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 / 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.**

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 standard dose 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]

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]

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.