Template Protocol for non-CTIMPs

Study Acronym

UGLOC as a method of fertility preservation.

Study Title

Intra-operative ultrasound guided laparoscopic ovarian cystectomy (UGLOC) as a method of fertility preservation in the management of benign ovarian cysts: Randomised Controlled Trial.

Version 7.0

09/08/21

Main Sponsor:

Imperial College London

Funders:

N/A

Study coordination centre:

Queen Charlotte's and Chelsea Hospital

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REC reference:

Protocol authorised by:

Name & Role	**Date**	**Signature**

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Clinical Queries

Clinical queries should be directed to Miss Lorraine Kasaven (Co-investigator) who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity at:

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Funder

This research project is sponsored by Imperial College London. There is no commercial partner involved in this Research Study. There is no conflict of interest declared in the study protocol.

This protocol describes the ***'Intra-operative ultrasound guided laparoscopic ovarian cystectomy (UGLOC) as a method of fertility preservation in the management of benign ovarian cysts: Randomised Controlled Trial'*** study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

IOTA	International Ovarian Tumour Analysis
UGLOC	Ultrasound Guided Laparoscopic Ovarian Cystectomy
AMH	Anti-Mullerian Hormone
AFC	Antral Follicle Count
BOT	Borderline Ovarian Tumour
FSS	Fertility Sparing Surgery
USO	Unilateral Salpingo-oophorectomy

KEYWORDS

- Fertility Preservation Surgery
- Intra-operative Ultrasound
- Benign Ovarian Cyst
- Anti-Mullerian Hormone

STUDY SUMMARY

TITLE	Intra-operative ultrasound guided laparoscopic ovarian cystectomy (UGLOC) as a method of fertility preservation in the management of benign ovarian cysts: Randomised Controlled Trial
DESIGN	A multi-centre prospective cohort non-blinded randomised controlled trial
AIMS	To assess whether intra-operative ultrasound is a significant method of fertility preservation surgery in the treatment of women of reproductive age with benign ovarian pathology.
OUTCOME MEASURES	Primary Outcome: Anti-Mullerian hormone (AMH) and Antral Follicle Count (AFC) measured at 3 and 6 months post-operatively Secondary Outcome: Surgical outcomes will be measured including: o Duration of hospital stay (days) o Duration of surgery (minutes) o Presence of intra-operative cyst rupture (Yes/No)
POPULATION	Females aged 18 -50 years old with a benign ovarian cyst requiring surgical management of pathology. Women with: Cyst size ≥3cm; ≤10cm
ELIGIBILITY	IOTA B features of an ovarian cyst: Unilocular, solid components: largest diameter ≤7mm, acoustic shadows, no blood flow, smooth multilocular cyst: largest diameter ≤100cm.
DURATION	3 years

REFERENCE DIAGRAM

See Appendices 1-3

1.0 INTRODUCTION

1.1 BACKGROUND

Over the last few decades, advancements within the field of reproductive medicine have facilitated the rapidly emerging sub-specialty in gynaecology known as fertility preservation. Fertility preservation includes various methods to preserve reproductive tissue or gametes such as medical, surgical or laboratory techniques, thus empowering women to preserve their fecundity with a view to achieving pregnancy at a later date.[1] Cancer is the second leading cause of death in women of reproductive age (<45 years old),[2] therefore focus within the specialty has predominantly concerned female cancer patients. This is because a number of treatment options for cancer including chemotherapy or radiotherapy are gonadotoxic in nature rendering women infertile. With survival rates of cancer in women of reproductive age as high as 70% in adults, a number of women are subsequently faced, albeit, with either cure or remission of disease, but also the burden of infertility.[2] The inability to bear children is associated with psychological distress and sequalae,[3] therefore fertility preservation is deemed an important quality of life matter.

Consequently, there has been an increasing demand for less radical surgical management of gynaecological cancers, with a shift towards conservative methods in order to preserve the reproductive organs. In appropriately selected women, this enables the opportunity to balance the risks of recurrence from disease with less radical surgery, whilst reserving the ability to conceive in the future. For example, previous management of borderline ovarian tumours [4], included radical debulking surgery which required bilateral salpingo-oophorectomy. Fertility sparing surgery (FSS), which now includes unilateral salpingo-oophorectomy (USO) or ovarian cystectomy is considered the mainstay treatment in women with early-stage disease, non-invasive implants or for those who wish to conceive. Evidence suggests that the 5-year overall survival following FSS is similar to that of debulking surgery.[5] However, the risk of relapse when ovarian cystectomy and USO are performed is increases from 13% to about 6%.[6] In the context of BOT, FSS is deemed safe when concurrent surveillance monitoring for detection of recurrence is carried out, allowing women the opportunity to conceive during interval monitoring of disease.[7]

There are many causes of infertility in women including benign pathology such as endometriosis or ovarian cysts. Infertility is caused either by the underlying pathology itself, or indirectly associated with the surgical intervention required to treat.[8] The latter is attributed to the fact that ovarian surgery, despite minimally invasive techniques, results in the resection of a number of healthy ovarian follicles and tissue.[9] Anti-Mullerian Hormone (AMH), a reliable marker of ovarian reserve, has been observed to be reduced post-operatively following surgery for endometriosis.[10] The lifetime risk of a women

undergoing surgery for the presence of benign ovarian pathology is 5-10%. It is understandable therefore, why an increasing demand for the implementation of fertility sparing surgical techniques for women with benign pathology is also prevalent.[11] Such demand is exacerbated further by the fact that the age of motherhood has increased over the last few decades.[12] Increasing age however, is associated with poorer oocyte quality and yield, therefore increases the risk of involuntary childlessness as a direct consequence of age related fertility decline.[13] If women delay attempting pregnancy to a later age, in addition to the risks of surgically induced impairment of ovarian tissue, overall chances of achieving pregnancy in the future maybe significantly reduced. It is imperative therefore, that fertility sparing techniques are implemented where possible in women of reproductive age, in order to optimize the chances of future successful conception.

1.2 RATIONALE FOR CURRENT STUDY

The use of intraoperative ultrasound has been widely implemented amongst other specialties.[14] However, within gynaecological surgery, it is not as commonly recognized, despite evidence that it can be used as an adjunct to improving minimally invasive surgical techniques.[15] This is primarily due to the improved visualization of the operative field which can assist more technically difficult surgical procedures, thus minimizing intraoperative complications.[16] The application of ultrasound guidance within gynaecological procedures have included predominantly ovarian cyst aspiration, in vitro fertilization and removal or insertion of intra uterine devices.[14] Although pre-operative imaging provides procedural planning, it cannot compare to the information gained from real time imaging. For example, in previous studies, intraoperative ultrasound detected more myomas during myomectomy than pre-operative transvaginal imaging.[17] Furthermore, it provides the potential to assess lesion margins, ensuring resection of pathology is complete with negligible damage to surrounding healthy tissues.[15] This is consistent with a recent systematic review, which also demonstrated that albeit a novel technique, amongst various case series, pathology can be safely resected without incurring injury to healthy reproductive tissue.[15] Therefore, intraoperative ultrasound has the potential to improve surgical accuracy, reduce complications and improve patient safety. The application of intraoperative ultrasound as an adjunct to fertility sparing surgery has not been widely researched, with only a few case series reporting surgical outcomes on patients undergoing treatment for pre-malignant or malignant pathology.[18] The aim of this study therefore, is to determine the efficacy of this surgical technique in the management of benign pathology including the surgical resection of ovarian cysts.

1.3 RESEARCH QUESTION

The primary objective of this study is to determine the efficacy of intraoperative ultrasound-guided ovarian cystectomy (UGLOC) for the management of benign ovarian cysts as an adjunct of fertility sparing surgery. This will be determined through assessment of post- operative AMH and AFC, which are both reliable measures of ovarian reserve. The secondary objective is to determine the surgical outcomes in women who have undergone intraoperative ultrasound guided ovarian cystectomy and compare this to the control group.

2.0 STUDY OBJECTIVES

Primary objectives

To determine the efficacy of intraoperative ultrasound guided ovarian cystectomy as an additional method of fertility preservation.

Secondary objectives

To determine the surgical outcomes in participants who have undergone intraoperative ultrasound guided ovarian cystectomy and compare to the control group.

3.0 STUDY DESIGN

This will be a multi-centre prospective cohort study carried out as a non-blinded randomised controlled trial. Participants will be allocated to either a control group of laparoscopic ovarian cystectomy performed without ultrasound guidance, or to the experimental ultrasound guided laparoscopic ovarian cystectomy (UGLOC) group. All surgeons operating and participants recruited to the study will be aware of which group they have been allocated to from the beginning of the study. The investigators aim for equal sample sizes in both groups (see power calculation below).

Participants will include all women of reproductive age diagnosed with a benign ovarian cyst requiring surgical management. The duration of the study from recruitment to end of data collection will be approximately 3 years (01/10/21-01/10/24).

Women referred to the outpatient gynecology clinic with a suspected ovarian cyst will be asked about their clinical history and undergo a pelvic transvaginal ultrasound scan (2D and 3D ultrasonography) as part of routine clinical care. If an ovarian cyst is seen on ultrasound, it will be assessed according to local protocols based on simple descriptors and international ovarian tumor analysis (IOTA) simple rules. Depending on the severity of symptoms, nature of the cyst and fulfilment of the inclusion criteria and if the woman is suitable for surgical management, she will then be invited to participate in the study.

Participants will be recruited from various general gynaecology clinics as well as specialist clinics including: ovarian cyst, the IOTA and rapid access clinics across Imperial and University College London Hospital.

Following consent of participation, the woman will then be assigned to either a control or experimental group. A separate research group, not directly affiliated with the project will perform the randomisation process. The research group will print x "control group" labels and x "experimental group," in which each label is then sealed into an individual envelope. All envelopes will be numbered and issued in sequence. During the recruitment process, once the participant has given consent to partake in the trial, a member of the research team will select the envelope in sequence, which will then assign the participant to a group. This will prevent the person performing the randomisation from selecting another envelope if they are not happy with the group allocation. For this study, it will not be necessary to postpone diagnostic procedures or treatment, and participation will not influence normal treatment.

Surgical Intervention

The same surgeons will operate on participants in both the control and experimental group. This will aim to exclude bias which may otherwise attribute findings to the surgeon operating. Surgery will be performed at Imperial Healthcare NHS Trusts and at the University College London Hospitals NHS Foundation Trust by an experienced clinician.

Data Collection

The investigators will collect the following data: patient demographics including age, BMI, gravida, parity and gynaecological surgical history. Pre-operative data will include findings from the diagnostic transvaginal scan and measure of ovarian reserve: AMH and AFC. Intra-operative data will include transvaginal findings during surgery (in the experimental group only), such as cyst location and size or any new lesions noted. Residual ovarian volume post cystectomy will also be measured intraoperatively. Histology data will include the histological diagnosis of the ovarian cyst and volume of normal ovarian tissue excised during the cystectomy measured as per margins in mm. Outcomes following surgery including duration of surgery (mins), length of hospital stay (days) and post op complications will be recorded.

Post operatively, participants will return to clinic for follow up at 3 and 6 months post -surgery, whereby a blood test will be taken to assess ovarian reserve by measuring the AMH level. The outpatient gynaecology nurse in clinic or research staff will be responsible for taking the blood sample

and will only require one EDTA bottle (yellow top) to be filled (20-40mls). The blood samples will be processed by Imperial College Healthcare Trust laboratories or University College London Hospitals NHS Foundation Trust, depending on the site taken, and will be discarded as per local protocol once the AMH has been determined. There are no specific storage or transfer requirements outside of normal practice. Therefore, samples will be 'podded' to the labs once taken in the usual way. In addition, an ultrasound will be performed during the follow up appointment to measure AFC and assess volume of preserved ovarian tissue. Follow up appointments should take approximately 20 minutes. The two blood tests and two ultrasound scans carried out during the follow up process are considered standard clinical practice, and therefore not considered additional investigations for the purpose of this research study.

3.1 STUDY OUTCOME MEASURES

Primary: AMH and AFC measurements at 3 and 6 months post-surgery.

Secondary: Surgical outcomes including:

- Duration of surgical procedure (minutes),
- Duration of hospital stay (days)
- Presence of intra-operative cyst rupture or spillage (Yes/No)

4.0 PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

All participants of the study will undergo routine pre-operative assessment including tests for Methicillin-resistant Staphylococcus aureus (MRSA) and COVID-19 and a full blood count. Given the indication for referral to the gynaecology clinic, all participants of the study will have an ultrasound scan to assess the nature and size of their ovarian cyst.

4.2 INCLUSION CRITERIA

All females of reproductive age with a diagnosis of a benign ovarian cyst requiring surgical management.

This includes cysts defined as dermoid, teratoma, simple cyst, functional, serous cystadenoma or mucinous cystadenoma from the initial diagnostic ultrasound.

A strict criterion for the US diagnostic features will include the following:

- Cyst size ≥3cm; ≤10cm
- International Ovarian Tumour Analysis Benign features (IOTA B):
    - Unilocular
    - Solid components: largest diameter ≤7mm
    - Acoustic shadows
    - No blood flow
    - Smooth multilocular cyst: largest diameter ≤10cm

Specifically:

- Pregnant participants can be included but will be analysed separately
- For participants selected for surgery, delay of surgery is not an exclusion criterion for this study, but for selected objectives we will use only those participants in whom surgery was performed within 180 days after the ultrasound examination
- With regards to age, participants can be selected only if 18-50 years old
- Participants whom only underwent transabdominal scanning can be included in the study, but will be analysed separately

4.3 EXCLUSION CRITERIA

- Cysts that are deemed to be clearly physiological and less than <3 cm in maximum diameter are not eligible for inclusion
- Cysts ≥11cm in maximum diameter
- Non-adnexal masses e.g. peritoneal inclusion cysts (where diagnosis is certain)
- Any cyst with features of malignancy
- The denial or withdrawal of written informed consent
- Females of post- menopausal or peri-menopausal status

4.4 WITHDRAWAL CRITERIA

All participants will be consented prior to enrolment, and will receive a full explanatory participant information leaflet. Signed participant consent will be obtained. The right of the participant to refuse to partake in the trial without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if it is in the participant's best interest, but the reasons for doing so should be recorded. In these

cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. All data captured in relation to their participation may be destroyed at their request.

5.0 ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and emailed to the chief investigator within 24 hours. However, relapse and death due to other pathology, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Chelsea Research and Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and,
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs

RGIT@imperial.ac.uk

CI email: joseph.yazbek@nhs.net

Fax: nil

Letters: For the attention of Miss Lorraine Kasaven

Queen Charlotte's and Chelsea Hospital, Du Cane Road, W12 0HS

Please send SAE forms to: L.kasaven@nhs.net

Tel: 02076366765 **(Mon to Fri 09.00 – 17.00)**

6.0 ASSESSMENT AND FOLLOW-UP

Follow up appointments at 3 and 6 months post -surgery will be carried out at the participants' respective hospital gynecology clinic responsible for the care and management of the ovarian cyst. During this appointment, the responsible physician will assess recovery post- surgery and perform a clinical assessment. A blood test to measure ovarian reserve including assessment of AMH will be taken by the outpatient gynaecology nurse or research staff assigned to the clinic. A transvaginal ultrasound scan will be performed during the appointment by an experienced gynaecology specialist trainee or Consultant to assess the AFC and preserved ovarian volume of tissue remaining. Any incidental findings identified on ultrasound scan of gynaecological pathology, will be managed by the responsible clinician and the participants GP will be informed by letter.

The majority of participants are likely to be discharged following the 2nd clinic appointment 6 months post- surgery, whereby no further involvement is required in the study. If a participant becomes pregnant during the follow up period, follow up will be deferred to 3 and 6 months post completion of pregnancy.

7.0 STATISTICS AND DATA ANALYSIS

A study by Kwon et al[19] investigated the impact of laparoscopic ovarian cystectomy for benign cysts on post-operative ovarian reserve, as measured by follow up AMH levels taken 3 months after surgery. This particular study is considered to be most applicable for determining the power calculation of our proposed randomised controlled trial based on the following principles: pathology of the ovarian cysts were benign in nature and the sample size of the paper is one of the largest reported in the literature review.

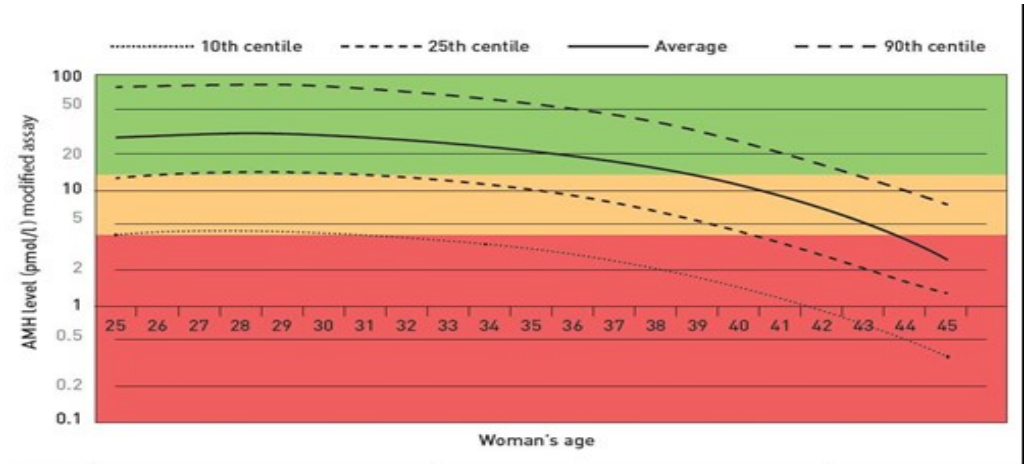
From a sample size of 100 women, this paper deduced that AMH levels decreased on average 30.58% (+/-29.66%) between the pre-operative value to the level assessed 3 months following surgery.[19] Specifically, the group of participants who underwent laparoscopic ovarian cystectomy for benign ovarian pathology had a mean (+/-SD) serum AMH of 1.59 (+/- 1.92)(ng/ml), which when converted to (pmol/L) is 3.57 (+/-4.31).

At present there are no reported studies assessing the change in AMH levels following ultrasound guided ovarian cystectomy. However, the investigators of this study have performed a small number of ultrasound-guided surgeries on 5 women, and therefore have a small data set, which can be considered a *pilot* study.

Amongst 5 women who have undergone ultrasound guided laparoscopic ovarian cystectomy, the mean difference (+/-SD) in AMH levels measured 3 months post operatively from pre-op levels is: 14.46 (+/- 21.02) pmol/L. This represents a substantial clinical difference according to previous research, and would imply women being less likely to experience fertility issues as they would be near the lower end of the normal range of AMH rather than in the lowest decile (ca. 0-4.5).

In order to calculate the sample size, the investigators have leveraged the pilot data to derive an estimate of the mean and standard deviation. From the literature, it can be assumed AMH is approximately log-normally distributed, as demonstrated from figure 1.[20] Using this figure, the investigators have determined the normed (percentile) transformation of values from the pilot study. **(Table 1)**

Figure 1: Normed percentile transformation of AMH Values[20]



Green zone	Above the 25th centile for younger, fertile women	Very likely normal ovarian reserve – age is the best predictor of your future fertility	80% chance of 6 or more eggs in IVF
Orange zone	Between the 25th and 10th centiles for younger, fertile women	Some women in this range will have reduced ovarian reserve	50% chance of 6 or more eggs in IVF
Red zone	Below the 10th centile for younger, fertile women	Very likely reduced ovarian reserve	20% chance of 6 or more eggs in IVF

Table 1: Estimated values of AMH differences based on normed percentile transformation

AMH Differences (pmol/L)		
	Treatment Group	Control Group
Mean	17.06	3.57
Standard Deviation (SD)	22.28	4.31
Coefficient of variation (CV) =(SD/Mean)	1.31	1.21
Number of participants	5	100

Using the pilot data, the investigators anticipate that 32 participants will be required to demonstrate a differential AMH level. (**Table 2)**

Table 2: Power Calculation

Sample Size Calculation		
	Treatment Group	Control Group
Mean (pilot)	17.06	3.57
Standard Deviation SD (pilot)	22.28	4.31
Standard Error (S.E)	6.18	1.08
Lower CI	4.70	1.42
Upper CI	29.42	5.73
Minimum (n)	**11**	**11**
Small sample margin	**2**	**2**
Attrition (assumed)	**3**	**3**
Total (n)	**16**	**16**

The minimum sample size is 11 participants. Considering the small size of the pilot and the very low risks thus far, the investigators include 2 more observations to boost power, and assume an attrition rate of approximately 25%. This leads to a total (n) of 16 participants per arm, with a power of 0.95 to detect a difference at the 5% level using a standard t-test on the log-transformed difference in means of AMH, the robust proxy for fertility. It will be necessary to perform an interim analysis given the low number of participants available for the power calculation.

With regards to further data analysis of the study, the investigators plan to use descriptive statistics (mean +/- standard deviation), two-sided tests, and Wilcoxon rank sum test to compare continuous variables in two groups. For more than two groups, the Kruskal-Wallis exact test will be used. For comparing a proportion with an expected value, a binominal exact test will be used. Results are considered significant at $p<0.05$. Analysis will be performed with SAS (version 9.2) and Statistical Package for Social Sciences for Windows (version 16). Statistical analysis will be performed under the supervision of Mr Srdjan Saso.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8.0 REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the London Chelsea Research Ethics Committee and the Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

This study does not require any specific funding

8.7 AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9.0 STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Miss Lorraine Kasaven (co-supervisor).

10.0 PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Study Management Group. The investigators will therefore be responsible for publication of the data. As such the investigators will co-author all clinically relevant papers, to which a significant contribution has been made. Co-authors will be included depending on the journals publication guidelines also.

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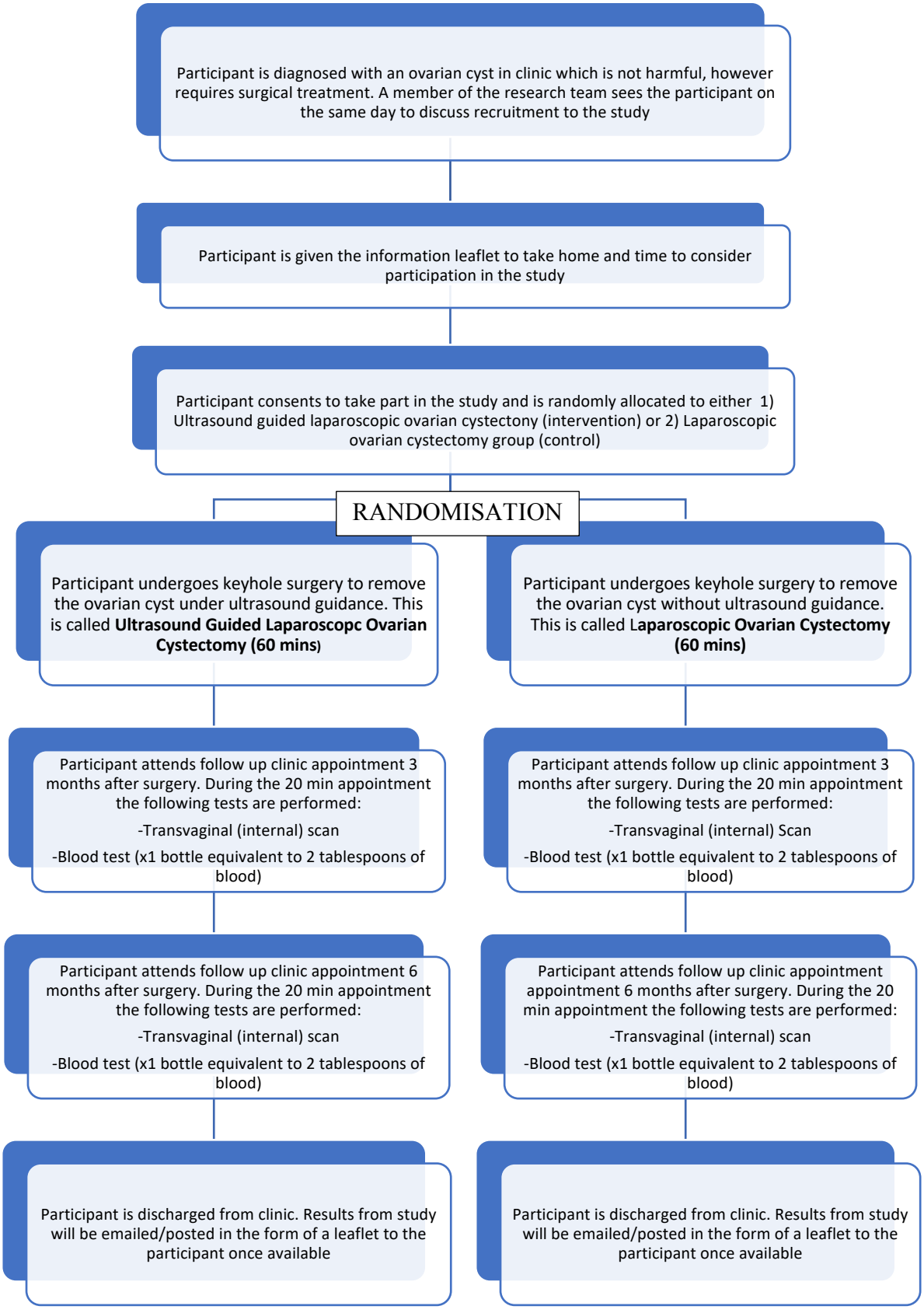
Appendix 1

Summary of investigations, treatment and assessments

Exam		**Month of Treatment**								
	Pre-treatment	1	2	3	4	5	6	7	8	9
Transvaginal Ultrasound	x			x			X			
Anti -Mullerian Hormone Blood test	x			x			x			
WHO performance status	X									
FBC/MRSA/COVID swab	X									
Informed consent	X			x			x			

Appendix 2: Flow Chart to explain participant involvement in the study:



Appendix 3
COSORT Flow Diagram:
Intra-operative Ultrasound Guided Laparoscopic Ovarian Cystectomy (UGLOC) as a method of fertility preservation surgery in the management of benign ovarian cysts: A Randomised Controlled Trial