STUDY PROTOCOL

FULL/LONG TITLE OF THE STUDY

Adipocytokines and their relationship to obesity and endometrial cancer

SHORT STUDY TITLE / ACRONYM

Adipocytokines in endometrial cancer

PROTOCOL VERSION NUMBER AND DATE

Version: 1.1
Dated: 27/04/2022

RESEARCH REFERENCE NUMBERS

IRAS Number	285863
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Sponsor's Number	SPON/2020/012/FHMS
Funder's Number	Irene Ray MD
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LIST OF CONTENTS

KEY STUDY CONTACTS

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STUDY SUMMARY

STUDY TITLE	Adipocytokines and their relationship with obesity and endometrial cancer
SHORT TITLE	Adipocytokines in endometrial cancer
STUDY DESIGN	exploratory biomarker study
STUDY PARTICIPANTS	Study population - patients presenting to Royal Surrey NHS Foundation Trust with endometrial cancer, identified at the MDT Control population - female patients without endometrial cancer, referred for benign condition.
PLANNED SIZE OF SAMPLE	100-120
FOLLOW UP DURATION	N/A
PLANNED STUDY PERIOD	36-48 months
RESEARCH QUESTION /AIM(S)	To investigate the relationship between adipocytokine level in blood and tissue (endometrial cancer tissue, adipose tissue and lymph node) in patients with endometrial cancer and co-relate with BMI to identify peripheral biomarkers that can be used as prognostic or diagnostic tools

FUNDING AND SUPPORT IN KIND

Funders (names and contact details of all organisations providing funding and /or support in kind for this study	GRACE (reg. no. 1189729)
Financial and non-financial support given	Financial support

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor is the University of Surrey. The sponsor, along with the Royal Surrey NHS Foundation Trust assumes overall responsibility for the initiation and the management of the study the funder provides financial support for the study.

PROTOCOL CONTRIBUTORS

- Irene Ray. Postgraduate research student, University of Surrey, and the Principal investigator (PI) of the study. Has been involved in protocol design and will conduct the research, data collection and analysis, interpretation of results, manuscript writing and dissemination of results.

- Patricia Ellis. Consultant Gynaecological Oncologist at Royal Surrey NHS Foundation Trust. Has been involved in protocol design and is also the clinical supervisor for the postgraduate research student and co-chief investigator of the study.

- Lisiane Meira. Lecturer in DNA Damage and Ageing, University of Surrey, Guildford. Has been involved in protocol design and is also the academic supervisor for the postgraduate research student and chief investigator of the study.

- Agnieszka Michael. Consultant Medical Oncologist at Royal Surrey NHS Foundation Trust and senior clinical lecturer at University of Surrey. Has been involved in protocol design and is also the academic co-supervisor for the post graduate research student.

STUDY FLOWCHART

Figure 1: Pathway for endometrial cancer patients undergoing surgery for endometrial cancer

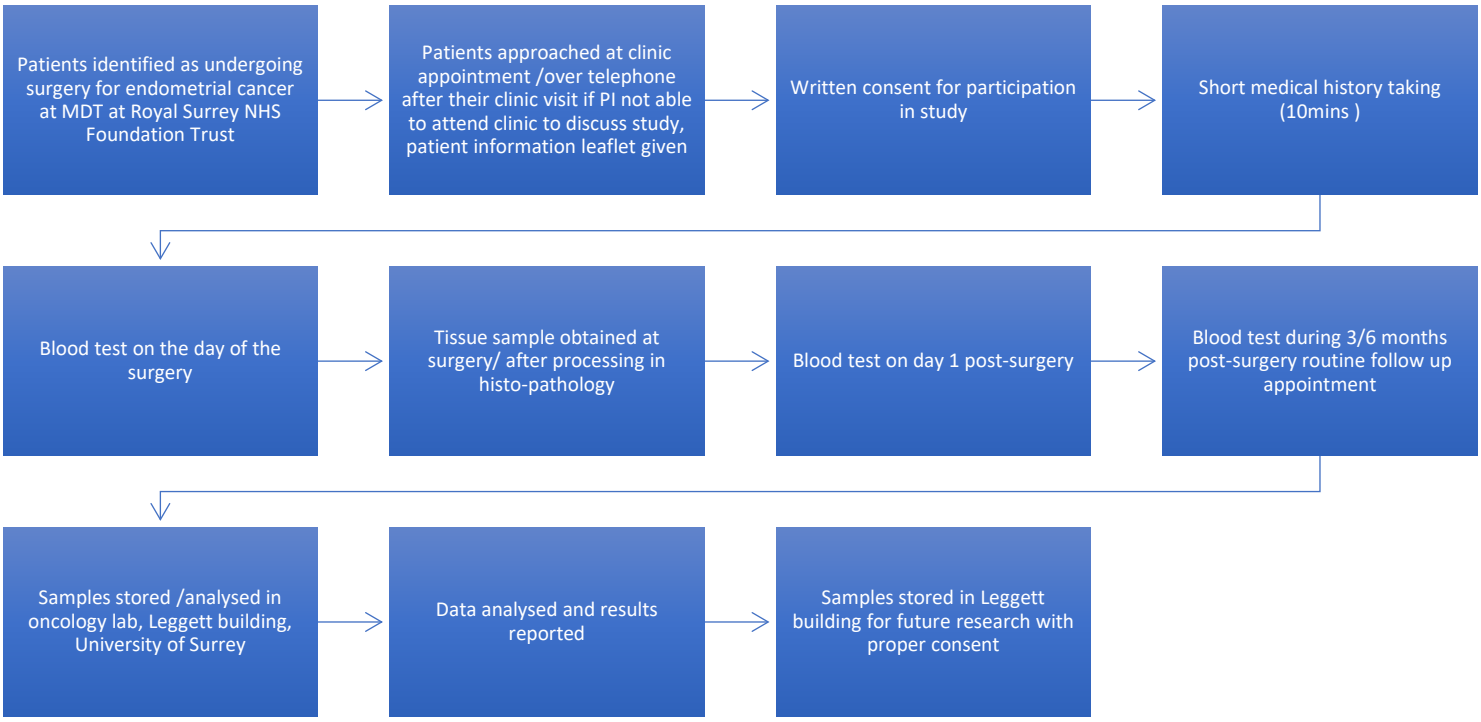
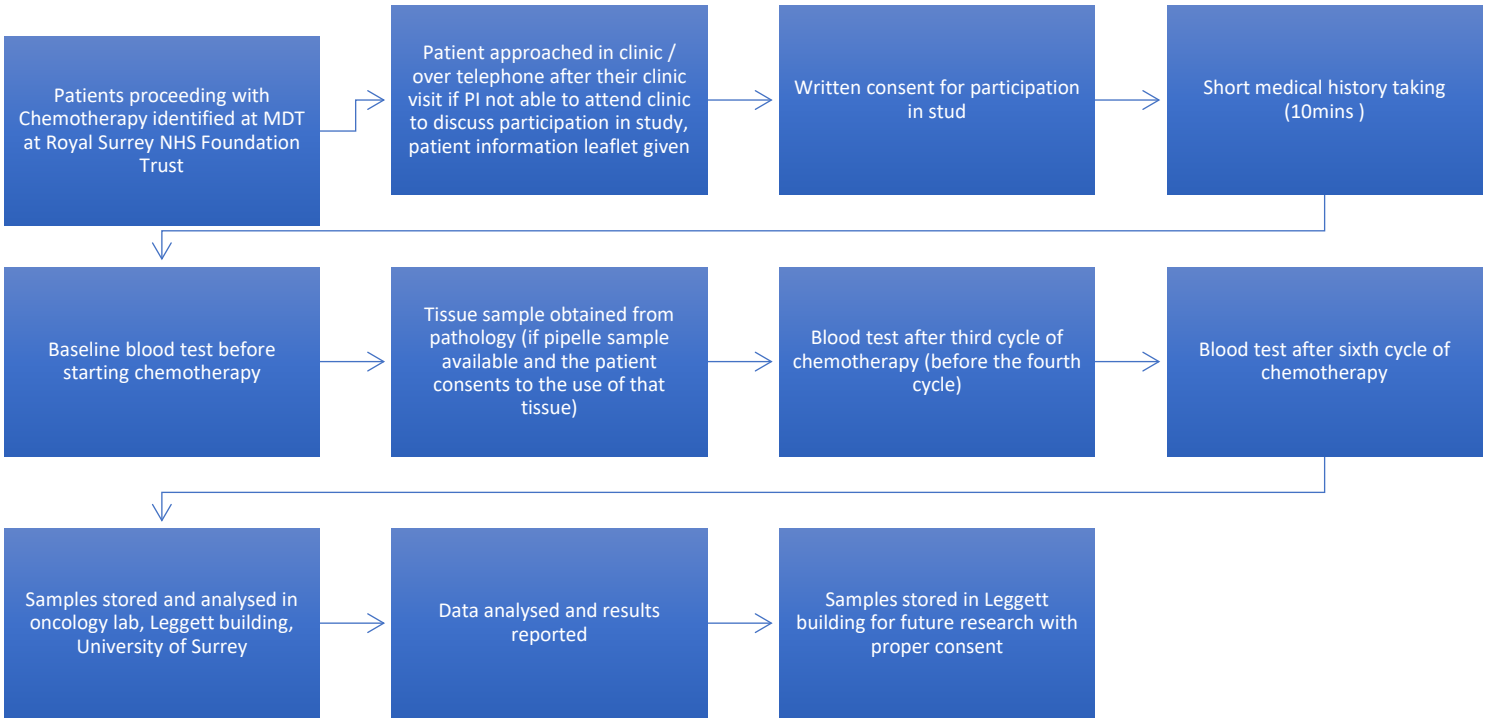


Figure 2: Pathway for patients undergoing chemotherapy for endometrial cancer



STUDY PROTOCOL

Adipocytokines and their relationship with obesity and endometrial cancer

KEY WORDS: Endometrial cancer, adiponectin, leptin, TNF α, IL 6, IGF 1, IGF 2, obesity

1. BACKGROUND

Endometrial cancer is the most common malignancy of the female genital tract. It is the fourth most common cancer in the UK with around 9,500 new cases in 2017, current lifetime risk being 1 in 36 women[1]. The number of women diagnosed with endometrial cancer continues to rise each year. Since the early 1990s, uterine cancer incidence rates have increased by almost three-fifths (55%) in the UK (2015-2017)[1]. The association between endometrial cancer and obesity is well documented. 7.5% of all cancers in women in UK are attributable to being overweight / obese (BMI ≥25 kg/m2). For endometrial cancer, this risk rises to 34%[2]. A review of meta-analyses showed endometrial cancer risk is 16% higher per 5 kg- gained during adulthood, 29% higher per 10cm increase in hip circumference and 27% higher per 10cm increase in waist circumference[3]. This higher endometrial cancer risk with raised BMI is present in both pre- and post-menopausal women. Moreover, patients who are obese tend to have a poorer outcome with more co-morbidities than their non-obese counterparts.

In the overweight and obese state, the function of the adipose tissue deteriorates resulting in a state of chronic inflammation[4]. In this inflammatory state, adipocytes and macrophages secrete several molecules, adipokines and inflammatory cytokines, which may promote tumour development and angiogenesis and stimulate adhesions and migration of cells[5]. Most implicated adipocytokines in the tumorigenesis pathway are adiponectin, leptin, tumour necrosis factor-α (TNF-α), Interleukin-6 (IL-6) and Insulin-like growth factor 1 and 2 (IGF 1 and 2).

Adipocytokine related signalling pathways are important in the development of an inflammatory microenvironment for tumours. This process is thought to increase the risk of endometrial cancer by inducing cell proliferation and preventing cell apoptosis. Adiponectin, the most abundant adipokine, has been suggested to have anti-angiogenic, anti-inflammatory, and anti-apoptotic properties. Raised leptin levels in obese state promotes inflammation by stimulating the production of IL-6, TNFα as well as IL-1 and IL-12[6]. Leptin and adiponectin secretion is counter-regulated in vivo. A study by Luhn et. al.[4] has shown adiponectin to have inverse relationship with the risk of endometrial cancer and leptin to have a direct co-relation.

Also, in an inflammatory environment, macrophages secrete potent proinflammatory cytokines such as TNF-α and IL-6, which are known to activate numerous transcription factors that regulate the expression of genes involved in immune responses, anti-apoptosis,

angiogenesis, and metastasis[7]. The mechanisms of tumorigenesis are thought to be involved are free-radical production that cause DNA damage and impaired DNA repair.

Research have further suggested that systemic levels of insulin-like growth factor (IGF) is dysregulated in obesity either due to increased IGF production or by down-regulation of IGF binding protein (IGFBP) prodution[8]. IGF 1 is a growth and proliferation promotor and has inhibitory effects on cell death and is a major contributor in many neoplastic transformation[9].

The above biomarkers are physiologically interrelated and are likely to reflect a more restricted number of underlying biological pathways[10]. Possibly, they work in a synergistic capacity to modulate the risk of developing endometrial cancer. If specific patterns of cytokine expression were found to be predictive of adverse outcome, then the specific receptors may be targeted as a therapeutic option for endometrial cancer[11]. No study so far has looked at all these markers together in the serum and tissue samples of the same endometrial cancer patients to give a more wholesome idea about their effect on tumour genesis, progression and outcome. Therefore, this study is designed to assess the prognostic significance of these six biomarkers in the blood and tissue of endometrial cancer patients and co-relating the levels with their BMI and tumour type, after adjusting for age, parity, smoking status, menopausal status, use of Hormone Replacement Therapy (HRT)/ hormonal contraception, and prevalence of diabetes and hypertension.

2. **RATIONALE**

Development of novel biomarkers for a variety of uses including diagnosis, treatment monitoring and prognostication is on the Cancer Reform Strategy agenda and actively encouraged by the National Cancer Research Institute and Medical Research Council.

Understanding how adipocytokines influence endometrial cancer risk may help to elucidate biological mechanisms important for the observed obesity-endometrial cancer association.

3. **THEORITICAL FRAMEWORK**

As the incidence of endometrial cancer continues to rise there is a health need for a better diagnostic and prognostic approach.

Studying the different biomarker levels in blood and cancer tissue will enable us to look for new targets that may be useful in the treatment and prognostication of this cancer.

Also, if the levels of these markers change significantly post-treatment, we can investigate if it will be possible to use these markers to assess response to treatment as follow-up for risk of recurrence forms an important part of the treatment protocol.

4. **RESEARCH QUESTIONS / AIM(S)**

4.1. **Objectives**

To assess the relationship between the endometrial cancer and blood and tissue biomarkers in patients referred for endometrial cancer management to Royal Surrey NHS Foundation Trust.

4.2. **Primary Outcomes**

1. To assess the circulating levels of adiponectin, leptin, tumour necrosis factor alpha (TNFα), interleukin 6 (IL-6), Insulin like growth factors 1 and 2 (IGF 1 and 2) in blood and at tissue level (endometrial tissue, adipose tissue, lymph node) from women with endometrial cancer (study population) and in the blood +/- endometrial tissue (control population) and to compare the results between the two groups.
2. Additional tests on the samples collected - looking at the cancer tissue microenvironment for infiltrating inflammatory cells +/- their secretions or other adipocytokines. We may also look at the tumour microbiome to look for any commensal bacteria or micro-organism and if available, to compare with tissue micro-environment and microbiome of normal endometrial tissue from control population.
3. To determine whether there is a correlation between these markers and obesity (classified by WHO category of BMI) after adjusting for confounding factors like age, parity, menopause, use of HRT/ hormonal contraception, smoking, diabetes and hypertension.

4.3. **Secondary Outcomes**

1. To determine if the markers have any prognostic significance by the expression profile with tumour grade, stage and histology.
2. To determine if the markers could be used as tools to assess effects of treatment.

5. **STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS**

5.1. **Study design**

All patients being referred to the Royal Surrey NHS Foundation Trust with diagnosed uterine cancer will be given the research information leaflet and invited to participate as the study

population of the research. Female patients being referred to Royal Surrey NHS foundation Trust for benign conditions (specifically not endometrial cancer) will be invited to participate as the control population.
Initially, an invitation letter will be sent alongside the patients' clinic appointment letter to inform them of the study and give them time for preliminary consideration of the study. Patients will then be approached in the outpatients' clinics after the initial consultation by the clinician. Alternatively, patients may be approached over phone and information about the study given at that time. The call will be scheduled after the clinic appointment visit so that the patient will have received the Invitation Letter that is sent out with the initial Appointment Letter, allowing patients sufficient time to consider the study. Patients will be given a participant information leaflet detailing the study rationale, methodology and analysis in clinic or alternatively the leaflet will be sent by post/ email (in case of telephone consultations). Patients who agree to participate in the study will be asked to sign a consent form after explanation at a later appointment.

Demographic data will be collected at the same time to correlate various risk factors associated with the development of uterine cancer. The data collected will include age, parity, smoking status, menopausal status, medications used, use of Hormone Replacement Therapy (HRT)/ hormonal contraception, and prevalence of diabetes and hypertension. This data will be collected by:

- Taking a medical history from the patient in clinic
- Patients' medical notes

This data will be directly entered into an existing departmental database for Gynaecological oncology which is password protected and stored on NHS computers.

Study participants will then have 30mls (2 ½ tablespoons) of venous blood taken on the day of the surgery and control participants will also have 30mls of venous blood collection alongside their clinic appointment.

Tissue samples from patients undergoing surgery will be collected as follows: For the study population, the PI will collect any fresh tissue (adipose tissue) directly from theatre before fixing as it is not needed for establishing diagnosis and the uterine cancer tissue and lymph node will be collected by the PI after histo-pathological examination from the histo-pathology department after the diagnosis is established. For the control population, if they are having uterine surgery, then the PI will collect some endometrial tissue after histo-pathological examination from the histo-pathology department after the diagnosis is established. All tissue processing will adhere to Human Tissue Authority (HTA) guidelines and will be performed at the Oncology laboratory at Leggett building at University of Surrey.

For study population only - the patients will have repeat blood tests (30mls of venous blood taken each time) on day 1 post-surgery and at their 3 or 6 months routine post-surgery follow up appointment. Control population will not have any repeat blood tests.

For the study population, women who are recommended chemotherapy, we will also ask consent to collect demographic data and baseline blood sample (30mls venous blood) at the time of consultation and after 3rd and 6th chemotherapy cycles to assess any changes in the markers that may correlate with progression or regression of disease.

We will also obtain archival serum samples and tissue blocks (of uterine cancer patients consented from a previous study for use during an appropriate ethics committee approved research) to help increase the number of recruitments for this study. Their demographic data with identification log will be made available to the PI only to assess for correlation between their data and the tissue diagnosis during analysis.

Timing of events including telephone contact events:

1. Send study Invitation Letter with Appointment Letter.
2. Clinic visit where patient is recruited/ phone call follow-up after clinic visit if the PI is not able to attend the clinic.
3. Enrolment of participant in study after consent.
4. Collection of blood and tissue sample as described above.

5.2. **Study flow-chart for patients undergoing surgery**

Procedures	Pre-study	Treatment period		
	Screening	Day of Sx	Day 1 Post Sx*	3/6 months post-Sx FU*
Visit Number	1	2	3	4
Written informed consent	X			
Demographic data	X			
Medical history	X			
Assessment of inclusion/ exclusion criteria	X			
Protocol restriction and continued eligibility check	X	X	X	X
Concomitant medication	X	X	X	X
Taking blood sample		X	X	X
Procuring tissue sample		X		
Recording AEs		Continuous		

*post surgery bloods relevant for study population only

5.3. **Study flow-chart for patients undergoing chemotherapy (CT)**

Procedures	Pre-study	Treatment period		
	Screening	Before starting CT	After 3rd CT cycle	After 4th CT cycle
Visit Number	1	2	3	4
Written informed consent	X			
Demographic data	X			
Medical history	X			
Assessment of inclusion/ exclusion criteria	X			
Protocol restriction and continued eligibility check	X	X	X	X
Concomitant medication	X	X	X	X
Taking blood sample		X	X	X
Recording AEs		Continuous		

5.4. **Sample analysis**

ELISA will be used to assay bio-marker levels in blood samples.

For tissue analysis we will set up a tissue microarray (TMA). This will allow more uniform staining of the sample for immunohistochemistry with no inter-specimen variation of the staining method. Each case will be reviewed, and the area of interest (tumour) marked on the slide. Cores from the areas of interest will be used to create the microarray block. Sections can then be cut from the microarray block and slides prepared for immune-staining. The advantage of using this method is that the samples are subjected to the same conditions while being stained and the same part of a tumour can be reliably stained for several markers. Tissue sections from the TMA will be used for immune-staining and the expression of the markers of interest will be scored.
Some tests have become available at the University of Surrey laboratory that can be done from the samples that are already being collected to maximise our information on endometrial cancer from the samples already available. These tests will be carried out at the University of Surrey laboratory and will not involve any resource implication on Royal Surrey NHS Foundation Trust.

The additional tests may include - looking at the cancer tissue microenvironment for infiltrating inflammatory cells and / or their secretions or any other adipocytokines. We may also look at the tumour microbiome to look for any commensal bacteria or micro-organism that may have a role in cancer onset, progression and drug response by secretion of small molecules and metabolites. Clinical data which is available on the cases will then be correlated with the histological and immunohistochemical results and statistical analysis will be carried out.

5.5. **Data analysis**

Standard statistical analytical tools will be used to analyse the data. Relation between different variables will be sought with odds ratio, confidence interval and significance with P value (<0.05 significant). The Mann–Whitney U test will be used to assess differential expression of immune markers between tissue types –blood and tumour tissue. Correlation with clinical characteristics will be determined using univariate log-rank and multivariable Cox proportional hazards adjusting for age, stage, grade and histology. Results will be compared between the study and the control populations.

6. **STUDY SETTING**

Study patients will be recruited when attending a clinic in the department of Gynaecological Oncology at Royal Surrey NHS Foundation Trust. Private consultation rooms are available here for discussing the study, history taking and consenting.

Blood sample will be collected on the day of the surgery when they are in the theatres and then repeated on day 1 post-operative in gynaecology ward and at 3 or 6 months post-surgery follow-up in clinic.

Tissue samples will be obtained from the following areas:

1. Adipose tissue from the main theatres at Royal Surrey NHS Foundation Trust
2. Uterine cancer tissue and lymph node from the histopathology department after they have finished analysis.

For those women recruited undergoing chemotherapy, blood sample will be procured at initial consultation and after 3rd (with the blood test before the fourth cycle of chemotherapy) and 6th cycles of chemotherapy. This can be performed in the Department of Gynaecological Oncology at Royal Surrey NHS Foundation Trust.
All samples (blood and tissue) will then be transferred to the Leggett Building at University of Surrey for processing and storage following HTA regulations. The samples will be double boxed for transfer. The outside box will be an icebox. The PI will personally transport the tissues by foot from the hospital to the Leggett building as they are very near geographically and it is a short 4 minutes' walk.

Control patients will be recruited when they attend a clinic appointment at Royal Surrey NHS Foundation Trust for any benign condition. Blood sample will be collected during their clinic appointment after written consent. If they are having any uterine surgery, endometrial tissue will be collected after histopathological diagnosis from the histo-pathology department.

Samples will also be stored anonymised (in case of patients who give consent) in Leggett building, University of Surrey following all regulations by HTA) for use in ethics approved future research project.

Historical samples / tissue blocks stored in the oncology department in the Leggett building, University of Surrey, from a previous study will also be used if appropriate consent is in place.

7. **SAMPLE AND RECRUITMENT**

Potential participants will be identified in the Royal Surrey NHS Foundation Trust – either seen here or referred here and receiving her treatment here.

7.1. **Inclusion criteria**

1. Study population- Women diagnosed with endometrial cancer
2. Control population – Women being seen in clinic for benign conditions
3. Age 18 or above
4. Of sound mind so they can give informed consent
5. Historical tissue sample/ blocks from previous cases in the oncology department in the Leggett building also be used if appropriate consent is in place.

7.2. **Exclusion criteria**

1. Under 18yrs age
2. Unable to give consent /denies consent

7.3. **Sample size**

We will aim to recruit 30-60 patients with diagnosed endometrial cancer in the study. This sample size will also include archived tissue sample (formerly consented and stored in Leggett building for use in future ethical research). We will aim to recruit as many patients in the control population as in the study population, aiming for a total (study + control population) of 100-120 patients.

7.4. **Recruitment**

All patients seen or referred with endometrial cancer at the Royal Surrey oncology Department will be invited to participate in the study as a part of study population. We will aim to get as many control population from the women referred to Royal Surrey NHS Foundation Trust with benign conditions.

Patients will not receive any payments for participation in the study. We aim to obtain all information and samples at the time of routine visits.

7.4.1. **Sample identification**

Patients diagnosed with endometrial cancer will be identified through the Gynaecological Oncology Multi-Disciplinary Team meeting or by the Gynaecological Oncology or Medical Oncology teams. Control population will be identified through the above route or from referral letters to Royal Surrey NHS Foundation Trust.

7.4.2. **Consent**

Written consent will be obtained after the patient has received the participant information leaflet and had the opportunity to discuss and ask questions about the study. Enough time will be given for the purpose. Patients must all have capacity to consent. Consent will be undertaken by clinicians on the Gynaecological Oncology team. If necessary, a translator or language line can be used.

Consent will also be taken for use of samples (anonymised and stored in Leggett building, university of Surrey following all regulations by HTA) for use in future research. However, the patient can still take part in this study even if she does not consent to her data/ samples to be used in a future study.

7.4.3 **Withdrawal of consent**

Participants are free to withdraw at any time and without giving a reason. A decision to withdraw or not take part will not affect the standard of care they will receive. Anonymised data or tissue already collected with consent would be retained and used in the study. Anonymised data or tissue already collected with consent would be retained and used in the study. This is because once anonymised, samples and data cannot be linked back to a participant and therefore we are unable to withdraw a participant's anonymised data or samples. No further data or tissue would be collected, or any other research procedures carried out on or in relation to the participant if they withdraw their participation.

8. **ETHICAL AND REGULATORY CONSIDERATIONS**

There is no direct benefit for the patients recruited into this study. They will be part of a research study which, in the future, may find ways of improving diagnosis of and survival from endometrial cancer.

Patients will not be disadvantaged in any way by participating in this research study – they will still receive standard clinical care for their condition.

Informed written consent will be taken from everyone who wishes to participate in the study. Written information leaflets will be given to the patients to read before they decide whether they wish to participate or not. Consent will be taken by doctors on the Gynaecological oncology team who have a clear and good understanding to this research and can take a valid informed consent.

All computers used to collect and save data will be stored in a securely locked room on NHS computer in NHS or University premises. Access to the computer will be password protected. Specific secure passwords will be needed to log onto these computers and this information will only be available to the researchers who are also part of the healthcare team. All computers will be encrypted to prevent access by any external source to the confidential information stored.

All personal information will be anonymised so that researchers except the PI will be blinded to this information. Information used for inference of prognostic outcomes will be based on generic data collected rather than individual information. At all times, the NHS Code of Confidentiality will be followed. Only the PI will have access to the 'key' to the patient identifiers. PI will be responsible for this.

All samples (blood and tissue) will then be transferred by the PI to the Leggett Building at University of Surrey for processing and storage following HTA regulations. The samples will be double boxed for transfer. The outside box will be an ice-box. The PI will personally transport the tissues by foot from the hospital to the Leggett building as they are very near geographically and it is a short 4 minutes walk.

Samples will be also be stored anonymised (in case of patients who give consent) in Leggett building, University of Surrey following all regulations by HTA) for use in future ethics approved research project. The patient will still be able to take part in this current study even if she does not consent to her data/ samples to be used in a future study.

8.1. **Assessment and management of risk**

Taking venous blood samples may involve a small amount of discomfort but is often a routine part of clinical assessment.
Tissue samples taken at the time of surgery will add no side-effect, discomfort or distress in addition to those of the clinically indicated surgery.

If any concerns are raised during consenting, with regards to the patients' wellbeing or safeguarding, the clinical team will be notified immediately, and appropriate steps will be taken to rectify the concerns.

8.2. **Research Ethics Committee (REC) and other regulatory review and reports**

Before the start of the study, a favourable opinion will be sought from the NHS REC for the study protocol, informed consent forms and other relevant documents.

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.

All correspondence with the REC will be retained by the PI. It is responsibility of the PI to produce the annual reports as required. The PI will notify the REC of the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the PI will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the PI will submit a final report with the results, including any publications/abstracts, to the REC.

8.3. **Amendments**

Should the protocol undergo any amendments, we will seek advice from the sponsor and submit them to the REC/HRA where applicable. Amendments will not be implemented until all relevant opinions and approvals have been received. Amendments to the protocol will be tracked in the amendments section in appendix.

8.4. **Supervisor/ Peer review**

The study protocol and other proformas have been reviewed by the clinical supervisor - Miss Ellis, consultant gynae-oncologist at the Royal Surrey NHS Foundation Trust and academic supervisors - Dr. Meira and Dr. Michael of the University of Surrey, who are all senior published authors. The study protocol has also been reviewed by the study sponsor (RIGO). The study has also been peer reviewed for enrolment into a public database – clinicaltrials.gov (ID No. NCT04697264).

8.5. **Patient and public involvement**

This research protocol was discussed with patients from Royal Surrey NHS Foundation Trust who also reviewed the patient information sheets and any suggestions/changes were incorporated.

8.6. **Protocol compliance, adverse events reporting and breaches**

The PI will be responsible for the conduct of the research. The research will be monitored by the supervisors involved. The sponsor can, at any time, audit the conduct of the study. The local R&D office regulations for maintaining research governance will apply.
Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the PI and sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.7. **Data protection and patient confidentiality**

All investigators and study site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.
Anonymised data will be stored on encrypted and password protected NHS and University computers.

All computers used to collect and save data will be stored in a securely locked room on NHS or University premises. Specific secure passwords will be needed to log onto these computers and this information will only be available to the researchers (they are also part of the healthcare team).

Any emails containing identifiable patient information will be sent to/from encrypted servers such as NHS mail.

All personal information will be anonymised so that the researchers will be blinded to this information. Information used for inference of prognostic outcomes will be based on generic data collected rather than individual information.

Only the principal investigator will have access to the 'key' to the patient identifiers.
Data from the interview will be directly entered into an existing departmental database for Gynaecological oncology which is password protected and stored on NHS computers. A file containing a copy of patient demographic data proformas that are completed at the initial interview will be stored in a locked office within the Leggett building, University of Surrey to be made available for source data verification, if required. The principal investigator will be the data custodian. All data will be stored for 10 years.

8.8. **Indemnity and insurance**

The University of Surrey (sponsor) has in force all relevant insurance for the design, conduct and the management of the study. The sponsor has arrangements in place for payment of compensation in the event of harm to the research participants where no legal liability arises.

8.9. **Access to final study dataset**

The final dataset will be accessible by the research team.
Study investigators and the sponsor may seek access to the data after approval.

9. DISSEMINATION POLICY

9.1. **Dissemination policy**

The study results will be published in international journals and presented at relevant conferences.
It will also be published as the MD thesis for the PI.
GRACE charity (funder) will be acknowledged in all publications as the funder of the research.

9.2. **Authorship eligibility guidelines any intended use of professional writers**

The PI will be the lead author on the final study report and any publications. The supervisors are senior authors and will take responsibility for the published data. Other protocol contributors will be listed as co-authors.

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12. **PROTOCOL HISTORY**

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	0.9	28/06/2021	Irene Ray (PI)	Provision for telephone consultation added
2.	1.0	16/09/2021	Irene Ray (PI)	1. Control population added. 2. Provision for performing other relevant tests from the samples collected.
3.	1.1	27/04/2022	Irene Ray (PI)	1. Increase in number of control population recruitment. 2. Extension of study duration to 36-48 months.