TRIAL PROTOCOL

LAVA

LAparoscopic Versus Abdominal hysterectomy (LAVA) trial

This protocol has regard for the HRA guidance

Version Number: 3.0

Version Date: 07th July 2021

Protocol development

NOTE: Regulatory requirements:
➢ As per EC guidance (ENTR/CT 2) the protocol should be signed by the CI and by the Sponsor to confirm approval of the protocol. NOTE: For University of Birmingham (UoB) sponsored trials, the sponsor will confirm approval of the protocol by signing the IRAS form and therefore a signature on the protocol is not required.

Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
AM02	**07/07/2021**	**3.0**	**Non-Substantial**	**minor changes to ensure consistent language throughout the protocol and with the CRFs/ Independent verification of classification of surgical complications is no longer required/ clarification of haemorrhage >/= 1L as a major surgical complication, ensuring consistency with CRFs / Change to scheduled window for completion of follow-up forms / Clarification of withdrawal types**

Funding and Support in Kind	
Funder (s) (Names and contact details of all organisations providing funding and/or support in kind for this trial)	**Financial and non-financial support given:**
National Institute of Health Research	
Funding Scheme (if applicable)	Health Technology Assessment Programme
Funder's reference number	128991
Department of Health disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health	

Protocol Sign Off

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been approved by:

Trial Name:	Laparoscopic Versus Abdominal hysterectomy (LAVA)
Protocol Version Number:	Version: 3.0
Protocol Version Date:	07th July 2021
CI Name:	Prof T Justin CLARK
Trial Role:	Chief Investigator
Signature and date:	

Sponsor statement:

By signing the IRAS form for this trial The University of Birmingham, acting as sponsor of this trial confirm approval of this protocol.

Reference Numbers	
Funder (NIHR HTA) reference number	NIHR128991
Sponsor number	RG_19-156
ISRCTN reference number	ISRCTN14566195
IRAS reference number	287988

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name:	Laparoscopic Versus Abdominal hysterectomy (LAVA)
Protocol Version Number:	Version: __ __
Protocol Version Date:	__ __ / __ __ / __ __ __ __
PI Name: Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor	
University of Birmingham	
Contact Details:	Contact Details: Research Governance University of Birmingham Edgbaston Birmingham, B15 2TT Email: researchgovernance@contacts.bham.ac.uk

Administrative Information

Chief Investigator	
Professor T Justin Clark	Consultant Gynaecologist
Birmingham Women's and Children's NHS Foundation Trust Mindelsohn Way Edgbaston Birmingham, B15 2TG	Telephone: 07967 724697 Email:tjustin.clark@nhs.net

Data Monitoring and Ethics Committee - DMEC
Simon Skene (CTU / statistician) Peter O'Donovan (Gynaecologist) Tyrone Carpenter (Gynaecologist)

Trial Steering Committee - TSC
Chair Patrick Chien (Gynaecologist) **Independent Members** Nicki Burnett (PPI) Elizabeth Ball (Gynaecologist) Soo Downe (Qualitative researcher) Gilly Macdonald (Gynaecology nurse)

Louise Linsell (Statistician) Lazaros Andronis (Health Economist) **Trial Management Group Member** Professor T Justin Clark (CI)

Trial Management Group - TMG
Prof T Justin CLARK (CI)
Mr Lee MIDDLETON (Statistics Lead)
Prof Peter BROCKLEHURST (Director of BCTU)
Mrs Jayne FULLARD (PPI)
Mrs Monique MORGAN (PPI)
Prof Kevin COOPER (Gynaecologist)
Mr Ertan SARIDOGAN (Gynaecologist)
Dr Laura JONES (Qualitative and Mixed-Methods Health Researcher)
Dr Paul SMITH (Gynaecologist)
Professor Tracy ROBERTS (Health Economist)
Dr William McKINNON (BCTU Team Leader)

BCTU Quality Assurance Team	
Maxwell Feltham	QA Lead
Birmingham Clinical Trials Unit School of Health and Population Sciences Public Health Building University of Birmingham Birmingham B15 2TT	Email m.g.feltham@bham.ac.uk Telephone 0121 414 7557

Trial Office Contact Details	
Birmingham Clinical Trials Unit School of Health and Population Sciences Public Health Building University of Birmingham Birmingham B15 2TT	LAVA@trials.bham.ac.uk
LAVA Trial Manager	LAVA@trials.bham.ac.uk
Randomisation website/ telephone number	https://bctu-redcap.bham.ac.uk/

	Tel: 0800 953 0274 (Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days)
Trial website	www.trials.bham.ac.uk/LAVA

ABBREVIATIONS

Abbreviation	Term
BCTU	Birmingham Clinical Trials Unit
BWCH	Birmingham Women's and Children's Hospital
CRF	Case Report Form
CRN	Clinical Research Network
DMC	Data Monitoring Committee
GP	General Practitioner
ICF	Informed Consent Form
ISF	Investigator Site file
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAP	Statistical Analysis
TMG	Trial Management Group
UoB	University of Birmingham

DEFINITIONS

Term	Abbreviation	Description
Policies	POL	Policies are developed to describe the approach of the University of Birmingham UoB on areas that heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the QMS or when procedures to be captured in the QMS address areas controversial within the UoB at the time of implementation. Policies explain why the UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant SOP. Policies that are not part of a Quality Manual are coded up as 'POL'.

Quality Control Documents	QCD	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System	QMS	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received
Related Event		An event which resulted from the administration of any of the research procedures
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening • Requires hospitalisation or prolongation of existing hospitalisation (with exceptions – see section 9.2) • Results in persistent or significant disability or incapacity • Or is otherwise considered medically significant by the Investigator
Unexpected and Related Event		An event which meets the definition of both an Unexpected Event and a Related Event

Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence
Source data		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
Birmingham Clinical Trials Unit	BCTU	The co-ordinating centre for the trial

TRIAL SUMMARY

Title LAparoscopic Versus Abdominal hysterectomy (LAVA) trial

Objectives To determine the clinical and cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy for women with a benign gynaecological condition

Trial Design A parallel, open, non-inferiority, multicentre, randomised controlled, expertise-based surgery trial with integrated health economic evaluation and an internal pilot with an embedded qualitative process evaluation.

Participant Population and Sample Size 3250 women who require a hysterectomy for a benign gynaecological condition

Eligibility Criteria Women with benign gynaecological conditions requiring a hysterectomy and who are suitable for either surgical technique are eligible for inclusion. The intervention is laparoscopic hysterectomy and the comparator is open, abdominal hysterectomy.

Interventions Laparoscopic hysterectomy compared to open abdominal hysterectomy

Outcome Measures Summary (full details given in section 8.1)

- **Primary** – Major surgical complications up to six completed weeks post-surgery
- **Key secondary -** Time from surgery to resumption of usual activities using the personalised PROMIS-SF (Patient-Reported Outcomes Measurement Information System Physical Function) questionnaire
- **Other secondary outcomes**
  - Duration of operation, estimated blood loss
  - In hospital post-operative pain (using a Numerical Rating Scale); analgesia use, quality of recovery (Quality of Recovery 15 - QoR-15) at 24 hours and time from operation to discharge;
  - Post-operative pain (using a Numerical Rating Scale) and analgesia use up to 14 completed days;
  - Minor complications, representation and readmission to hospital up to 6 weeks post-surgery
  - Generic quality of life at 6 and 12 weeks post-surgery (EuroQol-5D-5L and VAS); Time to return to work (if working) and work participation (Work Productivity and Activity Impairment Questionnaire - WPAI–GH) at 12 weeks post-surgery;
  - Satisfaction with hysterectomy (5-point Likert); symptoms of urogenital prolapse (pelvic organ prolapse symptom score – POP-SS); bladder function (Urogenital Distress Inventory – UDI); Bowel function questionnaire (Defecatory Distress Inventory - DDI); sexual function (Sexual Activity Questionnaire - SAQ); generic quality of life (EuroQol-5D-5L and VAS); body image (Body Image Scale – BIS); new gynaecological symptoms (abdominal pain [cyclical, non-cyclical and

dyspareunia] and vaginal bleeding) at 12 months post-surgery. (Note these outcomes will be collected also at 24 and 36 months post-surgery for subgroups of participants reaching these timepoints prior to close of the study i.e. when the last randomised patient reaches 12 months post-surgery)
- Contact with Community & Clinical Care Services i.e. outpatients or emergency visits, re-presentations / re-admissions to hospital for Health Economic assessment
- Serious Adverse Events

Trial Schema

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1. Background

Hysterectomy is common, with one in ten women undergoing the procedure in their lifetime, mostly for benign conditions[1-3]. 30,000 women undergo a hysterectomy every year in the UK for benign indications such as abnormal uterine bleeding and pelvic pain[1-3]. The procedure is associated with high rates of patient satisfaction and improvement in quality of life (QoL) but serious complications can arise[4, 5]. The morbidity arising from hysterectomy imposes a burden on women and the ubiquity of the procedure utilises a substantial amount of scarce health care resources[6-9]. Currently, most hysterectomies are performed abdominally because this traditional method is thought to minimise intra-operative complications but the increased trauma of an abdominal cut can prolong recovery[5]. This may be especially true in overweight and obese women, where morbidity is greater from mobility restrictions and wound infection[10].

Hysterectomy can be performed through large abdominal incisions (abdominal hysterectomy), through small 'key-hole' abdominal incisions (laparoscopic hysterectomy) or via the vagina without any abdominal incisions (vaginal hysterectomy). In contrast to vaginal hysterectomy, which is usually undertaken for uterine prolapse or when the uterus is not enlarged, both abdominal and laparoscopic hysterectomy can be performed in most women with benign disease. The morbidity associated with an abdominal incision, in particular wound infection and pain, has meant that abdominal hysterectomy requires longer inpatient stay and recovery times compared with laparoscopic hysterectomy. On the other hand, laparoscopic hysterectomy takes longer to perform, requires specialist surgical skills and is associated with more urological complications compared with traditional abdominal hysterectomy[4].

1.2. Trial Rationale

Several RCTs, mostly small and of low or moderate quality, have compared the surgical approach to hysterectomy for benign disease. The 2015 Cochrane review identified 25 trials (2983 women) comparing laparoscopic and abdominal hysterectomy[5]. Laparoscopic hysterectomy was found to have significantly more urinary tract injuries (bladder or ureter) but the available evidence was of low quality. The largest RCT included in this review was conducted over 15 years ago, when laparoscopic hysterectomy was in its infancy[11]. Smaller, but more recent trials of laparoscopic hysterectomy, have shown a trend towards a lower major complication rate[12-15]. The Cochrane review[5] identified no differences in any other outcomes apart from return to normal activities, which was shorter in the laparoscopic hysterectomy group by 14 days on average.

The 2015 Cochrane review found no difference in the costs of laparoscopic and abdominal hysterectomy[5]. A systematic review of cost-effectiveness studies of hysterectomy, found laparoscopic hysterectomy to be the least cost-effective but the authors felt that conclusions were difficult to draw due to variation in study design,

follow up times, and the QoL measurement used[16]. The Royal College of Obstetricians and Gynaecologists (RCOG) published national performance indicators of gynaecological care in 2018[7]. These data, collected in 2015 using Hospital Episode Statistics, showed that most women having a laparoscopic hysterectomy stayed less than 1 night in hospital whereas most women undergoing abdominal hysterectomy stayed for more than 2 nights without a difference in readmission rates. These cost-efficiencies may offset the higher equipment costs associated with laparoscopic hysterectomy.

In summary, the existing literature shows the recovery advantages of laparoscopic hysterectomy. However, earlier findings that laparoscopic hysterectomy took longer and had a higher complication rate may not be valid within the context of contemporary gynaecological practice. This is because surgical equipment and training has vastly improved since these studies were done and familiarity with laparoscopic hysterectomy has increased.

1.2.1. Justification for the trial and trial design from clinician surveys

A recent survey of clinician members of the British Society for Gynaecological Endoscopy (BSGE) showed that most 100/110 (91%) regularly undertook hysterectomy of which 91/100 (91%) regularly performed laparoscopic hysterectomy (mean 4.6/month) and 86/100 (86%) regularly undertook both laparoscopic and abdominal procedures. It should be borne in mind that the BSGE is a specialist society for laparoscopic surgery. Across the UK, three abdominal hysterectomies for benign disease are undertaken for every one laparoscopic hysterectomy[6], although a more recent analysis, which included malignant uterine disease, suggested that the relative rates of laparoscopic to abdominal hysterectomy, have narrowed[17]. Recruitment will take place from centres that are: (i) able to offer both laparoscopic and abdominal hysterectomy to their patients; and (ii) with gynaecological surgeons prepared to randomise between routes of hysterectomy. The BSGE clinician survey showed that each respondent worked in a unit with an average of 10 consultant gynaecologists. Of these gynaecologists, those competent in either laparoscopic, abdominal or equally proficient in both types of hysterectomy, will be able to undertake the allocated type of hysterectomy after randomisation.

A composite of major intra- and immediate post-operative complications was ranked as the most important outcome 20/54 (37%) to evaluate, and return to usual activities was ranked in the top three most important outcomes in the BSGE survey (along with quality of life). These outcomes will be our primary and key secondary outcome because they are in alignment with the views of the patients and public (see below). 63/100 (63%) of clinicians in the BSGE survey agreed an RCT was needed with 56/63 (89%) willing to participate.

1.2.2. Justification for the trial and trial design from patient surveys and focus groups

Our research has been developed with involvement of members of the RCOG Women's Voices group, the Hysterectomy Association, and the Birmingham Women's Hospital Hysterectomy Focus Group. A total of 945 women responded to our PPI survey. Major complications were ranked as the most important outcome for the trial to assess, with return to usual activities considered the second most important outcome (ranked in the top three most important outcomes in the BSGE survey). A measure of the speed and quality of recovery was also considered one of the most important outcomes to measure after major complications and improvement in QoL in the PPI survey.

Two focus groups felt the burden placed upon women from administering outcome questionnaires at 24 hours post-surgery and the frequency of dissemination post-operatively proposed was acceptable. Indeed, the consensus view was that measuring recovery against pre-set targets was a good thing (with tools already available on the internet). This frequency of contact was also supported by the PPI survey; 6 weeks 485/945 (51%) and 12 months 514/945 (54%) were the most popular time points.

Overall almost 50% (462/945) of PPI survey respondents were willing to consider taking part in the proposed trial. Excluding the 483 women declining to participate because they had already undergone a hysterectomy revealed that 63% (292/462) of respondents were willing to take part, with the remainder being "not sure". The embedded qualitative process evaluation will attempt to address potential facilitators and barriers to recruitment.

The importance and potential impact on clinical practice has been validated by the health professionals and patient surveys that have been conducted by our research team.

1.2.3. Choice of interventions

The LAVA trial will compare laparoscopic with conventional abdominal hysterectomy. Vaginal hysterectomy has been shown to be beneficial in terms of complications and recovery but this technique is largely confined to women with prolapse and where the uterus is not enlarged[18]. This leaves a choice between laparoscopic and conventional abdominal hysterectomy for the majority of hysterectomies for benign indications. However, there is uncertainty about the advantages and disadvantages of laparoscopic compared with abdominal hysterectomy, particularly the relative rate of complications of the two procedures. Whilst uptake of laparoscopic hysterectomy has been slow[17, 19], the situation is changing with greater familiarity, better training, better equipment and increased proficiency in the technique, such that nearly as many hysterectomies for benign disease are now being done laparoscopically as abdominally[17]. Thus, a large, robust, multi-centre RCT is needed to compare contemporary laparoscopic hysterectomy with abdominal hysterectomy to determine the safest and most cost-effective technique.

1.2.4. Research question

The research question has been framed as follows: What is the clinical and cost effectiveness of laparoscopic surgery compared to open abdominal hysterectomy for women with a benign gynaecological condition undergoing a hysterectomy?

- Population: Women with a benign gynaecological condition requiring a hysterectomy
- Intervention: Laparoscopic hysterectomy
- Comparator: Open abdominal hysterectomy
- Primary outcome: Major surgical complications

Current evidence-based guidance and recent systematic reviews have acknowledged the need for clinical trials to inform clinicians and patients regarding the relative merits of the route of hysterectomy[4]. Contemporary gynaecological practice has developed rapidly in response to technological advances facilitating less invasive surgical techniques for common operations aligned with innovations in pre, peri- and post-operative care designed to 'enhance' recovery[20]. The results of this trial will have a significant impact on day-to-day clinical practice in women's health care.

2. AIMS AND OBJECTIVES

2.1. Aims and Objectives

Main clinical objectives: To compare laparoscopic hysterectomy with open abdominal hysterectomy in terms of major intra-operative and post-operative surgical complications (up to six weeks). Post-operative recovery will also be evaluated by measuring the time from surgery to resumption of usual activities.

Economic objectives: To compare the relative cost effectiveness of laparoscopic hysterectomy with open abdominal hysterectomy in terms of cost per quality adjusted life year. Additional cost-effectiveness analyses will explore cost per major surgical complication avoided and cost per return to normal activities.

Qualitative process evaluation objectives:

(1) With women: to explore their views and experiences of the recruitment approach, randomisation, barriers and facilitators to participation, and acceptability of treatment allocations.

(2) with healthcare professionals: to explore their views and experiences of recruitment, randomisation, including perceived barriers and facilitators, equipoise, appropriateness and acceptability of treatment allocations, and perceptions of trial processes.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

A parallel, open, non-inferiority, multicentre, randomised controlled, expertise-based surgery trial with integrated health economic evaluation and an internal pilot with an embedded qualitative process evaluation to assess the ability of the study to recruit and randomise.

3.2. Trial Setting

Recruitment to the LAVA study will take place in gynaecology departments (general and relevant specialist clinics including menstrual disorders and pelvic pain clinics, hysteroscopy and colposcopy services) in up to 50 NHS Hospitals within the UK.

3.3. Identification of participants

Eligible women will be identified by a member of the clinical team responsible for the direct care of the potential participant in outpatient gynaecology clinics and pre-operative assessment clinics in each recruiting centre. The LAVA study will be introduced by a member of the clinical or research team, with full counselling about the trial (including provision of information about the qualitative process evaluation). The potential participant will be advised that participation in the study is entirely voluntary with the option of withdrawing from the study at any stage. It will be made clear that participation or non-participation will not affect their usual care.

3.4. Sub-studies

3.4.1. Qualitative evaluation

A qualitative process evaluation will be undertaken in parallel to the pilot phase. The primary aim of the qualitative study is to explore the feasibility, acceptability and appropriateness of the trial and intervention for women and healthcare professionals (HCPs). The results will inform decision-making around progression to a full trial, including study design and processes.

3.4.2. Health Economic evaluation

An economic evaluation alongside the RCT will explore the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy based on a primary outcome of quality-adjusted life years and secondary outcomes such as major surgical complications avoided. The analysis will adopt the perspective of the health service. All resource use will be collected prospectively and unit costs attached. Deterministic and probabilistic sensitivity analysis will be carried out.

3.5. Assessment of Risk

As both abdominal and laparoscopic hysterectomy are widely used, routine treatment options within the NHS, this trial is categorised as: Type A = No higher than the risk of standard medical care.

4. ELIGIBILITY

Women are eligible for recruitment to the LAVA trial if they meet the inclusion criteria and do not have any of the exclusion criteria set out below:

4.1. Inclusion Criteria

- Aged between 18-55 years of age and able to give informed consent to participate
- Have a benign gynaecological condition that is being treated with a hysterectomy
- This hysterectomy can be undertaken by either a laparoscopic or open abdominal routes

4.2. Exclusion Criteria

- Women with suspected malignant disease of the genital tract
- Women who require concomitant gynaecological surgery for bladder or other pelvic support
- Women who require concomitant gynaecological surgery for excision of deep endometriosis that requires dissection of the pararectal space

4.3. Co-enrolment

It is requested that any proposals for co-enrolment in additional or other studies be referred to the Trial Management Group for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.

5. CONSENT

It will be the responsibility of the Investigator to obtain informed consent (paper or electronic) for each participant prior to performing any trial related procedure. A research nurse, research midwife or clinician is able to take consent providing that local practice allows this and responsibility has been delegated by the Principal Investigator as captured on the Site Signature and Delegation Log.

A Participant Information Sheet (PIS) will be provided to facilitate this process either at the time of initial consultation / hospital visit or sent through the post, via email, or by text (i.e. short message service – SMS) with a link to download the PIS from

the trial website. Investigators or their delegate(s) will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to decline to take part and may withdraw from the trial at any time. The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions. If the woman agrees to be contacted at home after reading the PIS, she will receive a telephone or video call from the local Research Nurse, a member of the local clinical team or a clinical member of the central research team to discuss any queries. Women may make a decision to participate at home following this telephone / video counselling, or during a subsequent visit to hospital (e.g. a clinic appointment or a pre-assessment visit).

Women who agree to participate following telephone counselling or video consultation by a member of the local research team, will be able to provide consent in the following ways:

1) Wet sign, date and return the latest version of the REC approved paper Informed Consent Form (ICF) in the presence of a member of the local study team.

2) Sign, date and return the latest version of an electronic Informed Consent Form (ICF) via a secure on line web address provided by the Birmingham Clinical Trials Unit (BCTU), using email or SMS.

3) Provide consent verbally to a member of the research team during their VOIP, telephone, or video call. Before taking consent the member of the local research team will ensure that they have a witness present who can verify that informed consent was taken. This witness does not have to be named on the LAVA Delegation Log. The member of the local study team acting as a witness does not need to be named on the Delegation Log.

   The member of the local research team who is taking remote consent will read each of the statements on the ICF to the potential participant and will insert their initials in each of the associated boxes to confirm that the participant agrees with the statement.

   After consent has been taken the witness will countersign the ICF, and a copy of the completed form sent to the participant. The method by which this was done will be recorded at the end of the consent form. A copy of the ICF will be placed in the participants notes which will record the name of the person taking the consent, the witness, and the date this was done.

Oral confirmation of ongoing consent to participate in LAVA should be sought from the participant when they present for their procedure, and this should be recorded in the participant's medical notes.

4) Alternatively, the participant will be provided with a paper copy of the latest REC approved version of the ICF to complete, wet date and sign and send through the post to the local team at their treating hospital or bring it with them if they are returning to hospital for another consultation or surgery.

   Where direct access to patient medical records is required the participant will give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to their medical records.

The Investigator or their delegate will then countersign and date the ICF. A copy of the ICF will be given to the participant (electronic or hard copy), a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. In addition, if the participant has given explicit consent, a copy of the signed ICF will be sent to the Birmingham Clinical Trials Unit (BCTU).

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial at any time will remain.

Electronic copies of the PIS and ICF will be available from the Trials Office and will be printed or photocopied onto the headed paper of the local institution. Details of all patients approached about the trial will be recorded on the Participant

Screening/Enrolment Log and with the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6. RECRUITMENT, ENROLMENT AND RANDOMISATION

6.1. Recruitment

Potential participants will be identified and approached by medical staff who are responsible for the direct care of the potential participant in participating centres after having received appropriate training relating to the trial and who are delegated this task on the site delegation log. Recruitment will take place in gynaecology clinics in gynaecologist lead centres located across the United Kingdom. REC approved posters making potential participants aware of the study may be displayed in areas that will be accessed by them, such as waiting areas, clinics and consulting rooms.

The participant eligibility pathway to recruitment and randomisation is illustrated by the trial schema. Eligibility will be confirmed following discussions with the woman and a review of her medical notes by staff delegated this duty by the local PI.

Potential participants will be advised that taking part in the study is entirely voluntary and they may withdraw from the study at any stage without this affecting their usual care. Potential participants will be provided with a REC approved Study Participant Information Sheet (PIS) and given time to consider their involvement.

Women who give consent will proceed to randomisation if they are eligible to participate in the trial. Consent will be recorded on the approved consent form, the original of which must be retained in the site file with a copy given to the participant and a copy sent to the LAVA Trial Office at the BCTU. If electronic consent is taken, then copies will sent to the same recipients described for retention.

We will train medical staff at each site to facilitate recruitment. Recruitment will be supported by research nurses and midwives including those from the Clinical Research Network (CRN) in England. Local procedures at the participating hospitals are different and the timing and mode of approach to women and the consent process may vary in order to accommodate both the specific circumstances at each site and the needs of the women.

6.2. Enrolment and Screening

Women with benign gynaecological conditions requiring a hysterectomy and who are suitable for either surgical technique are eligible for inclusion in the LAVA trial.

Prior to clinical consultations, the medical records of potential participants may be screened for eligibility by clinic doctors, nurses, research nurses and research

midwives, after having received appropriate training relating to the trial. Clinic doctors will confirm eligibility for the trial.

6.3. Randomisation

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at http://www.trials.bham.ac.uk/lava). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study as detailed on the LAVA Trial Signature and Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A freephone telephone randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial. Randomisation Notepads will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Notepad must be answered before a Trial Number and allocation can be given. If data items are missing, randomisation will be suspended, but can be resumed once the information is available. Only when all eligibility criteria and baseline data items have been provided will a Trial Number be allocated.

Participants will be randomised at the level of the individual in a 1:1 ratio to undergo their hysterectomy by either a laparoscopic or open abdominal route.

A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- Previous caesarean section (yes / no)
- BMI (</=29.9, 30-34.9, >/=35 Kg/m^2)
- Uterine Size (<=12 weeks, >12 weeks)
- Planned retention of cervix (yes / no)
- Recruiting centre

A 'random element' will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the randomiser, the local PI and the trial co-ordinator, with the participant's unique trial number.

Investigators will keep their own study file log which links patients with their allocated trial number in the LAVA Patient Recruitment and Identification Log. The Investigator must maintain this document, which is not for submission to the Trials Office. The Investigator will also keep and maintain the LAVA Screening Log which will be kept in the ISF and which should be available to be sent to the Trials Office upon request. The LAVA Patient Recruitment and Identification Log and LAVA Participant Screening/Enrolment Log should be held in strict confidence.

6.4. Informing the participant's GP

If the participant has agreed, the participant's GP will be notified that they are in LAVA trial by using the LAVA GP Letter. If the woman does not want her GP to be aware of her participation in the LAVA study then she may opt out of this on the consent form.

6.5. Blinding

Due to the differing natures of the intervention it is impossible to blind either the care providers, investigators or participants to their allocated group.

7. TRIAL TREATMENT / INTERVENTION

7.1. Trial Treatment

Hysterectomy undertaken by either a laparoscopic or an open abdominal route, by a surgeon who has self-declared as having expertise in laparoscopic hysterectomy, abdominal hysterectomy or both approaches to hysterectomy. However, to participate in the LAVA trial, these gynaecological surgeons will have to meet minimum standards, regarding experience and case-load, to be considered competent in a particular type of hysterectomy. Satisfactory experience will require surgeons to have performed a minimum of 30 cases and to have a current caseload of at least 12 cases per year. For surgeons to conduct both procedures, these criteria will need to be met for both procedures. In light of the unprecedented restrictions on elective operating for benign conditions imposed by the Covid 19 pandemic, the required surgical caseload can be determined from the year preceding the SARS-COV-2 viral outbreak in March 2020.

The decision to remove or retain cervix (total or sub-total) or remove and retain ovaries will be left to the discretion of the participant in consultation with her gynaecologist.

The expertise design process for eligible centres is depicted in the figure on the next page:

Expertise-based surgery process

Confirm eligibility of participating centre

Members of the Local Surgical Unit (LSU)[1] should:

(1) Be able to provide laparoscopic AND open hysterectomy for benign conditions by surgeons who meet the threshold for expertise[2]
(2) Have at least one surgeon willing to randomise to LAVA
(3) Be able to agree local eligibility criteria (i.e. criteria to undertake either laparoscopic OR open hysterectomy)

Identify and confirm surgical expertise[2] within the participating centre

☐ Expert surgeon LAPAROSCOPIC
☐ Expert surgeon OPEN

Randomisation by local research team

Eligibility confirmed by a surgeon willing to randomise to LAVA[3]

Laparoscopic hysterectomy
Allocated LAPAROSCOPIC expert surgeon[4]

Open hysterectomy
Allocated OPEN expert surgeon[4]

1 Collective group of surgeons within a centre willing to operate on patients recruited into the LAVA trial. Not all surgeons within the LSU need to be willing to randomise but they should be prepared to perform a hysterectomy, according to their expertise, on patients following randomisation.
2 Surgeons to have performed a minimum of 30 cases and to have a current caseload of at least 12 cases per year. For surgeons to conduct both procedures, these criteria will need to be met for both types of hysterectomy. In light of the unprecedented restrictions on elective operating for benign conditions imposed by the Covid-19 pandemic, the required surgical caseload can be determined from the year preceding the SARS-COV-2 viral outbreak in March 2020.
3 The surgeon must consider the position for each individual patient. Only if they believe that either operation will be suitable for an individual patient can the patient then be recruited.
4 Participants must be made aware that their surgery may be conducted by another surgeon within the LSU with the appropriate expertise.

7.2. Accountability Procedures

The allocated intervention and the actual procedure that is undertaken will be recorded on a case report form (CRF). This completed CRF will be returned to the trials office where compliance will be monitored. Should any concerns arise then investigations will be undertaken to determine the reasons for changing the hysterectomy route or treatment and the findings presented to the TMG for their guidance. A summary of the compliance will be presented to the study oversight groups.

7.3. Treatment Modification

Modification of the hysterectomy pathway or treatment is undesirable but is allowed if there are legitimate medical reasons for this, or at the participant's request. The reasons why the hysterectomy pathway or treatment has changed will be recorded on a CRF that will be returned to the trial office.

Should any concerns arise then investigations will be undertaken to determine the reasons for changing the hysterectomy route, deviation from the planned surgery regarding removal of the ovaries and / or cervix or undertaking concomitant surgical procedures, or change to alternative surgical or medical treatment. The findings will be presented to the TMG for their guidance. A summary of the compliance will be presented to the study oversight groups.

The request to change treatment route, or the withdrawal of participants before the randomised treatment allocation has been performed should be an exception as women should be counselled as to the nature of the procedures before consenting to participate in the LAVA trial.

8. OUTCOME MEASURES AND STUDY PROCEDURES

Women who give consent in a face to face setting will subsequently complete their baselines questionnaires and then proceed to randomisation. Participants who consent remotely be sent the baseline questionnaires as paper copies to return in the post in self – addressed envelopes or in person if attending hospital for scheduled clinical visit. Alternatively, the baseline questionnaires will be made accessible via a secure weblink sent by email or SMS. These questionnaires can be completed and on-line.

The baseline questionnaires are self-explanatory but help to complete them will be provided by the local or central medical research teams on request using remote means (telephone / VOIP /video consultation) where feasible. Participants will be made aware of this resource by the local research teams. It is anticipated that some participants may need help to select their 8 personalised recovery targets from 29 options PROMIS-PF (Patient-Reported Outcomes Measurement Information System Physical Function) item bank v1.2 [16, 21-23]. Local research teams will offer remote (telephone, VOIP or video) contact, or exceptionally face to face appointments, to provide explanation.

Women will also have the opportunity to discuss all aspects of the proposed research with the local clinical team (staff at pre-admission clinics and ward staff while admitted), the Research Nurse, family and friends and, if appropriate, with their GP before admission.

8.1. Trial outcomes

8.1.1. Internal pilot outcome

We aim to recruit a minimum of 257 participants within 9 months of the first recruiting hospital being activated.

This is calculated on the assumption that 22 recruiting centres will be opened within this 9 month time-frame with a staggered starts and individual recruitment targets. If recruitment is =100% of expected (green), we will proceed to the main trial; if 67% to 99% of expected (amber), we will explore and implement methods to improve recruitment; if <67% of expected (red), and there are no obvious remedial factors, we will discuss with the TSC and consider stopping the trial. Any decision regarding the feasibility of the RCT, and remedial measures if necessary, will also be informed by the results for the embedded qualitative process

8.1.2. Primary Outcome

Major surgical complications. These will be objectively ascribed and largely in accordance with the validated and widely used Clavien-Dindo classification of surgical complications[24]. They will be defined as any of the following up to and including six full weeks post-surgery: i) all Clavien-Dindo grade III-V complications ii) Clavien-Dindo grade II complications of pulmonary embolus or blood transfusion or; iii) haemorrhage >/= 1L or; iv) major adverse anaesthetic event (see table below).

The most commonly anticipated major surgical complications are:

- Haemorrhage > / =1 L
- Blood transfusion
- Bladder injury
- Ureteric injury
- Bowel injury
- Vascular injury
- Unplanned removal of any other organ
- Any other complication not covered requiring surgical, endoscopic or radiological intervention
- Pelvic haematoma requiring radiological or surgical intervention
- Pelvic abscess requiring radiological or surgical intervention
- Life-threatening complication requiring admission to HDU/ITU

However, other less common major surgical or anaesthetic complications may arise and these will be ascribed in accordance with the appropriate Clavien-Dindo classification.

Definition of major surgical complications in the LAVA trial

Major haemorrhage	Haemorrhage >/= 1L
Clavien-Dindo grade II	Pulmonary embolus, blood transfusion
Clavien-Dindo grade III	Complication requiring surgical, endoscopic or radiological intervention
Clavien-Dindo grade IV	Life-threatening complication requiring management on a High Dependency Unit (HDU) / intensive therapy unit (ITU)*
Clavien-Dindo grade V	Death
Major anaesthetic event	Anaphylaxis, awareness, nerve injury (including epidural/spinal anaesthesia), hypoxic brain injury, malignant hyperthermia, iatrogenic complication (e.g. pneumothorax from central line, limb ischaemia from arterial line)

*Non-life threatening elective or precautionary admission to an HDU (e.g. because of medical co-morbidities) post-operatively will not be considered a grade IV complication.

Complication data occurring during and up to 6 weeks following hysterectomy will be collected from the relevant case report forms completed by the local research team:

- Day of Surgery CRF
    - Detailing the type of major peri-operative complications

- Post-operative inpatient CRF
    - Detailing the type and timing of major surgical complications occurring during inpatient stay up until hospital discharge)

- 6 week post-surgery complication and representation CRF
    - Detailing the type and timing of major post-operative complications, as well as any reattendance and / or readmissions to hospital up to 6 weeks post-surgery, will be recorded. The data will be acquired by the local research team from scrutiny of the hospital case-notes and / or follow up consultation (if conducted routinely at approximately 6 weeks post-hysterectomy). The "6 week follow up patient completed CRF" that reports overnight admission following hysterectomy will also be checked and corroborated by the TMG for consistency; see below.

The TMG will collate "6 week follow up patient completed CRFs" that report overnight admission following hysterectomy. If the corresponding "6 week post-surgery and representation CRF" does not record a major surgical complication then the local PI will be contacted by the TMG and asked to provide additional information to explain the apparent discrepancy (e.g. oversight by the local research team, invalid patient response, re-admission another hospital etc.), and the reason for the overnight hospital admission and any additional treatments. The local PI will be asked to record their response on a Data Clarification Form.

8.1.3. Secondary outcomes

8.1.3.1 Key secondary outcome

- Time from surgery to resumption of usual activities. To increase accuracy and to minimise recall bias, the validated, personalised PROMIS-PF (Patient-Reported Outcomes Measurement Information System Physical Function) item bank v1.2 will be used[16]. 29 items covering relevant activities for our study population will be used from the entire 121 item bank[21]. Every item contains five response categories.

At baseline participants will be asked to select 8 activities from this list of 29 that, in their view, would most reflect their day-to-day activities. In this way participants will create their personalised physical function short form. Participants will record when each activity is resumed, with full recovery being achieved once all 8 personalised activities have been resumed. Until all personalised activities have resumed participants will be asked to complete this weekly for the first 12 weeks, then fortnightly from week 13 to week 26 after which requests will cease.

8.1.3.2 Other secondary outcomes

- <u>Surgical outcomes:</u>
  - Duration of operation, (minutes)
  - Estimated blood loss, (ml)

- <u>In hospital stay:</u>
  - In hospital post-operative pain using a Numerical rating scale (NRS) (with 0 indicating no pain to 10 indicating maximum pain)*, measured daily
  - Total analgesia use*
  - Overall quality of recovery score taken from the Quality of Recovery 15 (QoR-15) questionnaire[25] (with 0 indicating worst recovery and 10 indicating best recovery), measured at approximately 24 hours post-operation*
  - Time from operation to discharge in days (the day of operation will be assumed to be day 1. i.e. discharge on day 2 = 2 days). Each part of a day will count as a whole day, e.g. discharge after 2.5 days = 3 days)

- <u>Up to 14 days after surgery:</u>
  - post-operative pain using a Numerical rating scale (NRS) (with 0 indicating no pain to 10 indicating maximum pain), measured daily
  - Total analgesia use

- Up to 6 weeks post-surgery:
    - Minor complications (Haemorrhage 500mL to </=1 L; pyrexia [presumed infection] requiring antibiotics; pain uncontrolled with usual analgesic management; urinary retention requiring re-catheterization; catheterisation for longer than 72 hrs; pelvic haematoma NOT requiring radiological or surgical intervention; pelvic abscess NOT requiring radiological or surgical intervention; wound infections/complications managed at the bedside or on the ward)
    - Representation to hospital
    - Readmission to hospital
    - Use of health services
    - Time away from normal activities

- 6 weeks post-surgery:
    - Quality of life score using EuroQol-5D-5L questionnaire[26] (with -0.285 indicating worst possible value and 1.0 as best possible value)
    - Quality of life score using EuroQol-5D-5L visual analogue scale (with 0 indicating worst possible score and 100 as best possible score)

- 12 weeks post-surgery:
    - Quality of life score using EuroQol-5D-5L questionnaire[26] (with -0.285 indicating worst possible value and 1.0 as best possible value)
    - Quality of life score using EuroQol-5D-5L visual analogue scale (with 0 indicating worst possible score and 100 as best possible score)
    - Time from surgery to work (if working) in days
    - Work productivity and activity impairment scores using WPAI-GH questionnaire[27] (absenteeism score; presenteeism score; work productivity loss score; activity impairment score – all scored 0 good to 100 bad) at 12 weeks only

- 12/24/36 months post-surgery:**
    - Satisfaction with hysterectomy (5-point Likert scale ranging from very satisfied to very unsatisfied)
    - Symptoms of urogenital prolapse using the Pelvic Organ Prolapse Symptom Score (POP-SS) questionnaire[28] (score ranging from 0 no symptoms to 28 maximum symptoms)
    - Bladder function using Urogenital Distress Inventory (UDI)[29, 30] questionnaire (score ranging from 0 good to 100 bad)
    - Bowel function using Defecatory Distress Inventory (DDI)[31] questionnaire (overall score ranging from 0 good to 100 bad)
    - Sexual function using the Sexual Activity (SAQ) questionnaire[32] (pleasure score ranging from 0 worst to 18 best; discomfort score

ranging from 0 worst to 6 best; habit score ranging from 0 worst to 3 best)
    - Quality of life score using EuroQol-5D-5L questionnaire (as scored above)
    - Quality of life score using EuroQol-5D-5L visual analogue scale (as scored above)
    - Body image using the Body Image Scale (BIS) questionnaire[33] (score ranging from 0 no disturbance to 30 maximum disturbance)
    - New gynaecological symptoms (abdominal pain [cyclical, non-cyclical and dyspareunia] and vaginal bleeding; yes/no)
    - Contact with Community Social and Clinical Care Services i.e. outpatients or emergency visits, and hospital services e.g. re-presentations, re-admissions, outpatient appointments and further medical treatment, time away from normal activities (collect to inform that Health Economic assessment [section 15]; not reported separately)

- <u>Throughout:</u> Serious adverse events (see section 9)

* Questionnaire may be completed at home if patient discharged on the same day as surgery

**The latter two time-points will only be collected for participants who reach these times prior to the study closes after all patients have been followed up for 12 months.

8.2. Schedule of Assessments

8.2.1. Site set-up

Centre eligibility

Recruiting centres must have eligible surgeons willing to participate in the LAVA trial such that both laparoscopic and open hysterectomy can be offered for the treatment of benign gynaecological conditions. This mandates that surgeons with specific expertise in either laparoscopic or open hysterectomy within each recruiting centre are prepared to refer patients to surgical colleagues, and vice-versa, according to the type of hysterectomy allocated post-randomisation. Some surgeons considering themselves equally adept in both types of hysterectomy, and who meet the eligibility criteria, will be able to undertake both procedures within the LAVA trial. Surgeons within recruiting centres willing to participate in the LAVA trial comprise the 'Local Surgical Unit' (see 'Expertise Based Process'). They should have at least one surgeon willing to randomise to LAVA and agree local eligibility criteria for undertaking either laparoscopic OR open hysterectomy.

Surgeon eligibility

For a surgeon to be considered expert in a particular type of hysterectomy (laparoscopic or open), minimum standards regarding experience and case load will need to be established as follows:

- A minimum of 30 cases conducted
- Current caseload of at least 12 cases per year.

(Note - these criteria will need to be met for laparoscopic and open hysterectomy for surgeons conducting both procedures in the LAVA trial)

In light of the unprecedented restrictions on elective operating for benign conditions imposed by the Covid 19 pandemic, the required surgical caseload can be determined from the year preceding the SARS-COV-2 viral outbreak in March 2020.

8.2.2. After consent but before randomisation

Baseline demographic and medical data ("Consent and randomisation CRF" - *local research team to complete*)

To include:

- Age
- Ethnicity
- BMI (</=29.9, 30-34.9, >/=35 Kg/m^2)
- Previous caesarean section (yes / no)
- Uterine Size - <=12 weeks, >12 weeks
- Planned retention of cervix yes / no

Baseline quality of life, symptom and physical functioning questionnaires (*participant to complete*)

- Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF) item bank v1.2 ("Baseline Personalised recovery CRF")
    - Selection of 8 activities, that in the participants view most reflect their day-to-day activities which will then will be used to assess return to usual activities.

- Baseline quality of life and symptom CRF:
    - Quality of life data (EQ-5D-5L and EQ VAS)
    - Sexual Activity Questionnaire (SAQ)
    - Urogenital Distress Inventory (UDI)
    - Defecatory Distress Inventory (DDI)
    - Pelvic organ prolapse symptom score (POP-SS)

8.2.3. Hospital stay

- Surgical details ("Day of surgery CRF" - *local research team to complete*)
    - to include Clavien-Dindo grade of surgical complications, anaesthetic complications (where applicable), surgical details such as duration, estimated blood loss, conversion to laparotomy, uterine weight

- Resource use ("Day of surgery CRF" and "Post-operative inpatient CRF to complete on discharge" - *local research team to complete*)
    - to include time for procedures, personnel present, equipment usage, time to discharge

- Quality of recovery CRF (Quality of Recovery 15 - QoR-15) at 24 hours post-surgery *(participant to complete) Note - if the patient is discharged as a day-case [i.e. within 24 hours] then they should be requested to complete this at home)*

- Post-operative pain diary CRF
    - Numerical rating scale (NRS) to measure post-operative pain, and analgesia use (*participant to complete in hospital and / or at home according to the day of discharge post-operatively*)

8.2.4. Days 1-14 after surgery

- Post-operative pain diary CRF
    - Numerical rating scale (NRS) to measure post-operative pain, and analgesia use (*participant to complete in hospital and / or at home according to the day of discharge post-operatively*)

8.2.5. Week 6 after surgery

- Six week follow up CRF
    - Post-surgery complication and representation form (*local research team to complete)*

8.2.6. At home weeks 1 to 26

- Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF) item bank v1.2
    - Patient to record the date when each of her 8 pre-selected physical activities is achieved using a text application that provides a link to the questionnaire on the BCTU trial database. Until attainment of all 8 pre-selected criteria participants will receive weekly text reminders to complete the PROMIS-PF during the first 12 weeks, fortnightly from 13 to 26 weeks after which requests will cease. It is anticipated that most participants will have resumed all their pre-selected activities between 6 and 9 weeks post-surgery (*participant to complete*).

8.2.7. At home week 6 post-surgery **

- Quality of life score and work assessment ("6 week follow up CRF")
    - EuroQol-5D-5L and VAS
    - Use of health services
    - Time away from normal activities

8.2.8. At home week 12 post-surgery **

- Quality of life score and work assessment ("12 week follow up CRF")
    - EuroQol-5D-5L and VAS
    - Time from surgery to work (if working) and work productivity and activity impairment scores using WPAI-GH questionnaire

8.2.9. At home week 12/24/36 months post-surgery* **

- 12/24/36 month post-hysterectomy CRF
    - Satisfaction with hysterectomy (5-point Likert scale ranging from very satisfied to very unsatisfied), assessment of new gynaecological symptoms, symptoms of urogenital prolapse (pelvic organ prolapse quantifications – POP-SS bladder function using Urogenital Distress Inventory (UDI), bowel function using Defecatory Distress Inventory (DDI) questionnaire, sexual function using the Sexual Activity (SAQ) questionnaire, quality of life score using EuroQol-5D-5L questionnaire and VAS, body image using the Body Image Scale (BIS) questionnaire,

contact with Community Social and Clinical Care Services and time away from normal activities.

*The latter two time-points will only be collected for participants who reach these times prior to the study closes after all participants have been followed up for 12 months.

**Participants will be offered the option to complete these questionnaires online, via a link sent to them in a text message. Participants will receive reminders to complete their questionnaires

8.2.10. Summary of schedule of assessments

	Pre-randomisation		*Rand*	*Surgery*	*Post-surgery*						
Visit	*Screening and recruitment*	*Baseline*		*Surgery*	*Hospital stay*	*Day 2-14*	*Weekly Week 1 to 12 (inc)*	*6 weeks + 28 days*	*12 weeks + 28 days*	*Fortnightly weeks 13 to 26 (inc)*	*Month 12 + 6 months* **
Eligibility check	*x*										
Valid informed consent	*x*										
Baseline demographic and medical questionnaire		*x*									
Urogenital Distress Inventory (UDI)		*x*									*x*
Defecatory Distress Inventory (DDI)		*x*									*x*
Sexual Activity Questionnaire (SAQ)		*x*									*x*
EuroQol (EQ-5D-5L and EQ VAS)		*x*						*x*	*x*		*x*
Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF)		*x*					*x*			*x*	
Randomisation			*x*								
Surgery CRF				*x*							
Resource use CRF					*x*						

Pain (Numerical Rating Scale - NRS) & analgesia questionnaire					*x*						
Time to discharge & complications					*x*						
*Quality of Recovery-15 questionnaire**					*x*						
Pain (NRS) symptom diary						*x*					
Six week post-surgery questionnaire including health care utilisation								*x*			
Work questionnaire / Work Productivity and Activity Impairment Questionnaire (WPAI-GH)									*x*		
Six week post-surgery complication and representation form								*x*			
Satisfaction with hysterectomy											*x*
New gynae symptoms											*x*
Pelvic organ prolapse quantifications – POP-SS		*x*									*x*
Body Image Scale (BIS)											*x*
Contact with Community Social and Clinical Care Services form											*x*
Serious Adverse Events				*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

** If patient discharged as a day-case then they should be instructed to complete at home at 24 hours post-surgery*

** *The same 12 month post-surgery questionnaires will be sent to all participants reaching 24 and 36 months of follow up post-surgery, prior to close of the LAVA study; defined as when the last randomised patient reaches 12 months follow up post-surgery*

8.3. Participant Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of) at any time.

LAVA has adopted an analysis based on a modified intention to treat principle, i.e. all participants will be followed up and analysed in the treatment group to which they were randomised provided a hysterectomy (of any type) was undertaken unless they withdraw from the study.

Types of withdrawal as defined are:

a) If for any reason the participant has not undergone a hysterectomy of any type they will be considered to have withdrawn from the study and not be followed up

b) The participant would like to withdraw from the allocated trial treatment pathway but is still having a hysterectomy of any type, and does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes)

c) The participant would like to withdraw from trial treatment but is still having a hysterectomy of any type, and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

or

d) The participant wishes to withdraw completely from the trial (i.e. from trial treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future trial analysis

*If the participant wishes to withdraw from the allocated trial treatment pathway but is still having a hysterectomy of any type, and is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis), they will **not** be considered as being withdrawn from the study*

The details of withdrawal (date, reason and type of withdrawal) will be clearly documented in the source data.

9. ADVERSE EVENT REPORTING

9.1. Reporting Requirements non-CTIMPs

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant this should be documented in the source data with reference to the protocol.

9.2. Adverse Events (AE) non-CTIMPs

All medical occurrences which meet the definition of an AE should be reported. Please note this includes abnormal laboratory findings.

Peri-operative and post-operative complications experienced by the participants are the primary outcomes of the LAVA study. Complications arising from the interventions will be collected on the relevant CRFs.

As these events are well characterised, it is highly unlikely that this trial will reveal any new safety information relating to this intervention. The recording of selected AEs will therefore not affect the safety of participants or the aims of the trial. As such the following will not be classed as adverse events and so do not need to be reported as AEs:

- Haemorrhage >/= 1L
- Surgical Complications (any factor that comprises the Clavien-Dindo grade [II-IV] with or without hospitalisation or prolongation of existing hospitalisation
- Anaesthetic complications
- Additional Medication required above that normally expected
- Emergency presentations / admissions
- Routine re-presentations / admissions for pre-planned events
- Prolonged hospitalisation without an associated adverse event
- Vaginal bleeding
- Pelvic organ prolapse
- Abdominal pain [cyclical / non-cyclical, and dyspareunia]
- Conditions / symptoms arising from altered bowel or bladder function

9.3. Serious Adverse Advents (SAE) non-CTIMPs

All events which meet the definition of serious, and that are not excluded above, will be collected and recorded as SAEs. These will be reported to the trials office immediately and within 24 hours of being made aware of the event.

9.4. Reporting period non-CTIMPs

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment (entering the anaesthesia suite) until woman exits the study.
SAEs that are not excluded above but that are judged to be at least possibly related to the intervention must still be reported in an expedited manner irrespective of how long after intervention the event occurred.

9.5. Reporting period – At Site non-CTIMPs

9.5.1. Adverse Events

Depending on their nature, AEs should be recorded in the relevant place, i.e. on the relevant CRFs or on the SAE reporting form, with a record being kept on the site Adverse Event Log.
Records of AEs should be returned to the BCTU trials team as soon as possible. The initial form should be returned to the BCTU by email. The data on the reporting form will be pseudo-anonymised by the person's trial number and their partial date of birth (month / year).

9.5.2. Serious Adverse Events

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form as soon as possible, but no later than 24 hours after the site has become aware of the adverse event. When completing the form, the PI will be asked to define the causality and the severity of the AE; according to the scale where a suspected causal relationship is definitely related; probably related; possibly related; unlikely to be related or unrelated.

Categorisation of causality (relatedness) for AEs and SAEs

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship, however, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship; there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Not related	There is no evidence of any causal relationship	

On becoming aware that a participant has experienced an SAE, the Investigator or their delegate should report the SAE to their own Trust in accordance with local practice and to the BCTU trials office.

To report an SAE to the BCTU trials office, the Investigator or their delegate must complete, date and sign the trial specific BCTU SAE form. The completed form should be scanned and emailed to the BCTU trials team using the trial mailbox address shown below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, email the SAE Form to:

LAVA@trials.bham.ac.uk

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from BCTU or if the SAE has not been assigned a unique SAE identification number, the site should contact the BCTU trials team within one working day. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Where an SAE Form has been completed by someone other than the Investigator, the original SAE form will be required to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

9.5.3. Provision of follow-up information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form, using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the original SAE form that was completed at site must be returned to the BCTU trials office and a copy kept in the Site File.

9.6. Reporting Procedure

On receipt of an SAE form from the site, the BCTU trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form. The SAE form (containing the unique reference number completed) will be forwarded to the site as proof of receipt within 1 working day of receipt. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the TMF.

On receipt of an SAE Form, the Chief Investigator (CI) or their delegate will independently determine the seriousness and causality of the SAE. An SAE judged by the PI, the CI or their delegate to have a reasonable causal relationship with the intervention will be regarded as a related SAE. The causality assessment given by the PI will not be downgraded by the CI or their delegates. If the CI or their delegates disagrees with the PI's causality

assessment, the opinion of both parties will be documented, and where the event requires further reporting, both opinions will be provided with the report.

The CI or their delegates will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

9.7. Reporting to the Research Ethics Committee

9.7.1. Unexpected and Related Serious Adverse Events

BCTU will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) and the University of Birmingham's Research Governance Team (RGT) within 15 days.

9.7.2. Other safety issues identified during the course of the trial

The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

9.8. Investigators non-CTIMPs

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to PI. A copy of any such correspondence should be filed in the site file and TMF.

9.9. Data Monitoring Committee non-CTIMPs

The independent Data Monitoring Committee (DMC) will review all SAEs.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained. Illustrative examples of source data are provided on the next page:

Data	Source
Participant Reported Outcomes	The original participant-completed CRF is the source and will be kept with the participant's trial record at site, whilst copies will be provided to the Trials Office
Lab results	The original lab report (which may be electronic) is the source data and will be kept and maintained in line with normal local practice. Information will be transcribed onto CRFs
Imaging	The source is the original imaging usually as an electronic file. Data may be supplied to the Trials Office as a password-protected, anonymised, copy of the electronic file, or as an interpretation of the imaging provided on a CRF. This will be transferred via fax or secure email, and stored on a secure computer server at the University of Birmingham. Where data is interpreted, the CRF onto which it is transcribed becomes the source. A copy of the CRF should be provided to the Trials Office.
Clinical event data	The original clinical annotation is the source data. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source data.
Health Economics data	Often obtained by interview directly with the participant for transcription onto the CRF.
Recruitment	The original record of the randomisation is the source. It is held on University of Birmingham servers as part of the randomisation and data entry system.
Drop out	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source data.

Source data will comprise of the hospital notes / electronic patient records, case report forms (e.g. surgical details and complications) and administered participant questionnaires to capture recovery and quality of life outcomes. Hospital source data is kept as part of the participants' medical notes generated and maintained at site.

10.2. Case Report Form (CRF) Completion

A CRF is required and should be completed for each individual participant. For the LAVA trial this will be in the form of a paper and / or electronic CRFs. The data held on the completed original CRFs are the sole property of the respective PIs whilst the data set as a whole is the property of the Sponsor and should not be made available in any form to third parties except for authorised representatives or appropriate regulatory authorities without written permission from the sponsor. Appropriate data sharing requests will be considered by the trial management group and the BCTU data sharing committee.

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to standard formats. Protocol and GCP non-compliances should be added to a Protocol Deviation Log, held by the site, and reported to the Trials Office on discovery. In all cases it remains the responsibility of the site's PI or their delegate to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI or their delegates on the CRF.

The completed originals will be submitted to the BCTU trials team and a copy filed in the Investigator Site File

10.3. Participant completed Questionnaires

Participant completed questionnaires can be completed in clinic, via post, online (including VOIP / video conferencing apps) or by telephone.

If completed in clinic, the questionnaire can be completed by the participant directly or by a member of the study team under the direction of the participant. The participant will be encouraged to answers the questions as fully as they can. A member of the study team will check the completed questionnaire and encourage the participant to complete any missed questions.

If completed via post, a paper questionnaire will be completed by the participant directly who will be asked to return it to the trials office in a pre-paid envelop. Upon receipt, a member of the study team will check the completed questionnaire and can contact the participant by telephone, post, text or email to query any missing data.

If completed on-line, an electronic version of the questionnaire will be completed by the participant directly. Upon submission, a member of the study team will check the completed questionnaire and can contact the participant by telephone, post, text or email to query any missing data.

If completed by remote video or telephone the questionnaire will be completed by a member of the study team under the direction of the participant. The participant will be encouraged to answers the questions as fully as they can. A member of the study team will check the completed questionnaire and encourage the participant to complete any missed questions.

10.4. Data Management

Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific data management plan. Coding and validation will be agreed between the trial's coordinator, statistician and programmer and the trial database will be signed off once the implementation of these has been assured.

Data can be entered onto the bespoke trial database by staff at BCTU, delegated staff at site or, in the case of participant completed questionnaires, the participant themselves if an on-line option is available. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries on the trial data will be raised using the integrated data query system in the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data queries will be requested on a monthly basis until receipt of the data or a file note to explain its absence.

10.5. Data Security

The security of the System is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act. The University will designate a Data Protection Officer upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate storage of non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).
- Data processing: Statisticians will only have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:

- Internal audit of the system
- An annual IT risk assessment

- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

10.6. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least ten years.

These essential trial and source documents must not be destroyed without express, written authorisation from a senior member of the management team at Birmingham Clinical Trials Unit.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

The CI is required to sign a UoB CI agreement to document the expectations of both parties. The UoB CI agreement document must be completed prior to participation. The CI is required to sign a Clinical Trials Task Delegation Log which documents the agreements between the CI and BCTU.

All local PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the CTU and supply a current CV and GCP certificate to BCTU. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

11.2. Monitoring

The monitoring requirements for this trial have been developed following trial specific risk assessment by BCTU and as documented in the monitoring plan.

11.3. Onsite Monitoring

For this trial we will monitor sites in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations (also defined in the monitoring plan). Investigators will allow the LAVA trial staff access to source documents as requested. The monitoring will be conducted by BCTU.

11.4. Central Monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Sites will be requested to send in copies of signed ICFs and other documentation for central review for all participants providing explicit consent. This will be detailed in the monitoring plan. Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

11.5. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.6. Notification of Serious Breaches

The Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the LAVA management and oversight committees and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

A copy of the notification will be sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

12. END OF TRIAL DEFINITION

The end of trial will be 9 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trials Office will

notify the REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the Trials Office will inform the REC within 15 days of the end of trial. The Trials Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report will also sent to the University of Birmingham Research Governance Team. At the same time these will be sent to the REC.

The BCTU trial team will notify the main REC and University of Birmingham Research Governance Team that the trial has ended within 90 days of the end of trial and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

13. STATISTICAL CONSIDERATIONS

13.1. Sample Size

To enable 90% power to test the non-inferiority hypothesis at a one-sided 2.5% significance level (two-sided 5% level) assuming a 3% margin of non-inferiority and a major surgical complication rate of 6% in the abdominal (control) group requires 2634 participants. The estimate of 6% is taken from a similar previous comparative study.[11] A 3% margin is justifiable because of the trade-off of potentially swifter recovery with laparoscopic surgery; a view shared by our patient focus group and is substantially less than the 5% difference observed in the previous major trial,[11] which led to the continued use of open abdominal hysterectomy.

An extra consideration is the potential for clustering by surgeon due to the expertise based design.[19 34] Under the assumption that each of the 50 centres will utilise 6 surgeons (operating on approximately 9 patients on average during the study), along with an intra-cluster correlation (ICC) estimate of 0.02, the sample size has been increased by 16% to 3055. This ICC estimate used - in the absence of precise estimates - is considered conservative given the outcome is clinical and of low prevalence, both of which are factors associated with low ICC.[35, 36] However, even varying these factors up to an ICC of 0.07 or average cluster size of 29, shows we will have at least 80% power to establish non-inferiority in these situations.

A final inflation of 6% to account for loss to follow-up (similar to the aforementioned previous study) brings the final sample size total to 3250 participants. This size of sample would give the ability to detect meaningful differences between groups in our key secondary outcome of time from surgery to resumption of usual activities. Assuming the median recovery time in the abdominal group is between 6 and 9 weeks[37] we will have high levels of power (>90%) to detect reductions of 1 week in all cases.

13.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those treated with laparoscopic hysterectomy versus those treated with open, abdominal hysterectomy. For all outcomes, analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation. For the primary outcome, given the nature of the non-inferiority design, supportive per-protocol and CACE analyses[38] will be considered alongside the intention-to-treat population. All outcomes will be adjusted for the minimisation variables listed in Section 6.3 where possible.

For all major outcome measures, summary statistics and differences between groups, e.g. relative risks, will be presented with 95% confidence intervals. For the primary outcome, this is equivalent to a one-sided 97.5% confidence interval and hence

conservative in terms of the non-inferiority margin. For the trial to declare non-inferiority of the laparoscopic approach, the lower margin of the absolute risk difference (see 13.2.1 for calculation method) confidence interval must not exceed 3%.

For the key secondary outcome of time from surgery to resumption of usual activities, we will incorporate a conditional hierarchical approach to interpretation of the 95% confidence interval to ensure we appropriately control for the overall rate of type I error[39]. If the primary outcome meets its non-inferiority objective we will then proceed to examine any differences between the two approaches for this outcome. For example, if the 95% confidence interval does not contain 1 (and favours laparoscopic) we will declare superiority of the laparoscopic approach.

Other secondary outcomes will be considered as exploratory; no adjustment for multiple comparisons will be made and hence significance should not be inferred from the confidence interval width. The exception is Serious Adverse Events may be subject to statistical testing without adjustment for multiple testing, as adjustment for multiplicity is counterproductive for considerations of safety.[39]

13.2.1. Primary Outcome Measure

We will use a mixed effect binomial regression model to estimate the absolute risk difference and 95% confidence interval (primary method). Relative risks will be calculated in a similar fashion. Parameters for treatment group as well as the minimisation variables (listed in Section 6.3) will be included in the model as fixed effects. We will explore methods to most appropriate account for both centre and surgeon variation; these elements will also be included in the model as random effect.

13.2.2. Secondary Outcome Measures

The key secondary outcome of time from surgery to resumption of normal activities will be analysed using a mixed effects ('frailty') Cox Proportional Hazard model[40], allowing the same minimisation variables and incorporating parameters for both centre and surgeon.

Linear regression models will be used to analyse response from continuous outcome measures such as, e.g. participant reported questionnaires, duration of surgery and pain via NRS; mean differences and 95% confidence intervals will be produced. Other binary and time-to-event analyses will be considered in the same fashion as the primary and key secondary outcomes. Satisfaction responses will be analysed using ordinal logistic regression. Serious adverse events will be summarised and analysed using a chi-squared test. Analgesia use will be summarised but not formally analysed. Appropriate summary statistics split by group will be presented for each outcome (e.g. proportions/percentages, mean/standard deviation or median/interquartile range).

13.2.3. Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see section 6.3; excluding centre), and performed on the primary and key secondary outcomes. Given they will have low power to assess non-inferiority on the primary outcome variable they will be treated as exploratory. Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the regression model) will be undertaken.

13.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. These are likely to involve multiple imputing techniques and 'tipping point' scenarios. Full details will be included in the Statistical Analysis Plan.

13.3. Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and key secondary outcome and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan. Further details of DMC arrangements are given in section 16.5.

13.4. Planned Final Analyses

The primary analysis for the study will occur once all participants have completed the assessments at 12 months post-surgery and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include data items up to and including this time-point only. The longer term data collected at 24 months and 36 months post-surgery will be restricted to the subgroup of patients who have reached these assessment points prior to study close and reported at a later date (see Trial Schema).

14. SUB STUDY 1: QUALITAIVE PROCESS EVALUATION

14.1. Aim

To qualitatively explore the feasibility, acceptability and appropriateness of the trial and intervention for women and healthcare professionals (HCPs).

14.2. Objectives

(1) With women: to explore their views and experiences of the recruitment approach, randomisation, barriers and facilitators to participation, and acceptability of treatment allocations

(2) With healthcare professionals: to explore their views and experiences of recruitment, randomisation, including perceived barriers and facilitators, equipoise, appropriateness and acceptability of treatment allocations, and perceptions of trial processes.

14.3. Outcomes

This pragmatic qualitative process evaluation is aligned with the MRC framework for evaluation of complex interventions[41]. The primary outcome of the qualitative process evaluation is to explore the feasibility, acceptability and appropriateness of the trial and intervention for women and healthcare professionals (HCPs). The results will dynamically informing decision-making around progression to a full trial and study design and processes. In addition, the results may help to (a) inform improvements to NHS care for women requiring hysterectomy for benign gynaecological conditions; (b) inform future gynaecology guidelines.

14.4. Eligibility

14.4.1. Inclusion

- All women eligible for LAVA and who are approached about the trial, irrespective if they agree to participate or not.
- All healthcare professionals caring for women in and involved in the delivery of the LAVA trial
- Those able and willing to give informed consent

14.4.2. Exclusion

- Participants who would be unable to take part in an interview due to language barriers (interviews will be undertaken in English)

14.5. Participant identification and treatment

Women will be approached to participate in an interview after they are approached to participate in the trial, whether they consent to the trial or not. If they verbally consent to potentially taking part in an interview, they will be asked to provide their contact details (via a consent to contact form) to the recruiting clinician who will pass these details on to the qualitative research team.

In addition, recruiting clinicians or research midwives will review their site specific screening logs and notes of all women approached about the trial. Where there is no documented evidence of discussion about the qualitative study or where women have asked to be contacted about the qualitative study at a later time the research midwives will follow up women with a letter specific to their decision about participating in the trial (e.g. decliner or randomised). The notes review and follow up letters will be sent within approximately 4 weeks of the approach about the trial. Women who have clearly declined participation in the qualitative study will not be contacted via letter.

HCPs will be approached directly by the qualitative research team after being identified from the delegation logs, snowballing within sites, and through collaborator events and established clinical networks.

14.6. Consent and withdrawal

A written record of informed consent to participate will be sought wherever possible. However, for example, in cases where the study related paperwork has not been received, not fully completed, or there are issues around literacy then we will seek alternative forms of informed consent including electronically completed (e.g. electronic completion of the form and scanning/photo of the completed consent form returned) or verbal (e.g. where the consent form will be read out in full and audio recorded at the start of the interview).

Informed consent (including written, electronically completed and/or verbal (that is audio recorded) will include agreement to participate, demographic data collection, audio recorded discussion, and anonymised data sharing.

At the beginning of each audio recording, participants who have completed written or electronic consent processes will be asked to verbally re-confirm consent. Were formal verbal informed consent is being sought at the start of a virtual interview then two separate audio file recordings for each participant will be created. The first audio file will just cover the consent discussion and record verbal consent. The consent form will be read out, and the participant asked to consent to each statement. Should the participant not consent to any of the statements then the interview will be terminated at that point having explained to that participant that data collection cannot continue, as they did not consent to participate. Once verbal consent has been sought the first audio file will be closed. A member of the Qualitative research team within the University of Birmingham will transcribe the consent audio file to create formal record of consent or declined consent. This transcript will be stored securely and separately from the transcript of the main interview (if consent was gained)

If the participant does give consent then the study interview will commence and be recorded in a second audio file. Only this second file will be sent to a third party company for transcription.

Interview participants will be free to withdraw at any time without having to explain or justify their decision. However, data already obtained may be retained and use for the purpose for which it was collected.

14.7. Data collection

In the first instance, participants will be invited to participate in an interview via telephone/video conference (e.g. Zoom, Skype or WhatsApp). To ensure inclusivity, where participants are unable to participate virtually, we may consider face to face interviews in the clinic where they were treated/work, at the University of Birmingham (if local to Birmingham), in the participant's home or in an appropriate public space. We will ensure that we are following appropriate COVID related guidance if interviews are undertaken face to face, and the relevant guidance from the University of Birmingham, such as that relating to working in participant's homes, is adhered to. From experience, we anticipate that the vast majority will be done virtually.

For women, we will aim to conduct interviews within four to six weeks of them being approached to participate (decliners) or being randomised (women who consent to randomisation). This will however remain flexible to accommodate the needs of the women.

A discussion guide to facilitate the interviews will be developed informed by existing literature (for example the domains proposed in the Theoretical Framework for Acceptability of Healthcare Interventions[42], patient and public involvement, and discussions within the LAVA team. Interviews will be conducted in a participant focused manner allowing issues and perspectives important to participants to arise naturally[43].

For women, interviews will explore their views and experiences of the treatment options, the recruitment approach, randomisation, barriers and facilitators to participation, acceptability of randomisation, and experiences of care pre- and post-intervention. For healthcare professionals, interviews will explore their familiarity with, and exposure to, different types of hysterectomy; views and experiences of recruitment, randomisation, including perceived barriers and facilitators, equipoise, appropriateness and acceptability of the intervention, and perceptions of trial processes.

14.8. Anticipated sample sizes

We aim to undertake semi-structured one to one interviews across the sites involved in the trial and will attempt to purposively recruit participants from the following groups (number of interviews per group provided in brackets):

a. women who decline to participate (n~4-6)
b. women randomised to the laparoscopy treatment group (n~8-12)

c. women randomised to abdominal surgery treatment group (n~8-12)
d. healthcare professionals involved in recruitment and randomisation (n~8-10)

The Pilot study will be open for 9 months across approximately 25 trial sites. Based on recruitment projections for the trial, approximately 200 women will have been recruited and randomised during the 7 months of qualitative data collection. Our aim is therefore to interview roughly 15% of these women.

From experience, we expect the final sample to include approximately 30-40 interviews (both women and HCPs) but the numbers will remain flexible to ensure that we collect sufficiently rich data to address the aim and objectives of the study.

14.9. Data analysis

Verbal consent and interviews will be audio recorded using a password protected encrypted dictaphone with data collection and initial analysis taking place iteratively[44]. Data collection will continue until the research team judge that the data and sample had sufficient depth and breadth to address the study aim[45]. The main interview audio files will be transcribed clean verbatim by an external specialist transcription company (who has an appropriate contract with the University of Birmingham that will include a confidentially and data protection agreement) and the framework approach[46] used to facilitate a systematic and flexible approach to the analysis.

14.10. Management of risk

Given the nature of the discussions, it is unlikely that the participants in this study will be distressed as a result of participating in an interview. However, it will be clearly stated in the participant information sheet, by the person introducing the potential participant to the study, as well as being reiterated by the researcher at the beginning of the interview that participants are free to withdraw at any time up to two weeks after the data collection event without having to explain or justify their decision.

All participants will self-select to take part. The welfare of the participants will always be placed ahead of the knowledge to be gained and emotionally distressing topics will be handled with sensitivity and sympathy. The interviewer will also signpost the distressed participant towards services for additional support should this be appropriate. Information on support services is also provided in the participant information leaflet. We have sought PPI input to ensure that all participant facing materials and the interview questions are appropriate.

If a participant raises issues about their care that the qualitative research team deem as potentially harmful to them (or others) then the researcher will advise them to contact their local Patient Advice and Liaison Service (PALS) (or equivalent) whose contact details are provided in the PIS. The lead for the qualitative sub-study, Dr Laura Jones, will also inform the CI, Prof T. Justin Clark. The CI, where appropriate, will ensure that the local unit PI is aware of the woman and potential concerns so that follow-up can be arranged if required. Should a participant have questions about their clinical care then the qualitative research team will advise the woman to contact her clinical team and/or her GP.

14.11. Nesting within the LAVA Trial

Recruitment to the qualitative study will begin in parallel with the pilot trial with qualitative data collection for 7 months. This will include dynamic feedback in real time to allow the TMG to be adaptive to any problems identified and increase the likelihood of the pilot moving to full RCT. Final analysis and initial write up will be undertaken in month 8, prior to the pilot review DMC meeting.

15. SUB STUDY 2: HEALTH ECONOMIC EVALUATION

Aim

To carry out an economic evaluation to assess the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy in the management of benign gynaecological conditions.

Rationale

If laparoscopic hysterectomy is non-inferior to open abdominal hysterectomy as a method of treatment for benign gynaecological conditions, significant economic implications may be seen for the health sector. For example, laparoscopic hysterectomy may result in fewer intra-operative and post-operative complications. Furthermore, there may be cost implications; the intervention may be more costly or less costly compared to open abdominal hysterectomy. Any additional cost would need to be justified and shown to provide good value for the public health care resources, or any cost saving (for the same outcome), could be effectively spent elsewhere in the health system.

Methods

A within trial-based economic evaluation will explore the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy.

The principal outcomes for the economic evaluation will be cost per QALY at 12 months post-surgery.

A secondary analyses will be undertaken to generate costs per major surgical complication avoided and costs per return to normal activities.

Data Collection for Economics Evaluation

Resource use data will be collected prospectively from an NHS perspective, through case report forms (CRF) in order to estimate the overall cost of the alternative strategies. The cost of the laparoscopic hysterectomy and the comparator of open abdominal hysterectomy will be sourced from the routine Health Resource Group data. Additional resource use such

as that associated with additional inpatient stay (beyond that assumed in HRG data) as a result of complications, and any follow-up care up to the end of follow up at 12 months will collected through additional case report forms, collecting interactions related to the procedure with health services following discharge from hospital.

In addition we will undertake micro costing of both laparoscopic hysterectomy and abdominal hysterectomy to ensure the assumptions associated in routine Health Resource Group Data accurately reflects the interventions as carried out in the trial.

To achieve this we will record time the time for the procedures in both arms of the trial, record the personnel present during the procedures and record the use of any specific different equipment required. In addition we will collect observational data to further quantify resources consumption using a time and motion study that will be conducted over a two week period from a random subgroup of actively recruiting centres.

The main resource categories to be monitored include

1. Resource use associated with the procedures in both arms of trial (for micro-costing), personnel present, specific additional equipment and disposable, and length of time taken to carry out the procedure.
2. Resource use associated with adverse events and complications and length of stay beyond that expected and additional medication beyond that expected for an inpatient.
3. Resource use associated with outpatient or emergency visits and re-presentation / re-admission to hospital arising from complications.
4. Contacts with community and social care services, such as consultation with a general practitioner or practice nurse.

In order to value health care resource use to estimate the overall cost of each trial-arm, unit costs will be applied to each resource item. Information on unit costs will be obtained from key UK national sources, such as the NHS reference costs, the Unit Costs of Health and Social Care[47] the British National Formulary, and the Office for National Statistics. Given the potential impact on physical and, particularly, psychological health, health-related quality of life data will be obtained based on participants responses to the EQ-5D-5L at baseline and at each clinical review. A preference-based index of health-related quality of life will be derived using the recently published English value set (and appropriate crosswalk as per 3L), and Quality-Adjusted Life-Years (QALYs) will be calculated using the area under the curve approach.

Economic analysis: A within trial-based economic evaluation will explore the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy.

Initially, the base-case analysis for the within trial analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost and the important consequences as assessed in the trial.

The principal outcomes for the economic evaluation will be presented in term of Incremental Cost effectiveness Ratios (ICER) in term of cost per QALY at 12 months post randomisation. Secondary analyses will be undertaken to generate costs per major surgical complication avoided and costs per return to normal activities.

In the base case analyses, we will consider costs that were stipulated in the NHS reference costs. Although these costs are representative of the expenses incurred in the UK, to make the results more generalisable we will calculate the cost of the procedures by breaking them down to the individual components involved and then adding up all the costs to obtain an overall cost (i.e. bottom- up costing). Thus, in addition to the base case analysis we will conduct additional analysis based on micro costing the procedure. Given the skewness inherent in most cost data and the concern of economic analyses with mean costs, we shall use a bootstrapping approach in order to calculate confidence intervals around the difference in mean costs[48].

The incremental economic analysis will be conducted on both the primary outcome and confidence intervals generated to estimate uncertainty. The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also use both simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.

16. TRIAL ORGANISATIONAL STRUCTURE

16.1. Sponsor

The Sponsor for this trial is the University of Birmingham. The Head Organisation (i.e. the contracting party with the funder) is Birmingham Women's and Children's Hospital.

16.2. Coordinating Centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit, based at the University of Birmingham.

16.3. Trial Management Group

The Trial Management Group will take responsibility for the day-to-day management of the trial, and will include (but is not limited to) the CI, co-applicants, statistician, team leader and trial manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

16.4. Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or

equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

A single TSC will be created for the LAVA trial and, unless in exceptional circumstances, will meet *via* teleconference as required depending on the needs of the trial office.

Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will provide overall oversight of the trial, including the practical aspects of the study, as well as ensuring that the study is run in a way which is both safe for the participants and provides appropriate feasibility data to the sponsor and investigators.

16.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet at regular intervals that will allow them to effectively monitor the trial unless there is a specific reason (e.g. safety phase) to amend the schedule.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Steering Committee who will convey the findings of the DMC to the Trial Management Group, the funders, and the sponsors. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

16.6. Finance

Funding for the LAVA trial is provided by an award from the National Institute of Health Research Health Technology Assessment program Ref: 128991

17. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998) and the Principles of GCP. The protocol will be submitted to and approved by the main REC prior to circulation.

Before any participants are enrolled into the trial, the PI at each site will obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

18. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998.

Participants will always be identified using their unique trial identification number and partial date of birth (month / year) on the Case Report Form and correspondence between BCTU and local centres. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process".

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. laboratory staff, competent authority, sponsor). Representatives of the LAVA trial team and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

19. Financial and other competing interests

Members of the TMG or study oversight committees will be required to declare any financial or other competing interests. These will be recorded in specific documents recording any competing interests based upon the DAMOCLES declaration.

20. Insurance and Indemnity

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's,

or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

21. Amendments

The decision to amend the protocol and associated trial documentation will be initiated by the TMG. As sponsor, The University of Birmingham will be responsible for deciding whether an amendment is substantial or non-substantial. Substantive changes will be submitted to REC for approval. Once this has been received, R&D departments will be notified of the amendment and requested to provide their approval. If no response is received within 35 days, an assumption will be made that the site has no objection to the amendment and it will be implemented at the site. All amendments will be tracked in the 'Protocol Amendments' section of the protocol.

22. Post-trial care

All patients will continue to receive standard medical care following participation in the clinical trial. There are no interventions that participant's will be prevented from accessing after their participation in the trial has been completed.

23. Access to the final trial dataset

During the period of the study only the trial steering group will have access to the full trial dataset in order to ensure that the overall results are not disclosed by an individual trial site prior to the main publication.
Following publication of the findings, the final trial dataset will be made available to external researchers upon approval from the trial management group and the BCTU data sharing committee in line with standard data sharing practices for clinical trial data sets.

24. Publication Policy

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the CI and authorship will be determined by the trial publication policy.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG prior to wider circulation. Manuscripts must be submitted to the TMG in a timely fashion and well in advance of being submitted for publication to allow time for review and resolution of any outstanding issues.

Authors must acknowledge that the trial was performed with the support of the University of Birmingham and Birmingham Clinical Trials Unit. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

The trial question is important and has the potential to change clinical practice. This view has been validated by the health professionals and patient surveys that have been conducted by our research team and from research recommendations arising from systematic reviews and national, evidence-based guidelines. We have prioritised methods to ensure rapid, clinical impact once the results of the LAVA trial are available. These include:

Guidelines: The information is expected to be rapidly incorporated into guidelines by the Royal College of Obstetricians and Gynaecologists (RCOG), the British Society of Gynaecological Endoscopy (BSGE), the National Institute of Health and Care Excellence (NICE) and international guidelines and disseminated nationally for implementation. This will be facilitated by the coinvestigator group who hold senior positions in many of these bodies.

All current systematic reviews and guidance have acknowledged the need for research and we therefore believe that authors will be receptive to these new findings Patient information resources: Production of lay information with links to appropriate patient organisations, particularly the Hysterectomy Association and the RCOG (RCOG Women's Voices and patient information department). With our PPI co-applicants and contacts we will produce effective, contemporary formats for dissemination e.g. the use of video podcasts and social media outlets. Conferences: The findings will be presented and disseminated via the BSGE, RCOG and other national and international conferences.

Peer reviewed publications: We will aim to publish the findings in high impact peer reviewed journals. We will disseminate the completed paper to the Department of Health, the Scientific Advisory Committees of the RCOG, the Royal College of Nurses (RCN) and the BSGE.
NIHR Journals Library: A copy of the monograph will be lodged with the NIHR Journals Library will help with dissemination of findings and will provide an important, permanent and comprehensive record of the study.

Media: In consultation with the investigators and appropriate journal, a press release will be issued to the media upon publication of the results.

Results of the study will be shared with study participants, staff members at research sites and investigators of other studies related to hysterectomy and benign gynaecological surgery. A formal notification to the ethics committee, Department of Health, key partners and sponsors will be made. Outreach to other key stakeholders (trial networks, health advocates) involved in related trials is planned. The trial team has key individuals to optimise the dissemination of results.

25. Reference List

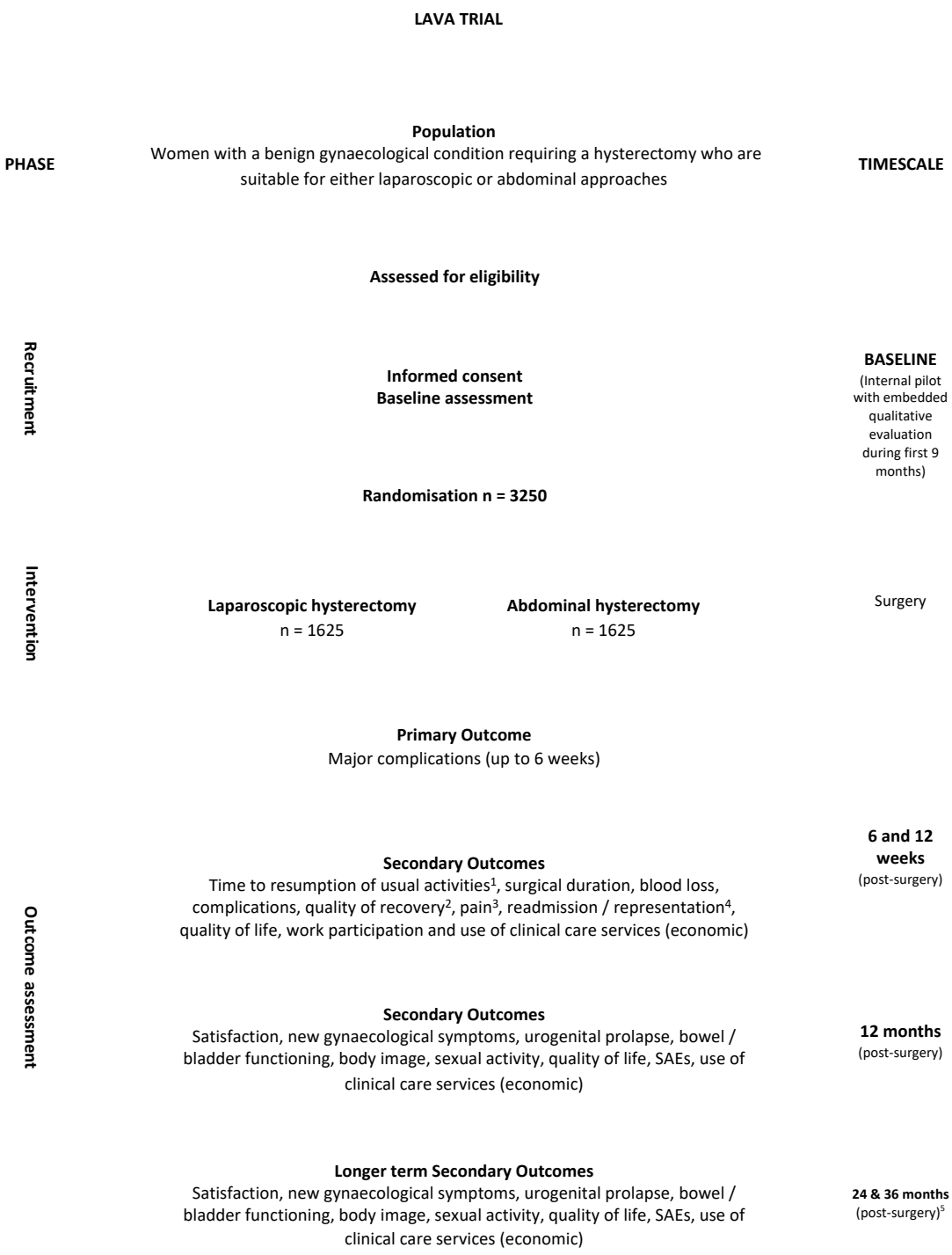
1. Ruiz de Azua Unzurrunzaga G, Brewster DH, Wild SH, Sivalingam VN. Declining hysterectomy prevalence and the estimated impact on uterine cancer incidence in Scotland. *Cancer Epidemiol* 2019;**59**:227-31. https://doi.org/10.1016/j.canep.2019.02.008
2. ACOG Committee Opinion No. 444: choosing the route of hysterectomy for benign disease. *Obstet Gynecol* 2009;**114**:1156-8. https://doi.org/10.1097/AOG.0b013e3181c33c72
3. Nieboer TE, Johnson N, Lethaby A, Tavender E, Curr E, Garry R*, et al.* Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev* 2009; 10.1002/14651858.CD003677.pub4:CD003677. https://doi.org/10.1002/14651858.CD003677.pub4
4. Middleton LJ, Champaneria R, Daniels JP, Bhattacharya S, Cooper KG, Hilken NH*, et al.* Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients. *BMJ* 2010;**341**:c3929. https://doi.org/10.1136/bmj.c3929
5. Aarts JW, Nieboer TE, Johnson N, Tavender E, Garry R, Mol BW*, et al.* Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev* 2015; 10.1002/14651858.CD003677.pub5:CD003677. https://doi.org/10.1002/14651858.CD003677.pub5
6. Royal College of Obstetricians and Gynaecologists LSoHTM, Ipsos MORI. *National Heavy Menstrual Bleeding Audit: Final report. London, UK*. RCOG Press; 2014. URL: https://www.rcog.org.uk/globalassets/documents/guidelines/research--audit/national_hmb_audit_final_report_july_2014.pdf (accessed).
7. Royal College of Obstetricians and Gynaecologists LU. *Patterns of Benign Gynaecology Care in English NHS Hospital Trusts 2015/16.*; 2018. URL: https://www.rcog.org.uk/en/guidelines-research-services/audit-quality-improvement/clinical-indicators-programme/benign-gynaecological-care/benign-gynaecology-report-2015-16/ (accessed).
8. Liu Z, Doan QV, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. *Value Health* 2007;**10**:183-94. https://doi.org/10.1111/j.1524-4733.2007.00168.x
9. Frick KD, Clark MA, Steinwachs DM, Langenberg P, Stovall D, Munro MG*, et al.* Financial and quality-of-life burden of dysfunctional uterine bleeding among women agreeing to obtain surgical treatment. *Womens Health Issues* 2009;**19**:70-8. https://doi.org/10.1016/j.whi.2008.07.002
10. Blikkendaal MD, Schepers EM, van Zwet EW, Twijnstra AR, Jansen FW. Hysterectomy in very obese and morbidly obese patients: a systematic review with cumulative analysis of comparative studies. *Arch Gynecol Obstet* 2015;**292**:723-38. https://doi.org/10.1007/s00404-015-3680-7
11. Garry R, Fountain J, Mason S, Hawe J, Napp V, Abbott J*, et al.* The eVALuate study: two parallel randomised trials, one comparing laparoscopic with abdominal hysterectomy, the other comparing laparoscopic with vaginal hysterectomy. *BMJ* 2004;**328**:129. https://doi.org/10.1136/bmj.37984.623889.F6
12. Ghezzi F, Uccella S, Cromi A, Siesto G, Serati M, Bogani G*, et al.* Postoperative pain after laparoscopic and vaginal hysterectomy for benign gynecologic disease: a randomized trial. *Am J Obstet Gynecol* 2010;**203**:118 e1-8. https://doi.org/10.1016/j.ajog.2010.04.026
13. Song T, Cho J, Kim TJ, Kim IR, Hahm TS, Kim BG*, et al.* Cosmetic outcomes of laparoendoscopic single-site hysterectomy compared with multi-port surgery: randomized controlled trial. *J Minim Invasive Gynecol* 2013;**20**:460-7. https://doi.org/10.1016/j.jmig.2013.01.010
14. Paraiso MF, Ridgeway B, Park AJ, Jelovsek JE, Barber MD, Falcone T*, et al.* A randomized trial comparing conventional and robotically assisted total laparoscopic hysterectomy. *Am J Obstet Gynecol* 2013;**208**:368 e1-7. https://doi.org/10.1016/j.ajog.2013.02.008
15. Janssen MF, Bonsel GJ, Luo N. Is EQ-5D-5L Better Than EQ-5D-3L? A Head-to-Head Comparison of Descriptive Systems and Value Sets from Seven Countries. *PharmacoEconomics* 2018;**36**:675-97. https://doi.org/10.1007/s40273-018-0623-8

16. Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware JE, Jr. The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J Clin Epidemiol* 2014;**67**:516-26. https://doi.org/10.1016/j.jclinepi.2013.10.024
17. Madhvani K, Curnow T, Carpenter T. Route of hysterectomy: a retrospective, cohort study in English NHS Hospitals from 2011 to 2017. *BJOG* 2019;**126**:795-802. https://doi.org/10.1111/1471-0528.15539
18. Lee SH, Oh SR, Cho YJ, Han M, Park JW, Kim SJ*, et al.* Comparison of vaginal hysterectomy and laparoscopic hysterectomy: a systematic review and meta-analysis. *BMC Womens Health* 2019;**19**:83. https://doi.org/10.1186/s12905-019-0784-4
19. Cook JA, Elders A, Boachie C, Bassinga T, Fraser C, Altman DG*, et al.* A systematic review of the use of an expertise-based randomised controlled trial design. *Trials* 2015;**16**:241. https://doi.org/10.1186/s13063-015-0739-5
20. Barber EL, Van Le L. Enhanced Recovery Pathways in Gynecology and Gynecologic Oncology. *Obstet Gynecol Surv* 2015;**70**:780-92. https://doi.org/10.1097/OGX.0000000000000259
21. Crins MHP, Terwee CB, Klausch T, Smits N, de Vet HCW, Westhovens R*, et al.* The Dutch-Flemish PROMIS Physical Function item bank exhibited strong psychometric properties in patients with chronic pain. *J Clin Epidemiol* 2017;**87**:47-58. https://doi.org/10.1016/j.jclinepi.2017.03.011
22. Terwee CB, Roorda LD, de Vet HC, Dekker J, Westhovens R, van Leeuwen J*, et al.* Dutch-Flemish translation of 17 item banks from the patient-reported outcomes measurement information system (PROMIS). *Qual Life Res* 2014;**23**:1733-41. https://doi.org/10.1007/s11136-013-0611-6
23. van der Meij E, Anema JR, Leclercq WKG, Bongers MY, Consten ECJ, Schraffordt Koops SE*, et al.* Personalised perioperative care by e-health after intermediate-grade abdominal surgery: a multicentre, single-blind, randomised, placebo-controlled trial. *Lancet* 2018;**392**:51-9. https://doi.org/10.1016/S0140-6736(18)31113-9
24. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205-13. https://doi.org/10.1097/01.sla.0000133083.54934.ae
25. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;**118**:1332-40. https://doi.org/10.1097/ALN.0b013e318289b84b
26. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199-208. https://doi.org/10.1016/0168-8510(90)90421-9
27. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics* 1993;**4**:353-65. https://doi.org/10.2165/00019053-199304050-00006
28. Hagen S, Glazener C, Sinclair L, Stark D, Bugge C. Psychometric properties of the pelvic organ prolapse symptom score. *BJOG* 2009;**116**:25-31. https://doi.org/10.1111/j.1471-0528.2008.01903.x
29. Groenendijk AG, Birnie E, Roovers JP, Bonsel GJ. Contribution of primary pelvic organ prolapse to micturition and defecation symptoms. *Obstet Gynecol Int* 2012;**2012**:798035. https://doi.org/10.1155/2012/798035
30. Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. *Neurourol Urodyn* 1995;**14**:131-9. https://doi.org/10.1002/nau.1930140206
31. van Brummen HJ, Bruinse HW, van de Pol G, Heintz AP, van der Vaart CH. Defecatory symptoms during and after the first pregnancy: prevalences and associated factors. *Int Urogynecol J Pelvic Floor Dysfunct* 2006;**17**:224-30. https://doi.org/10.1007/s00192-005-1351-0
32. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. *Qual Life Res* 1996;**5**:81-90. https://doi.org/10.1007/BF00435972

33. Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. *Eur J Cancer* 2001;**37**:189-97. https://doi.org/10.1016/s0959-8049(00)00353-1
34. Roberts C. The implications of variation in outcome between health professionals for the design and analysis of randomized controlled trials. *Stat Med* 1999;**18**:2605-15. https://doi.org/10.1002/(sici)1097-0258(19991015)18:19<2605::aid-sim237>3.0.co;2-n
35. Gulliford MC, Adams G, Ukoumunne OC, Latinovic R, Chinn S, Campbell MJ. Intraclass correlation coefficient and outcome prevalence are associated in clustered binary data. *J Clin Epidemiol* 2005;**58**:246-51. https://doi.org/10.1016/j.jclinepi.2004.08.012
36. Pagel C, Prost A, Lewycka S, Das S, Colbourn T, Mahapatra R*, et al.* Intracluster correlation coefficients and coefficients of variation for perinatal outcomes from five cluster-randomised controlled trials in low and middle-income countries: results and methodological implications. *Trials* 2011;**12**:151. https://doi.org/10.1186/1745-6215-12-151
37. Vonk Noordegraaf A, Anema JR, Louwerse MD, Heymans MW, van Mechelen W, Brolmann HA*, et al.* Prediction of time to return to work after gynaecological surgery: a prospective cohort study in the Netherlands. *BJOG* 2014;**121**:487-97. https://doi.org/10.1111/1471-0528.12494
38. Hewitt CE, Torgerson DJ, Miles JN. Is there another way to take account of noncompliance in randomized controlled trials? *CMAJ* 2006;**175**:347. https://doi.org/10.1503/cmaj.051625
39. Huque MFD, A. ; D'Agostino, R. Multiplicity Issues in Clinical Trials With Multiple Objectives. *Statistics in Biopharmaceutical Research* 2013;**5**.
40. Austin PC. A Tutorial on Multilevel Survival Analysis: Methods, Models and Applications. *Int Stat Rev* 2017;**85**:185-203. https://doi.org/10.1111/insr.12214
41. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W*, et al.* Process evaluation of complex interventions: Medical Research Council guidance. *BMJ* 2015;**350**:h1258. https://doi.org/10.1136/bmj.h1258
42. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Serv Res* 2017;**17**:88. https://doi.org/10.1186/s12913-017-2031-8
43. Clarke VaB, V. *Successful qualitative research: a practical guide for beginners.* Sage; 2013. URL: http://www.uk.sagepub.com/books/Book233059.
44. Dicicco-Bloom B, Crabtree BF. The qualitative research interview. *Med Educ* 2006;**40**:314-21. https://doi.org/10.1111/j.1365-2929.2006.02418.x
45. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res* 2016;**26**:1753-60. https://doi.org/10.1177/1049732315617444
46. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC medical research methodology* 2013;**13**:117. https://doi.org/10.1186/1471-2288-13-117
47. Curtis L.A B, A. *Unit Costs of Health and Social Care 2017*. University of Kent; 2017. URL: https://kar.kent.ac.uk/65559/40/65559_rep_UCR-2017-v13finalKAR.pdf (accessed; https://doi.org/10.22024/UniKent/01.02/6555). https://doi.org/https://doi.org/10.22024/UniKent/01.02/6555
48. Briggs AH, O'Brien BJ. The death of cost-minimization analysis? *Health Econ* 2001;**10**:179-84. https://doi.org/10.1002/hec.584

26. APPENDICES

26.1 Appendix 1: Trial Schema



[1] Time from surgery to resumption of usual activities will continue to be evaluated until all 8 selected activities have been resumed
[2] 24 hours post-surgery
[3] Daily, up to and including 14 days post-surgery
[4] 6 weeks post-surgery only
[5] Restricted to subgroups of participants reaching these timepoints prior to close of the study i.e. when the last randomised patient reaches 12 months post-surgery