Refining Adjuvant treatment IN endometrial cancer Based On molecular features (RAINBO) No Specific Molecular Profile (NSMP)-ORANGE trial

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Protocol v1.0 Authorisation signatures:

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Katie Wilkinson Senior Project Manager		

Please note: This trial protocol must not be applied to patients outside the RAINBO NSMP-ORANGE trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate aminotransferase
AUC	Area Under the Curve
CCC	Country Coordinating Centre
CI	Chief Investigator
CLS	Country Lead Site
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
DSUR	Development Safety Update Report
EC	Endometrial cancer
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDTA	Ethylene Diamine Tetra Acetate
EEA	European Economic Area
ER	Estrogen (oestrogen) Receptor
EUCT No.	European Union Clinical Trial Number
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FBC	Full Blood Count
FFPE	Formalin-fixed paraffin-embedded (tissue blocks)
GDPR	General Data Protection Regulation (i.e. UK GDPR (as defined in section 3(10) (as supplemented by section 205(4)) of the Data Protection Act 2018)); and (to the extent that it applies) the General Data Protection Regulation (EU)2016/679 (EU GDPR)
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HRA	Health Research Authority
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
LFT	Liver Function Tests
LVSI	Lymph-vascular Space Invasion
MRI	Magnetic Resonance Image
MHRA	Medicines and Healthcare products Regulatory Agency
OS	Overall Survival

PI	Principal Investigator
PR	Progesterone receptor
PR-QoL	Patient Reported Quality of Life
REC	Research Ethics Committee
RFS	Recurrence Free Survival
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre

1 PROTOCOL SUMMARY

1.1 Summary of Trial Design

Title:	Refining Adjuvant treatment IN endometrial cancer Based On molecular feature (RAINBO) No Specific Molecular Profile (NSMP) – ORANGE Trial
Short Title/acronym:	RAINBO NSMP-ORANGE
Sponsor name & reference:	University College London
Funder name & reference:	NIHR154244
ISRCTN/Clinicaltrials.gov no:	NCT05255653-3
Design:	International multi-centre, randomised phase III non-inferiority trial
Overall aim:	RAINBO NSMP-ORANGE aims to investigate if adjuvant radiotherapy with oral progestin tablets is as effective as radiotherapy with chemotherapy, whilst reducing toxicity and thus improving quality of life, in patients with high-risk NSMP endometrial cancer. Patients will be randomised to radiotherapy with chemotherapy (standard of care), or radiotherapy followed by oral progestin tablets.
Primary endpoint:	3-year recurrence free survival rate (RFS)
Secondary endpoints:	• 5-year RFS • Vaginal RFS • Pelvic RFS • Para-aortic nodal RFS • Distant RFS • Cancer-specific survival • Overall survival • Treatment-related toxicity (using the Common Terminology Criteria for Adverse Events [CTCAE] version 5) • Health-related quality of life (using the validated common and endometrial cancer European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaires C30 and EN24)

Exploratory Biological Studies:	Retrospective archival tissue blocks, and blood for ctDNA will be collected
Countries and number of sites:	UK, Netherlands, France, Canada, Germany, Switzerland, India, Italy, Brazil, Greece, Czechia, Norway Approximately 50 sites in total
Target accrual:	300 patients across UK sites and an anticipated 300 across international sites. Total of 600 patients
Inclusion & exclusion criteria:	**Inclusion criteria** 1. Written informed consent and consent for data sharing for the overarching RAINBO programme 2. Histologically confirmed diagnosis of endometrial cancer (EC) of the following histotypes: endometrioid endometrial carcinoma, serous endometrial carcinoma, uterine clear cell carcinoma, dedifferentiated and undifferentiated endometrial carcinoma, uterine carcinosarcoma and mixed endometrial carcinomas of the aforementioned histotypes 3. Full molecular classification performed following the diagnostic algorithm described in WHO 2020 (5th Edition, IARC, Lyon, 2020, adapted from Vermij et al. 2020). See Appendix 2 4. Hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy or sentinel node biopsy, without macroscopic residual disease after surgery. See Section 8.3.1 5. No distant metastases as determined by pre-surgical or post-surgical imaging (CT scan of chest, abdomen and pelvis within 8 weeks of randomisation). Whole-body PET-CT scan is acceptable if this is part of standard of care at participating sites. 6. Age ≥ 18 years 7. WHO performance status 0 or 1 8. Expected start of adjuvant treatment within 10 weeks after surgery 9. Patients must be accessible for treatment and follow-up 10. Consent for the donation of a tissue block for translational research for the overarching RAINBO programme 11. FIGO (2018) stage II EC with substantial LVSI or stage III NSMP tumours 12. p53 wildtype, MMR proficient EC with no somatic pathogenic POLE variant (i.e. NSMP)

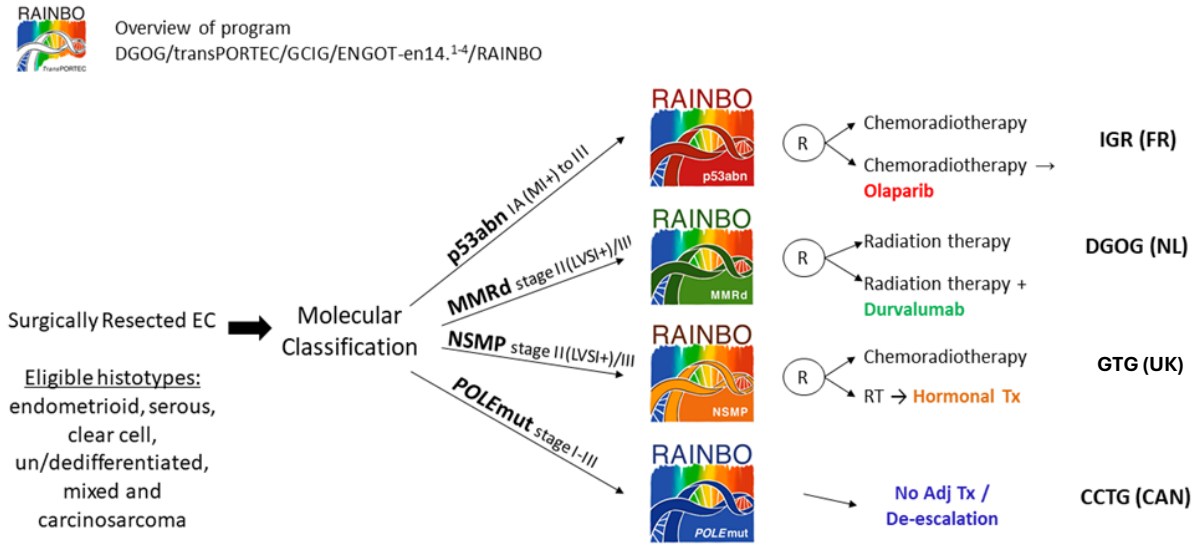
	13. ER+ by IHC (10% threshold applied) or Allred score of ≥3 14. Absolute neutrophil count (ANC) ≥1.5 x 10^9/l 15. Platelets ≥ 100 x 10^9/L 16. Bilirubin ≤ 1.5 x UNL (or ≤ 3 x ULN for cases of known Gilbert's syndrome) 17. AST/ALT ≤ 2.5 x UNL **Exclusion criteria** 1. Previous malignancy, except for non-melanoma skin cancer, in the past 5 years 2. Prior pelvic radiation 3. Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction) within previous 6 months 4. Thromboembolic event, e.g. pulmonary embolism or deep vein thrombosis, within previous 6 months 5. Impaired renal function: ≤50ml/min (EDTA clearance, or measured creatinine clearance) or creatinine clearance ≤60 ml/min (calculated according to Cockcroft gault) 6. Uncontrolled cardiac disease (defined as cardiac function which would preclude hydration during cisplatin administration and any contraindication to paclitaxel) 7. Peripheral neuropathy, ≥ grade 2 8. Inflammatory bowel disease 9. Known history of porphyria 10. History of active immune deficiency syndromes or uncontrolled HIV infection: HIV positive patients receiving effective antiretroviral therapy and CD4 count >200 may be included 11. Patients who have received a live attenuated vaccine within 2 weeks prior to planned treatment start Any other condition which as per section 4.3 of the relevant SmPC or in the opinion of the investigator contraindicates the use of chemotherapy, radiotherapy and/or oral progestin tablets 12. The patient is currently participating in another interventional clinical trial or has received an investigational drug (either approved or not approved) in any prior clinical study within 5 half-lives prior to screening

Treatment summary:	Following surgery for endometrial cancer patients with ER+ NSMP tumours will be randomised 1:1 to one of the following 2 arms: Arm A Adjuvant pelvic radiotherapy +/- vaginal brachytherapy followed by oral progestin tablets for 24 months *(investigational arm)* Arm B Adjuvant pelvic radiotherapy +/- vaginal brachytherapy with chemotherapy *(cisplatin, carboplatin and paclitaxel; standard of care arm)*
Duration of recruitment:	Five years
Duration of follow-up:	Arm A 6 monthly for 1 year following end of oral progestin tablets, then annually for 5 years Arm B 6 monthly following end of treatment for 3 years then annually to 5 years *Following disease recurrence survival status, additional treatment, further recurrence/s and new malignancies should be recorded on the eCRF annually from the date of recurrence*
Definition of end of trial:	Last patient last visit
Other related research:	Refining Adjuvant treatment IN endometrial cancer Based On molecular profile (RAINBO) is a collaborative international umbrella programme of four adjuvant treatment trials in high-risk endometrial cancer: • RAINBO MMRd-GREEN trial: Patients with mismatch repair deficient tumours will be randomised to radiotherapy alone (SOC) or radiotherapy with concurrent and adjuvant durvalumab for 1 year. • RAINBO p53abn-RED trial: Patients with p53 abnormal tumours will be randomised to chemoradiation (SOC) or chemoradiation with adjuvant olaparib for 24 months. • RAINBO POLE-BLUE trial: Patients with POLE mutant tumours will be given no adjuvant treatment or a de-escalation of treatment. RAINBO Translational work: A biobank of FFPE-blocks from hysterectomy will be sent to a central RAINBO biobank.

1.2 Trial Schema

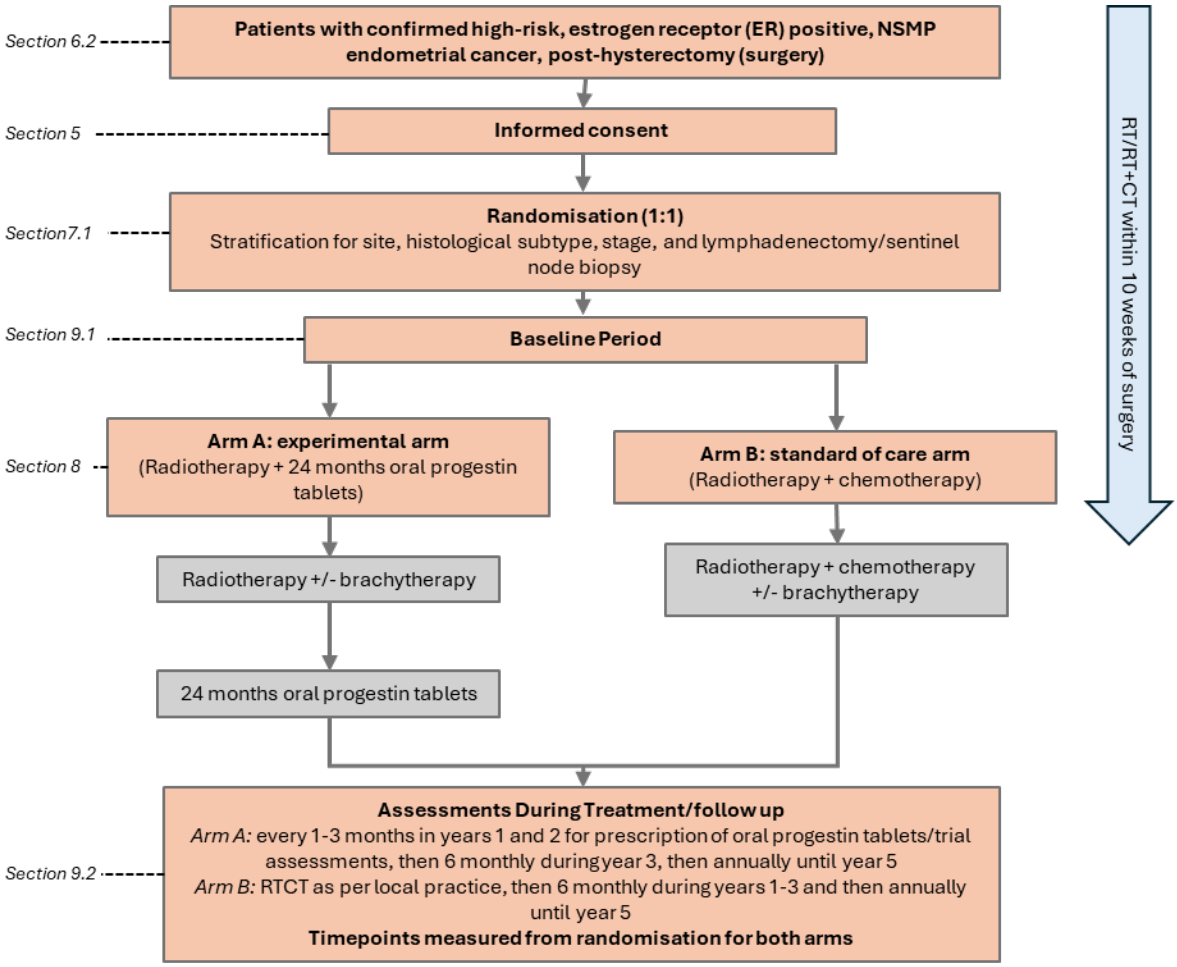
1.2.1 *RAINBO program overall design*

Refining Adjuvant treatment IN endometrial cancer Based On molecular profile (RAINBO) is a collaborative international umbrella programme of four adjuvant treatment trials in high-risk endometrial cancer:



RAINBO program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group

1.2.2 *RAINBO NSMP-ORANGE design*



2 INTRODUCTION

2.1 Background

Endometrial cancer (EC) is the 4th most common cancer in women in the UK, with almost 10,000 cases and 2,400 deaths/year [1]. Diagnoses and deaths from endometrial cancer are rising and few advances in treatment have been made over the last 20 years. The cornerstone of treatment is surgery, with adjuvant radiotherapy (RT) and sometimes chemotherapy (CT) offered to women with high-risk clinico-pathological features. The PORTEC-3 trial tested the addition of CT during and after RT (CTRT) vs RT alone in high-risk endometrial cancer in a phase III, international, randomised controlled trial. The trial published in 2018/19 and was practice-changing, showing improved overall survival (5-year OS; 81.4% vs 76.1%, HR=0.70, p=0.034) and recurrence-free survival with CTRT (5-year RFS; 76.5% vs 69.1%, HR=0.70, p=0.016) [2, 3]. This was at the expense of CT-related harms and a temporary reduction in women's quality of life [4]. In GOG-258, CTRT offered similar RFS rates to CT alone (5-year; 59% vs 58%, HR=0.90, p=0.20) but there were more nodal relapses in the CT arm, supporting the role of pelvic RT [5].

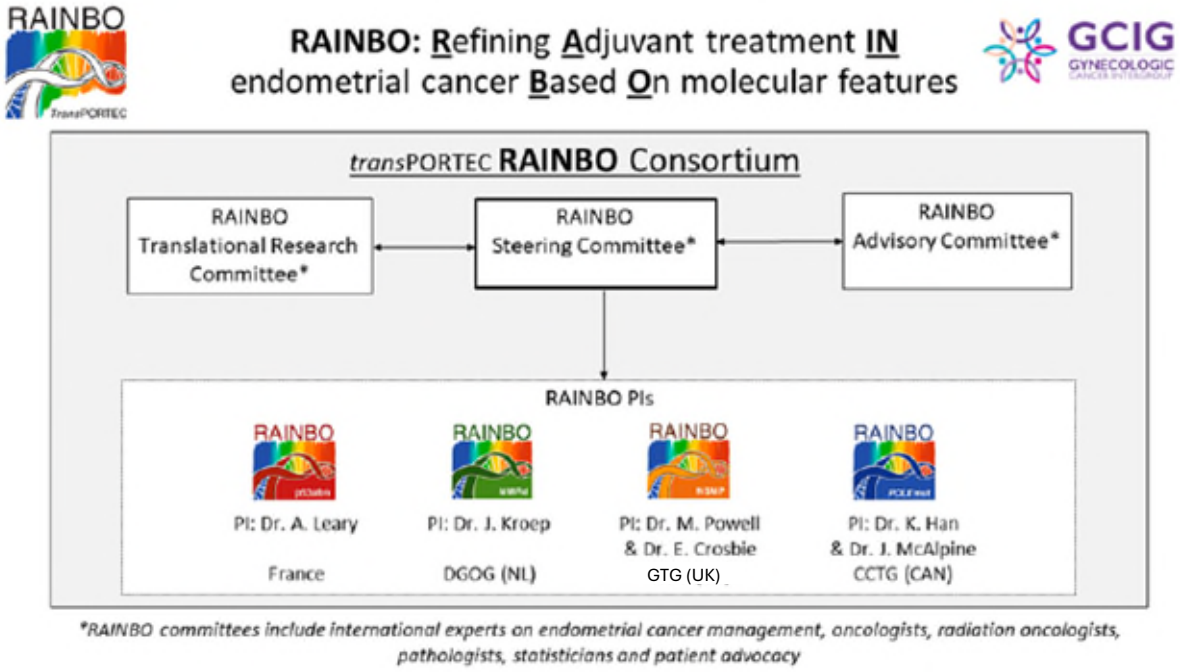
Molecular classification identifies four molecular groups of endometrial cancer with distinct prognostic profiles: p53-abnormal (p53abn), POLE-ultramutated (POLEmut), mismatch repair-deficient (MMRd) and no specific molecular profile (NSMP) [6-8]. The international TransPORTEC Consortium retrospectively classified 423/660 (64%) PORTEC-3 tumours into p53abn (23%), MMRd (33%), NSMP (31%) and POLEmut (12%) groups. Molecular classification had strong prognostic value with 5-year RFS of 48% for p53abn, 72% for MMRd, 74% for NSMP and 98% for POLEmut tumours (p<0.001) [9]. It showed for the first time that molecular group predicts benefit from adjuvant CTRT. Patients with p53abn tumours derived significant benefit from CTRT (RFS HR=0.52, p=0.02; OS HR=0.55, p=0.049), while those with POLEmut tumours had excellent outcomes anyway (5-year RFS and OS both 100% vs 97%). No benefit was found from CTRT for MMRd tumours (RFS HR=1.29, p=0.43; OS HR=1.33, p=0.45 and a trend towards benefit for NSMP tumours was seen although this was not statistically significant (RFS HR=0.68, p=0.25; OS HR=0.68, p=0.43) [9].

Molecular classification has been integrated into the 2020 World Health Organization (WHO) diagnostic classification and European (ESGO/ESTRO 2022) treatment guidelines and provides direction towards more effective and less toxic adjuvant treatment strategies for women with endometrial cancer [1]. However, there are no prospective data regarding the use of molecular group for adjuvant therapy decisions in high-risk endometrial cancer.

For the 32% of women included in PORTEC-3 with NSMP endometrial cancer, a 5-year RFS of 80% after CRT and 68% after RT was found [9]. This apparent improvement in RFS did not reach statistical significance (HR 0.68, 95% CI 0.36 to 1.30, p=0.25). This leaves uncertainty as to the clinical benefit of CT, particularly when considering the potential negative impact on functioning and symptoms[4]. For example, in PORTEC-3, grade ≥3 toxicity was observed in 61% after CRT compared with 13% after RT alone (p<0.0001) and, even 5 years after CRT, women still reported significantly more grade 2 toxicity[4, 10]. Therefore, research into less toxic alternatives for CT is important. Hormonal treatment has a relatively mild toxicity profile and is an attractive alternative because the majority of high-risk NSMP endometrial cancers are of the endometrioid

histotype and hormone receptor positive (estrogen receptor 85%, progesterone receptor 73%)[11]. Hormonal treatment is currently the first-line systemic therapy in patients with recurrent and metastatic endometrial cancer without rapidly progressive disease. Progestins are generally recommended[12], and yield an objective response in ~25% of patients and clinical benefit in ~50%[13]. There are no recent trials of adjuvant hormone therapy in endometrial cancer. A meta-analysis of seven randomised studies from the 1980s showed no significant impact on overall survival (OS)[14]. However, most of the participants had low- and intermediate-risk disease. It is also likely that ~50% of included patients had molecular profiles less likely to benefit from hormonal treatment (p53abn, MMRd, POLEmut). The most comparable study was the COSA trial [15], which included over 1,000 women who received adjuvant progestogen for three years. A duration of 24 months was selected for this study to balance potential efficacy with the risk of toxicity, while also aiming to optimise patient compliance.

2.1.1 *RAINBO consortium structure*



3 TRIAL DESIGN

The UK-led RAINBO NSMP-ORANGE trial is an international, randomised-controlled Phase III non-inferiority trial. Eligible patients with estrogen receptor positive (ER+) (using a cut-off of 10%), stage II NSMP endometrial cancer (EC) with substantial LVSI or with stage III NSMP EC (POLE wild type, MMR proficient and p53 wild type) will be randomised 1:1 to radiotherapy with oral progestin tablets for 24 months (investigational arm) or radiotherapy with chemotherapy (standard of care arm) with stratification for site, histological subtype, stage, and lymphadenectomy/sentinel node biopsy. The oral progestin tablets used will be either medroxyprogesterone acetate or megestrol acetate, according to local practice.

3.1 Trial Objectives

RAINBO NSMP-ORANGE aims to investigate whether adjuvant radiotherapy with oral progestin tablets is as effective as radiotherapy with chemotherapy, whilst reducing toxicity and thus improving quality of life, in patients with high-risk NSMP endometrial cancer.

3.2 Trial Endpoints

Primary Endpoint

- 3-year recurrence-free survival (RFS)

Secondary Endpoints

- 5-year RFS
- Vaginal RFS
- Pelvic RFS
- Para-aortic nodal RFS
- Distant RFS
- Cancer-specific survival
- Overall survival
- Treatment-related toxicity (using Common Terminology Criteria for Adverse Events [CTCAE] Version 5)
- Health-related quality of life (using the validated common and endometrial cancer European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaires C30 and EN24)

3.3 Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
- **'**Adoption' into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4 SELECTION OF SITES/SITE INVESTIGATORS

4.1 Site Selection

In this protocol, trial "site" refers to a hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow-up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority and the Medicines for Human Use Clinical Trials) Regulation (SI 2004/1031) and all amendments
- Data collection requirements, including adherence to eCRF submission timelines as per Section 11
- Biological sample collection, processing and storage requirements
- Monitoring requirements, as outlined in protocol Section 14
- Non-UK sites: all local regulations governing clinical trials

4.1.1 *Selection of Principal Investigator and other investigators at sites*

Each site must appoint an appropriate Principal Investigator (PI), i.e., a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of the site. Co-investigators must be trained and approved by the PI. All PIs and co-investigators must be medical doctors and have experience of treating endometrial cancer**.** The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. **If a PI plans to take a leave of absence, UCL CTC must be informed promptly.** For absences greater than three months, or where the PI is no longer able to perform their duties at the site, a new suitable replacement PI must be identified by the site and UCL CTC notified.

UCL CTC may terminate recruitment at a site where a suitable replacement PI has not been identified within three months.

4.1.2 *Training requirements for site staff*

All site staff must be appropriately qualified by education, training and experience to perform the trial-related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up to date, signed and dated, and copies held in the Investigator Site File (ISF). A current, signed copy of the CV with evidence of GCP training (or copy of GCP certificate) for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or two yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.1.3 *Site initiation*

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site-by-site visit or video conference. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient.

4.1.4 *Required documentation*

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- A signed and dated copy of the PI's current CV (with documented up to date GCP training, or copy of GCP training certificate)

In addition, the following agreements must be in place:

- For UK sites: a signed site agreement between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)
- For non-UK sites: a signed international site agreement.
- For countries with a country coordinating centre (CCC):
    - a signed international country coordinating centre agreement
    - a signed clinical trial agreement between the CCC and the relevant institution (site)

4.1.5 *Site activation*

Once the UCL CTC trial team has received all required documentation and the site has been initiated, notification of site activation will be issued to the PI, at which point the site may start to approach patients.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol
- all relevant site staff are trained in the protocol requirements
- appropriate recruitment and medical care of patients in the trial
- timely completion of eCRFs (including assessment of all adverse events)
- prompt notification and assessment of all serious adverse events
- that the site has facilities to provide **24-hour medical advice** for trial patients

5 INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheets, are fully informed about the trial, and have confirmed their willingness to take part in the trial by signing the current approved consent form.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an independent interpreter/NHS approved translator would be required to ensure fully informed consent. If a patient requires an interpreter and none are available prior to consent, and for the duration of the potential patient's time on the trial, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheets for the trial should be discussed with the patient.

A minimum of twenty-four (24) hours must be allowed for the patient to consider and discuss participation in the trial. However, to prevent unnecessary return visits, patients may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and its implications. A member of the research team at the site must then phone the patient in the following days to confirm that they are still willing to participate in the trial.

Written informed consent on the current approved version of the consent forms for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient medical notes.

Site staff are responsible for:

- checking that the current approved version of the patient information sheets and consent forms are used
- giving the patient a copy of the patient information sheet
- checking that information on the consent forms is complete and legible
- checking that the patient has completed and initialled all relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the consent forms to confirm that they provided information to the patient
- giving the patient a copy of their signed consent form
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)
- following creation on the OpenClinica database, adding the patient's trial number to all copies of the consent forms, which should be filed in the patient's medical notes and investigator site file

- following randomisation, giving the patient a copy of the patient diary and patient contact card

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to Section 15.

Additionally, non-UK Sites will need to consent patients to the trial according to any other local practice and regulatory and/or ethical requirements.

6 SELECTION OF PATIENTS

6.1 Screening

A screening log must be maintained and appropriately filed at site. Sites should record each patient screened for the trial/all patients identified with ER+ NSMP endometrial cancer and the reasons why they were not consented in the trial if this is the case. The log must be sent to UCL CTC when requested.

Note: ER+ NSMP patients that are found not to be eligible for the RAINBO NSMP-ORANGE trial may be considered for additional RAINBO NSMP-ORANGE studies. Please contact UCL CTC for further information.

6.2 Patient Eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria must be addressed prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patients' eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to randomising the patient. Confirmation of eligibility must be documented in the patients' medical notes and on the randomisation eCRF.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to Section 9.1 for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1 *Inclusion criteria*

Key inclusion criteria for RAINBO program:

1. Written informed consent and consent for data sharing for the overarching RAINBO programme
2. Histologically confirmed diagnosis of endometrial cancer (EC) of the following histotypes: endometrioid endometrial carcinoma, serous endometrial carcinoma, uterine clear cell carcinoma, dedifferentiated and undifferentiated endometrial carcinoma, uterine carcinosarcoma and mixed endometrial carcinomas of the aforementioned histotypes
3. Full molecular classification performed following the diagnostic algorithm described in WHO 2020 (5th Edition, IARC, Lyon, 2020, adapted from Vermij et al. 2020). See Appendix 2
4. Hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy or sentinel node biopsy, without macroscopic residual disease after surgery. See Section 8.3.1
5. No distant metastases as determined by pre-surgical or post-surgical imaging (CT scan of chest, abdomen and pelvis within 8 weeks of randomisation). Whole-body PET-CT scan is acceptable if this is part of standard of care at participating sites

6. Age ≥ 18 years
7. WHO performance status 0 or 1
8. Expected start of adjuvant treatment within 10 weeks after surgery.
9. Patients must be accessible for treatment and follow-up
10. Consent for the donation of a tissue block for translational research for the overarching RAINBO programme

Inclusion criteria specific for RAINBO NSMP-ORANGE Trial:

11. FIGO (2018) stage II EC with substantial LVSI or stage III NSMP tumours
12. p53 wildtype, MMR proficient EC with no somatic pathogenic POLE variant (i.e. NSMP)
13. ER+ by IHC (10% threshold applied) or Allred score of ≥3
14. Absolute neutrophil count (ANC) ≥1.5 x 10^9/l
15. Platelets ≥ 100 x 10^9/L
16. Bilirubin ≤ 1.5 x UNL (or ≤ 3 x ULN for cases of known Gilbert's syndrome)
17. AST/ALT ≤ 2.5 x UNL

6.2.2 *Exclusion criteria*

Exclusion criteria for RAINBO Program

1. Previous malignancy, except for non-melanoma skin cancer, in the past 5 years
2. Prior pelvic radiation

Exclusion criteria specific for RAINBO NSMP-ORANGE Trial:

3. Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction) within previous 6 months
4. Thromboembolic event, e.g. pulmonary embolism or deep vein thrombosis, within previous 6 months
5. Impaired renal function: ≤50ml/min (EDTA clearance, or measured creatinine clearance) or creatinine clearance ≤60 ml/min (calculated according to Cockcroft gault)
6. Uncontrolled cardiac disease (defined as cardiac function which would preclude hydration during cisplatin administration and any contraindication to paclitaxel)
7. Peripheral neuropathy, ≥ grade 2
8. Inflammatory bowel disease
9. Known history of porphyria
10. History of active immune deficiency syndromes or uncontrolled HIV infection: HIV positive patients receiving effective antiretroviral therapy and CD4 count >200 may be included

11. Patients who have received a live attenuated vaccine within 2 weeks prior to planned treatment start
12. Any other condition which as per section 4.3 of the relevant SmPC or in the opinion of the investigator contraindicates the use of chemotherapy, radiotherapy and/or oral progestin tablets
13. The patient is currently participating in another interventional clinical trial or has received an investigational drug (either approved or not approved) in any prior clinical study within 5 half-lives prior to screening

6.3 Pregnancy and birth control

Patients in the RAINBO NSMP-ORANGE Trial will have had previous hysterectomy for endometrial cancer (inclusion criteria 4, Section 6.2.1). Therefore, no women of childbearing potential (WOCBP) will be enrolled in the study.

Guidance for pregnancy and birth control is not applicable on this study.

7 RANDOMISATION PROCEDURES

7.1 Randomisation

Randomisation method	Minimisation
Stratification factors	Site Histological subtype (grade [1-2] vs high grade [3] and non-endometroid or mixed carcinomas) Stage (II vs III) Lymphadenectomy/sentinel node staging (yes vs no)
Ratio	1:1
Trial arms	Arm A Adjuvant pelvic radiotherapy +/- vaginal brachytherapy followed by oral progestin tablets for 24 months (investigational arm) Arm B Adjuvant pelvic radiotherapy +/- vaginal brachytherapy with chemotherapy (cisplatin, carboplatin and paclitaxel; standard of care arm)

Patient randomisation will be undertaken via a remote data capture system called OpenClinica (OC) hosted by UCL CTC. This must be performed following consent, screening assessments and confirmation of the eligibility of a patient at site, and prior to commencement of any trial treatment. Screening assessments should be carried out at sites as detailed in Section 9.1.

Please refer to the Trial Guidance Document (a separate document) for details on how training on OpenClinica is provided, the process of randomisation, and how confirmation of randomisation will be provided to site.

Site staff responsible for patient randomisation must request access to the OpenClinica database by completing their contact details on the Database User Access Form (see also The Trial Guidance Document). They must also be assigned this responsibility on the site staff delegation log. Access to the database will be provided by UCL CTC upon receipt of completed forms. Sites should contact UCL CTC via e-mail if there are any difficulties in accessing the randomisation database (OpenClinica).

UCL CTC Telephone number and email for queries relating to Randomisation:	0207 679 9808 ctc.nsmp-orange@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays (UK Time)

Once a patient has been randomised onto the trial they must be provided with the following:

- **A patient contact card.** Site contact details for 24-hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial.

- **Patients in Arm A:**
    - A patient diary. Patients may use this to record any missed doses of medroxyprogesterone or megestrol acetate, and any adverse events or other issues they may experience.

- **Patients in Arm B:**
    - A patient diary. Patients may use this to record any adverse events or other issues they may experience.

After randomisation into the trial, the patient's general practitioner (GP) should be informed of the patient's involvement in the trial by the site completing and sending the completed GP letter.

7.2 Initial Trial Drug Supply

All trial drugs are to be supplied from Hospital Commercial Stock as detailed in the Pharmacy Manual document.

8 TRIAL TREATMENT

Investigational Medicinal Products (IMPs)

For the purpose of this protocol, the IMPs are:

- Medroxyprogesterone acetate **or** megestrol acetate (dependent on local practice)
- Cisplatin
- Carboplatin
- Paclitaxel

There are no restrictions on the brand of IMP.

Please also refer to the Pharmacy Manual for full arrangements for the trial.

Non-Investigational treatment

The following is administered as part of standard of care:

- Radiotherapy (+/- vaginal brachytherapy)

8.1 Investigational Medicinal Products

Medroxyprogesterone acetate and megestrol acetate are currently licensed for use in the treatment of endometrial cancer. They will **not be** provided for the trial and so hospital stock should be used. The MHRA have granted an Annex 13 labelling exemption to medroxyprogesterone acetate and megestrol acetate. Cisplatin, carboplatin and paclitaxel are currently licensed for use in the treatment of endometrial cancer. They will **not be** provided for the trial; hospital stock should be used. An Annex 13 label is not required for cisplatin, carboplatin or paclitaxel.

8.2 Treatment Summary

Patients with surgically resected stage II endometrial cancer and substantial LVSI or stage III endometrial cancer and who meet all eligibility criteria will be randomised to receive either:

- Arm A: Adjuvant pelvic radiotherapy +/- vaginal brachytherapy followed by oral progestin tablets for 24 months *(investigational arm)*
- Arm B: Adjuvant pelvic radiotherapy +/- vaginal brachytherapy with chemotherapy *(cisplatin, carboplatin and paclitaxel; standard of care arm)*

8.3 Trial Treatment Details

8.3.1 *Surgery*

Surgery is carried out as part of standard of care prior to study entry. The standard surgical procedure is open, laparoscopic, or robot-assisted total hysterectomy with bilateral salpingo-oophorectomy and biopsy with histological verification in case of any clinically suspicious lesions (such as peritoneal deposits or lymph nodes). Diagnostic staging lymphadenectomy and/or sentinel node biopsy are at the discretion of the participating centre or group.

Lymph node debulking with or without para-aortic lymph node sampling is recommended in case of macroscopic positive pelvic nodes and/or para-aortic nodes, as detected on pre-surgical CT or MRI scans or intra-operatively. Other extra-uterine tumour deposits should also be completely removed.

At the completion of the operation there should be no remaining macroscopic tumour.

8.3.2 *Arm A: investigational arm*

Adjuvant pelvic radiotherapy (external beam +/- brachytherapy) followed by oral progestin tablets, either medroxyprogesterone acetate or megestrol acetate. (Figure 1)

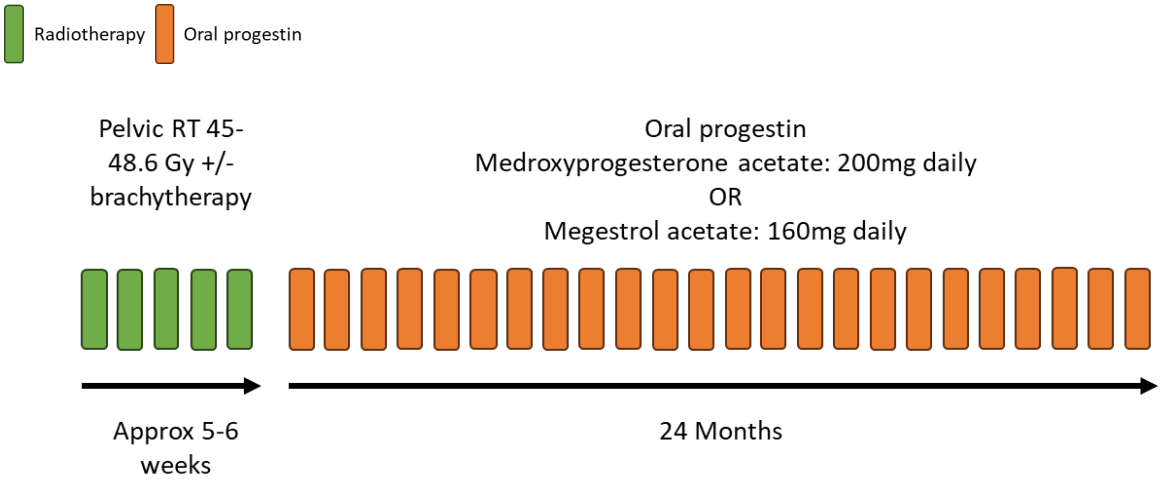
Treatment with radiotherapy (external beam +/- brachytherapy) should commence within 6 to 8 weeks after surgery, but no later than 10 weeks. Oral progestin tablets should commence on completion of radiotherapy. Start may be delayed until radiation toxicity is less than grade 2 but should commence within 4 weeks following completion of radiotherapy.

Radiotherapy and brachytherapy
See Section 8.3.4 and 8.3.5 for details of radiotherapy and brachytherapy.

Oral progestin tablets
Medroxyprogesterone acetate or megestrol acetate will be given in the doses and schedule illustrated below, according to standard practice in the participating centre. The choice of oral progestin tablets will be as per local practice.

Agent	Dose/day	Route	Time /Days
Medroxyprogesterone acetate	200mg OD	oral	24 months (days 1-730)
Megestrol acetate	160mg OD	oral	24 months (days 1-730)

8.3.2.1 Figure 1: radiotherapy and oral progestin tablets



Arm B, standard of care arm, can be found on the next page.

8.3.3 *Arm B: standard of care arm*

Sequential radiotherapy and chemotherapy is preferably given according to the PORTEC-3 regimen and should be started within 6 to 8 weeks after surgery and no later than 10 weeks: two cycles of intravenous cisplatin 50mg/m² in the first and fourth week of the pelvic external beam radiotherapy (EBRT) +/- vaginal brachytherapy followed by four cycles of intravenous carboplatin AUC 5 and paclitaxel 175 mg/m² at 21-day intervals. (Figure 2, overleaf)

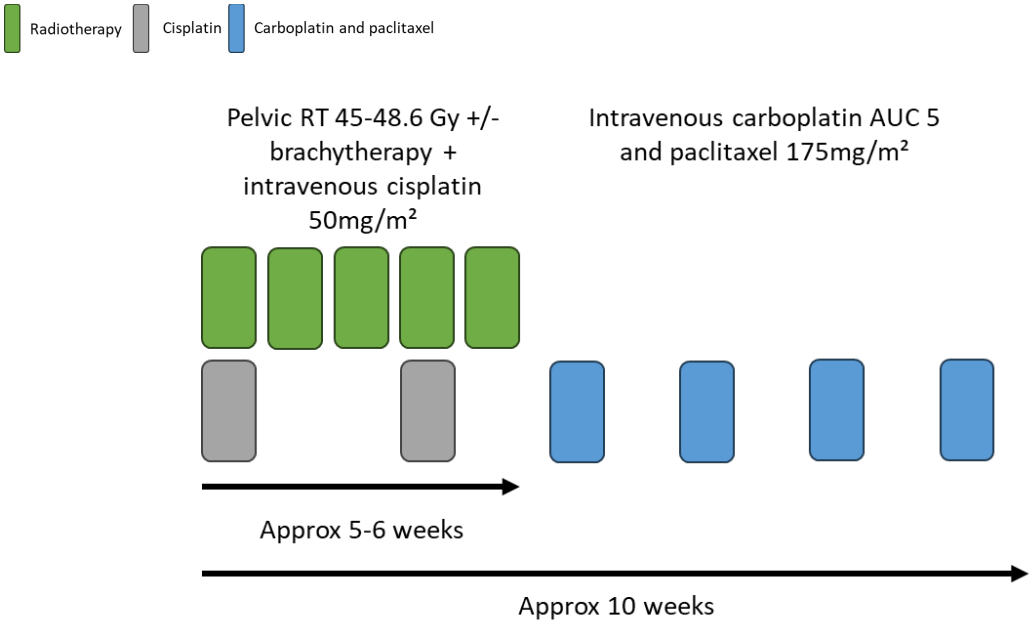
However the sequence of chemotherapy, number of cycles and inclusion of cisplatin may be altered according to local practice at the investigator's discretion.

This may include;

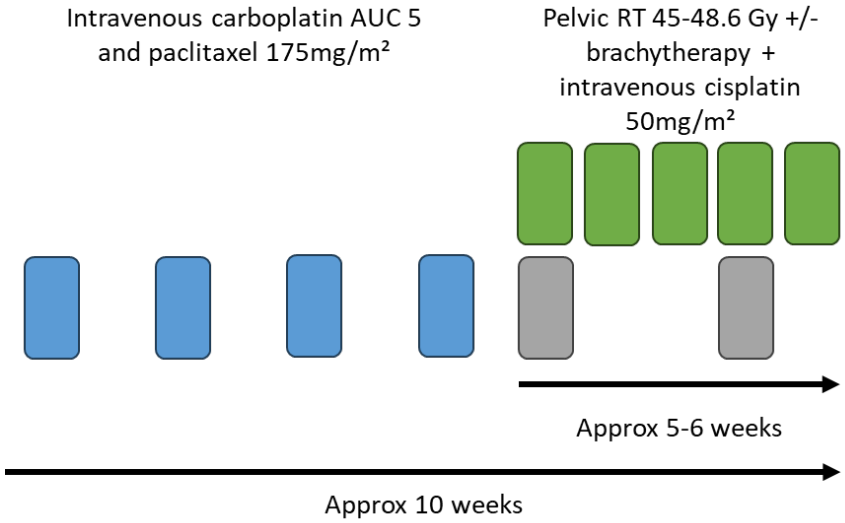
- 4 cycles carboplatin & paclitaxel before or after radiotherapy with 2 cycles cisplatin
- 4 cycles carboplatin & paclitaxel before or after radiotherapy (no cisplatin)
- 6 cycles carboplatin & paclitaxel before or after radiotherapy (no cisplatin)

If chemotherapy is to be given before radiotherapy it should be started within 6 to 8 weeks after surgery and no later than 10 weeks. This should be followed 3 to 4 weeks later with EBRT +/- vaginal brachytherapy with or without cisplatin in weeks 1 and 4. Radiotherapy planning should be commenced shortly before or just after infusion of the final cycle of carboplatin and paclitaxel to avoid unnecessary delay. See Figure 3 for example of an alternative schedule.

8.3.3.1 Figure 2: Radiotherapy with chemotherapy: PORTEC-3 schedule



8.3.3.2 Figure 3: Radiotherapy with chemotherapy: example of an alternative schedule



Details of the radiotherapy with chemotherapy schedule must be recorded on the eCRF.

Radiotherapy and brachytherapy
See Section 8.3.4 and 8.3.5 for details of radiotherapy and brachytherapy.

8.3.4 *External Beam Radiotherapy (EBRT)*

The dose schedule for adjuvant EBRT should range between 45-48.6 Gy, with fraction size of 1.8-2.0 Gy per fraction, 5 fractions a week. Treatment should preferably be started within 6 to 8 weeks after surgery, but no later than 10 weeks. Treatment breaks should be avoided, and treatment time for EBRT should be kept within 5-6 weeks. Treatment prolongation due to public holidays and machine maintenance should not exceed 2-4 days.

Target volume and technique

Radiotherapy planning will use intensity-modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT) or tomotherapy with appropriate QA according to the treating centre's standard policy.

Planning scans will be obtained in treatment position with (comfortably) full bladder; if desired full and empty bladder scans may be used to create an internal target volume (ITV) to account for movement of the vaginal vault region [Small 2021]. The full bladder scan should be used for treatment planning.

Individualised target volume and organ-at-risk contouring must be done for all patients.

Contouring of the Clinical Target Volume (CTV) should be done according to literature data and atlases and taking
institutional preferences and practices into account. Useful guidelines and contouring atlas can be found at:

- RTOG website (NRG Oncology/RTOG consensus guidelines)
- and in the publications by Small and Taylor (Small IJROBP 2021; Taylor 2005; Taylor 2007)

Organs at risk to be contoured are the bladder, rectum, sigmoid, bowel bag (excluding sigmoid) and the femoral heads.

The CTV includes the proximal half of the vagina and the paravaginal/parametrial soft tissues. Where vaginal tumour has been removed the full length of the vagina should be encompassed.

In node negative cases the nodal CTV includes the internal and external iliac lymph node regions, as well as the distal third to half of the common iliac lymph node region. Inclusion of the subaortic pre-sacral nodes is recommended for tumours with pelvic lymph node involvement, cervical stromal involvement, or vaginal involvement.

In case of external or internal iliac lymph node involvement the common iliac lymph node regions are to be included up to the aortic bifurcation.

In case of common iliac node involvement, the entire para-aortic region should be considered for inclusion in the target volume. At the very least the lower para-aortic region must be included.

In case of para-aortic involvement, the para-aortic lymph node region should include the higher para-aortic region at least 1cm above the renal vessels (ideally a margin of at least 2 cm above the highest lymph node region involved). [Small et al. IJROBP 2021]

Dose specification, planning and homogeneity requirements should be done according to ICRU-report 83. The dose in the CTV, Planning Target Volume (PTV) and organs at risk should be recorded and DVHs should be generated. At least 95% of the prescribed dose should cover >98% of the PTV (aiming for >99%). The maximum dose received by 2% of the PTV should not exceed 107 % of the prescribed dose. Suggested dose constraints for organs at risk are provided in Table 1, below.

PTV consists of the CTV/ITV with a 5-7 mm margin, depending on the type of position verification and institutional practice. Daily position verification using cone beam CT is strongly recommended. A ‘library of plans’ technique with daily selection of the most appropriate treatment plan is permitted if standard for the treating centre.

Dose aims and constraints can be found on the next page

Organ at risk	Dose Volume	Limit	Type
Bowel			
- RT pelvic area	V30Gy	< 500 cc	constraint
- RT pelvic + PAO area	V30Gy	< 650 cc	constraint
	V30Gy	< 350 cc	aim
	V40Gy	< 250 cc	aim
Sigmoid	V45Gy	< 60%	aim
Bladder	V40Gy	< 75%	aim
	V30Gy	< 85%	aim
Rectum	V30Gy	< 95%	aim
	V40Gy	< 80%	aim
Spinal canal	V48Gy	< 0.03 cc	constraint
Femur head	Dmax	< 48.6 Gy	aim
Kidney	Dmean	< 15 Gy	constraint
		< 10 Gy	aim
	V12Gy	< 55%	constraint
Body	Dmax	107%	constraint

TABLE 1. RAINBO dose aims and constraints for external beam radiotherapy. Abbreviations: D = dose; PAO = para-aortic; RT = radiotherapy; V = volume

8.3.5 *Brachytherapy*

A brachytherapy boost is recommended in patients with documented cervical involvement, and otherwise is as per the investigator's choice. Brachytherapy should be either incorporated within the last week of EBRT (not giving both on the same day) or be given in the first week after completion of EBRT (high dose-rate [HDR] sessions ideally immediately following completion of EBRT). Overall treatment time for radiotherapy (EBRT and brachytherapy) should not exceed 49 days. Brachytherapy is given with a vaginal cylinder or vaginal ovoids or ring applicator, according to the centre's standard technique. When using a cylinder, the active length will ideally be 2-4 cm, with the reference isodose covering the proximal 2.5-4cm of the vagina. In the case of vaginal involvement a longer length is likely to be treated.

High-dose-rate (HDR) and pulse-dose-rate (PDR) schedules are permitted, delivering an EQD2 equivalent dose of 8-14 Gy at 5 mm from the vaginal mucosa (to obtain a cumulative EDQ2 of 60 Gy at 5 mm). Example of a schedule: HDR 8-10 Gy in 2 fractions.

8.3.6 *Toxicity of irradiation*

Irradiation can give acute and late reactions, such as irritation of the bladder, mucous membranes and bowel. Patients should be regularly reviewed during radiotherapy with acute toxicity managed according to local practice. This may include dietary measures, anti-diarrhoea medication and analgesia.

8.3.7 *Radiotherapy Quality Assurance*

There is no formal radiotherapy quality assessment in this study. It is assumed that the majority of participating centres have extensive experience with quality assessment of external beam radiotherapy and brachytherapy in clinical trials for both endometrial (PORTEC trials) and cervical cancer (EMBRACE and INTERLACE). Guidance in line with these trials and standard international practice is provided in this protocol for both external beam radiotherapy and brachytherapy. If required, additional assistance for individual centres can be obtained by contacting UCL CTC.

8.4 Dose Modifications

8.4.1 *Medroxyprogesterone acetate/megestrol acetate*

In the case of a suspected toxicity, medroxyprogesterone acetate/megestrol acetate can be stopped for up to 28 days. Medroxyprogesterone acetate/megestrol acetate can be re-introduced at the same dose once the patient has recovered or at the site investigator's discretion.

Any treatment breaks of 5 days or over should be recorded on the eCRF. See the Trial Guidance Document for further information.

8.4.2 *Radiotherapy and brachytherapy*

Treatment toxicity can be managed according to local practice.

Treatment delays should be recorded on the eCRF. See the Trial Guidance Document for further information.

8.4.3 *Chemotherapy*

Treatment toxicity can be managed according to local practice.

Treatment delays should be recorded on the eCRF. See the Trial Guidance Document for further information.

Please contact UCL CTC for further advice regarding trial treatment if required.

8.5 Management of Adverse Events

Medroxyprogesterone acetate and megestrol acetate toxicities are well recognised. A list of expected toxicities can be found in the approved reference safety information (SmPC) at the time of clinical trial application and subsequent amendments, if applicable.

Cisplatin, carboplatin and paclitaxel are in routine clinical use and toxicities are also well recognised. A list of expected toxicities can be found in the approved reference safety information (SmPC) at the time of clinical trial application and subsequent amendments, if applicable.

If guidance is required regarding management of adverse events, please contact UCL CTC.

8.6 Supportive Care

Supportive care during chemotherapy and radiotherapy +/- brachytherapy can be managed according to local guidelines. The use of G-CSF for neutropenia during chemotherapy is permitted.

If guidance is required regarding supportive care, please contact UCL CTC.

8.7 Contraindications

Any other concurrent anti-cancer therapy, including investigational agents, while on study treatment.

- Any investigational anticancer therapy other than those under investigation in this study
- Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study
- Immunosuppressive medications including, but not limited to methotrexate, azathioprine, and tumour necrosis factor-α blockers
- Live attenuated vaccines should not be given whilst the patient receives chemotherapy or for 3 months after
- Patients should not donate blood while participating in this study, or for at least 90 days following the last hormone tablet
- Natural/herbal products or other traditional remedies should be discouraged

Medroxyprogesterone acetate and megestrol acetate

Contraindications can be found in the approved reference safety information (SmPC) at the time of clinical trial application and subsequent amendments, if applicable. Also refer to the exclusion criteria for the trial (Section 6.2.2).

Cisplatin, Carboplatin and Paclitaxel

Contraindications can be found in the approved reference safety information (SmPC) at the time of clinical trial application and subsequent amendments, if applicable. Also refer to the exclusion criteria for the trial (Section 6.2.2).

8.8 Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

8.8.1 *Drug supply*

All IMPs will be supplied from hospital stock.

Please refer to the Pharmacy Manual for further information relating to the following:

- suppliers
- ordering
- labelling
- storage
- preparation and handling
- destruction of each IMP

8.8.2 *IMP accountability*

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include participant accountability logs for medroxyprogesterone acetate and megestrol acetate, including dispensing, returned medication, reconciliation, and destruction of returned/unused medication. Participant accountability forms will be supplied, and must be used, unless there is prior agreement from UCL CTC to use alternative in-house records.

Copies of completed participant drug accountability logs must be submitted to UCL CTC for all trial patients upon request. Also refer to Section 14.1.As cisplatin, carboplatin and paclitaxel are supplied from hospital stock as part of standard of care, copies of accountability logs will not be collected by UCL CTC.

The site pharmacy will be required to ensure that appropriate records are maintained, according to their local policies and procedures, to ensure traceability of the movement and administration of all IMPs to patients.

8.9 Clinical Management after Treatment Discontinuation

If a patient discontinues trial treatment early, they will remain on trial for follow-up purposes unless they explicitly withdraw consent. Also refer to Section 9.3 and Section 15 for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

9 ASSESSMENTS

9.1 Baseline Period

The following are required in order for the patient to be considered for the trial:

- Molecular classification of either pre-operative biopsy or hysterectomy specimen (ER+ NSMP). See Appendix 2
- Availability of either pre-operative biopsy or hysterectomy FFPE (formalin-fixed paraffin-embedded) sample, to be shipped to central labs following informed consent (see the Trial Guidance Document for shipping instructions)

The above assessments are part of the standard of care, therefore availability of a suitable tissue block and confirmation of molecular classification can be confirmed prior to study entry/informed consent. **The tissue block for translational research should only be retrieved and sent to central labs following provision of informed consent**.

Progesterone receptor (PR) status should also be recorded on the eCRF if available: this does not confirm eligibility but may inform likelihood of treatment success.

The following assessments are required to evaluate the suitability of patients for the trial and should be obtained **within 28 days prior to randomisation and following provision of informed consent:**

- WHO Performance status
- Age, height, and weight
- Physical and pelvic examination
- Chest/abdomen/pelvis CT (**within 8 weeks of randomisation**)
- Medical history/co-morbidity (NCI, Appendix 5)
- Review of concomitant medication
- Vital signs including blood pressure
- Full blood count – including ANC, haemoglobin and platelets
- Biochemistry – CA125, urea, creatinine/GFR, sodium, potassium, total bilirubin, alkaline phosphatase, ALT, AST
- Demographics (*age, ethnicity and post-code* - collected on the consent form and to be recorded on the eCRF)

The following assessments should be completed **at the time of randomisation:**

- PR-QoL (EORTC QLQ C30 and EN24)
- **Optional** NIHR Equality Diversity and Inclusion (EDI) Survey (see Section 19.5)
- Treatment characteristics (details of surgery and planned radiotherapy, chemotherapy/oral progestin tablets to be recorded on the eCRF)

- Adverse events/toxicity (CTCAE v4.03, including grade). Patients on both arms should also be given a patient diary to record any adverse events while on the trial, and for Arm A patients to record any missed doses of oral progestin tablets.

9.2 Trial Specific Assessments

Please also see Schedule of Events (Table 2, Section 9.5 on page 42).

During initial radiotherapy (Arms A and B) and chemotherapy (Arm B) patients should be seen as per routine clinical practice/as required. Clinical examination, blood tests and other investigations should be as per standard of care.

Any suspicious findings, however, should be investigated in accordance with routine clinical care and may, for example, include additional imaging and biopsy.

Recurrence will be classified as vaginal, pelvic nodal, para-aortic nodal or distant (metastatic) according to site. RFS is defined as the length of time from date of randomisation to date of any recurrence (local or distant) or date of death due to any cause. See Appendix 3 for further details.

Patients will be seen for trial specific procedures and assessments at the following timepoints. All trial visits are calculated from the date of randomisation:

Timepoint	***Assessments***	***Notes***
Month 2-3 following randomisation: visit must be completed on completion of radiotherapy, or within 4 weeks following completion of radiotherapy.	• Physical and pelvic examination • Review of concomitant medication • WHO performance status • Weight • QoL (EORTC QLQ C30 and EN24) • Adverse events/Toxicity • **Arm A only:** collection of blood tube for ctDNA (20ml) and first prescription of oral progestin	Oral progestin tablets: start may be delayed until radiation toxicity is less than grade 2 but should commence within 4 weeks following completion of radiotherapy. See Section 8.3.2 for further information on oral progestin tablets Concomitant medication should be reviewed but entry on to the eCRF is not required. Toxicity/AEs should be entered on to the eCRF See Trial Guidance Document for further instructions for ctDNA collection

Every 1-3 months for 24 months **(<u>Arm A only</u>)**	• Prescription of oral progestin tablets according to local practice (patients remain on oral progestin treatment for 24 months following completion of RT) • Toxicity and concomitant medication assessment	Concomitant medication should be reviewed but entry on to the eCRF is not required Toxicity/AEs should be entered on to the eCRF QoL completion is not required at these interim visits
Month 6	• Physical and pelvic examination • Review of concomitant medication • WHO performance status • Weight • QoL (EORTC QLQ C30 and EN24) • Adverse events/Toxicity • **Arm A:** blood tests **(***see notes column*) • **Arm A:** blood pressure **Arm B only:** collection of blood tube for ctDNA (20ml) – this must be taken following completion of RTCT	Concomitant medication should be reviewed but entry on to the eCRF is not required. Toxicity/AEs should be entered on to the eCRF See Trial Guidance Document for further instructions for ctDNA collection Arm A: monitoring of renal and liver function with blood tests to include urea, creatinine, sodium, potassium, total bilirubin, alkaline phosphatase, ALT, AST
Months 12, 18, 24, 30, 36 and then **months 48** and **60**	• Physical and pelvic examination • Review of concomitant medication • WHO performance status • Weight • QoL (EORTC QLQ C30 and EN24) • Adverse events/Toxicity • CT chest, abdomen and pelvis **months 12, 24 and 36** • CA125 **months 12, 24 and 36**	Concomitant medication should be reviewed but entry on to the eCRF is not required. Toxicity/AEs should be entered on to the eCRF See Trial Guidance Document for further instructions for ctDNA collection Arm A: monitoring of renal and liver function with blood tests to include urea, creatinine, sodium, potassium, total bilirubin, alkaline phosphatase, ALT, AST

	• **collection of blood tube for ctDNA (20ml) month 12 for both trial arms** • **Arm A:** blood tests **(***see notes column*) • **Arm A:** blood pressure	
28 days following completion of oral progestin tablets (+/- 7 days) **(Arm A only – safety visit)**	• Telephone or on-site visit • Toxicity assessment	Treatment characteristics (details of oral progestin tablets) to be recorded on the eCRF Toxicity/AEs should be entered on to the eCRF

9.3 Assessments after Disease Recurrence

- In the event of recurrence during the trial period, assessments should be carried out according to local practice. Alternative treatments may be prescribed according to local practice and should be documented where possible
- Recurrence will be classified as vaginal, pelvic nodal, para-aortic nodal or distant (metastatic) according to site
- RFS is defined as the length of time from date of randomisation to date of any recurrence (local or distant) or date of death due to any cause
- Patients who have disease recurrence are no longer required to attend for study visits or complete QoL questionnaires**,** however **the following details should be recorded on the eCRF Follow-up Form annually from the date of recurrence while the trial remains open:**
    - Survival status
    - Additional treatment for endometrial cancer
    - Further recurrences
    - New malignancy

Detailed recurrence criteria and guidance can be found in Appendix 3.

9.4 Patient reported outcome measures (PROM)/Quality of Life Questionnaires

Patient Reported Quality of Life (PR-QoL) will be assessed at baseline, following treatment with radiotherapy, and at follow-up visits. The validated European Organization for Research and Treatment of Cancer's (EORTC) QLQ-C30 and the EN24 quality of life questionnaires will be used to assess quality of life of patients.

Patient reported Quality of Life (PR-QoL) questionnaires for this trial will be completed by patients in a module of OpenClinica called Participate. Patients will be asked to consent to providing their contact details (name, email and mobile telephone number) in order to receive the link via email or text to complete these online. (See also Section 19.5 Patient Confidentiality & Data Protection)

Hard copies of the questionnaires may be provided to patients if completion on paper is preferred. Once completed and returned, the data will be entered on to the eCRF.

9.5 Table 2: schedule of assessments

RAINBO NSMP-ORANGE trial	Time since randomisation in months																		
	All Trial patients		Arm A: radiotherapy and oral progestin tablets (RT+HT)										Arm B: radiotherapy with chemotherapy (RTCT)						
	<0 Baseline*	0 Randomisation	M2-3 on end of RT**	Every M1-3 from end of RT[6]	M6	M12	M18	M24	28 days following completion of HT[7]	M30	M36	M48, M60	M2-3 on completion of RT**	M6	M12	M18	M24	M30	M36	M48, M60
Informed Consent[1]	X																			
Molecular classification and details of EC [1, 8]	X																			
ER and PR positivity [1, 9]	X																			
Tumour tissue collection for biobank[1]	X																			
Patient weight, WHO performance status	X		X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Patient age, height	X																			
Physical and pelvic examination	X		X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Chest/abdomen/pelvis CT[2]	X					X		X			X				X		X		X	
Medical history/co-morbidity (NCI) [10]	X																			
Review of concomitant medication	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs and blood pressure	X				X	X														
Pathology assessment[3]	X				X	X														
CA125	X					X		X			X				X		X		X	
Demographics	X																			
PR-QoL (EORTC QLQ C30 and EN24)		X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Treatment characteristics[4]		X							X					X						
Selected toxicities (CTCAE v5.0)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for ctDNA[5]			X			X								X	X					
Prescription (HT)[6]			X	X																
Follow-up endpoints	Vaginal, pelvic, para-aortic lymph node and abdominal/distant (metastatic) recurrence, additional treatment, date of death and cause of death Following disease recurrence, survival status, additional treatment for endometrial cancer, further recurrences and new malignancies should be recorded on the eCRF annually from the date of recurrence																			
Off study	Date and reason (e.g. withdrawal/loss of follow-up, death)																			

* If not otherwise specified, baseline study procedures must be performed within 28 days prior to randomisation
** 2-3 months following randomisation on completion of radiotherapy (or within 4 weeks following completion of radiotherapy)
[1] The 28 day prior to randomisation window is not applicable but must be obtained prior to randomisation
[2] CT chest/abdomen/pelvis at baseline (within 8 weeks of randomisation) and at 12, 24 and 36 months
[3] **Screening:** FBC inc. ANC, Hb and platelets, biochemistry inc. liver and bone profile (bilirubin, ALT, AST, creatinine/GFR) **Follow up (M6, M12):** monitoring of renal and liver function with blood tests to include urea, creatinine, sodium, potassium, total bilirubin, alkaline phosphatase, ALT, AST
[4] Details of surgery, radiotherapy, chemotherapy/oral progestin tablets recorded on the eCRF following randomisation (planned treatment) and at end of treatment (actual treatment received)
[5] Blood tube for ctDNA occurs once at the first visit following completion of radiotherapy for Arm A (2-3 month visit) and following completion of radiotherapy and chemotherapy for Arm B (6 month visit), then at the 12 month visit for both arms
[6] Medroxyprogesterone acetate 200mg OD or megestrol acetate 160mg OD prescribed every 1-3 months (as per local guidelines) for 24 months to commence on completion of radiotherapy. Start may be delayed until radiation toxicity is less than grade 2 but should commence within 4 weeks following completion of radiotherapy. Details including treatment breaks of 5 days or over should be recorded on the eCRF
[7] 28 days (+/- 7 days) following completion of 24 months of oral progestin tablets. Telephone or on-site visit
[8] The following details should be entered on to the eCRF: grade, histological subtype (including MMR, POLE, p53, NSMP status), FIGO stage, details of surgery for EC (including size of tumour, complications, biopsies, lymph nodes, LVSI, cervical stromal involvement, serosal invasion, metastases)
[9] ER (estrogen receptor) status required for eligibility. PR (progesterone status) if known
[10] See NCI criteria (Appendix 5). Details of any myocardial infarction, congestive heart failure, peripheral/ cerebrovascular vascular disease, chronic obstructive pulmonary disease, dementia, hemiplegia/paraplegia, diabetes, renal/liver/peptic ulcer/rheumatological disease, other malignancies

10 TRANSLATIONAL RESEARCH / EXPLORATORY BIOLOGICAL STUDIES

All patients randomised to RAINBO NSMP-ORANGE will have consented to the collection of tissue for translational research.

Translational research studies will use archival tissue collected from primary surgery for the RAINBO translational research programme. Clinically annotated tumour blocks will be collected and stored at the central RAINBO Tissue Repository* Leiden, Netherlands for future trial-specific and overarching translational research programmes.

Blood will also be collected for ctDNA analysis following completion of initial treatment. For patients on Arm A this means at the first visit following completion of radiotherapy and for patients on Arm B this means at the first visit following completion of radiotherapy with chemotherapy.

The process for sample acquisition, processing, labelling storage and shipment is described in the Trial Guidance Document.

*RAINBO Tissue Repository (P1-33)
Department of Pathology
Leiden University Medical Center (LUMC)
Albinusdreef 2
2333 ZA Leiden
The Netherlands

11 DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites using an electronic case report form OpenClinica (eCRF) created and maintained by UCL CTC. Data must be accurately transcribed on to trial eCRFs and must be verifiable from source data at site. Examples of source documents are hospital records, which include patient's medical notes, laboratory, and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending, to maintain confidentiality.

Please note that, for this trial, patients must consent to their name, email address, contact telephone number and NHS number being supplied to UCL CTC. This is:

- for flagging with national data registries e.g. NHS England and National Radiotherapy Dataset*
- in order to send QoL forms directly to patients for completion via OpenClinica Participate

* the trial may apply for future data collection from national data sources and registries e.g. NHS England and National Radiotherapy Dataset.

11.1 Entering data into the eCRF

The eCRF must be completed by site staff who have been appropriately trained, are listed on the site staff delegation log, and authorised by the PI to perform this duty. Each authorised staff member will be issued with their own unique login details for the eCRF by UCL CTC, and a list of current users at each site will be maintained by UCL CTC. Site staff must never share their login details with other staff as the eCRF audit trail will record all entries/changes made by each user. The PI is responsible for the accuracy of all data reported in the eCRF.

The use of abbreviations and acronyms must be avoided.

11.2 Corrections to eCRF Forms

Where necessary, corrections can be made by site staff to data on the eCRF, as long as the eCRF has not been locked/frozen by UCL CTC. The eCRF audit trail will record the original data, the change made, the reason for the change, the user making the change and the date and time. Site staff should contact UCL CTC if changes need to be made to a locked/frozen eCRF.

11.3 Timelines for Data Entry

The relevant eCRF forms must be completed as soon as possible after a patient visit.

Sites who persistently do not enter data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and this may trigger a monitoring visit. See Section 14.2 for details.

11.4 Data Queries

Data entered onto the eCRF will be subject to some basic checks at the time of entry, and any discrepancies will be flagged to the user in the form of a warning. The data can be corrected immediately, or where this is not possible the data amended at a later stage.

Further data review will be carried out at UCL CTC and queries raised where necessary. Further guidance on the process for handling data queries can be found in the eCRF completion guidance.

There may be times when data queries require a rapid response e.g. when an Independent Data Monitoring Committee (IDMC) meeting is due. UCL CTC will contact sites if this is the case and provide as much notice as possible.

12 PHARMACOVIGILANCE

12.1 Definitions

The following definitions have been adapted from the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and subsequent amendments, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6.

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with an IMP. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an IMP), whether or not related to that IMP. See Section 12.3.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. A causal relationship between an IMP and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

See Section 12.3.2 for SAE Reporting procedures.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction - the nature or severity of which is not consistent with the applicable reference safety information.

i.e., an adverse event that meets all the following criteria:

- **Serious** – meets one or more of the serious criteria, listed under the definition of SAE above
- **Related** – assessed by the local PI or designee, one or more elements of the trial treatment
- **Unexpected** – the event is not consistent with the applicable reference safety information

12.2 Management of Overdoses, Investigational Treatment Error, Misuse, Abuse, or Occupational Exposure

Overdose

Overdose is administration of a quantity of an IMP either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can either be evaluated as overdose by the trial team at site or by the Sponsor upon review.

- **Medroxyprogesterone acetate**

  There is no specific treatment in the event of an overdose with medroxyprogesterone acetate. In cases of suspected overdose medroxyprogesterone acetate should be discontinued.

- **Megestrol acetate**

  There is no specific treatment in the event of an overdose with megestrol acetate. In case of overdose, appropriate supportive measures should be taken.

- **Cisplatin, carboplatin and paclitaxel**

  There are no specific antidotes for these drugs. Patients should be closely monitored and offered supportive treatment as needed.

Overdoses should be reported on an incident report (see Section 13.1). Any adverse events resulting from an overdose should be reported as an SAE (see Section 12.3.2 for reporting procedures).

Medication error / Investigational treatment error

A medication error/investigational treatment error is any unintentional error in prescribing, dispensing, or administration of an IMP while in the control of a healthcare professional or consumer. The error can be identified either by the trial team at site or by the Sponsor upon review.

If the medication error is an overdose, refer to the section above. Otherwise, medication errors should be reported on an Incident report (see Section 13.1). Any adverse events resulting from a medication error should be reported as an SAE (see Section 12.3.2 for reporting procedures).

Misuse

Situations where the trial treatment is intentionally and inappropriately used in a way that is not in accordance with the protocol.

Any instances of intentional misuse should be reported on an incident report (see Section 13.1). Any adverse events resulting from misuse should be reported as an SAE (see Section 12.3.2 for reporting procedures).

Abuse

The persistent or sporadic, intentional, excessive use of an IMP which is accompanied by harmful physical or psychological effects.

Any instances of abuse should be reported on an incident report (see Section 13.1). Any adverse events resulting from abuse should be reported as an SAE (see Section 12.3.2 for reporting procedures).

Occupational exposure

Exposure to an IMP as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see Section 13.1).

12.3 Reporting Procedures

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 should be used. This is available online at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Severity grade

Severity grade of each adverse event must be determined by using CTCAE v5.0.

Causality

The relationship between the treatment and an adverse event will be assessed.

For AEs (including SAEs) the local PI or designee will assess whether the event is causally related to each IMP.

Causal relationship to each IMP must be determined as follows:

- Related (reasonable possibility) to an IMP
- Not related (unlikely/no reasonable possibility) to an IMP

UCL CTC will consider events evaluated as related to be adverse reactions.

12.3.1 *Reporting Adverse Events (AEs)*

All adverse events that occur between informed consent and the end of the follow up period (5 years following randomisation) must be recorded in the patient medical notes and the trial eCRFs.

The following adverse events should be reported: **all adverse events**.

Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the SAE Report eCRF in the OpenClinica (OC) database. Also see Section 12.3.2 (Reporting of Serious Adverse Events (SAEs).

Pre-existing conditions (i.e. conditions present at informed consent) do not qualify as adverse events unless they worsen or recur (i.e. improves/resolves and then worsens/reappears again). e.g. an AE could be an exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition (worsening of the event). Another example of an AE is when a pre-existing condition improves during the trial (e.g. from grade 3 to grade 1) and then it worsens again (e.g. from grade 1 to grade 2), even if the event is of severity equal or lower to the original condition (improvement and recurrence of the event).

NB: The disease(s) under study and its anticipated day-to-day fluctuations would not be an AE.

12.3.2 *Reporting Serious Adverse Events (SAEs) to UCL CTC*

All SAEs that occur between the signing of informed consent and 30 calendar days post last IMP **(or after this date if the site investigator feels the event is related to an IMP)** must be reported to UCL CTC by completing the SAE report eCRF in OpenClinica (OC) within **24 hours** of observing or learning of the event.

Sites must notify UCL CTC when an SAE report has been submitted in OC by sending an email notification to the trial mailbox **ctc.nsmp-orange@ucl.ac.uk**, quoting the patient study ID, SAE term and event onset date.

All sections on the SAE Report eCRF must be completed. If the event is **not being reported to UCL CTC within 24 hours**, the circumstances that led to this delay must be detailed in the SAE Report eCRF to avoid unnecessary queries.

SAEs must be reported to UCL CTC by completing an SAE Report eCRF in OC within 24 hours of becoming aware of the event:

Link to the OC database:
https://ucl.openclinica.io/OpenClinica/MainMenu

and sending an email notification to:
ctc.nsmp-orange@ucl.ac.uk

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE report eCRF, **unless the event has been exacerbated or accelerated by the IMPs**:

- Grade 1-3 adverse events for patients on **Arm B (control arm) only**
- disease recurrence (including disease-related deaths)
- events that occur more than **30 calendar days** post last IMP

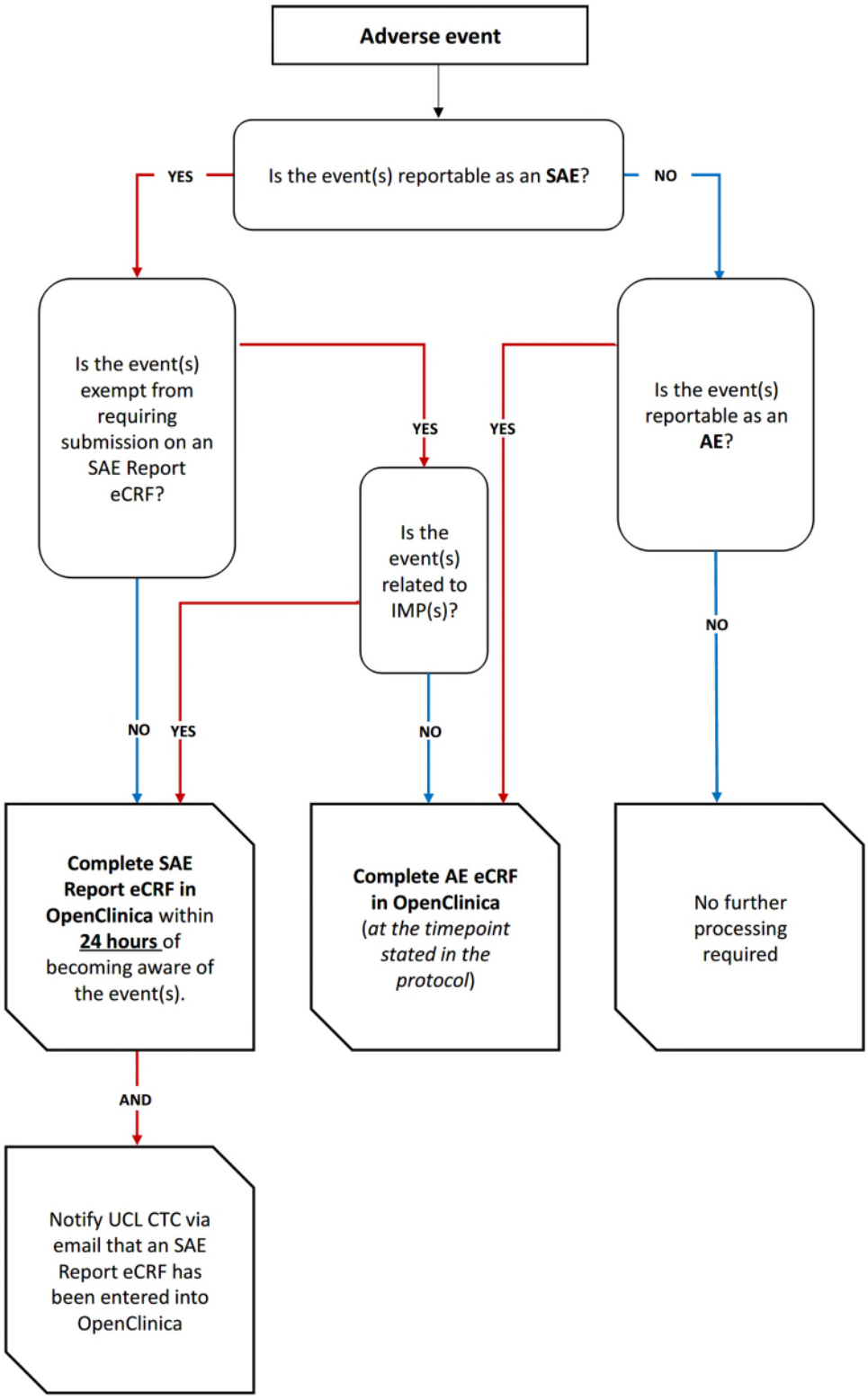
Please note that hospitalisation for elective treatment, palliative care, socio-economic or logistic reasons does not qualify as an SAE.

SAE Follow-Up Reports

UCL CTC will follow up all SAE/SARs until resolution and until there are no further queries.

Sites must ensure any new and relevant information is reported to UCL CTC by updating the SAE Report eCRF in OC within 24 hours of learning of the new information. If an event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to this delay must be detailed in the SAE Report eCRF to avoid unnecessary queries.

SAE and AE Reporting Flowchart



SAE Processing at UCL CTC

On receipt of an SAE Report eCRF in OpenClinica, UCL CTC will check for completeness, accuracy and consistency. UCL CTC will evaluate expectedness, to determine whether the case qualifies as a SUSAR for expedited reporting, using the approved RSI in section 4.8 of the SmPCs for medroxyprogesterone acetate or megestrol acetate, cisplatin, carboplatin and paclitaxel.

The CI, or their delegate (e.g. a clinical member of the TMG), will review the SAE. If UCL CTC has considered expectedness difficult to determine, the reviewer will be consulted for their opinion at this time.

12.4 SUSARs

If the event is evaluated as a SUSAR, i.e. an unexpected event that is related (reasonable possibility) to the trial drug(s), UCL CTC will submit a report to the MHRA, REC and applicable regulatory authorities in the EU/EEA within 7 calendar days for initial reports of fatal/life threatening events (with a follow-up report within a further 8 calendar days) and 15 calendar days for all other events.

Where a Country Coordinating Centre (CCC) will be submitting SUSAR reports in a non-UK country, UCL CTC will provide the report to the CCC before the submission deadline, allowing sufficient time for local reporting. The CCC will be responsible for forwarding SUSAR reports to their ethics committee(s), as required, their regulatory authority and any other organisations as identified in the agreement between UCL and the CCC.

Informing Sites of SUSARs

UCL CTC will inform all UK sites of any SUSARs that occur on the trial. Sites will receive a quarterly line listing which must be processed according to local requirements.

For participating countries outside the UK, UCL CTC will submit line listings to CCCs/CLSs to forward to the sites in their country. Where there is no CCC, UCL CTC will submit SUSAR reports directly to sites in that country.

12.5 Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

The IDMC will review the following trial safety data:

- Disease-related events (exempt from SAE reporting as per Section 12.3.2) according to treatment allocation to identify whether disease-related events appear to be enhanced by the IMP
- Line listing of adverse reactions to the individual IMP to identify new adverse reactions

The IDMC and TMG will review trial safety data to identify:

- A higher incidence of rare serious adverse reactions than is stated in the RSI for an IMP

- Trial related events or incidents that may lead to changes to the trial documents.

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary, the issue will be referred to the IDMC.

12.6 OpenClinica Systems Failure

In the event of OpenClinica systems failure, SAEs should be reported to UCL CTC by sending the following information in an email to ctc.nsmp-orange@ucl.ac.uk.

- Trial name
- Patient's trial number
- Reporter's name
- SAE details (event term, grade, seriousness criteria)
- Randomised arm
- Assessment of causal relationship for SAEs

An SAE Reporting eCRF must be promptly submitted in OC once notified by UCL CTC that the system is operational.

12.7 Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs (Annual Safety Report) that UCL CTC will submit to the MHRA, the UK REC and all CCCs/CLSs. CCCs/CLSs must forward all reports to the regulatory authority, ethics committee(s) and any other organisations as identified in the agreement between UCL and the CCC/CLS in that country according to the timelines outlined in the agreement between UCL and the CCC/CLS.

13 INCIDENT REPORTING AND SERIOUS BREACHES

13.1 Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. When an incident report is requested by UCL CTC this should be provided, but an equivalent document (e.g. Trust Incident form) is acceptable where already completed. Where an equivalent document is being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers redacted prior to sending, to maintain confidentiality.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

Where the incident has occurred in a site outside the UK, the CCC/CLS in that country must also notify the relevant ethics committee in accordance with local requirements. Where UCL CTC identifies an incident at a site outside the UK, the CCC/CLS in the country where the incident occurred will be informed.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2 Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the MHRA and REC within 7 calendar days of becoming aware of the breach.

The serious breach report may also be forwarded to CCCs/CLSs for submission to their regulatory authorities and any other organisations as identified in the agreement between UCL and the CCC/CLS, as required.

UK Sites must have written procedures for notifying the Sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

The serious breach report may also be forwarded to CCCs/CLSs for submission to their ethics committees and any other organisations as identified in the agreement between UCL and the CCC/CLS, as required.

14 TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Where permitted by site policy, remote access to source data/documents may also be provided by participating sites for remote monitoring by UCL CTC or its representatives.

Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form. UCL CTC or its representatives will conduct all monitoring in compliance with the patient consent, site policy and data protection requirements.

UCL CTC will determine the appropriate level and nature of monitoring required, based on the objective, purpose, phase, design, size, complexity, endpoints, and risks associated with the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

Details of monitoring activities will be included in the trial monitoring plan and conveyed to sites during initiation. The trial monitoring plan will be kept under review during the trial and updated information provided to sites as necessary.

14.1 Centralised Monitoring

UCL CTC performs centralised monitoring, which requires the submission of documents by sites to UCL CTC for review, including but not limited to:

- Delegation Log, Screening Log, Samples Log, Drug Accountability Logs etc.

Expectations for document submission will be explained during site initiation and UCL CTC or its representatives will send emails to sites requesting the documents when required.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency determined for the trial. Checklists detailing the current version/date of version-controlled documents will be provided by UCL CTC for this purpose.

14.2 On-Site/Remote Monitoring

On-site/remote monitoring may be triggered following UCL CTC centralised monitoring or data review and/or where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements.

Sites will be sent an email in advance of any on-site or remote monitoring visits outlining the reason(s) for the visit and confirming when it will take place. The email will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Monitoring Follow-up

Following on-site/remote monitoring, the Trial Monitor/Trial Manager will provide a follow-up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

14.3 Escalation of monitoring issues

Where monitoring indicates that a patient may have been placed at risk the matter will be raised urgently with site staff and escalated as appropriate.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitutes a serious breach. Refer to Section 13 for details.

14.4 Oversight Committees

14.4.1 *Trial Management Group (TMG)*

The TMG will include the Chief Clinical Investigator and Chief Scientific Investigator, clinicians and experts from relevant specialties and RAINBO NSMP-ORANGE trial staff from UCL CTC (see page 4). The TMG will be responsible for overseeing the trial. The group will meet regularly (2-3 times per year) and will send updates to PIs (via newsletters or at Investigator meetings).

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA and CCCs/CLSs for submission to their ethics committees and regulatory authorities. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

All members of the TMG external to UCL CTC will be required to read and sign a UCL CTC TMG Charter.

14.4.2 *Trial Steering Committee (TSC)*

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

All TSC members will be required to read and sign a UCL CTC TSC Charter.

14.4.3 *Independent Data Monitoring Committee (IDMC)*

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held annually to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

All IDMC members will be required to read and sign a UCL CTC IDMC Charter.

14.4.4 *Role of UCL CTC*

UCL CTC, on behalf of the Sponsor, will be responsible for the day-to-day coordination and management of the trial and the UCL CTC Director will act as custodian of the data generated in the trial (on behalf of UCL).

15 WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples, follow-up, and data collection.

15.1 Patients who do not start Trial Treatment

If a patient does not start treatment the reasons for this must be recorded in the patient's medical notes and on the relevant eCRF(s). Reasons that a patient may not start treatment include:

- Deterioration in health
- Patient decision
- No longer eligible

If a patient does not start treatment, then the patient should be withdrawn from the trial. Data collected about the patient so far will be used in the trial analysis, where appropriate. Biological samples collected may still be used unless the patient explicitly withdraws consent to this.

15.2 Discontinuation of Trial Treatment

A patient may discontinue trial treatment if the treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patient's medical notes and on the relevant eCRF(s). Reasons for discontinuing treatment may include:

- Disease recurrence whilst on trial treatment
- Unacceptable toxicity
- Intercurrent illness that prevents further treatment
- Patient decision not to continue with trial treatment
- Any alterations in the patient's condition that justifies the discontinuation of trial treatment in the site investigator's opinion
- Non-compliance with the trial treatment and/or procedures

In these cases, patients will remain on the trial for the purposes of follow-up and will be included in appropriate data analysis, unless they explicitly withdraw consent to this.

If a patient expresses their wish to discontinue trial treatment, sites should explain the importance of remaining on trial follow-up, or of at least allowing routine follow-up data and data already collected to be used for trial purposes. If the patient gives a reason for wishing to discontinue trial treatment this should be recorded.

The following eCRFs should be completed if a patient discontinues trial treatment early:

- Treatment Summary
- Treatment forms for all cycles of treatment received

(continued next page)

Thereafter, unless the patient has withdrawn consent for data collection, the following CRFs should continue to be completed:

- SAE reports
- Adverse event form
- Month 2-3 and months 6, 12, 18, 24, 30, 36, 48 and 60 forms with any available data
- Additional treatment
- Death

15.3 Withdrawal of Consent

If a patient withdraws consent for any aspect of the study, UCL CTC should be notified and the Withdrawal of Consent form should be completed.

15.3.1 *Withdrawal of consent for follow-up*

If a patient withdraws consent for trial follow-up, but is happy to continue with future data collection from hospital medical notes:

- The patient will no longer have trial-specific visits and assessments. Follow-up forms should be completed based on the routine visit nearest the due date for the follow-up form
- The following CRFs/data must be completed at time of withdrawal:
    - Withdrawal of Consent form
    - All CRFs up to and including the date of withdrawal of consent
- Thereafter, the site should report AEs/SAEs as per Section 12.3 and follow-up forms, including notifications of relapse, death and new primary malignancies.

15.3.2 *Withdrawal of consent for data collection*

If a patient **explicitly** states they do not wish to contribute further data to the trial their decision must be respected. The following CRFs must be completed at the time of withdrawal of consent:

- Withdrawal of Consent form
- All CRFs up to and including the date of withdrawal of consent

Thereafter, no further data should be submitted, with the exception of SAE reports as per Section 12.3 (due to the regulatory requirement for oversight of IMP safety).

15.3.3 *Withdrawal of consent for use of samples*

If a patient withdraws consent for the use of some, or all, of their samples in the trial, or for future research, this should be reported on the Withdrawal of Consent form. Unless the patient has also withdrawn from trial treatment/follow-up, management and data collection should continue as per protocol.

15.4 Losses to Follow-up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for the patient to be followed up via the patient's GP. Details of participating trial sites can be obtained from the UCL CTC trial team, who must be informed of the transfer of care and follow-up arrangements. If it is not possible to transfer to another participating site, the registering site remains responsible for submission of CRFs.

If a patient is lost to follow-up, every effort should be made to contact the patient's GP to obtain information on the patient's status.

UK patients who are lost to follow-up will be tracked by UCL CTC via NHS England.

At the time of loss to follow-up, the following CRFs should be completed:

- Lost to Follow-up form
- All eCRFs due up to and including the date of loss to follow-up

If contact is re-established with the patient, further follow-up forms should be sent, including notifications of disease recurrences and new malignancies. A death form should also be completed if the site becomes aware that the patient has died.

Prior to primary analysis and presentation/publication of the primary endpoint data, UCL CTC may ask sites to attempt to re-establish contact with patients who were lost to follow-up and/or check hospital records for evidence of when the patient was last known to be alive and evidence of death, disease recurrences or new malignancies.

15.5 Loss of Capacity

Patients who lose capacity during the trial would continue in the trial for the purposes of data collection, if appropriate. If the patient regained capacity, an Investigator would discuss with the patient their continued participation in the trial and together, the patient and Investigator would decide what action, if any, to take.

16 TRIAL CLOSURE

16.1 End of Trial

For regulatory purposes the end of the trial will be defined as the date of the last visit of the last patient. At this point the 'declaration of end of trial' form will be submitted to the MHRA, participating regulatory authorities and Ethics Committee(s), as required, and sites notified.

UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the end of trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

16.2 Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3 Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see Section 14.4.2 Trial Steering Committee [TSC] and Section 14.4.3 Independent Data Monitoring Committee [IDMC]). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow-up of patients.

16.4 Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow-up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the site agreement.

Should a non-UK site choose to close to recruitment the PI must inform UCL CTC in writing. Follow-up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the agreement with the site and/or CCC.

17 QUALITY ASSURANCE

The participating centres of the RAINBO program have extensive experience with quality assessment of external beam radiotherapy and brachytherapy in clinical trials for endometrial cancer because of the preceding series of PORTEC trials. In addition, many centres have participated in the EMBRACE and INTERLACE trials on cervical cancer which are renowned for their stringent EBRT and brachytherapy planning criteria and intensive assessments. This protocol is based on those experiences and provides the participating centres with a detailed description of the requirements for EBRT and brachytherapy that should fit current practices. Therefore, there will be no formal radiotherapy quality assessment control in the RAINBO trials.

18 STATISTICS

18.1 Sample Size Calculation

The RAINBO NSMP-ORANGE trial is an international, Phase III non-inferiority trial wherein patients will be randomised with a 1:1 allocation ratio to adjuvant radiotherapy followed by oral progestin tablets for two years (intervention) or adjuvant chemoradiation (control).

The primary endpoint is 3-year recurrence-free survival (RFS) rate. Assuming a 3-year RFS rate of 82.5% in the control arm [9], a non-inferiority margin of 7.5% is of interest to exclude a rate below 75.0% in the intervention arm. A total of 600 randomised patients are required in total, recruited over 5 years with 3 years of additional follow-up to observe 153 events, for 80% power at the one-sided 5% significance level after allowing for up to 5% common exponential dropout per year.

The non-inferiority design was discussed extensively with patients and clinicians, who considered evidence from the PORTEC-3 trial as well as the harms and benefits of each treatment approach (including that a survival benefit of at least 10% was needed for the addition of CT to be worthwhile given its toxicity [4, 16, 17]).

Sample size calculations were carried out using PASS 2023 Power Analysis & Sample Size Software version 23, and nQuery version 9.

18.2 Statistical Analysis

18.2.1 *Analysis of main endpoint*

RFS is defined as the time from date of randomisation to date of recurrence or death from any cause, censoring will occur at the date last known to be alive. This will be described using the Kaplan-Meier method and analysed using a Cox proportional hazards model to adjust for the randomisation stratification factors. Sensitivity analyses will be carried out censoring non-endometrial cancer deaths, and a competing risk model can be used in which death due to other causes is considered a competing risk to endometrial cancer death or recurrence.

Interpretation of non-inferiority will be based on the one-sided 95% (or two-sided 90%) confidence interval for the difference in 3-year RFS rate, i.e. whether this excludes the non-inferiority margin. The absolute risk difference will be estimated by applying the hazard ratio and confidence interval to the observed RFS rate in the control arm. A non-inferiority p-value can also be provided from a test to compare the difference in two event rates with consideration of the allowable margin (a one-sided $p<0.05$ would indicate non-inferiority).

Analysis will be carried out on an intention-to-treat basis, to preserve randomisation, and also on a per-protocol basis to ensure that primary findings are robust and any potential difference between trial arms is not underestimated due to non-compliance. Replacing chemotherapy with oral progestin tablets is not a simple de-escalation question, therefore the impact of any post-

randomisation deviations and non-adherence will be considered under the estimands framework and detailed in the Statistical Analysis Plan.

18.2.2 *Analysis of secondary endpoints and secondary analyses*

If the primary endpoint of non-inferiority is met, then toxicity between the trial arms will be compared formally to ensure that this treatment de-escalation approach leads to a corresponding benefit in this regard (CTCAE v5.0). Utilising a fixed sequence gatekeeping procedure, based on the closed test principle to control familywise error rate, the proportion of patients experiencing a grade 3 or higher adverse event in each arm will be compared at the two-sided 5% significance level. In the chemoradiation control arm, 61% of patients would be expected to experience a grade 3 or higher adverse event within 2-years [4], a reduction of at least 12.5 percentage points to 48.5% or lower in the investigational arm [18] can be detected with >85% power at the two-sided 5% significance level with N=600.

Toxicity at any time will be described by trial arm in the safety population which will include all patients who receive any trial treatment. The proportion of grade 3 or higher adverse events and exact 95% confidence intervals will be described, both the maximum grade per patient and for individual adverse event terms, and compared using Fisher's exact tests.

Similar methods to the primary endpoint analysis of RFS will be used for the secondary time-to-event endpoints:

- vaginal RFS, defined as the time from date of randomisation to date of vaginal recurrence;
- pelvic RFS, defined as the time from date of randomisation to date of pelvic recurrence;
- para-aortic nodal RFS, defined as the time from date of randomisation to date of para-aortic nodal recurrence;
- distant RFS, defined as the time from date of randomisation to date of distant recurrence;
- cancer-specific survival, defined as the time from date of randomisation to date of cancer-related death;
- overall survival, defined as the time from date of randomisation to date of death from any cause.

Competing risks analyses will also be carried out for vaginal RFS, pelvic RFS, para-aortic nodal RFS, distant RFS and cancer-specific survival, in which death from other causes (and/or non-simultaneous pelvic/vaginal/distant recurrences) before the specific event of interest will be considered a competing risk, as detailed in the Statistical Analysis Plan.

Quality of Life (QoL) outcomes (EORTC QLQ-C30 & EN24, and associated subscales) will be analysed using linear mixed models. Repeated measurements over time will be modelled with individual patient random effects, and treatment, time and the treatment by time interaction as fixed effects. Estimates of treatment effects for QoL outcomes will be reported with 99% confidence intervals to guard against false-positive results due to multiple testing.

Exploratory subgroup analyses of efficacy, safety and QoL endpoints will be carried out by the stratification variables used in the randomisation procedure, presented using forest plots and with p-values from interaction tests where appropriate.

The overarching RAINBO program will combine data and tumour material of all participants to perform translational research and evaluate molecular class-based adjuvant therapy in terms of efficacy, toxicity, QoL, and cost-utility.

18.3 Interim Analyses

The trial will be regularly monitored by trials unit staff, with input from members of the Trial Management Group. A report will be provided to the Independent Data Monitoring Committee (IDMC), who will review accrual, compliance, safety and efficacy. The first review by the IDMC will be once the trial is in set up, and at least once each year thereafter or more regularly if required. The IDMC will make recommendations on whether the trial should continue or stop recruitment, or the protocol modified. Any decision to stop the trial will be communicated to Trial Steering Committee (TSC).

No formal interim analyses are planned as part of the design, which would otherwise increase sample size. However, given the length of the accrual and follow-up periods a pragmatic approach using conditional power will be utilised to ensure that the trial will not continue if the primary objective is unlikely to be reached. This is informative because it indicates the probability of obtaining a statistically significant result at the end of the study given the accumulated data observed and assuming that the future data is consistent with the original target. Conditional power will be calculated and presented to the IDMC on an annual basis; if this drops below 15% then a further check will be made after 6 months and if conditional power remains <15% then the IDMC may recommend major changes to the protocol or closing of the trial [19].

19 ETHICAL AND REGULATORY CONSIDERATIONS

This trial will adhere to the conditions and principles of GCP as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended.

For sites in the EU/EEA, this trial will adhere to the GCP requirements as outlined in Directives 2001/20/EC and 2005/28/EC and all laws implementing these in the relevant country(ies), as amended, and, once applicable, the EU Clinical Trials Regulation No. 536/ 2014.

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with the protocol and with all relevant guidance, laws and statutes, as amended, applicable to the performance of clinical trials and research including, but not limited to:

- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority
- Human Rights Act 1998
- Data Protection Act 2018
- UK GDPR (as defined in section 3(10) (as supplemented by section 205(4)) of the Data Protection Act 2018); all applicable law about the processing of personal data and privacy; and (to the extent that it applies) the General Data Protection Regulation (EU)2016/679 (EU GDPR)
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)
- EU Clinical Trials Regulation No. 536/ 2014
- Medicines Act 1968
- Good Manufacturing Practice
- The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (SI 2019/775)

All non-UK sites shall comply with all their local laws and statutes applicable to the performance of clinical trials and research.

19.1 Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the [REC name] Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

Favourable opinion will also be obtained in all participating countries outside the UK in compliance with all local laws, statutes and requirements.

19.2 Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA and relevant international Regulatory Authorities.

19.3 Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

All non-UK sites must provide confirmation of approval of their local institution(s).

19.4 Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals, as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

19.5 Patient Confidentiality & Data Protection

Patient identifiable data, including initials and date of birth will be collected by UCL CTC via OpenClinica (OC), an electronic data capture system used in clinical research. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be directly identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR, with the Data Protection Officer at UCL.

Twilio and Sinch (under the brand Mailgun) are sub-processors of OC. Patient identifiable data will be provided to Twilio (patient name and mobile telephone number) and Sinch (patient name and email address). They will use these details in order to send text messages (Twilio) and/or emails (Sinch) to invite patients to complete online quality of life questionnaires. Twilio will process data in the US, where data protection laws have different levels of protection to those in the UK and EU/EEA. Sinch will process data in the EU, which has equivalent levels of data protection to the UK. Twilio and Sinch are required not to use patient identifiable data for any purposes other than those detailed above. They will not share personal information with any other organisation, they will hold it securely and retain it for only for the period required to process the data. UCL CTC will not have access to the patient identifiable data provided for this purpose.

NIHR Equality, Diversity and Inclusion (EDI) Survey

The National Institute of Health Research (NIHR) is the British Government's major funder of clinical, public health and social care research in the UK. The NIHR would like to understand

whether research is reaching under-represented groups to help shape future research. To help us with this, we will ask participants to answer the **optional, anonymous** questionnaire.

Participants are informed that the information they are providing in these questions is anonymous (not linked to their name or another identifier) and may be used for other educational and research purposes in the future.

The optional NIHR EDI Survey should be completed by trial participants at randomisation, if the participant agrees. The information collected for the optional questions will not be linked to the other research data collected in the study and will be used to monitor equality, diversity and inclusion (EDI) in study participants. The questionnaire data will be manually entered into a separate password protected spreadsheet by UCL CTC. These data will be stored separately from the rest of the study data and will be stored **anonymously** without participant IDs. These data may be merged with demographic data from other research projects and stored for at least 5 years as part of a larger dataset, which may then be shared with the NIHR for EDI monitoring purposes.

20 SPONSORSHIP AND INDEMNITY

20.1 Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office 4th Floor, West 250 Euston Road London NW1 2PG
Contact:	Managing Director, UCLH/UCL Research
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937
Legal Representative in EU:	UCL Research Limited 70 Sir John Rogerson's Quay Dublin 2 D02 R296 Ireland

20.2 Indemnity

University College London (UCL) holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if it is proven that UCL has been negligent. However, as this clinical trial/study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office. Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

21 FUNDING

The National Institute for Health and Care Research, Efficacy and Mechanism Evaluation (EME) Programme is supporting the central coordination of the trial in the UK through UCL CTC.

Research costs will be reimbursed to sites as per the finance section of the site agreement.

Country coordinating centres and/or non-UK sites will be sourcing, obtaining and managing distribution of any additional local funding for the trial outside the UK.

22 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group (TMG). The first publication of the trial results will be in the name of the TMG on behalf of the trial participants. The writing committee will be formed by contributing members of the TMG. The Chief Clinical Investigator and Chief Scientific Investigator will be named as joint lead authors in publications and presentations. Investigators who have significantly contributed to the trial will also be added as co-authors. Authors will be cited by name if published in a journal where this does not conflict with the journal's policy. Trial participants and funders will be acknowledged. Data from all sites will be analysed together and published as soon as possible. Participating sites and laboratories may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG.

A summary of the results will be published on the UCL CTC website, and a lay summary will be sent to site investigators to pass on to trial participants.

The Clinicaltrials.gov number and NIHR unique award identifier allocated to this trial will be quoted in any publications based upon its results. The trial data are owned by UCL.

Patient samples and the future translational work arising will be published separately. These data will not be owned by UCL. Publications, presentations and authorship will be defined according to the funders and employers of the relevant researchers and will be conducted independently of the RAINBO NSMP-ORANGE clinical trial. Trial participants, PIs, the TMG and the UCL CTC will be acknowledged.

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APPENDIX 1: ECOG PERFORMANCE STATUS

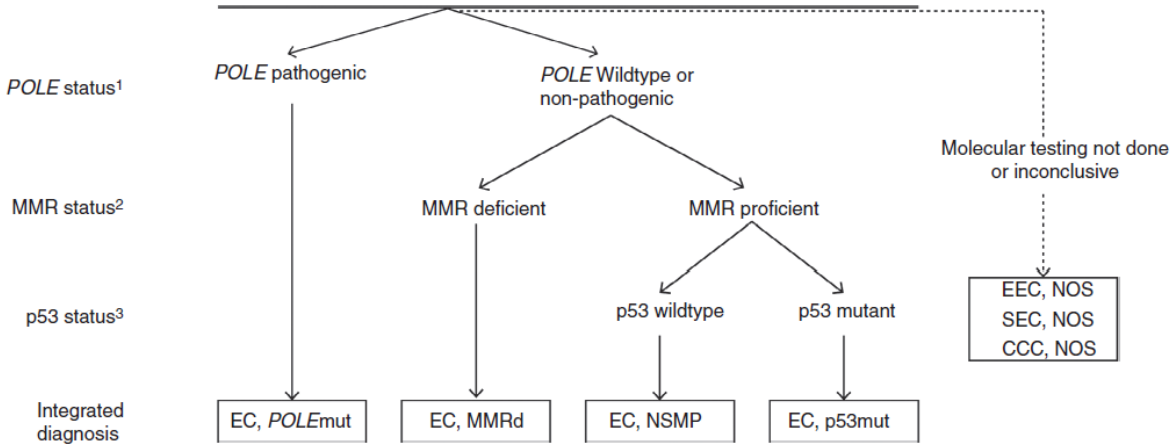
GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

APPENDIX 2: MOLECULAR CLASSIFICATION OF ENDOMETRIAL CANCER

Prior to inclusion in one of the RAINBO trials **complete** assessment of the molecular classification must be performed on the EC (endometrial cancer) specimen. This can be either the tumour containing hysterectomy (preferred) specimen or the preoperative specimen. In many institutes assessment of the molecular profile is done as part of standard care.

Molecular classification includes mutational status assessment of the exonuclease domain of DNA polymerase epsilon (POLE), MMR immunohistochemistry (IHC) and p53 IHC or TP53 sequencing. These tests should be performed in a (pathology) laboratory with ISO-15189 accreditation (or equivalent certification). For molecular class assignment the diagnostic Vermij algorithm is used, which is also incorporated in the WHO 2020 pathology endometrial cancer guideline [20] (Figure 4). This algorithm also provides support for cases that have more than one classifying feature; sometimes referred to as multiple or double classifiers).

Figure 4: Molecular classification of endometrial cancer according to WHO 2020 guideline



Assessment of the EC molecular classification should be performed according to the WHO 2020 guideline, which is based on the algorithm published by Vermij et al. [20]. For inclusion in the RAINBO program, some additional criteria apply, which are described in this protocol.

***POLE* status**

There are a variety of validated technologies available to assess the status of *POLE* in EC. Acceptable technologies for RAINBO include:

1) targeted NGS covering exon 9-14,

2) Sanger sequencing covering exon 9-14. Use of other technologies such as *POLE* hotspot analysis by for example (multiplex) qPCR or SnAPShot could be granted by the RAINBO steering committee after proper validation against golden standard NGS. For all techniques, adequate assessment of preferably the mutational status of all 11 hotspots, but at least the five most frequent hotspots within the exonuclease domain of *POLE* is required (Table 3.1). POLE variants outside the exonuclease domain are not considered.

Table. 3.1 Pathogenic *POLE* EDM mutations in the exonuclease domain according to Léon-Castillo et al. [21]

Order of frequency	Protein change	Nucleotide substitution	Assessment for RAINBO program	Interpretation molecular class
1.	P286R	c.857C > G	Mandatory	*POLE*-mutant
2.	V411L	c.1231G > T or C	Mandatory	*POLE*-mutant
3.	S297F	c.890C > T	Mandatory	*POLE*-mutant
4.	S459F	c.1376C > T	Mandatory	*POLE*-mutant
5.	A456P	c.1366G > C	Mandatory	*POLE*-mutant
6.	F367S	c.1100T > C	Strongly recommended	*POLE*-mutant
7.	L424I	c.1270C > A	Strongly recommended	*POLE*-mutant
8.	M295R	c.884T > G	Strongly recommended	*POLE*-mutant
9.	P436R	c.1307C > G	Strongly recommended	*POLE*-mutant
10.	M444K	c.1331T > A	Strongly recommended	*POLE*-mutant
11.	D368Y	c.1102G > T	Strongly recommended	*POLE*-mutant

Besides the pathogenic *POLE* mutations in the exonuclease domain listed in Table 3.1, Léon-Castillo et al. [21] also defined a list of non-pathogenic *POLE* mutations in the exonuclease domain which are presented in Table 3.2. The presence of one or more of these non-pathogenic mutation does neither affect the assessment of the *POLE* status nor assignment of the molecular class.

Table 3.2 Non-pathogenic *POLE* mutations in the exonuclease domain according to Léon-Castillo et al [21]

Protein change	Nucleotide substitution	Interpretation for assignment molecular class in RAINBO
S461L	c.1382C>T	Not relevant, ignore for molecular class assignment
R114*	c.340C>T	Not relevant, ignore for molecular class assignment
F990C	c.2969T>G	Not relevant, ignore for molecular class assignment
W1824C	c.5472G>T	Not relevant, ignore for molecular class assignment
E396G	c.1187A>G	Not relevant, ignore for molecular class assignment
A1140T	c.3418G>A	Not relevant, ignore for molecular class assignment
Y1889C	c.5666A>G	Not relevant, ignore for molecular class assignment
A781S	c.2341G>T	Not relevant, ignore for molecular class assignment
R34C	c.100C>T	Not relevant, ignore for molecular class assignment
E1461V	c.4382A>T	Not relevant, ignore for molecular class assignment
R976S	c.2926C>A	Not relevant, ignore for molecular class assignment
V2025M	c.6073G>A	Not relevant, ignore for molecular class assignment
A566T	c.1696G>A	Not relevant, ignore for molecular class assignment
R1386Q	c.4157G>A	Not relevant, ignore for molecular class assignment
D368*	c.1101dupT	Not relevant, ignore for molecular class assignment
R1321K	c.3962G>A	Not relevant, ignore for molecular class assignment
Q1049H	c.3147G>T	Not relevant, ignore for molecular class assignment
R764M	c.2291G>T	Not relevant, ignore for molecular class assignment
E1698D	c.5094G>T	Not relevant, ignore for molecular class assignment
A1010T	c.3028G>A	Not relevant, ignore for molecular class assignment
C402R	c.1204T>C	Not relevant, ignore for molecular class assignment
T906I	c.2717C>T	Not relevant, ignore for molecular class assignment

Q352H	c.1056G>T	Not relevant, ignore for molecular class assignment
Q453R	c.1358A>G	Not relevant, ignore for molecular class assignment

Finally, *POLE* variants of unknown significance in the exonuclease domain have also been discovered by Léon-Castillo et al. [21], a non-exhausting list is provided in Table 3.3. These variants will be regarded as non-pathogenic in the RAINBO program, and patients will be included in either the GREEN, RED or ORANGE trial according to their MMR and p53 status and eligibility.

Table 3.3 *POLE* variants of unknown significance in the exonuclease domain according to Léon-Castillo et al [21]

Protein change	Nucleotide substitution	Interpretation for participation in RAINBO
M1754V	c.5260A>G	Non-pathogenic, ignore for molecular class assignment
K1070N	c.3210G>T	Non-pathogenic, ignore for molecular class assignment
L424V	c.1270C>G	Non-pathogenic, ignore for molecular class assignment
A428T	c.1282G>A	Non-pathogenic, ignore for molecular class assignment
R742H	c.2225G>A	Non-pathogenic, ignore for molecular class assignment
Q1335*	c.4003C>T	Non-pathogenic, ignore for molecular class assignment
T278M	c.833C>T	Non-pathogenic, ignore for molecular class assignment
A465V	c.1394C>T	Non-pathogenic, ignore for molecular class assignment

In case of the detection of a novel POLE variant within the exonuclease domain that is not listed above in Table 3.1, 3.2 and 3.3, the case should be regarded as *POLE* wildtype.

For the inclusion into the POLEmut-BLUE trial the endometrial cancer must contain a pathogenic variant in the exonuclease domain of POLE. Assignment of an EC as being POLEmut EC is independent of any of the other test results.

Q. Can a patient enter one of the RAINBO trials, without POLE status assessment?
No. This is not possible, as can be derived from the WHO 2020 diagnostic algorithm, successful *POLE* status assessment is required for all patients for final molecular class assignment.

In the unlikely case that a patient has a pathogenic *POLE* mutation but assessment of MMR status and/or p53 status has failed, the patient is not eligible for participation in the RAINBO program either, even though such patients can be classified into the POLEmut molecular class according to the WHO 2020 algorithm.

MMR status
For the purpose of all RAINBO trials MMR status must be determined by IHC. When MMR-IHC is performed, MSH6 and PMS2 (two-antibody approach) is the minimal requirement. Cases with positive nuclear staining of MSH6 and PMS2 can be regarded is MMR proficient. In all cases with ambiguous MSH6 and/or PMS2 staining, MLH1 and MSH2 are required for final MMR status assignment. A cancer is considered MMR deficient when at least one of the MMR proteins show loss of expression with positive internal control. In most MMR deficient cases the complete tumour will show loss of expression, however subclonal loss of MMR expression can be

observed. In cases of subclonal/partial MMR protein loss there might be a pathogenic driver mutation in *POLE*. If the EC appears to be *POLE*-wild type, the cancer is considered MMR deficient when >10% of the tumour volume shows subclonal loss. In ambiguous MMR-IHC cases or failed MMR IHC it is recommended to perform an analysis of MSI status for definitive assignment. MSI-high is then considered equal to MMRd. If both tests failed, then MMR status and final molecular class cannot be assigned, and therefore the patient is not eligible for the RAINBO trials. For the assignment of an EC as MMR deficient *POLE* status must be wildtype as can be deducted.

The RAINBO program encourages to execute the Lynch Syndrome triage following international guidelines. It is therefore recommended to perform *MLH1* methylation assay in cases with loss of MLH1/PMS2 expression in order to pre-screen patients for germline testing. The *MLH1* methylation assay is however NOT a requirement for entering in one of the RAINBO trials, as it has no impact on the molecular EC classification.

p53 status

p53 status is preferably determined by immunohistochemistry (p53-IHC). Abnormal p53 IHC is defined as 1) complete loss of expression with positive internal control or 2) strong nuclear and/or cytoplasmic overexpression. When the p53-IHC stain is well interpretable, TP53 sequencing is not required for molecular subgroup assignment. In cases with an ambiguous IHC result, p53 status cannot be assigned by p53-IHC. In these instances, it is recommended to use sequencing (NGS or Sanger) to assign p53 status. Upfront assessment of p53 status by *TP53* mutational analyses (e.g. by NGS or Sanger) instead of IHC is allowed under the condition that 1) the complete *TP53* gene is covered by the sequencing panel and 2) only pathogenic p53 mutations are considered. We refer to the following two public databases to determine the pathogenicity of any detected TP53 mutations:

- International Agency for Research on Cancer (IARC) TP53 database [22]; https://p53.iarc.fr/TP53GeneVariations.aspx)
- ClinVar database [23]; https://erepo.clinicalgenome.org/evrepo/ui/classifications?matchMode=exact&gene=TP53).

Sometimes sequencing detects TP53 mutations that are not present in these two databases. Often these are secondary mutations in a MMRd or POLE ECs that can be disregarded. If the tumour is MMR proficient and POLE wild type, we recommend performing p53 IHC and rely on the IHC result to classify the EC.

If both IHC and sequencing of the whole TP53 gene are performed upfront, disconcordances between these two techniques can be observed in 7.7-9.3% across all EC molecular types and in 4.9-5.5% in POLE-wild type and MMR-proficient ECs [24, 25]. The majority of these discordant cases can be resolved by reviewing the p53-IHC (missed subclonal areas, missed “null=pattern”?) and reviewing the sequencing data (is the variant truly pathogenic, has there not been a mix-up, what is the allele-frequency?). If in such cases IHC shows convincing abnormality and sequencing did not detect a pathogenic variant, the cases should be considered p53 abnormal. If sequencing

shows a pathogenic TP53 variant but IHC shows a convincing wild type staining pattern, other aspects can be considered for final molecular subgroups assignment. One can for example look at the other molecular alterations (Her2amplification, PTEN status, histologic subtype) to support a subgroup assignment. We estimate that this will only be needed in ~1% of cases and would advise to send these specific cases out for consult to the national RAINBO pathology expert for assistance with the interpretation and assignment of molecular class.

Abnormal p53 patterns may be observed in only a part of the tumour while the remaining tissue shows wild-type p53 staining; this is called subclonal abnormal p53 expression and has been observed in 5-7% of high-risk ECs [24, 25]. This phenomenon is often the result of secondary p53 mutations and usually occurs in POLE-mutant or MMRd ECs. According to the WHO 2020 guideline, those cases must be assigned to respectively the POLEmut or MMRd EC molecular class. Hence, subclonal p53 abnormality in POLEmut and MMRd EC does not affect eligibility for respectively the RAINBO-BLUE and RAINBO-GREEN trials. However, in POLE-wild type and MMR proficient ECs, the presence of subclonal p53 abnormality will determine whether the EC is classified as a p53-abn EC or an NSMP EC. Because this situation is very rare (<1% of ECs) current literature does not provide solid evidence for a threshold for the percentage of subclonal p53 abnormality [25]. For the RAINBO program, it was decided based on consensus that POLE-wild type, MMR-proficient ECs with subclonal p53 abnormality in >50% of the tumour should be regarded as p53-abn ECs and are eligible for participation in the RAINBO-RED trial. POLE-wild type, MMR-proficient ECs with subclonal p53 abnormality in <10% of the tumour should be regarded as NSMP ECs and are eligible for participation in the RAINBO-ORANGE trial. The very small group of patients who have a POLE-wild type, MMR-proficient EC with 10-50% subclonal p53 abnormality cannot be assigned to a molecular class and are not eligible for participation in any of the 4 RAINBO clinical trials. Nonetheless, collection of data on clinical outcome and FFPE tumour blocks of this specific subgroup is encouraged to enable future research on molecular class assignment.

For further details on the interpretation of p53-IHC we refer to the following publications: Köbel et al. [26], Singh et al. [24] and Vermij et al. [25]. To finally assign an EC as p53abn EC the endometrial cancer must show abnormal p53 expression and be MMR proficient and *POLE* wildtype.

APPENDIX 3: REGISTRATION OF THE ENDPOINTS (RECURRENCE CRITERIA)

Vaginal, pelvic and para-aortic recurrences: all tumour recurrences in the pelvic area (up to and including the common iliac bifurcation), including vaginal recurrences and para-aortic nodal recurrences. Nodal recurrences above the aortic bifurcation are considered para-aortic. These recurrences should be registered regardless of the presence of abdominal and/or distant recurrences.

Check all that apply:

- None
- Yes, vaginal recurrence: inside radiotherapy planning target volume (PTV)
- Yes, vaginal recurrence: outside radiotherapy PTV
- Yes, vaginal recurrence: patient had no radiotherapy
- Yes, pelvic recurrence, nodal/side wall: inside radiotherapy PTV
- Yes, pelvic recurrence, nodal/side wall: outside radiotherapy PTV
- Yes, pelvic recurrence, nodal/side wall: patient had no radiotherapy
- Yes, pelvic recurrence, other including central: inside radiotherapy PTV
- Yes, pelvic recurrence, other including central: outside radiotherapy PTV
- Yes, pelvic recurrence, other including central: patient had no radiotherapy
- Yes, para-aortic nodal recurrence (above the aortic bifurcation): inside radiotherapy PTV
- Yes, para-aortic nodal recurrence (above the aortic bifurcation): outside radiotherapy PTV
- Yes, para-aortic nodal recurrence (above the aortic bifurcation): patient had no radiotherapy

Abdominal / distant recurrence: includes all tumour recurrences at distant sites; examples are peritoneal carcinomatosis, malignant ascites, metastasis in liver, lung, bone and other distant localisations.

Check all that apply:

- No
- Yes, isolated
- Yes, oligometastatic (max 5 metastases)
- Yes, multiple

Continued next page

Site(s) of metastasis:

Check all that apply:

- Peritoneum/omentum
- Liver
- Lung
- Bone
- Brain
- Distant lymph nodes (e.g. supraclavicular, mediastinal nodes)
- Other(s), specify: …

Assessment of recurrences: it should be registered how the recurrence was assessed.

Check all that apply:

- Imaging (new compared to baseline, or serial imaging)
- pathologically (cytology or histology)

APPENDIX 4: NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilised for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

APPENDIX 5: NCI COMBINED COMORBIDITY INDEX

Comorbidity will be systematically assessed at baseline using the NCI combined comorbidity index to be able to correct for its confounding effect in the quality of life and toxicity analyses of the four trials and overarching research project. The conditions that make up the NCI and the weights assigned to them to calculate the score are listed below [27]. Conditions that are (highly) unlikely to be present among trial participants (such as dementia) will be assumed to be absent and can be left out of the CRFs to reduce administrative burden. This may differ by trial as each trial has trial-specific inclusion and exclusion criteria on top of the overarching inclusion and exclusion criteria.

Table 4: NCI combined comorbidity index

Condition	Weights
Moderate/severe renal disease	3
Congestive heart failure	2
Dementia	3
Chronic pulmonary disease	2
Cerebrovascular disease	2
Paralysis	1
Diabetes	2
Diabetes with complications	1
Peripheral vascular disease	1
Rheumatologic disease	2
Acute myocardial infarction	1
Old myocardial infarction	1
Ulcer disease	1

Interpretation according to Klabunde et al [27].

Four-tiered comorbidity classifier:

Low	0 points
Medium	1-2 points
High	3-4 points
Very high	≥5 points

Dichotomous comorbidity classifier:

None or mild	0-1 point
Moderate or severe	≥2 points

APPENDIX 6: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version**
1.0	14Jul2025	N/A		