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LAparoscopic Versus Abdominal hysterectomy (LAVA): Protocol of a randomised controlled trial

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Abstract

Introduction

There is uncertainty about the advantages and disadvantages of laparoscopic hysterectomy compared with abdominal hysterectomy, particularly the relative rate of complications of the two procedures. Whilst uptake of laparoscopic hysterectomy has been slow, the situation is changing with greater familiarity, better training, better equipment and increased proficiency in the technique. Thus, a large, robust, multi-centre randomised controlled trial (RCT) is needed to compare contemporary laparoscopic hysterectomy with abdominal hysterectomy to determine the safest and most cost-effective technique.

Methods and analysis

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. A within trial-based economic evaluation will explore the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy. We will aim to recruit 3250 women requiring a hysterectomy for a benign gynaecological condition and who were suitable for either laparoscopic or open techniques. The primary outcome is major complications up to six completed weeks post-surgery and the key secondary outcome is time from surgery to resumption of usual activities using the personalised PROMIS-SF (Patient-Reported Outcomes Measurement Information System Physical Function) questionnaire. The principal outcome for the economic evaluation is to be cost per QALY at 12 months' post-surgery. A secondary analysis is to be undertaken to generate costs per major surgical complication avoided and costs per return to normal activities.

Ethics and dissemination

The study was approved by the West Midlands-Edgbaston Research Ethics Committee,18th February-2021 (Ethics ref: 21/WM/0019). We will present the findings in national and international conferences. We will also 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.

Trial registration: University of Birmingham, ISRCTN14566195.

Strengths and limitations of this study

- The LAVA trial is larger than all the previous 25 RCTs evaluating laparoscopic and open hysterectomy and of higher quality, addressing the methodological deficiencies of previous trials; namely their power to show a meaningful difference, accounting for surgical expertise bias and the ensuring the validity of outcomes assessments, especially the key secondary outcome of personalised recovery
- In the LAVA trial a novel, validated, personalised recovery tool is used via SMS and an expertise-based design to mitigate against surgical expertise bias employed.
- Third part randomisation is to be performed balancing important prognostic variables.
- Due to the differing natures of the intervention it is impossible to blind either the care providers, investigators or participants to their allocated group.

Introduction

Hysterectomy is common, with one in ten women undergoing the procedure in their lifetime, mostly for benign conditions [1,2,3]. 30,000 women undergo a hysterectomy every year in the UK for benign indications such as abnormal uterine bleeding and pelvic pain [1,2,3]. 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 [6,7,8,9]. Currently, most hysterectomies are performed by laparotomy, through a vertical or transverse incision because this traditional method is thought to minimise intra-operative complications but the increased trauma of an abdominal incision 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].

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 [12,13,14,15]. The Cochrane review [5] identified no differences in the costs or outcomes apart from return to normal activities, which was shorter in the laparoscopic hysterectomy group by 14 days on average.

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]. Thus, we designed a large RCT to determine the clinical and cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy for women with a benign gynaecological condition.

Methods and analysis

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.

Study design and setting

The study is designed as 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.

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.

Patient and Public Involvement (PPI)

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".

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. 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.

Participants

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

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

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 para-rectal space

Choice of intervention

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 [17]. Whilst the uptake of laparoscopic hysterectomy has been slow [18], 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 [18].

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.

Recruitment and randomisation

Women with benign gynaecological conditions requiring a hysterectomy and who are suitable for either surgical technique are eligible for inclusion in the LAVA trial. Potential participants will be provided with a REC approved Study Participant Information Sheet (PIS) and given time to consider their involvement.

After participant eligibility is confirmed and informed consent received, the baseline questionnaires are to be completed and then the participant randomised into the trial. Baseline data collected includes demographic and medical data (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); Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF) item bank v1.2 [16] (see "key secondary outcome"); quality of life, symptom and physical functioning questionnaires, EuroQoL EQ-5D-5L and EQ VAS [15], Urogenital Distress Inventory (UDI) [28], Pelvic organ prolapse symptom score (POP-SS) [28], Defecatory Distress Inventory (DDI) [31], Sexual Activity Questionnaire (SAQ) [32].

Randomisation is provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at http://www.trials.bham.ac.uk/lava). 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/m2)
- Uterine Size (<=12 weeks, >12 weeks)
- Planned retention of cervix (yes / no)
- Recruiting centre

Interventions and expertise-based surgery

Hysterectomy is undertaken by either a laparoscopic or an open abdominal route, by a surgeon who had self-declared as having expertise in laparoscopic hysterectomy, abdominal hysterectomy or both approaches to hysterectomy. Satisfactory experience requires 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. The decision to remove or retain cervix (total or sub-total) or remove and retain ovaries was left to the discretion of the participant in consultation with her gynaecologist. The expertise design process for eligible centres is depicted in (Figure 1)

Outcome Measures

Women who give consent in a face to face setting will subsequently complete their baselines questionnaires and then proceed to randomisation. 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], [21,22,23]. Local research teams will offer remote (telephone, VOIP or video) contact, or exceptionally face to face appointments, to provide explanation.

Trial Outcomes

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.

However, other less common major surgical or anaesthetic complications may arise and these will be ascribed in accordance with the appropriate Clavien-Dindo classification shown in (Table 1)

TABLE 1

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:

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 were 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 created 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.

Other secondary outcomes

1- Surgical outcomes:
   - Duration of operation, (minutes)
   - Estimated blood loss, (ml)

2- In hospital stay:
   - 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

3- Up to 14 days after surgery:

- 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) questionnaire25 (with 0 indicating worst recovery and 10 indicating best recovery), measured at approximately 24 hours post-operation*
- Time from operation to discharge in days

4- 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

5- 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)

6- 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
- 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

7- 12/24/36 months post-surgery:**

- Satisfaction with hysterectomy
- Symptoms of urogenital prolapse using the Pelvic Organ Prolapse Symptom Score (POP-SS) questionnaire [28]
- Bladder function using Urogenital Distress Inventory (UDI) [29,30] questionnaire
- Bowel function using Defecatory Distress Inventory (DDI) [31] questionnaire
- Sexual function using the Sexual Activity (SAQ) questionnaire [32]
- Quality of life score using EuroQol-5D-5L questionnaire
- Quality of life score using EuroQol-5D-5L visual analogue scale
- Body image using the Body Image Scale (BIS) questionnaire [33]
- 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.

8- Throughout: Serious adverse events

* 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.

A SUMMARY OF THE SCHEDULE OF ASSESSMENTS IS SHOWN IN (TABLE 2) AND THE TRIAL FLOW DIAGRAM SHOWN IN (FIGURE 2)

TABLE 2

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	6 weeks +28	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

Rand = randomisation

* 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

Statistical consideration

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. 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.

Analysis of outcome measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. 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 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 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].

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 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.

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).

Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm, 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.

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.

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.

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) (Figure 2)

Sub-studies

Full details of these sub-studies are available from the authors on request

Qualitative process evaluation

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

Health economic evaluation

An economic evaluation was designed to assess the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy in the management of benign gynaecological conditions. A within trial-based economic evaluation was to explore the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy. The principal outcomes for the economic evaluation was cost per QALY at 12 months post-surgery. A secondary analyses was planned
to generate costs per major surgical complication avoided and costs per return to normal activities.

Discussion

The LAVA trial protocol was designed in 2019 and amended during 2020 before funding and ethical approval was granted. The trial commenced recruitment in September 2021 but failed to meet its RAG (‘red; amber; green) criteria for site set up and recruitment rate and so for

this reason and the recognition by the funder (The NIHR HTA Programme) of insufficient NHS clinical and Research & Development capacity post the Covid-19 pandemic, the trial was closed. The research question remains relevant, given that almost 30,000 hysterectomies are undertaken per year [7,18] and especially now that the laparoscopic approach to hysterectomy is being facilitated further by advances in instrumentation including robotic surgery [41,42]. Our research group plans to analyse qualitative and quantitative data acquired from the commencement of the trial to inform future surgical trials and aid future researchers wishing to undertake comparative trials in hysterectomy. We believe that our carefully considered protocol will be of value to future researchers working in the field of optimising clinical outcomes for women undergoing hysterectomy.

Strengths and limitations

The LAVA trial was larger than all the previous 25 RCTs evaluating laparoscopic and open hysterectomy and of higher quality, addressing the methodological deficiencies of previous trials; namely their power to show a meaningful difference, the validity of outcomes assessment, especially the key outcome of recovery and a failure to account for surgical expertise. In the LAVA trial we used a novel, validated, personalised recovery tool [17,21,22], and employed an expertise-based design to mitigate against surgical expertise bias [19,34]. Third part randomisation was performed balancing important prognostic variables. Due to the differing natures of the intervention it is impossible to blind either the care providers, investigators or participants to their allocated group.

Potential impact and implications

Hysterectomy is common, with one in ten women undergoing the procedure in their lifetime, mostly for

benign conditions [12,13,14]. The operation imposes substantial morbidity upon women, disrupts families and impacts upon wider society through utilisation of scarce health care resources and lost productivity [3,4,5,6] [15]. These burdens could potentially be reduced with safe, less invasive surgery allowing quicker recovery. Currently, most hysterectomies are performed abdominally because this traditional method is thought to minimise intra-operative complications but the increased trauma of an abdominal incision can prolong recovery [2]. This may be especially true in overweight and obese women, where morbidity is greater from mobility restrictions and wound infection [16].

Laparoscopic hysterectomy avoids the need for a large surgical incision speeding recovery for most women but has been associated with serious complications and specialist surgical skills. However, scientific advances in imaging and equipment, has made laparoscopic surgery easier as well as more accessible to general gynaecologists [11] [17,18]. Furthermore, laparoscopic surgery forms an integral part of modern packages of nursing, anaesthetic and surgical care designed to enhance recovery and allow 24 hour hospital discharge [20].

The wider adoption of contemporary laparoscopic hysterectomy has the potential to minimise morbidity, expedite recovery and improve clinical outcomes for women in the short-term and longer-term. Furthermore, enhanced recovery has the potential to be economically advantageous to the NHS through resource efficiencies and wider society via increased productivity.

Ethics and dissemination

The study was approved by the West Midlands-Edgbaston Research Ethics Committee. All participants gave informed consent before participation. The trial was being 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.

The findings will be presented and disseminated via the BSGE, RCOG and other national and international conferences. We will also 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.

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Statements

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Figure 1
The expertise design process for eligible centres

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

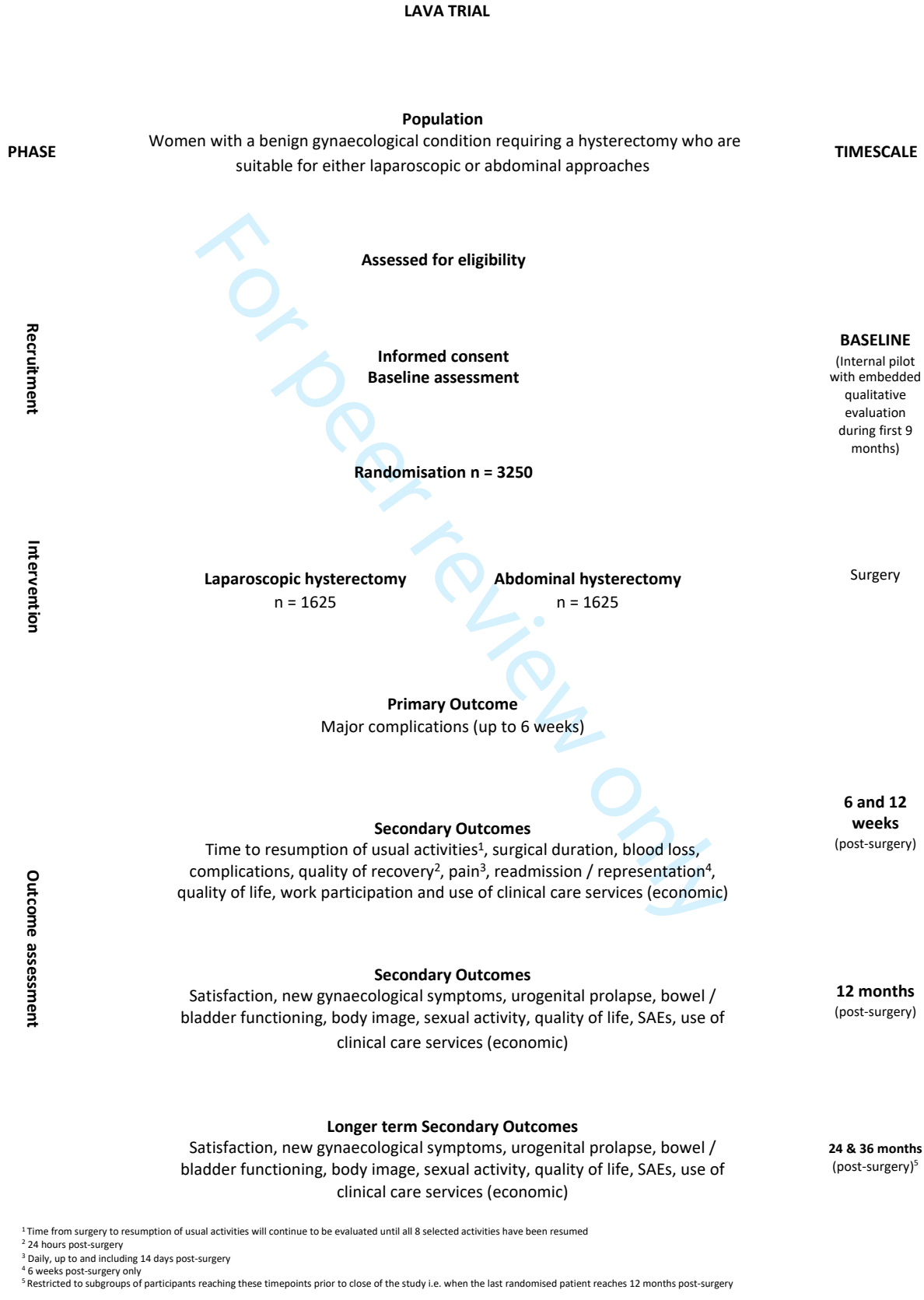
Allocated LAPAROSCOPIC expert surgeon[4]

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.

Figure 2
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

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LAparoscopic Versus Abdominal hysterectomy (LAVA): Protocol of a randomised controlled trial

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LAparoscopic Versus Abdominal hysterectomy (LAVA): Protocol of a randomised controlled trial

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Abstract

Introduction

There is uncertainty about the advantages and disadvantages of laparoscopic hysterectomy compared with abdominal hysterectomy, particularly the relative rate of complications of the two procedures. Whilst uptake of laparoscopic hysterectomy has been slow, the situation is changing with greater familiarity, better training, better equipment and increased proficiency in the technique. Thus, a large, robust, multi-centre randomised controlled trial (RCT) is needed to compare contemporary laparoscopic hysterectomy with abdominal hysterectomy to determine the safest and most cost-effective technique.

Methods and analysis

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. A within trial-based economic evaluation will explore the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy. We will aim to recruit 3250 women requiring a hysterectomy for a benign gynaecological condition and who were suitable for either laparoscopic or open techniques. The primary outcome is major complications up to six completed weeks post-surgery and the key secondary outcome is time from surgery to resumption of usual activities using the personalised PROMIS-SF (Patient-Reported Outcomes Measurement Information System Physical Function) questionnaire. The principal outcome for the economic evaluation is to be cost per QALY at 12 months' post-surgery. A secondary analysis is to be undertaken to generate costs per major surgical complication avoided and costs per return to normal activities.

Ethics and dissemination

The study was approved by the West Midlands-Edgbaston Research Ethics Committee,18th February-2021 (Ethics ref: 21/WM/0019). REC approval for the protocol version 2.0 dated 02nd February 2021 was issued on 18th February 2021.

We will present the findings in national and international conferences. We will also 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.

Trial registration

University of Birmingham, ISRCTN14566195.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The LAVA trial is larger than all the previous 25 RCTs evaluating laparoscopic and open hysterectomy and of higher quality, addressing the methodological deficiencies of previous trials; namely their power to show a meaningful difference, accounting for surgical expertise bias and the ensuring the validity of outcomes assessments, especially the key secondary outcome of personalised recovery
- In the LAVA trial a novel, validated, personalised recovery tool is used via SMS and an expertise-based design to mitigate against surgical expertise bias employed.
- Third part randomisation is to be performed balancing important prognostic variables.
- Due to the differing natures of the intervention it is impossible to blind either the care providers, investigators or participants to their allocated group.

1. Introduction

Hysterectomy is common, with one in ten women undergoing the procedure in their lifetime, mostly for benign conditions [1,2,3]. 30,000 women undergo a hysterectomy every year in the UK for benign indications such as abnormal uterine bleeding and pelvic pain [1,2,3].

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 [6,7,8,9]. Currently, most hysterectomies are performed by laparotomy, through a vertical or transverse incision because this traditional method is thought to minimise intra-operative complications but the increased trauma of an abdominal incision 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].

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 [12,13,14,15]. The Cochrane review [5] identified no differences in the costs or outcomes apart from return to normal activities, which was shorter in the laparoscopic hysterectomy group by 14 days on average.

The uptake of laparoscopic hysterectomy is increasing with greater familiarity and increased proficiency in the technique aided by improved training and better surgical equipment [16, 17,18]. Patient's values and preferences, especially around speed of recovery may also be driving this trend.

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 [19,20]. Thus, we designed a large RCT to determine the clinical and cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy for women with a benign gynaecological condition.

2. Aims and objectives

2.1. Main clinical objective

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.

2.2. 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.

3. Study design and setting

3.1. Trial design

The study is designed as 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).

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. Patient and Public Involvement (PPI)

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".

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. 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.

4. Participants

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

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. The feasibility, and appropriateness of both routes of hysterectomy for women were to be decided pragmatically, the operating surgeon deciding where their equipoise was taking into consideration factors such as the size of the uterus, likelihood of pelvic adhesions and anticipated surgical complexity for either approach.

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 para-rectal space

4.1. Choice of intervention

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 [16]. Whilst the uptake of laparoscopic hysterectomy has been slow [17], 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 [18,19].

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.

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 (Supplementary file). 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.

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. Research Ethics Committee (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

6.2. Enrolment

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, and research nurses, after having received appropriate training relating to the trial.

Potential participants will be provided with a REC approved Study Participant Information Sheet (PIS) and given time to consider their involvement. Clinic doctors will confirm eligibility for the trial. After participant eligibility is confirmed and informed consent received, the baseline questionnaires are to be completed and then the participant randomised into the trial. Baseline data collected includes demographic and medical data (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); Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF) item bank v1.2 [19] (see “key secondary outcome"); quality of life, symptom and physical functioning questionnaires, EuroQoL EQ-5D-5L and EQ VAS [15], Urogenital Distress Inventory (UDI) [21], Pelvic organ prolapse symptom score (POP-SS) [21], Defecatory Distress Inventory (DDI) [22], Sexual Activity Questionnaire (SAQ) [23].

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

6.3. Randomisation

Randomisation is provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at http://www.trials.bham.ac.uk/lava). 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/m2)
- Uterine Size (<=12 weeks, >12 weeks)
- Planned retention of cervix (yes / no)
- Recruiting centre

6.4. 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.

6.5. Interventions and expertise-based surgery

Hysterectomy is undertaken by either a laparoscopic or an open abdominal route, by a surgeon who had self-declared as having expertise in laparoscopic hysterectomy, abdominal hysterectomy or both approaches to hysterectomy

The decision to remove or retain cervix (total or sub-total) or remove and retain ovaries was left to the discretion of the participant in consultation with her gynaecologist. The expertise design process for eligible centres is depicted in (Figure 1).

Satisfactory experience requires surgeons to have performed a minimum of 30 cases [24] and to have a current caseload of at least 12 cases per year [25,26,27]. For surgeons to conduct both procedures, these criteria will need to be met for both procedures. These thresholds are evidence-based. In a series of over 10,000 laparoscopic hysterectomies, surgeons who had performed more than 30 laparoscopic hysterectomies had a significantly lower incidence of ureteric and bladder injuries (0.5% and 0.8% respectively) compared with those performing 30 operations or fewer (2.2% and 2.0% respectively) [24].

The importance of surgical experience as a predictor of successful surgical outcome has been shown in other studies [25]. Surgical volume is well recognised to correlate with safety in hysterectomy [26]. A systematic review and meta-analysis of studies including 741,760 patients reported complication rates according to surgical volume. High volume surgeons were defined as performing at least one of a particular type of hysterectomy per month on average (i.e. a minimum of 12 per year). Low volume surgeons performed fewer than 12 hysterectomies per year and had higher major complication rates (total complications (odds ratio [OR] 1.3, 95% CI 1.2- 1.5%), intraoperative complications (OR 1.6, 95% CI, 1.2%-2.1%) and postoperative complications (OR 1.4 95% CI 1.3%-1.4%) [27].

7. Outcome Measures

Women who give consent in a face to face setting will subsequently complete their baselines questionnaires and then proceed to randomisation. 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 [19], [21,22,23]. Local research teams will offer remote (telephone, VOIP or video) contact, or exceptionally face to face appointments, to provide explanation.

7.1. Trial Outcomes

7.1.1. 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 [28]. 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. The specific type of major complication will be presented in addition to the Clavien-Dindo grade III-V classification.

However, other less common major surgical or anaesthetic complications may arise and these will be ascribed in accordance with the appropriate Clavien-Dindo classification shown in (Table 1)

TABLE 1

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).

7.1.2. 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 [19]. 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 were 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 created 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.

7.1.3. Other secondary outcomes

- Surgical outcomes:
  - Duration of operation, (minutes)
  - Estimated blood loss, (ml)
- In hospital stay:
  - 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
- Up to 14 days after surgery:
  - 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

- 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 [29] (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 [29] (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
  - Time from surgery to work (if working) in days
  - Work productivity and activity impairment scores using WPAI-GH questionnaire [30] (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
  - Symptoms of urogenital prolapse using the Pelvic Organ Prolapse Symptom Score (POP-SS) questionnaire [31,32]
  - Bladder function using Urogenital Distress Inventory (UDI) [33,34] questionnaire
  - Bowel function using Defecatory Distress Inventory (DDI) [35] questionnaire
  - Sexual function using the Sexual Activity (SAQ) questionnaire [36]
  - Quality of life score using EuroQol-5D-5L questionnaire
  - Quality of life score using EuroQol-5D-5L visual analogue scale
  - Body image using the Body Image Scale (BIS) questionnaire [37]
  - 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.
- Throughout: Serious adverse events

* 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.

A summary of the schedule of assessments is shown in (Supplementary Table 1) and the trial flow diagram shown is (Figure 2)

8. Statistical consideration

8.1. 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 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.

8.2. Analysis of outcome measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. 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 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 upper margin of the absolute risk difference 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].

8.3. 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 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.

8.4. 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.

We will capture recovery more fully with the other included validated outcome measures (e.g. PROMIS-PF (Patient-Reported Outcomes Measurement Information System Physical Function) item bank v1.2 [19], [21,22,23] Quality of Recovery 15 (QoR-15) questionnaire [25], numerical rating scales. The variation in analgesia type and use (secondary outcome) over the 14 day post-operative diary will presented descriptively because meaningful quantitative analysis is compromised due to the variation in type of analgesia and how to aggregate such data to allow valid comparison because meaningful quantitative analysis is compromised due to the variation in type of analgesia and how to aggregate such data to allow valid comparison. Appropriate summary statistics split by group will be presented for each outcome (e.g. proportions/percentages, mean/standard deviation or median/interquartile range).

8.5. Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm, 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.

8.6. 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.

8.7. 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.

8.8. 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) (Figure 2)

9. Sub-studies

Full details of these sub-studies are available from the authors on request

9.1. Qualitative process evaluation

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

9.2. Health economic evaluation

An economic evaluation was designed to assess the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy in the management of benign gynaecological conditions. A within trial-based economic evaluation was to explore the cost-effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy. The principal outcomes for the economic evaluation was cost per QALY at 12 months post-surgery. A secondary analyses was planned

to generate costs per major surgical complication avoided and costs per return to normal activities.

9.3. 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

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.

9.4. Management of risk

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 will also inform the CI. 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.

10. 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.

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.

DATA SOURCE CAN BE FOUND IN (TABLE 2)

TABLE 2

DATA SOURCE

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.

11. Discussion

The LAVA trial protocol was designed in 2019 and amended during 2020 before funding and ethical approval was granted. The trial commenced recruitment in September 2021 but failed to meet its RAG ('red; amber; green) criteria for site set up and recruitment rate and so for this

reason and the recognition by the funder (The NIHR HTA Programme) of insufficient NHS clinical and Research & Development capacity post the Covid-19 pandemic, the trial was closed. The research question remains relevant, given that almost 30,000 hysterectomies are undertaken per year [7,18] and especially now that the laparoscopic approach to hysterectomy is being facilitated further by advances in instrumentation including robotic surgery [40,41]. Our research group plans to analyse qualitative and quantitative data acquired from the commencement of the trial to inform future surgical trials and aid future researchers wishing to undertake comparative trials in hysterectomy. We believe that our carefully considered protocol will be of value to future researchers working in the field of optimising clinical outcomes for women undergoing hysterectomy.

12. Strengths and limitations

The LAVA trial was larger than all the previous 25 RCTs evaluating laparoscopic and open hysterectomy and of higher quality, addressing the methodological deficiencies of previous trials; namely their power to show a meaningful difference, the validity of outcomes assessment, especially the key outcome of recovery and a failure to account for surgical expertise. In the LAVA trial we used a novel, validated, personalised recovery tool [16,21,22], and employed an expertise-based design to mitigate against surgical expertise bias [18,34]. Third part randomisation was performed balancing important prognostic variables. Due to the differing natures of the intervention it is impossible to blind either the care providers, investigators or participants to their allocated group.

13. Potential impact and implications

Hysterectomy is common, with one in ten women undergoing the procedure in their lifetime, mostly for benign conditions [12,13,14]. The operation imposes substantial morbidity upon women, disrupts families and impacts upon wider society through utilisation of scarce health care resources and lost productivity [3,4,5,6] [15]. These burdens could potentially be reduced with safe, less invasive surgery allowing quicker recovery. Currently, most hysterectomies are performed abdominally because this traditional method is thought to minimise intra-operative complications but the increased trauma of an abdominal incision can prolong recovery [2]. This may be especially true in overweight and obese women, where morbidity is greater from mobility restrictions and wound infection [16].

Laparoscopic hysterectomy avoids the need for a large surgical incision speeding recovery for most women but has been associated with serious complications and specialist surgical skills. However, scientific advances in imaging and equipment, has made laparoscopic surgery easier as well as more accessible to general gynaecologists [11] [16,17]. Furthermore, laparoscopic surgery forms an integral part of modern packages of nursing, anaesthetic and surgical care designed to enhance recovery and allow 24 hour hospital discharge [20].

The wider adoption of contemporary laparoscopic hysterectomy has the potential to minimise morbidity, expedite recovery and improve clinical outcomes for women in the short-term and longer-term. Furthermore, enhanced recovery has the potential to be economically advantageous to the NHS through resource efficiencies and wider society via increased productivity.

14. Ethics and dissemination

The study was approved by the West Midlands-Edgbaston Research Ethics Committee. REC approval for the protocol was issued on 18th February 2021. All participants gave informed consent before participation. The trial was being 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 findings will be presented and disseminated via the BSGE, RCOG and other national and international conferences. We will also 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.

15. Confidentiality

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.
The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence.

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).

16. Trial organisational structure

16.1. Sponsor

University of Birmingham.

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

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.

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.

17. Amendments

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.

18. 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. 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.

19. 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.

20. Publication policy

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.

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.

21. Auditing

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

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Statements

Author's contribution: TJC, LM, PB, JF, MM, KC, ES, LJ, PS, TR, WM, SB, RW were involved in conception and trial design. TJC, LA and were involved in drafting of the article. TJC reviewed and critiqued the article for intellectual content. All the authors were involved in final approval of the article.

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Figure 1
The expertise design process for eligible centres

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

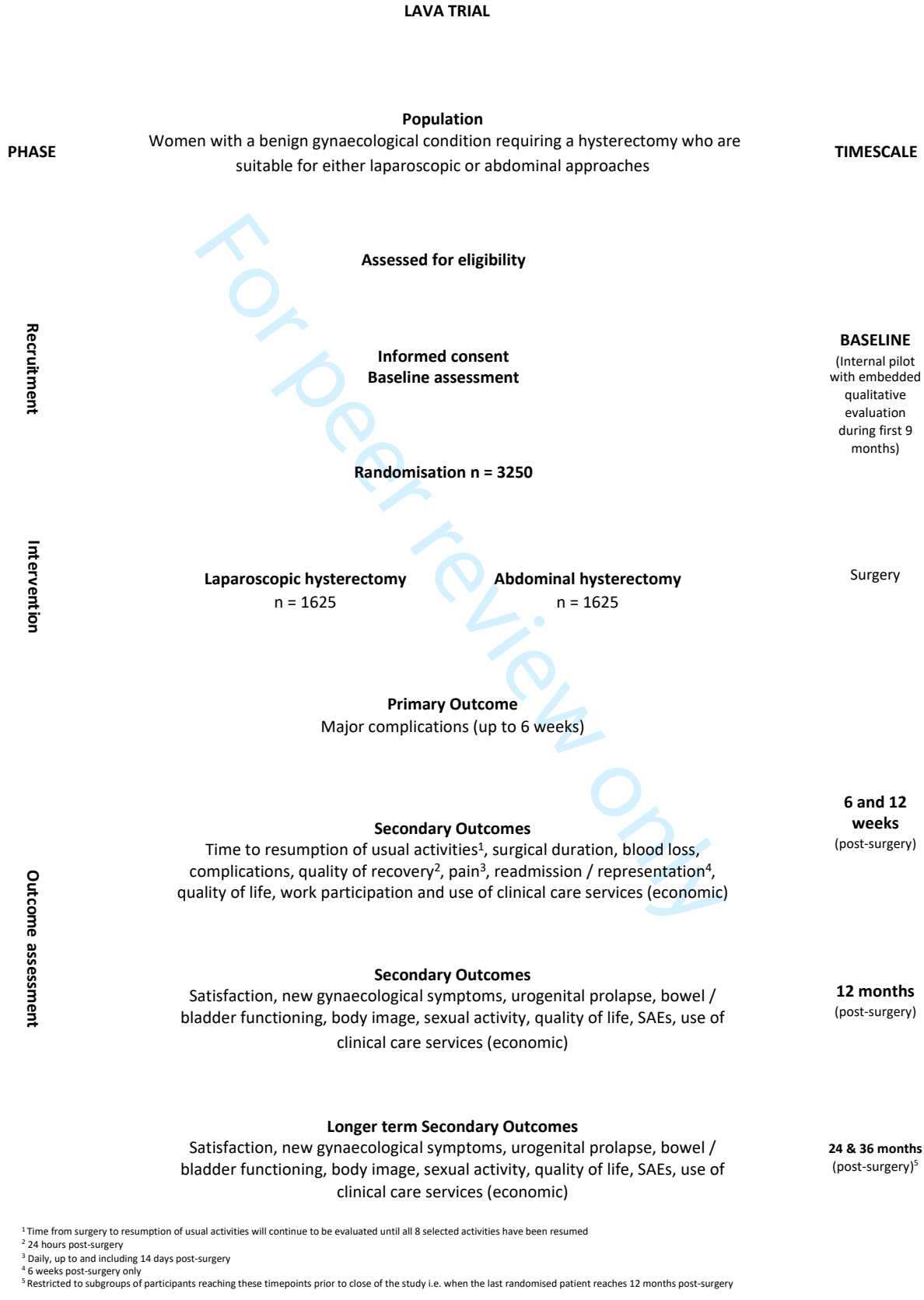
Allocated LAPAROSCOPIC expert surgeon[4]

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.

Figure 2
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

Supplementary Table 1

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	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

Rand = randomisation

* 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

Birmingham Women's and Children's NHS Foundation Trust

Participant Trial | | | | | | | |

LAparoscopic Versus Abdominal hysterectomy (LAVA)

Participant Consent Form

Please initial inside each box to provide your consent to participate in each part of the study.

Please initial inside each box that you agree to take part in

1	I confirm that I have read and understand the participant information sheet (version__.__ and date _ _ / _ _ / _ _ _ _) for the LAVA trial. I agree that I have had the opportunity to take time to consider my involvement in the trial and I have had the chance to ask questions, all of which have been answered to my satisfaction.	
2	I agree that my involvement in the LAVA trial is voluntary, and I am free to withdraw at any time without the quality of my medical care or my legal rights being affected. I agree that if I decide to withdraw from the trial, any information that has already been analysed cannot be withdrawn. I understand that should I want to withdraw from the study then I will be contacted by a member of the study team and given the options described in the above participant information sheet about what other data can be collected from me and what happens to it, and that my response will be recorded on a withdrawal form.	
3	I agree that my hospital research team can provide a copy of my consent form, and relevant personal information, including my name, home address, date of birth, telephone number, ethnicity, Body Mass Index (BMI), if I have had any caesarean sections, the size of my womb and other relevant details of my medical history including my hysterectomy to the researchers based at the University of Birmingham for use in the LAVA trial	
4	I agree that relevant sections of my medical notes, and all of the information provided by me in trial related questionnaires will be transferred to members of the LAVA research team at the University of Birmingham. I agree that collaborators of the LAVA trial, and authorised representatives from the study sponsor (The University of Birmingham), regulatory authorities and my NHS trust can access my data where relevant such as my taking part in this research and safety monitoring.	
5	I agree that my data will be anonymised and used in combination with that of others to produce research outputs such as reports, presentations, publications and websites connected to the LAVA trial. I understand that I will not be individually identified in any publicly available output.	

Birmingham Women's and Children's NHS Foundation Trust

Participant Trial

6	I understand that all information collected from me for this study will be subject to the General Data Protection Regulation and Data Protection Act 2018. This information will be stored securely by the University of Birmingham, which is the data controller for the LAVA trial, for a minimum period of 10 years.	
7	I give consent for members of the LAVA trial team to contact me by telephone, mobile, post, voice over the internet protocol - VOIP (e.g. Skype, Facetime etc) or email to request additional information such as missing data on questionnaires that I have completed.	
8	I agree that some anonymous information collected from me may be shared and/or made publicly available for other researchers to support other research in the future.	
9	I agree that my general practitioner(GP) is informed of my participation in the LAVA trial.	
10	I agree to my study number and mobile telephone number being passed to an external company (Textlocal) who will send me text messages containing a link that will take me to a questionnaire hosted by the University of Birmingham telling them which of the recovery goals I set before my operation I have reached. I understand that only my study number and mobile telephone number will be passed to Textlocal and that these, will be securely encrypted whilst being stored by Textlocal. I understand that my data will not be used by Textlocal for any other purpose. I understand that Textlocal will securely delete all the information they hold on me at the end of the LAVA study.	
11	I understand the information that has been given to me about the LAVA trial and I agree to take part in this study.	

Name of Participant	*Date*	*Signature*
Name of Person taking Consent	*Date*	*Signature*

Master copy for Site File, 1 copy for participant notes, 1 copy for Participant, 1 copy for LAVA Trial Office

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1, lines (1-2)
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry Page 4, line 76
Protocol version	3	Date and version identifier Page 2, lines (43,44)
Funding	4	Sources and types of financial, material, and other support Page 35, lines (792-793)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Pages (1-2), lines (4-34)
	5b	Name and contact information for the trial sponsor Page 31, lines (702-705)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Page 26, lines (600-602) Page 32, lines (737-744) Page 33, lines (764-766) Table 3 (data source): please check imaging, and recruitment

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Pages (31,32), lines (708-725)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Page 6, lines (92-125)
	6b	Explanation for choice of comparators Pages 11, lines (225-232)
Objectives	7	Specific objectives or hypotheses Page 7, lines (130-134)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 8, lines (144-176)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Page 8, lines (150-153)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Pages (10-11), lines (206-223) Page (14), lines (303-308) The expertise design process for eligible centres is depicted in (Figure 1)

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Page 14, lines (302-311)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Page 12, lines (279-283)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Page 13, lines (264-278) Page 31, lines (712-716)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Page 11, lines (218-223)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Pages (15-20), lines (327-446)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Trial schema (Figure 2)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Pages (21-22), lines (449-472)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Page 13, lines (262-266)

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Page 14, lines (286-296)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Page 13, lines (267-278)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Pages (12-14), lines (253-296)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Page 14, lines (298-300)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A- See above (17a)

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Page 26, lines (577-585) Page 24, lines (516-525)

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Page 13, lines (279-283)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Pages (26-27), lines (598-608) Table 3- Data Source
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Page (21-24), lines (481-525)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Pages (24-25), lines (527-575)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Page 24, lines (534-538)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Page 32, lines (727-734)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Page 24, lines (540-546)

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Page 26, lines (587-595)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Page 34, lines (773-776)
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 30, lines (669-676)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Pages (32-33), lines (737-744)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 12, lines (241-247)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Pages (30-31), lines (684-697)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 34, line 790

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Page 33, lines (747-752)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Page 33, lines (755-759)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Page 30, lines (678-681) Page 34, lines (768-770)
	31b	Authorship eligibility guidelines and any intended use of professional writers Page 34, lines (785-788)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Page 33, lines (749-752) Page 34, lines (768-770)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Please see supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.