Appendices

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

Key: Prescribed estrogen dose for ultra-low, low, standard, moderate and high dose regimens

	Ultra-low dose	Low Dose	Standard dose	Moderate dose	High dose
Oestrogel	½ pump	1 pump	2 pumps	3 pumps	4 pumps
Sandrena	0.25 mg	0.5 mg	1 mg	1.5-2 mg	3 mg*
Lenzetto spray	1 spray	2 sprays	3 sprays	4-5 sprays*	6 sprays*
Patch	12.5 µg	25 µg	50 µg	75 µg	100 µg
Oral estradiol	0.5 mg	1 mg	2 mg	3 mg^	4 mg^

* Off-license use
mg = milligrams
^ Off-license use – rarely required to achieve symptom control
µg = micrograms

Progestogen dose per licensed estrogen dose in the baseline population

Estrogen dose	Micronised Progesterone		Medroxy progesterone		Norethisterone		LNG-IUD (52mg)
	continuous	sequential	continuous	sequential	continuous	sequential	
Ultra/Low	100 mg	200 mg	2.5 mg	10 mg	5 mg*	5 mg*	One – for up to 5 years of use
Standard	100 mg	200 mg	2.5-5 mg	10 mg	5 mg*	5 mg*	
Moderate	100 mg	200 mg	5 mg	10 mg	5 mg	5 mg	
High	200 mg+	300 mg+	10 mg^	20 mg^	5 mg	5 mg	

*1 mg provides endometrial protection for ultra-low to standard 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 moderate dose estrogen.
+There are limited evidence in relation to optimal micronised progesterone dose for moderate or high dose estrogen; until evidence is available to guide practice, the advised dose is based on studies reporting 100 mg/day providing protection with up to standard dose estrogen. If unscheduled bleeding occurs with ultra-low to moderate dose estrogen, and other progestogens are not acceptable, offer micronised progesterone at the dosage recommended for high dose estrogen.

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

- 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"

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