable or efficacious.
  - If separate oral norethisterone leads to cessation of bleeding but the 5 mg dose causes adverse progestogenic side effects, consider daily off-license use of x3 noriday tablets (1.05 mg norethisterone in total) in combination with low or medium dose estrogen.
  - Re-offer the 52 mg LNG-IUD.
  - If at 4 years of use, new unscheduled bleeding develops, offer a change of 52 mg LNG IUD, if cancer exclusion investigations are normal – particularly in women using more than high dose estrogen and in those with a BMI ≥ 40.

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- Oral preparations may achieve greater cumulative rates of amenorrhoea than transdermal. If older than age 60, oral preparations are a risk factor for thrombosis, but if stopping HRT and switching to non-hormonal alternatives is not acceptable, because of quality-of-life effects, then the pros and cons of combined low dose oral preparations, which contain micronised progesterone or dydrogesterone (lower breast and thrombotic effects), may be of benefit.
- If unscheduled bleeding persists, despite trying multiple adjustments, discuss changing to a sequential regimen for 6-12 months.
- Discuss reducing the estrogen dose and offer non-hormonal alternatives (lifestyle, complementary, pharmacological).

Surgical options

Hysteroscopic myomectomy

This can be considered an option in women with heavy bleeding and a normal endometrial assessment who have submucosal fibroids which prevent insertion of a 52 mg LNG-IUD. Consider if changes to the HRT preparation are not acceptable or efficacious. After informed counselling, small, non-vascular and mostly intracavity submucosal fibroids (FIGO type 0 and 1) may be suitable for resection in an outpatient setting with appropriate pain-relief. However, most submucosal fibroids require removal as a day case procedure under regional or general anaesthesia. Preparation for hysteroscopic myomectomy may require assessment of fitness for a general anaesthetic, a degree of intravascular fluid absorption as well as a laparoscopy if uterine perforation occurs. It may also require down-regulation (GnRH analogues) with a potential reduction in estrogen dose if high dose preparations are currently used (which can affect menopause symptom control).

Endometrial Ablation

This day case / outpatient procedure is not recommended as a management option in women who have recurrent unscheduled bleeding. Uterine cavity adhesions after endometrial ablation often prevent further endometrial evaluation with ultrasound, hysteroscopy and/or endometrial biopsy if further episodes of unscheduled bleeding occur (which may then necessitate a hysterectomy).

Hysterectomy

This is a major operation and risks of the procedure (bleeding, infection, hernia formation, risk of prolapse and bladder dysfunction, plus injury to surrounding structures including bladder, bowel and ureters) need to outweigh the benefits (management of unscheduled bleeding). All avenues of managing the bleeding pattern, including reducing the estrogen dose, stopping HRT with consideration of non-hormonal options / lifestyle measures and reasons for 52 mg LNG-IUD non-acceptability, if relevant, should be explored and documented before considering hysterectomy. Medical and individual comorbidities (such as an elevated BMI) can increase intraoperative and postoperative surgical and anaesthetic risks; these factors would need to be optimised before considering major elective surgery (which may in itself improve unscheduled bleeding episodes).

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Abbreviations and key terms

Term	Description
BGCS	British Gynaecological Cancer Society
BSGE	British Society for Gynaecological Endoscopy
Direct access	When an assessment is done by primary care, who then retain clinical responsibility throughout, including acting on the result
BMS	British Menopause Society
ccHRT	Continuous combined HRT: estrogen and progestogen every day
ET	Endometrial thickness
HRT	Hormone replacement therapy
Hyperplasia	Precancerous change
LNG IUD	52 mg levonorgestrel Intrauterine Device
MP	Micronised progesterone
NICE	National Institute of Clinical Excellence
PMB	Postmenopausal bleeding
Progestogen	Encompasses synthetic progestogens and progesterone unless specifically stated otherwise
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised control trial
sHRT	Sequential (also known as cyclical) HRT: estrogen every day and, depending on the specific preparation, a progestogen for 10 to 14 days per month
Synthetic progestogens: NET MPA Livial	 Norethisterone Medroxyprogesterone acetate Tibolone
TCRF	Transcervical resection of fibroids
Tricycling / Long-cycle	Estrogen daily and a reduced progestogen course (every three months)
TVS	Transvaginal ultrasound
TAS	Transabdominal ultrasound
Urgent pathway	Investigation to be complete within 6 weeks
USCP	Urgent suspicion of cancer pathway
VTE	Venous thromboembolism

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This BMS Guideline will be updated when guidance changes and/or new data becomes available.

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Appendices

Appendix 1: Licensed estrogen dose and proportionate progestogen dose

Appendix 2: Endometrial ultrasound reporting criteria for women with unscheduled bleeding

Appendix 3: Recommendations pertaining to investigation outcomes in women taking HRT

Appendix 4: Auditable topics

Appendix 5: Research priorities

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Appendix 1: Licensed estrogen dose and proportionate progestogen dose

'The dose of the progestogen should be proportionate to the dose of estrogen. Women who require high dose estrogen intake should consider having their progestogen dose increased to ensure adequate endometrial protection.'
BMS 2022 Recommendation

Prescribed estrogen dose for low, medium and high dose regimens

Approximate equivalent doses of estradiol products for those of average menopause age with symptoms (45-55 yrs)

Product	Low	Medium	High†
Oestrogel (gel pump)	1 pump	2-3 pumps	4 pumps
Sandrena (gel sachet)	0.5 mg	1 mg 2 mg*	2.5-3 mg* *See note 2*
Lenzetto (spray)	1-2 sprays	3 sprays 4 sprays*	5-6 sprays* *See note 3*
Patch	25/30/37.5 mcg	40/50/75 mcg	100 mcg
Oral estradiol	0.5 mg	1-2 mg	3 mg* *See note 4*

** Outside of Summary of Product Characteristic licensing.*
† High doses and doses outside of product license should only be considered in exceptional individualised cases and after full discussion about the relative lack of evidence of additional benefit and risks with these doses. If response has not been assessed with other options, consider offering a change of estrogen preparation before increasing the dose above license.

Notes

1. The table has been drawn up as a practical guide based on a combination of pharmacokinetics, clinical trials and clinical experience. The dose equivalents are subject to significant individual variations in absorption and metabolism, so cannot be precise.
2. Sandrena: high doses have been extrapolated from other gel preparations.
3. Lenzetto has a unique mode of action so data cannot be extrapolated: the excipient pushes estradiol through the skin into a reservoir from which it slowly releases. If going above 3 sprays, advise applying these additional sprays to the contralateral side.
4. Oral estradiol: high doses are rarely used in this age group.
5. Doses for those with premature ovarian insufficiency (POI) are not included in this table.

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Stand-alone progestogen dose per licensed estrogen dose in the baseline population

Estrogen dose	Micronised progesterone *Continuous*	Micronised progesterone *Sequential*	Medoxyprogesterone *Continuous*	Medoxyprogesterone *Sequential*	Norethisterone *Continuous*	Norethisterone *Sequential*	Dydrogesterone *Continuous*	Dydrogesterone *Sequential*	LNG-IUD, 52 mg
Low	100 mg	200 mg	2.5-5 mg	10 mg	5 mg*	5 mg*	10 mg‡	10 mg	for up to 5 years of use
Medium	100 mg	200 mg	5 mg	10 mg	5 mg	5 mg	10 mg‡	10 mg	
High	200 mg	300 mg	10 mg†	20 mg†	5 mg	5 mg	10 mg	20 mg	

* *1 mg provides endometrial protection for low to medium dose estrogen but the lowest stand-alone dose currently available in the UK is 5 mg (off license use of three Noriday POP, i.e. 1.05 mg, could be considered if 5 mg is not tolerated).*

† *There is limited evidence in relation to optimal MPA dose with high dose estrogen; the advised dose is based on studies reporting 10 mg providing protection with up to medium dose estrogen.*

‡ *2.5 mg provides endometrial protection for low dose estrogen and 5 mg for medium dose estrogen but the lowest stand-alone dose currently available in the UK is 10 mg.*

Notes

Drospirenone (DRSP): RCT data suggests 0.5 mg daily DRSP provides endometrial protection with 1 mg oral estradiol over 12 months of use. Extrapolation suggests 4 mg of DRSP should provide protection for up to high dose estrogen (but no dose specific studies have been completed). Dosages of 2 mg DRSP per 1 mg estradiol have been shown to provide better bleed control. Whilst no direct evidence, efficacy has been demonstrated with a dose of 3 mg DRSP when combined with 30 mcg of ethinyl estradiol which is equivalent to high dose estradiol. DRSP 4 mg (Slynd) is licensed in the UK as a progestogen only contraceptive. It can be used off license as the progestogen component of HRT by taking one active hormone tablet 4 mg daily on a continuous basis (omitting the 4 hormone free pills in the pack).

Desogestrel: earlier studies have reported that desogestrel 150 mcg is effective as the progestogen component of HRT with no increase in the risk of endometrial hyperplasia. There is lack of evidence on the use of desogestrel 75 mcg as the progestogen component of HRT. If desogestrel 75 mcg is used as contraception in women receiving HRT, it would be recommended to add further progestogen (e.g. micronised progesterone 100 mg daily or 200 mg for 12 days a month) to provide adequate endometrial protection.

Dienogest: 2 mg can be considered as an option (off license) if other measures have been ineffective.

*(*see the BMS Tool for Clinicians *on Progestogens and endometrial protection).*

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Appendix 2: Endometrial ultrasound reporting and referral criteria for unscheduled bleeding with HRT

Referral criteria for endometrial thickness (ET) on ultrasound

HRT preparation	≤ 4 mm	> 4 to ≤ 7 mm	> 7mm	Incomplete endometrial assessment but visualised ET within normal limits
ccHRT (Postmenopausal – daily estrogen and progestogen)	Result considered normal but interpreted by referring clinician in context of patient's cancer risks	USCP	USCP	Endometrial assessment on an urgent pathway (within 6 weeks)
sHRT (Perimenopausal – daily estrogen and a progestogen for 10 to 14 days of the month)	Result considered normal but interpreted by referring clinician in context of patient's cancer risks	Result considered normal but interpreted by referring clinician in context of patient's cancer risks	USCP	Endometrial assessment on an urgent pathway (within 6 weeks)

USCP – urgent suspicion of cancer pathway **sHRT** – sequential HRT **ccHRT** – continuous combined HRT

Continuous combined HRT (ccHRT): daily progestogen & estrogen
Preparation given to postmenopausal women i.e. 'bleed free' preparation

All patients should be offered a transvaginal ultrasound scan if possible, if transabdominal please indicate on the report.

- The upper limit for AP measurement for patients with unscheduled bleeding on ccHRT is 4 mm. If > 4 mm advise an urgent suspicion of cancer pathway referral, if not already under their care.
  "The endometrium is thickened and measures XX mm: malignancy should be excluded and referral to the gynaecology urgent suspicion of cancer pathway is advised"

- If the measurements are ≤ 4 mm report the endometrial thickness using the following phrasing:
  "The endometrium measures XX mm: This result is considered reassuring for patients taking ccHRT but should be interpreted by the referring clinician in the context of the patient's individual risk factors for endometrial cancer and bleeding pattern."

Sequential / cyclical HRT (sHRT): daily estrogen and progestogen for 10-14 days of the month
These women are perimenopausal and are still having monthly withdrawal bleeds.

All patients should be offered a transvaginal ultrasound scan if possible, if transabdominal please indicate on the report

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- The upper limit for AP measurement for patients with unscheduled bleeding on sequential HRT (progestogen for 10-14 days days of the month) should be ≤ 7 mm because of the additional progestogen from mid-cycle. If > 7 mm, advise an urgent suspicion of cancer pathway referral, if not already under their care.
  "The endometrium is thickened and measures XX mm: malignancy should be excluded and referral to the gynaecology urgent suspicion of cancer pathway is advised"

- If the AP measurements are ≤ 7 mm report the endometrial thickness using the following:
  "The endometrium measures XX mm. This result is considered reassuring for patients taking sHRT but should be interpreted by the referring clinician in the context of the patient's individual risk factors for endometrial cancer and bleeding pattern."

Endometrium appears within normal limits but not entirely visualised

If it is not possible to accurately assess the endometrium, or obtain an AP measurement of the endometrial thickness owing to factors such as fibroids, IUCD, prior ablation etc, then use:
"The endometrium cannot be assessed in its entirety because of the presence of XXXXXX, therefore endometrial pathology cannot be excluded; the visualised portion measures XX mm. Referral *to the gynaecology urgent suspicion of cancer pathway,* for endometrial assessment, is advised if the visualised portion is thickened (> 4 mm for ccHRT and >7 mm if sHRT) or on an urgent pathway (within 6 weeks) if the visualised portion is within normal limits"

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Appendix 3: Recommendations pertaining to investigation outcomes in women taking HRT

Investigation Result	Pathway	Management Recommendation
TVS: Endometrial thickness (ET) ≤ 4 mm if ccHRT and ≤ 7 mm if sHRT	N/A	Offer adjustments to the HRT preparation for 6 months
TVS: ET > 4 mm if ccHRT and > 7 mm if sHRT (thickened endometrium)	USCP	Endometrial assessment (endometrial biopsy and / or hysteroscopy)
TVS: Incomplete assessment of the endometrium (e.g. fibroids/IUD obscuring) but visualised portion within normal ultrasound limits	Urgent (within 6 weeks)	Endometrial assessment (endometrial biopsy and / or hysteroscopy)
TVS: Asymptomatic (no unscheduled bleeding) with incidental ET ≥ 10 mm and *no* risk factors for endometrial cancer.	Urgent	Hysteroscopy + biopsy (preferable) or blind biopsy alone – resources dependent
TVS: Asymptomatic (no unscheduled bleeding) but incidental ET ≥ 10 mm with risk factors for endometrial cancer (x1 major or x2 minor)	USCP	Hysteroscopy + biopsy (preferable) or blind biopsy alone – resources dependent
TVS: Normal ET (≤ 4 mm if ccHRT and ≤ 7 mm if sHRT) but, • Recurrent unscheduled bleeding six months after HRT adjustments or, • Heavy or Persistent (almost daily) bleeding or, • Intracavity fluid and x1 major or x2 minor risk factors for endometrial cancer	Urgent	Endometrial assessment (endometrial biopsy and / or hysteroscopy)
Blind endometrial biopsy: Normal (inactive/atrophic if ccHRT use or inactive / proliferative for sHRT)	N/A	Offer adjustments in HRT preparation for 3 months
Blind endometrial biopsy: Normal but bleeding ongoing 3 months later	Urgent	Hysteroscopy + / – targeted biopsy
Blind endometrial biopsy: Inadequate sample and thickened ET on TVS.	USCP	Hysteroscopy + targeted biopsy
Blind endometrial biopsy: Proliferation in women using ccHRT who have x1 major or x2 minor risk factors for endometrial cancer	Urgent	Hysteroscopy + / – targeted biopsy
Hysteroscopy and biopsy: Normal but bleeding ongoing 6 months later	Urgent	TVS: endometrial assessment if thickened endometrium
Blind or targeted endometrial biopsy: Hyperplasia (with or without atypia)	USCP	Management: RCOG endometrial hyperplasia guideline

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Appendix 4: Auditable topics

1. Women prescribed stand-alone estradiol products (oral / transdermal) with concurrent issue of appropriate dose and total days per month progestogen or progesterone (100%)

2. Women prescribed stand-alone estradiol products (oral / transdermal) in the presence of an 'in-date' 52 mg LNG–IUD (five or less years since insertion) (100%)

3. Women who started HRT ≥ 45 years of age switched to ccHRT after 5 years of sequential HRT or by age 54 (whichever occurs first) (100%)

4. Percentage of women presenting with unscheduled bleeding meeting criteria for USCP referred by a USCP (100%)

5. Percentage of women presenting with unscheduled bleeding on HRT meeting the criteria for referral on USCP meeting 28-day faster diagnosis target (85%)

6. Percentage of women referred for urgent (6 week) TVS seen by 6 weeks (85%)

7. Percentage of women referred on an urgent (6 week) pathway, with endometrial assessment by 6 weeks (85%)

Appendix 5: Research Priorities

1. Assessment of endometrial cancer risk in women who have unscheduled bleeding on ccHRT including variables relating to high dose estrogen and/or micronised progesterone.

2. Assessment of endometrial cancer risk in perimenopausal women who have unscheduled bleeding on sHRT including variables relating to high dose estrogen and/or micronised progesterone.

3. Acquire evidence assessing endometrial cancer risk dependent upon total duration of HRT use. This should be stratified by progestogen type and dose (with priority given to micronised progesterone).

4. Assessment of endometrial protection with LNG IUD as progestogenic component of HRT:
   a. When lower dose (13.3 and 19.5 mg) LNG IUD is used
   b. When 52 mg LNG IUD is sited in the lower endometrial cavity (more than 2 cm from the fundus)
   c. When 52 mg LNG IUD is used in conjunction with estrogen use above high dose.

5. Acquire evidence correlating endometrial thickness (ET) with endometrial disease (hyperplasia with / without cytological atypia and endometrial cancer) in women who have unscheduled bleeding on HRT. Priority should be given to women taking sequential HRT; assessment of ultrasonographic variation at different intervals in the cycle, with histological correlation, may enable higher cut-offs at the end of the progestogen phase which would reduce the number of women offered invasive testing.

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6. Assessment of optimal interval for endometrial reassessment (ultrasound or biopsy) in women who have recurrent unscheduled bleeding, despite progestogen adjustments, and a normal biopsy and / or hysteroscopy.

7. Assessment of the prevalence of endometrial hyperplasia / cancer in hysteroscopically diagnosed focal endometrial pathology in women with unscheduled bleeding on HRT.

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